MARCH 2017 # 28

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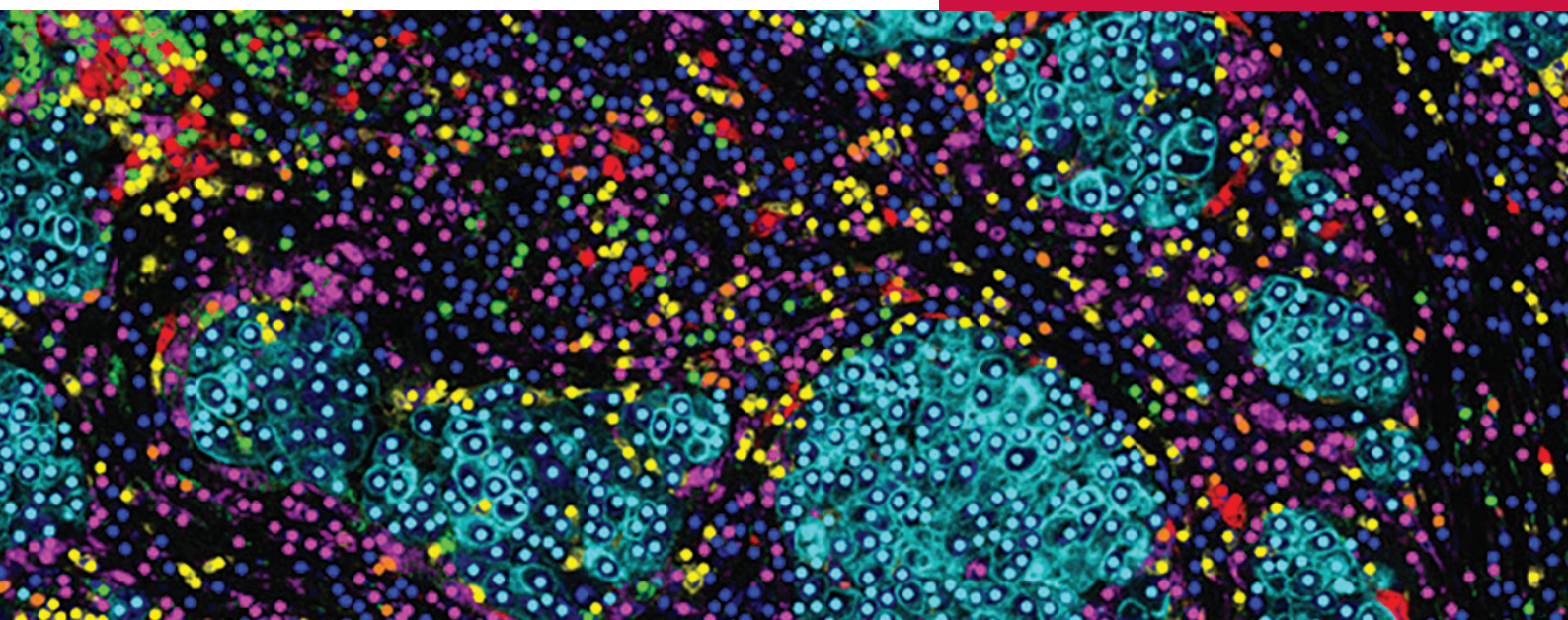
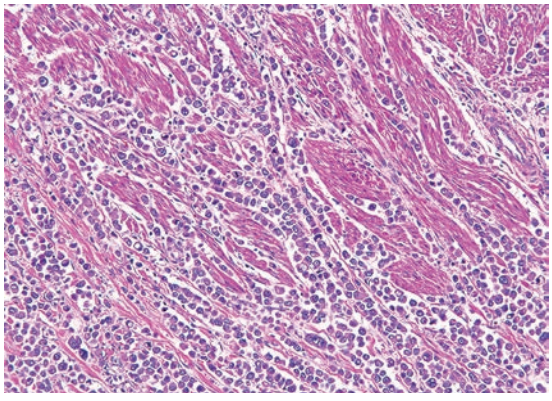
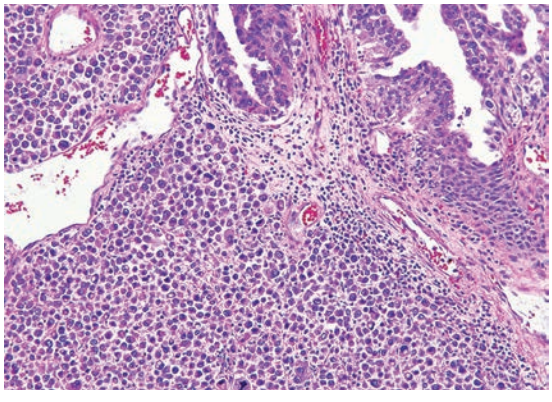
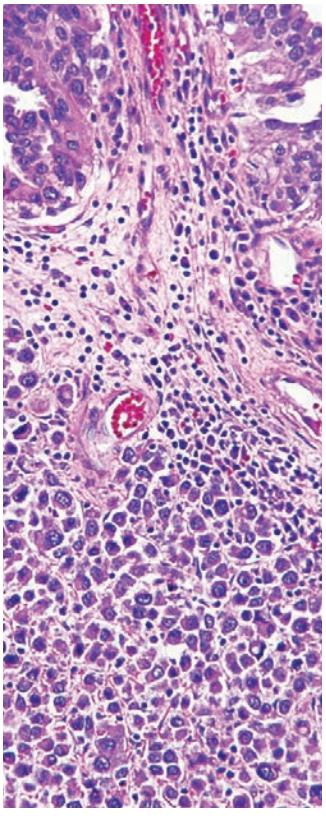


Case of the Month







Credit: Ivan Damjanov, Kansas Histopathology Club

Urinary bladder tumor

The tumor shown here was removed by radical cystectomy from a 72-year-old man. The tumor cells were positive for cytokeratin 7 and weakly positive for CD138, but were negative for immunoglobulins and mucins.

What is the most likely diagnosis?

- *A* Urothelial carcinoma
- *B* Adenocarcinoma of urachal origin
- *C* Plasmacytoma
- *D* Plasmacytoid carcinoma
- *E* Metastatic breast carcinoma

Do you think you have a good case of the month? Email it to edit@thepathologist.com

To register your guess, please go to http://tp.txp.to/0317/case-of-the-month
We will reveal the answer in next month's issue!

Answer to last month's Case of the Month…

C: Malignant perivascular epithelioid cell tumor (PEComa)

PEComas are soft tissue tumors composed of nests of clear or granular eosinophilic cells that have the immunohistochemical features of perivascular epithelioid cells. These cells may be epithelioid- or spindle-shaped. The tumor nests are typically surrounded by capillary vessels. Typical PEComas may show occasional pleomorphism, but mitotic figures are usually rare or absent. Malignant PEComas are characterized by brisk mitotic activity, necrosis, marked nuclear atypia, and significant pleomorphism as in this case. Tumor cells are positive for melanoma markers, such as microphthalmia transcription factor, Melan A, and HMB45, and smooth muscle cell markers, such as smooth muscle actin or calponin. Desmin and S100 are less often positive (1).

Submitted by Wei Cui, The University of Kansas School of Medicine, Kansas City, Kansas, USA.

Reference

1. *JL Hornick, CC Pan, "PEComas", WHO classification of tumours of soft tissue and bone. IARC Press: 2013.*

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A microscope constructed from cardboard, representing low-cost tools for developing regions.

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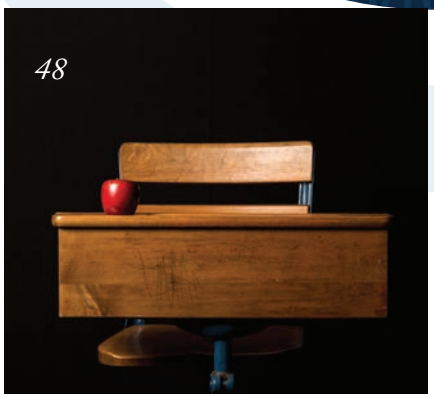

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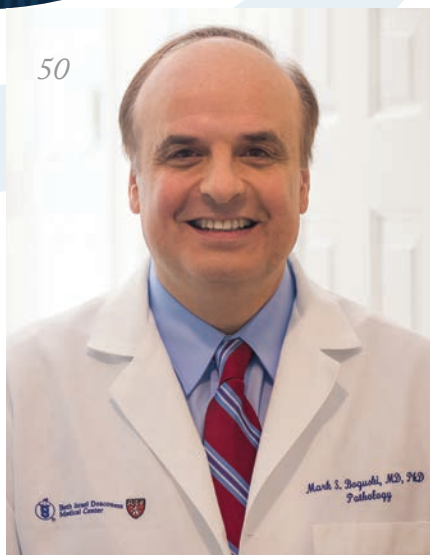

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In Practice

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Sitting Down With

the **Pathologist**

ISSUE 28 - MARCH 2017

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PHOTON IS OUR BUSINESS

Everything's Bigger in Texas

... including the welcome. But meeting you – our readers – was the real highlight in San Antonio

As I write this editorial, I am just about shaking off the desynchronosis from yet another fantastic USCAP event – this year, held in the wonderful city of San Antonio, Texas. I can't emphasize how pleased I was to meet so many of you there; the feedback I received was simply amazing! (And, I'll be honest, I was happy that my boss was there to hear some of the praise...)

A big thanks goes out to all of you who stopped by our stand to let us know what you think of The Pathologist and, in one (slightly reluctant) case, to sign a copy of a Sitting Down With for a fan (...you know who you are, Jerad Gardner!).

One item that seems to have gone down well is our relatively new reader-requested section, Case of the Month. In fact, someone told me that January's case was the subject of a lengthy conversation between a group of people at an evening event during the USCAP congress. That conversation then led to a direct connection between a person at the event and the submitter of the case – and I believe those people are now discussing a potential informal collaboration! My sincere thanks to Ivan Damjanov for getting this initiative up and running. I urge the rest of you to get involved. If you think you've got a case that may stump your peers, please email us. If we feel it's strong or curious enough (and assuming you have a high-resolution image), we'll publish it and let you know how many of our readers got it right.

I hope Case of the Month demonstrates our commitment to listening to our readers. On that note, one female senior pathologist who I spoke with recently requested that we publish an article on a somewhat delicate subject: sexism and bullying in the workplace – something that she told me was more common than one might believe. Testament to our vow to cover the issues that matter to you – even the controversial ones – I want to know if any of you have experienced such negativity or witnessed it in your workplace. If so, please do get in touch (we will gladly respect anonymity where requested).

Being aware of topics that you want to see covered – or aspects that could be improved – helps our development and growth (and makes us more useful to you!) I'll admit that it's more than a little flattering to listen to praise for our beloved publication, but I am also more than happy to hear constructive feedback and requests. My inbox is always open to feedback and new ideas: edit@thepathologist.com.

On a final note, thank you to everyone for making us feel so welcome in San Antonio. I'm already looking forward to Vancouver 2018!

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?

Email: edit@thepathologist.com

The Castleman Criteria

A novel ruleset may give hope to iMCD patients who remain undiagnosed

When your symptoms belong to a rare illness, such as Castleman disease (a lymph node disorder), the diagnostic outlook is bleak. Idiopathic multicentric Castleman disease (iMCD) is a life-threatening subtype that affects multiple lymph nodes. With no established diagnostic protocol in place, sufferers may remain undiagnosed – or misdiagnosed with lymphoma or autoimmune disorders – for years. To offer a solution, a multinational team of investigators banded together to pioneer a set of identification criteria (1).

The journey began with a review of 244 clinical cases and 88 lymph node biopsies from iMCD patients. Fifteen months of investigation yielded a set of major and minor criteria for diagnosis (see Table 1). To confirm iMCD, patients must exhibit at least two major and two minor criteria, including at least one abnormal laboratory result.

Next, the investigators used their criteria to retrospectively diagnose patients from a clinical trial of siltuximab, a therapeutic tested on iMCD patients. Trial participants who did not meet the criteria had no response to the drug, while those who did had a 43 percent response rate.

The outcome seems to show the effectiveness of the criteria, but that doesn't mean the job is done. Using ACCELERATE, a research platform that collates iMCD clinical data, the researchers aim to keep fine-tuning their method. But even in this early stage, the investigators believe their Castleman criteria could help turn the tide in the fight against iMCD. *WA*

Reference

1. *DC Fajgenbaum et al., "International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease", Blood, [Epub ahead of print] (2017). PMID: 28087540.*

Major Criteria

Histopathological features consistent with iMCD on excisional lymph node biopsy
Enlarged (≥1 cm) lymph nodes in two or more lymph node stations

Minor Criteria

Clinical	*Laboratory*
Constitutional symptoms	Elevated C-reactive protein
Hepatosplenomegaly	Anemia
Edema or effusions	Hypoalbuminemia
Eruptive cherry hemangiomatosis or violaceous papules	Thrombocytopenia or thrombocytosis
	Renal dysfunction
Lymphocytic interstitial pneumonitis	Polyclonal hypergammaglobulinemia

Table 1. Major and minor criteria for the diagnosis of iMCD.

FOSL1 Fuels Cancer?

Unveiling a potential new biomarker for lung and pancreatic tumors

KRAS mutations are responsible for a large number of human cancers – but why? Clearly, more insight into the mechanisms involved could deepen our understanding of certain cancers, as well as offer up new diagnostic and therapeutic possibilities. Silve Vicent co-led a team of researchers who saw the opportunity to delve deeper into the mechanisms of *KRAS*-mutated tumors – and their findings showed that transcription factor FOSL1 is highly expressed in lung and pancreatic cancer patients (1), implicating the protein as a possible diagnostic biomarker. To further unzip what information the gene may hold, we spoke with Vicent, assistant professor at the University of Navarra's Center for Applied Medical Research.

What was your goal during the investigation?

We aimed to expose common core elements of *KRAS* oncogene signaling relevant for the homeostasis of *KRAS*-mutated tumors. To do this, we followed a two-tiered "zoom-in" strategy. The first part involved identifying *KRAS*-regulated genes by a cross-species meta-analysis of laboratory data, and the second included selecting genes frequently upregulated across human *KRAS*-driven cancers. We did this by contrasting the cross-species signature against a panel of five different tumor types where *KRAS* is frequently mutated. We chose FOSL1 for follow-up experiments because it was the only gene whose high expression was a marker of poor survival in *KRAS*-related lung and pancreatic cancer patients.

How did you further elucidate the protein's role?

To follow up on the role of FOSL1 in those cancers, we carried out in vitro and in vivo studies of human and mouse cancer cell line panels, where FOSL1 was inhibited via RNA*i*. We investigated the characterization of FOSL1 expression levels in patient-derived xenografts, the genetic abrogation of FOSL1 in genetically engineered mouse models, and the pharmacological inhibition of FOSL1 targets in combination with *KRAS* inhibition (using inhibitors that are under investigation in clinical trials).

Could FOSL1 could play a role in non-*KRAS* cancers?

We have shown that FOSL1 expression can be regulated through several kinase modules downstream of the *KRAS* oncogene. It is likely that non-*KRAS* genetic alterations may trigger activation of such kinase modules to upregulate FOSL1 expression in other tumors. For example, you can find genetic alterations that increase FOSL1 expression in the Wnt pathway in colon cancer, and in the *NF1* gene in gliomas and glioblastomas.

What's next?

At this stage, we are focusing on two main goals. First, we are working to discern which FOSL1 transcriptional targets mediate its deleterious effects in *KRAS*-mutated tumors. Second, we are looking for inhibitory strategies that target *KRAS*-mutated tumors – involving depletion of FOSL1 in conjunction with chemotherapy and/or targeted therapies currently in the clinic.

Reference

1. *A Vallejo et al., "An integrative approach unveils FOSL1 as an oncogene vulnerability in KRAS-driven lung and pancreatic cancer", Nat Commun, 8, (2017). PMID: 28220783.*

Sticking Our Noses into Lung Cancer

A nasal swab could be an effective diagnostic for pulmonary malignancy

Lung cancer kills over 1.5 million people per year worldwide (1) – and even though its prevalence has slowly declined over the last few decades, the five-year survival rate after diagnosis is still only 17.7 percent (2). At the moment, lung cancer lesions are detected via costly CT scan or by lung biopsy, which is both expensive and invasive. Better screening for the disease could boost survival rates – and The Boston University School of Medicine may have the solution – a simple nasal swab (3).

In 2015, a BU group conducted research showing that bronchial airway epithelia outside a cancerous site can carry the genetic signature of lung cancer (4). Following on from that study, the investigators hypothesized that those malignant traces might present themselves even farther away from the cancer – in the nasal airway – in smoking-induced instances of the disease.

They evaluated the nasal epithelia of current and former smokers going through diagnostic evaluation for pulmonary lesions and discovered that 535 genes in those samples were linked with diagnosis of lung cancer (3).

More research is needed to validate the findings, but the investigators are confident that their discovery could eventually lead to a novel noninvasive test for lung cancer detection. But even without a current diagnostic to take advantage of their efforts, these findings are significant. *WA*

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2. *National Cancer Institute, "Cancer stat facts: lung and bronchus cancer", (2017). Available at: http://bit.ly/2mWbmbd. Accessed March 16, 2017.*
3. *For the AEGIS Study Team, "Shared gene expression alterations in nasal and bronchial epithelium for lung cancer detection" J Natl Cancer Inst, 109, (2017).*
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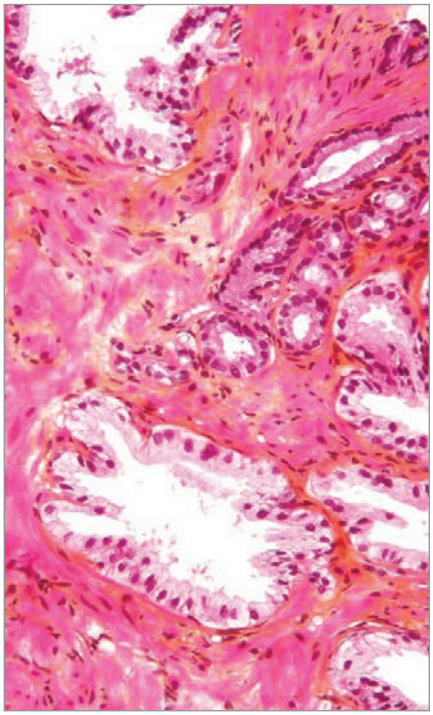
DESNT: Poor Prognosis Prostate Cancer

Could unnecessary surgery soon be confined to (medical) history?



"There is currently no proper classification of prostate cancer," says Colin Cooper, Professor of Cancer Genetics in Norwich Medical School at the University of East Anglia. "This is a major problem for people who are diagnosed with the disease, because only a small proportion is actually fatal. This leads to massive overtreatment – particularly in the USA, where many men are made impotent unnecessarily. We urgently need a test that can distinguish aggressive from non-aggressive cancers so treatments can be targeted." The strong sentiment kick-started Cooper into co-leading a study to create a classification framework for prostate cancers (1).

During conventional prostate cancer diagnosis by blood test or rectal exam, categorization of the disease is difficult because of its highly heterogeneous nature. What if the problem were approached from a mathematical perspective instead of a purely medical one? The investigators used a Bayesian model – latent process decomposition – to analyze the transcriptomic data of prostatectomy patients. The model revealed 45 genes that show low levels of expression in what the researchers call "DESNT" prostate cancers – a subcategory with a poor prognosis.

Does this mean there's a new prostate cancer diagnostic? Not according to Cooper. "Designation of a cancer as DESNT is not a biomarker. The category was identified before we linked it to clinical data and found it had poor prognosis. It is a new classification of prostate cancer." He adds, "Much of the data that we used has been around for over 10 years. It's just that the wrong math has been used to analyze the results. When you use the right math, it's easy to see the DESNT poor-prognosis cancers."

As for the classification's future, the researchers plan to develop a test to identify DESNT cancers in the clinic. And Cooper's lab is also setting up a review to determine how easily histopathologists can distinguish DESNT cancers from more benign ones. If implemented, proper classification could not only save resources in cases that don't require treatment, but also save men from unnecessary pain and suffering. *WA*

Reference

1. *BA Luca et al., "DESNT: A Poor Prognosis Category of Human Prostate Cancer", Eur Urol Focus, (2017).*

Cancer Comes Unglued

Loss of cellular adhesion may be a red flag for imminent metastasis

One of the key aspects of understanding cancer behavior is predicting when it may metastasize. Previous research suggests that, rather than exploring the intricacies of genetics, epigenetics, or biochemistry, it's possible that we may gain some insight by simply measuring cancer cell adhesion (1). Could the intricate mechanisms of metastasis really be predicted by observing cellular stickiness? "Probably," say investigators from the University of California, San Diego (2).

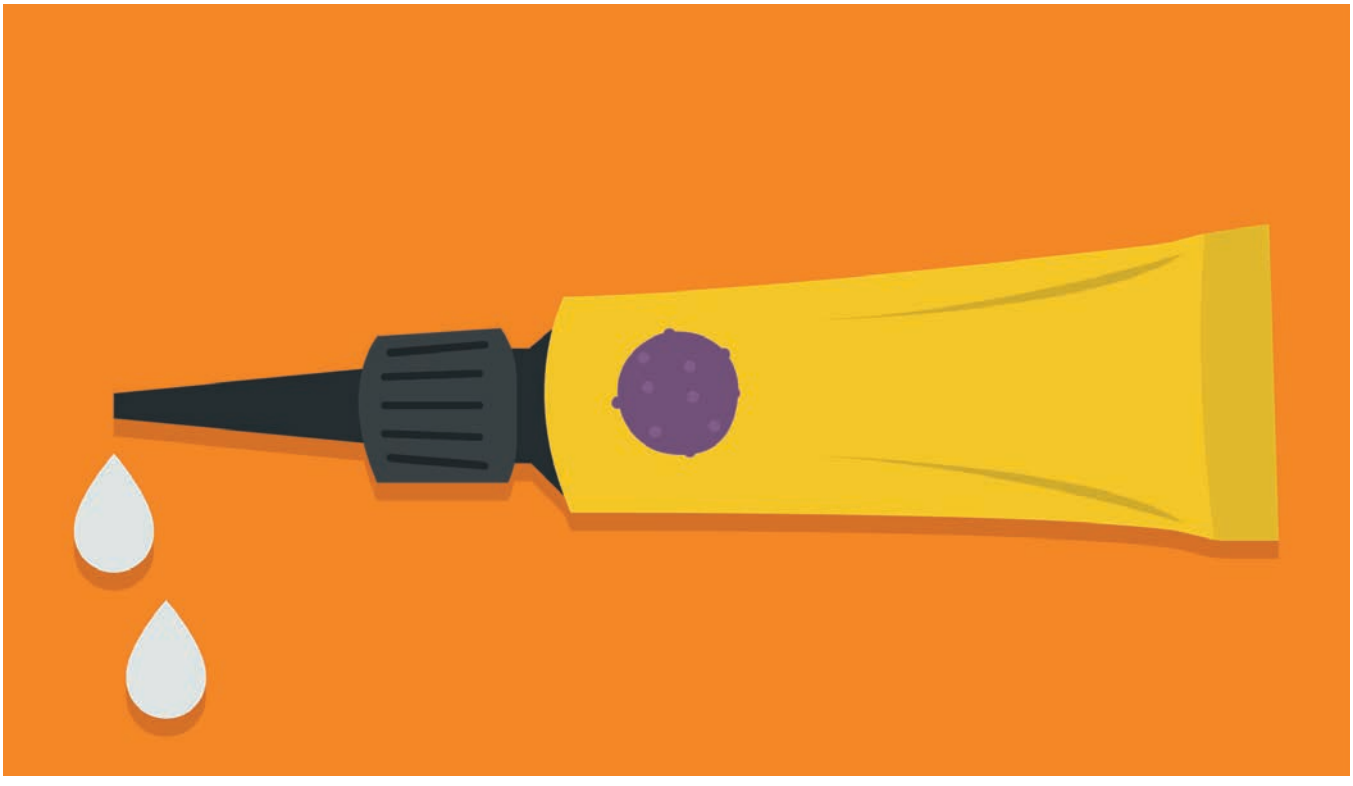
The heterogeneous nature of cancer confounds attempts to identify biomarkers that can predict metastasis, so the researchers decided to approach the problem from a different angle – morphology. Determined to find out whether there is indeed a strong correlation between cell stickiness and cancer spread, the UCSD team built a device to measure the adhesive strength of breast and prostate cancer cells. It consists of a spinning disc attached to a coverslip coated with extracellular matrix (ECM) proteins, to which the researchers then stuck cancerous cells. The apparatus was able to quantify the force required to unbind the cells from the ECM.

Compared with very adhesive cells, they found that less sticky malignant cells are more likely to metastasize. The research quantified relative adhesion, factored in the heterogeneity within cell lines, and assessed the magnesium and calcium concentrations in stromal tumors, which are higher than in non-cancerous cells. All these factors together should help identify the role that cellular adhesion plays in the metastatic state of a cancer cell.

To keep moving forward, the team has also developed another device to identify migratory cells with lower adhesive properties than surrounding tissue. They believe this device may ultimately lead to an actual indicator for metastatic potential – if only they can stick with it… *WA*

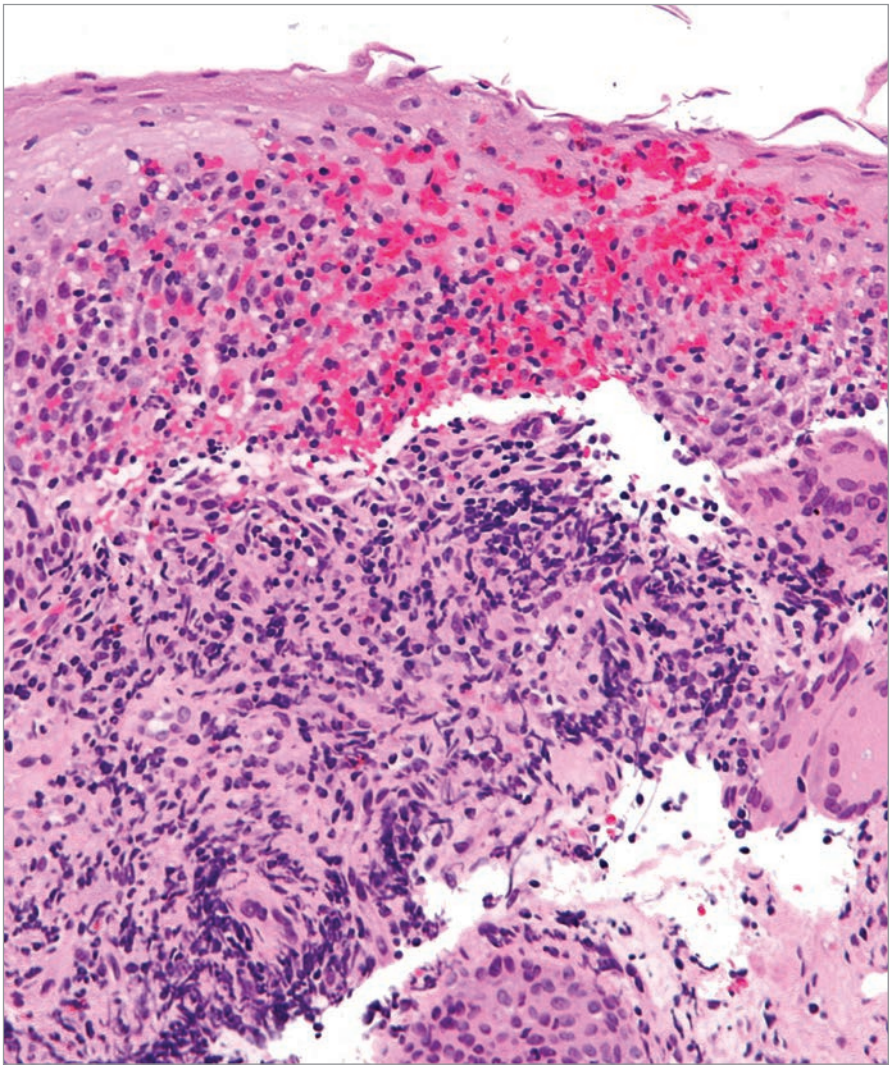
References

1. *NE Reticker-Flynn et al., "A combinatorial extracellular matrix platform identifies cell-extracellular matrix interactions that correlate with metastasis", Nat Commun, 3, (2012). PMID: 23047680.*
2. *A Fuhrmann et al., "Metastatic state of cancer cells may be indicated by adhesion strength", Biophys J, 112, 736–745 (2017). PMID: 28256233.*



Cracking the Case of Crohn's

Immunoproteomics offer a new diagnostic test – and potentially a route to better understanding of the disease



Abdominal pain, diarrhea, anemia, weight loss... all symptoms of Crohn's disease. But the cause? It has eluded pathologists and clinicians since the illness was first described over a century ago. Now, researchers at Arizona State University and the Mayo Clinic have teamed up to create an autoantibody biomarker panel for the condition (1) – one that may not only help unveil new diagnostics for the condition, but possibly even pave the way to discovering its roots.

"There are currently no gold standard tests for the diagnosis and prognosis of Crohn's disease," says Joshua LaBaer, Director of the Biodesign Institute at Arizona State University. "Delay in diagnosis – and misdiagnosis – postpones the initiation of appropriate treatment, and there is also a lack of means to distinguish between patients with aggressive or non-aggressive forms of the disease." The current de facto methods of identifying the immunological disorder involve expensive equipment (MRI) or invasive surgical procedures (biopsy).

The investigators believed there had to be a better way to serve patients and began searching for an efficient, noninvasive clinical tool to diagnose Crohn's disease. The result? A novel system called NAPPA – nucleic acid programmable protein arrays – that profiles Crohn's-associated autoantibodies against more than 1,900 blood-borne human proteins. After further validation by an ELISA, their results revealed a panel of IgA antibodies that could be used as a diagnostic test for Crohn's disease.

It's one of the first investigations to explore the immuno-proteomics of the disease, and the researchers are optimistic that the approach may shine a light on its cause. Moreover, the array can also be applied to other illnesses; LaBaer says, "We have already applied NAPPA in the study of many other diseases involving autoimmunity (type 1 diabetes, rheumatoid arthritis), cancers (breast and lung), neurodegeneration (Alzheimer's disease), and infectious disease (tuberculosis)."

"We hope our pilot study in Crohn's disease will serve as a springboard to allow us to carry out a more comprehensive study," says LaBaer, who hopes it will eventually lead to a product that can improve clinical management of patients. *WA*

Reference

1. *H Wang et al., "Identification of antibody against SNRPB, small nuclear ribonucleoprotein-associated proteins B and B', ad an autoantibody marker in Crohn's disease using an immunoproteomics approach", J Crohns Colitis, [Epub ahead of print] (2017). PMID: 28204086.*

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 editors at edit@thepathologist.com

Change is Here, But Are We Ready for It?

Our approach to clinical research and translation must change if we are to deliver truly patient-centric healthcare

By Giorgio Stanta, Head of the Molecular Histopathology Laboratory, University of Trieste, Italy

The National Institutes of Health (NIH) defines clinical research as "Research with human subjects that is: Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. It includes: (a) mechanisms of human disease, (b), therapeutic interventions, (c) clinical trials, or (d) development of new technologies" (1).

This seems clear and straightforward; however, as we continue to discover more about the genetic basis of disease and move ever more towards a personalized approach to diagnostics and therapeutics, the boundaries between what is defined as clinical research, and basic and translational research, are becoming blurred.

We have entered a new era in healthcare and medicine where patients' tests are being used to not only inform treatment decisions, but also to develop our knowledge of disease and drive new research. Recent advances in oncology – for example in molecular intratumor heterogeneity and its impact on the pathogenesis of disease and treatment resistance – have given rise to patient-centric clinical research performed on solid tissues or blood (the so-called liquid biopsies), with the results being very specific to that donor patient. In this scenario, molecular analyses are performed to verify clinical cases and to assess efficacy of new treatment opportunities. This analysis is not limited to a few defined biomarkers only, though, it gives rise to subgroups of patients, whereby some may have intrinsic resistance to therapy from the beginning, and others later present an acquired resistance. This type of knowledge supports the need for ongoing molecular analysis through a patient's treatment pathway with the definition of increasingly small groups of patients and suggestion of very specific combinatorial therapies. However, it also provides valuable information for the development of new therapeutics.

In anticipation of the growing importance of clinical research, the Organisation of European Cancer Institutes (OECI) (2) has developed a specific accreditation and designation programme for comprehensive cancer institutes. This accreditation takes into account not only the organization, diagnosis and therapeutic aspects of this molecular testing, but also what clinical research can be performed on what type of patient. The objective of the program is to guarantee that the patient has the most advanced treatment possibilities available, with a higher level of personalized analysis.

Accreditation is crucial for this type of research to ensure accuracy and reproducibility of results which, in my opinion, can be affected by at least three different factors. The first is the preclinical conditions of patients' material. For example, with fixed and paraffin-embedded tissues, long ischemia times before fixation must be avoided, and sample acquisition and fixation should

be performed with correct procedures in line with the recently developed CEN recommendations (3). The second aspect is the analytical methods used. These must be standardized and specific standard operating procedures should be followed, which include accurate internal and external quality control procedures. The third cause of irreproducible results is tissue and intratumor molecular heterogeneity, which is at the basis of clonal tumor evolution and acquired resistance to new therapies. This must be studied in depth, using tissues and "liquid biopsies" to define spatial and temporal development.

Understandably, this new approach to clinical research requires specialist facilities and is now viewed as an integrated activity in high-level clinical institutions. Not every hospital has direct access to these facilities though, and for this reason there is a real need for organized reference centres as an alternative for patients who need more sophisticated types of analysis and treatment.

Something else that needs to be very carefully considered is the bioethics of this type of approach. The fact is that we are using patient donor tissue or blood to support their own effective treatment, but also to perform clinical research, so this raises a number of bioethical issues. It's very important that this matter is discussed together with patient associations and an agreement reached on how to deal with it.

Overall, I strongly believe that new organizational changes are needed in health institutions. Clinical research must be central in this new vision, which must be developed together with patient organizations. Our new approach must support the training and continuous development of clinical researchers so that they amass experience and expertise in applying the results of clinical research to a single patient. In order to do this, however, we will need to create national and even international networks of reference centers, so that this level of patient-centric care can be made available to everyone, irrespective of their location.

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Measuring the Microbiome

Untangling the complex web of relationships between humans and the trillions of microbes who share our bodies is a daunting task, but novel application of modern analytical techniques at least gives us a chance.

By Liam M Heaney, postdoctoral scientist in the Department of Cardiovascular Sciences, University of Leicester, UK

The symbiotic relationship between humans and microbes is important for maintaining good health. And according to mounting evidence, dysfunctional relationships could increase susceptibility to disease (1). Here, I will use the example of trimethylamine [N-oxide] (TMA[O]), a molecule mediated through metabolism of dietary components by gut microbes, to illustrate the complexity of the microbiome.

TMAO can be measured in biofluids and, in 2011, was found to be elevated in the plasma of patients diagnosed with coronary artery disease (2). Later, it was demonstrated to be elevated in patients at higher risk of major adverse cardiac events (for example, stroke, myocardial infarction) within three years (3). Most systemically circulating TMAO is formed by metabolism of dietary components, such as L-carnitine and free choline, by the gut microbiota (4). These molecules are readily available in red meat and dairy, and TMAO has been identified as a possible mediator in the link between red meat and cardiovascular disease. But the relationship is complex. Paradoxically, TMAO is present in relatively high quantities in fish, yet populations with seafood-rich diets are considered at lower risk of heart disease than other western populations (5). We, and others, are attempting to unravel the relationship between diet, TMAO and heart disease.

TMAO is a non-volatile small molecule (molecular weight 75.11), and liquid chromatography-mass spectrometry (LC-MS) methods have been developed to measure circulating concentrations in plasma and serum, and excreted concentrations in urine. Though previous methods have predominantly employed multiple reaction monitoring on triple-quadrupole MS systems, our lab has developed a protocol employing the quadrupole-traveling wave-time of flight setup on a Waters Synapt G-2S instrument (6). The inclusion of a dilution step, using an isotopically labeled internal standard (D9-TMAO), allows a highly specific and selective analysis of samples with accurate quantification. Additionally,

the inherent ability for selected/multiple reaction monitoring measurements using LC-MS allows for simultaneous analysis of other molecules related to gut microbial metabolism, without loss of sensitivity or selectivity. For example, analyses may include additional molecules, such as L-carnitine, choline, betaine and γ-butyrobetaine, allowing an improved understanding of the dynamics and kinetics of these molecular/metabolic relationships.

Using these methods, we have shown that elevated levels of TMAO are associated with poor prognosis in acute hospitalizations of heart failure (7) and myocardial infarction (8). These experiments support previous data from gene knockout mice models, which showed that high levels of TMAO induced atherosclerosis (9) and worsened conditions associated with heart failure (for example, left ventricular ejection fraction) (10). Interestingly, we (and others) have also reported a strong correlation between circulating TMAO levels and markers of renal dysfunction. It is crucial that we ascertain whether elevated TMAO levels cause increased cardiovascular risk, or whether elevated TMAO is a side effect of renal dysfunction (11). In the latter case, increases in TMAO may be a surrogate biomarker for severity of cardiovascular/renal disease, rather than a direct cause. I'm confident that ongoing studies into the metabolic pathways involved will give us the evidence we need to establish the nature of these relationships.

Whether TMAO acts as a direct toxin on human cardiac/renal tissue or exists merely as a surrogate biomarker, this small molecule offers valuable prognostic information for a range of cardiovascular conditions, and we hope eventually to see it in clinical use.

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Quicker, Cheaper, Better

Cytology offers reliable and earlier diagnosis of malignant mesothelioma

By Anders Hjerpe, Professor Emeritus at the Department for Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden

Malignant mesothelioma (MM) is considered difficult to diagnose. Indeed, it is among the first solid tumors requiring mandatory immunohistochemistry for reliable diagnosis. In an effort to assist, guidelines for MM diagnosis using histological material have been presented by the International Mesothelioma Interest Group (IMIG) (1,2).

However, several laboratories have demonstrated that it is also possible to diagnose MM reliably with cytology, which is clearly a less invasive approach. For example, Segal and coworkers recently presented a 20-year audit that shows MM diagnosis can be established based on cytological examination of effusions with 73 percent sensitivity and 100 percent positive predicted value (ppv), i.e., without any false positive diagnosis (3). The main reason for this new diagnostic ability has been the development of ancillary techniques, some of which are now standard procedures in clinical cytology. In fact, we can now say that MM is no longer difficult to diagnose, not even when based on exfoliated cells in an effusion.

Corresponding guidelines for cytological diagnosis of MM are now adopted by IMIG, endorsed by both the International Academy of Cytology and the Papanicolaou Society of Cytopathology, and have been published by various cytological journals (4–6). According to the guidelines, the

diagnosis must be supported by ancillary techniques. In most cases, immunocytochemistry is sufficient, but certain cases may require additional support from fluorescence in situ hybridization (FISH) analysis. Additional techniques such as soluble biomarker analysis and electron microscopy are useful for improving sensitivity. However, unlike immunochemistry, these optional techniques are not available to many laboratories.

In cytological diagnosis, the sensitivity (73 percent) is somewhat less than for that for biopsy examination. Here, the important measure is the ppv! The 20-year audit demonstrates that the diagnosis is reliable, and the accuracy is sufficient for clinical handling. In most cases, the patient is not eligible for surgery, and cytological diagnosis is sufficient for selecting a chemotherapeutic regimen, making biopsy redundant.

So, what does this mean to a patient with MM?

The first symptom of a tumor is the development of an effusion. This is withdrawn to alleviate associated symptoms, primarily dyspnea. The diagnostic material is therefore available without any additional invasive sampling, eliminating the need for a biopsy, with its potential for morbidity and increased risk of tumor seeding (7,8). Although the disease is often in an advanced stage when the first effusion appears, the approach enables an earlier diagnosis with the possibility of a better response to chemotherapy. The diagnosis also requires fewer resources, which is economically beneficial.

Cytology alone, however, cannot diagnose sarcomatoid MM. Here, an indication for a biopsy is necessary when (a) cytology is inconclusive and (b) information on a possible sarcomatoid component is required for clinical handling. The three main reasons for not being able to diagnose MM with epithelioid components by examining an effusion are: (i) the low yield of the diagnostic cells; (ii) a cytopathologist's lack of experience; and (iii) lack of awareness of this diagnostic possibility. Therefore, a liberal use of immunocytochemistry is advocated, particularly in effusions rich in mesothelial cells (8).

Clearly, the current cytological guidelines show how to diagnose MM accurately. Moreover, most of the recommended techniques are common to both histopathology and cytopathology. Therefore, in my view, it would be advantageous to merge both guidelines into a single document.

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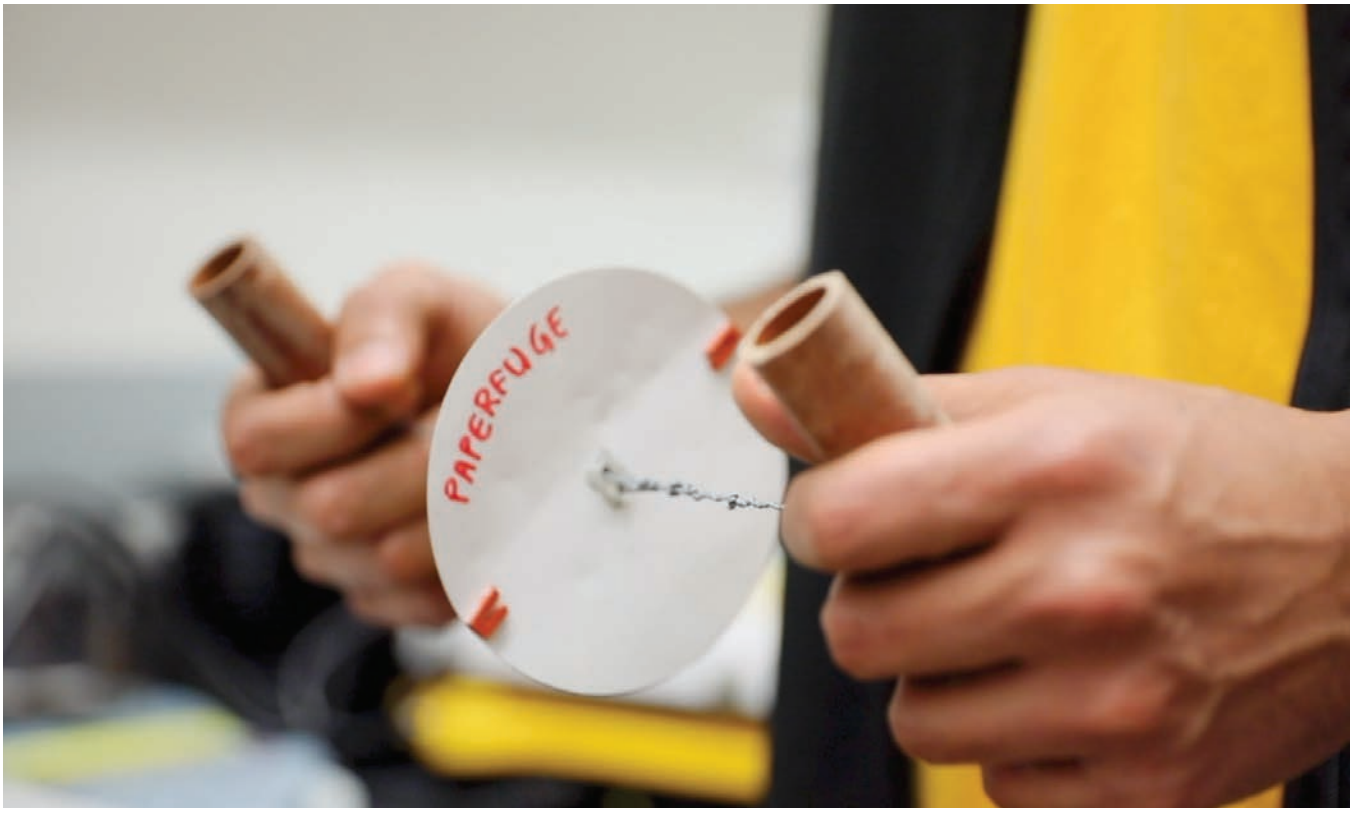
Pathology on a Shoestring

Pathologists and laboratory medicine professionals share their efforts to provide top-level care to those with the fewest resources

The slides are unclear… Patient information is unavailable… We don't have the right equipment or expertise to make a definitive diagnosis… All too often, diagnostic pathology is fraught with challenges. How much more challenging must it be to try to provide these services with limited resources? Pathologists in such areas face all the same difficulties as their western colleagues – and more – but their commitment to providing excellent patient care is no less absolute. So what creative methods have these determined doctors devised to overcome their unique obstacles? And what advice do they have for others facing the same challenges?



In a Spin

Introducing the paperfuge: a hand-powered, low-cost alternative to the centrifuge

How can a length of string, two pieces of paper, and a couple of handles become a low-cost alternative to a traditional centrifuge? Researchers at Stanford University have the answer (1), and their efforts could have positive implications for diagnostics in resource-poor areas.

The "paperfuge" was inspired by whirligigs – toys invented thousands of years ago – and, rather suitably, it appears to be child's play to operate. How does it work? A plastic capillary tube is used to collect a blood sample before being sealed and securely fixed to a circular piece of paper with two holes in the center. A similar piece of paper is secured on top to trap the capillary between the two sheets. String is then threaded through the holes in the paper, and held via a grip at each end. The disc is "wound" up and then unwound by pulling the grips apart; the inertia allows the disc to rewind once more before the cycle begins again.

Despite the featherweight device being simple to put together and operate – and costing a mere 20 cents to produce – it is highly effective, spinning up to 125,000 rpm (the authors cite 1,000,000 rpm as the theoretical maximum!) and reaching g-forces of approximately 30,000. Such force allows the separation of blood cells from plasma in less than two minutes, and malaria parasites can be isolated in 15 minutes. The investigators noted that in regions without access to traditional centrifuges, researchers and medical professionals often use eggbeaters or salad spinners as alternatives – but those solutions don't spin rapidly enough to be effective substitutes – and they are bulkier than the paperfuge.

As the Stanford investigators have shown, sometimes to move forward, you need to look back – even thousands of years. Simple, cost-effective tools like the paperfuge (and the paper-based biosensor on page 21) have the potential to open up modern diagnostic capabilities to the people and places that often need them most.

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Paper Versus Pancreatitis

A new biosensor detects β-glucosidase and lipase for less than a penny

As the pursuit to develop more sophisticated and sensitive diagnostics continues, the cost of producing those tools and techniques tends to increase, making them inaccessible to low- and middle-income countries. But moving forward doesn't always have to come with a hefty price tag, as researchers from the Indian Institute of Science have shown with their new paper-based biosensor, which uses photoluminescence to detect lipase (1).

Why is this biomarker important? High levels of lipase in blood can indicate pancreatic inflammation. A quick, affordable diagnostic could aid in the preliminary diagnosis of pancreatitis, especially in low-and middle-income countries (LMICs) that may lack conventional diagnostic equipment – or even the electricity to power it.

The apparatus consists of a paper disc embedded in a terbium gel that contains a pro-sensitizer (a chemical that liberates the sensitizer). It costs approximately one and a half cents to produce five discs, making it an extremely cost-effective technique.

How exactly does the biosensor work? "Upon activation of the specific enzymes, the 2,3-dihydroxynaphthalene sensitizer is liberated, resulted in the 'turning-on' of green luminescence, detectible under UV light," says Uday Maitra, study author and Professor in the Department of Organic Chemistry at the Indian Institute of Science. "The main idea with this is to chemically modify the sensitizer with an enzyme-cleavable group. The advantage, we felt, was that as long as we are able to design appropriate pro-sensitizers, all enzymes will be detected with the same fluorescence."

Indeed, the investigators have big plans for the ultra-cheap biosensor. "At present, we have half a dozen pro-sensitizers, and we are developing more artificial substrates to detect more enzymes. On top of that, we're improving the sensitivity, and fabricating a handheld device that can be used for imaging and quantifying the enzyme-triggered luminescence of the paper discs. So a lot of work remains to be done!"

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The Best Things Come In Small Packages

The story behind the miniature molecular diagnostic device that will offer simple, affordable pathology in low-resource settings

By Jonathan O'Halloran

Molecular diagnostics are often key to unlocking the mysteries of disease – but the techniques required are often complex and time-consuming, and the equipment can be bulky and expensive. Those issues can be frustrating even in the most well-resourced laboratories, and the difficulties are significantly magnified when pathologists face resource limitations. So I decided to do something about it.

I began by defining what I thought were the ideal specifications for a point-of-care (POC) molecular diagnostic device – something that could remove the frustration I felt when processing samples. Once I had decided exactly how such a device should look, I set to work creating it – building, changing, building again, changing again. That early work, all done at home in my garage, is the foundation on which QuantuMDx's technology is now built.

A sample's journey

Once entered into Q-POC, the portable, simple-to-use testing platform, a patient sample is lysed and purified in a three-minute step that uses a novel filter to capture cellular components, such as carbohydrates and proteins, leaving the DNA in solution. It takes a further seven to nine minutes to amplify the DNA – a task accomplished by microfluidic PCR. How can your device do PCR? Q-POC uses static heat blocks at two or three distinct temperatures, moving the reaction mix back and forth between them to create the necessary thermal cycling. We then employ a world first: a two-method integrated detection system. The first method takes advantage of sensitive in-line optics to observe the generation of fluorescence as the target region is amplified, providing a six-channel quantitative PCR (qPCR) read-out in just over 10 minutes from sample input. The second method – hybridization to a microarray – adds another five minutes to the overall process, but enables us not only to quantitate up to six markers with the qPCR, but also allows us to genotype alleles or mutations within the amplicons – an important consideration for drug resistance testing.

The foundation of Q-POC's development – and our end goal – was to create a platform that was quicker and more portable than current gold-standard tests. We also wanted to ensure that the devices were suitable for the economies and environments where they can be of greatest use. As a result, we have had to reinvent each stage of the molecular testing workflow. For example, when we were in the early stages of development, we reviewed the molecular diagnostic process and found that it wasn't suited to microfluidic platforms. Our team has innovated each step in the process to overcome these issues and find a solution. For instance, the standard BOOM method of DNA extraction involves binding the nucleic acid to a silica surface, washing away the cellular constituents, and then eluting the DNA – but to do that, you need a number of wash and elution buffers, all of which cost money and take up space. Q-POC, in contrast, requires one buffer and no valving or waste management. Thermal cycling is another example of our innovation; rather than heat and cool a reaction mix, we move the mix itself back and forth between different temperature zones to create the necessary cycling. Not only does that save significant time in ramping, but it also preserves battery life to let the device run for much longer.

> "Experts in the field of molecular diagnostics thought we were crazy to take on a project like this."

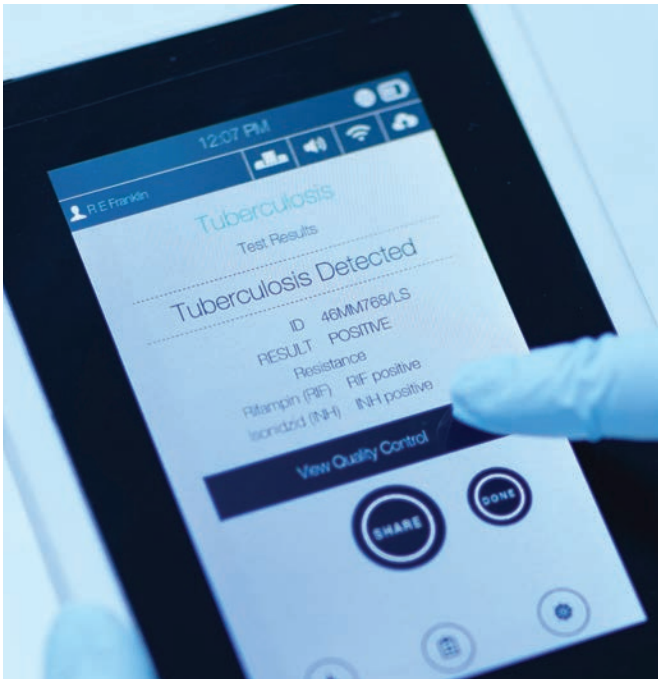
Surviving a rocky road

Clearly, any novel approach to improve complex technologies is going to be fraught with difficulties. Given that we had to reinvent nearly every aspect of the molecular testing process – not to mention miniaturize it without losing speed or effectiveness – we knew we had set ourselves a near-impossible task. Then we added the challenge of keeping the cost extremely low and things really got interesting. Despite all of that, I think the biggest challenge was integrating everything. Why? Each process of the molecular diagnostic workflow uses totally different chemistries and buffers to the others, so linking them together is a huge headache. Then add in a significant change to the reaction environments and dynamics, and different device materials, and you can see that the task seems impossible!

While we were in early development, experts in the field of molecular diagnostics thought we were crazy to take on a project like this. And many thought it was simply impossible...

But we have already demonstrated our first Q-POC test, a warfarin


testing
4 mins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Defeating HPV: A Partnership for Global Good

Who?
A collaborative project between the Global Good charity and QuantuMDx.

What?
A sample (swab or cervical brush transfer buffer) that can be run on a disposable microarray on the Q-POC platform. The assay amplifies several regions of the human papillomavirus (HPV) genome to first confirm the presence of HPV, and second identify whether the virus is one of the 13 oncotypes. Almost all cervical cancer is caused by HPV infection, so the assay gives health workers the ability to screen and treat for the virus in a single visit.

Why?
It is estimated that more than 80 percent of cervical cancer deaths occur in low-resource settings (1). Current methods for screening in those settings are limited or nonexistent because they require considerable training and diagnostic quality is hard to maintain. In contrast, the assay is cost-efficient, easy to use, and accurate. It's an especially timely intervention because recent changes in the FDA have dramatically decreased the number of new diagnostics for HPV. We felt a responsibility to act, and our new assay is a result of that feeling.

Where?
The assay will be trialed in low- and middle-income countries like Uganda and Kenya.

When?
We've already begun transferring the assay, and we're aiming to begin field trials in the first half of 2018.

Reference

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genotyping assay, and we are currently working on a number of infectious disease tests. These include tuberculosis, HPV and CT/NG/TV – although we're still in the early stages with those tests. We have the Bill and Melinda Gates Foundation to thank for a grant that will support the further development of our tuberculosis assay and the preclinical data gathering required to support the optimization of our device ahead of clinical trials. We will then go through a process validation phase and then onto clinical trials, which we anticipate beginning in 2018. After the clinical trials are complete, we hope to apply for regulatory approval for each of the countries we wish to market in.

In the future, our challenges will be more familiar. We'll need to scale up to manufacture Q-POC in large quantities, and we'll have to predict sales volumes as accurately as possible. We have worked hard to ensure that we avoid the potential pitfalls in that part of the process, and that's why we have brought on strong partners who have either the finances, knowledge or both to ensure the device reaches commercialization successfully. I'd recommend the same to anyone else looking to bring a novel device to market – find allies whose strengths complement yours, because it makes the entire journey easier and less risky.

The Internet of Life
Q-POC aims to speed up, simplify and automate the day-to-day workflow of molecular pathologists and laboratory professionals. Without laborious sample preparation, we'll be able to just load the sample and press go! And we've designed the device to function in most situations and environments, so that it will work in countries with few other options. Those regions tend to have a high burden of diseases such as tuberculosis, malaria and STIs. Our ideal scenario is that Q-POC reaches the individuals whose countries lack a strong healthcare system – or even those who cannot access healthcare at all.

One really exciting feature is that all Q-POC devices will be connected to the cloud. Globally distributed devices will then be able to anonymize and geotag the data they collect so that it can be used for real-time disease and drug resistance monitoring. We hope that we can use this data to create a real-time map of disease prevalence, transforming the way non-governmental organizations, health ministries and even the World Health Organization monitor and control outbreaks. Of course, that's still in the future – but we're looking forward to distributing as many devices as possible so that we can begin to create this "Internet of Life." That's the first step – so any pathologists interested in adopting Q-POC are welcome to contact us. We'd be happy to help facilitate!

Now that we've achieved our initial goals, we know that all our early struggles and growing pains were worth it – after all, they brought us several steps closer to bringing quality pathology to the people who need it most.

Jonathan O'Halloran is co-founder and Chief Scientific Officer at QuantuMDx.

Mobile Phone Microscopy

Can smartphones help bring molecular diagnostics to low- and middle-income countries?

Molecular diagnostics are a pillar of pathology, but as the technologies and methods evolve, we need increasingly complex assays and equipment. Unfortunately, in LMICs, where such diagnostics may be sorely needed, new technology isn't always tenable. The solution? Smartphones, according to researchers from Sweden and California, who have developed an affordable attachment that transforms a phone into a biomolecular analysis and diagnostics microscope (1).

By combining the device's optomechanical lasers and algorithmic "brain" with a smartphone's camera and a special app, the researchers were able to carry out in situ analysis via fluorescence microscopy. Could the instrument's simplicity and power help bring one of our most essential biomedical tools to the places that need it most?

To find out, we spoke with the lead researchers – Aydogan Ozcan, Professor of Electrical Engineering and Bioengineering at UCLA, and Mats Nilsson, Professor and Scientific Director of the Science for Life Laboratory at Stockholm University.

UCLA, Stockholm University and Uppsala University.

Why did you focus on smartphones?

AO: There are several aspects that make today's phones rather unique for conducting, sensing, and diagnostic measurements. The massive quantity of the devices – over eight billion at the time of writing (2) – drives rapid improvements in hardware, software, and high-end imaging/sensing technologies for daily use. This also transforms them into a cost-effective, yet extremely powerful platform able to run various tasks – such as biomedical tests and scientific measurements – that would normally require advanced laboratory instruments. I think this rapidly evolving trend in mobile phones will help us transform how medicine, engineering, and other sciences are practiced and taught globally.

MN: I think it's a trend in society in general. We'll see more wireless applications and less need for traditionally large infrastructure. I've been involved in other projects where we've looked at point-of-care diagnostic approaches, and it seems to be very important that the devices cannot rely on wired electricity or networks to serve not only LMICs but also modern, developed environments – it's often difficult to find an available power socket in Swedish hospitals.

Did you develop the device particularly with LMICs in mind?

MN: That has definitely been our major objective: to make molecular diagnostics affordable in low-income settings. During our investigation, we demonstrated the molecular diagnosis of tumors with sequencing and KRAS mutations, both in the tissue and in the liquid sample of a tissue – showing the practical utility of the device in regions with few options. I also think that a more urgent, short-term need for molecular diagnosis is in the field of infectious diseases. That's another area in which I think this platform is important.

AO: Our work is significant because mobile DNA sequencing and tumor biopsy analysis can greatly decrease the cost of diagnosis and make it more accessible globally. I believe we've taken a real step toward the next generation of DNA sequencing and mutation analysis, as well as toward better technologies for point-of-care settings and resource-limited environments. Beyond its current capabilities, I believe our platform could eventually also be used to identify disease-causing microorganisms and measure the genetic signatures of antibiotic resistance.

What's next for your labs?

AO: We are very much interested in mobile imaging, sensing, diagnostic techniques, and their applications in biomedicine and environmental monitoring. We have several exciting projects that will soon reveal how powerful – and how fit for purpose – these smart mobile systems can get, including in developing countries.

MN: We want to remove the laser from the current sequencer to make it even faster and simpler. We'll also apply the current setup to infectious disease diagnostics. For example, we could investigate tuberculosis diagnosis – if we develop ways of profiling tuberculosis patients with our platform, we can further add to its use in LMICs.

Just as this collaborative project focused on device size to increase accessibility, others have been heading in the same direction. One example is Oxford Nanopore's MinION (3), which recently traveled to the International Space Station as a tool for sequencing experiments (4). It's exciting that such devices appear to be just the start of a portable diagnostic revolution.

> "If we spend more time and resources on the ways we can best use both old and new methods, it will definitely pay off."

But the answer needn't lie solely with developing new diagnostic tools. Nilsson says, "We probably do need to develop novel diagnostics, but we should also focus on how old diagnostics can be used. If we spend more time and resources on the ways we can best use both old and new methods, it will definitely pay off for pathologists and patients alike."

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A Viral Vision

Meet the new miniature biosensor that aims to enhance HIV diagnostics in the field

Over 35 million people have died of HIV since the epidemic's peak in the 1980s (1). Today, the disease still affects tens of millions of patients per year, with sub-Saharan Africa – where one in 25 adults lives with the virus – being the hardest hit. As the battle against HIV rages on, new vaccines and treatments are being proposed (2) – but the field of diagnostics has an important role to play. Investigators from the Spanish National Research Council (CSIC) have developed a tiny but sensitive chip-based biosensor to detect HIV-1 (3).

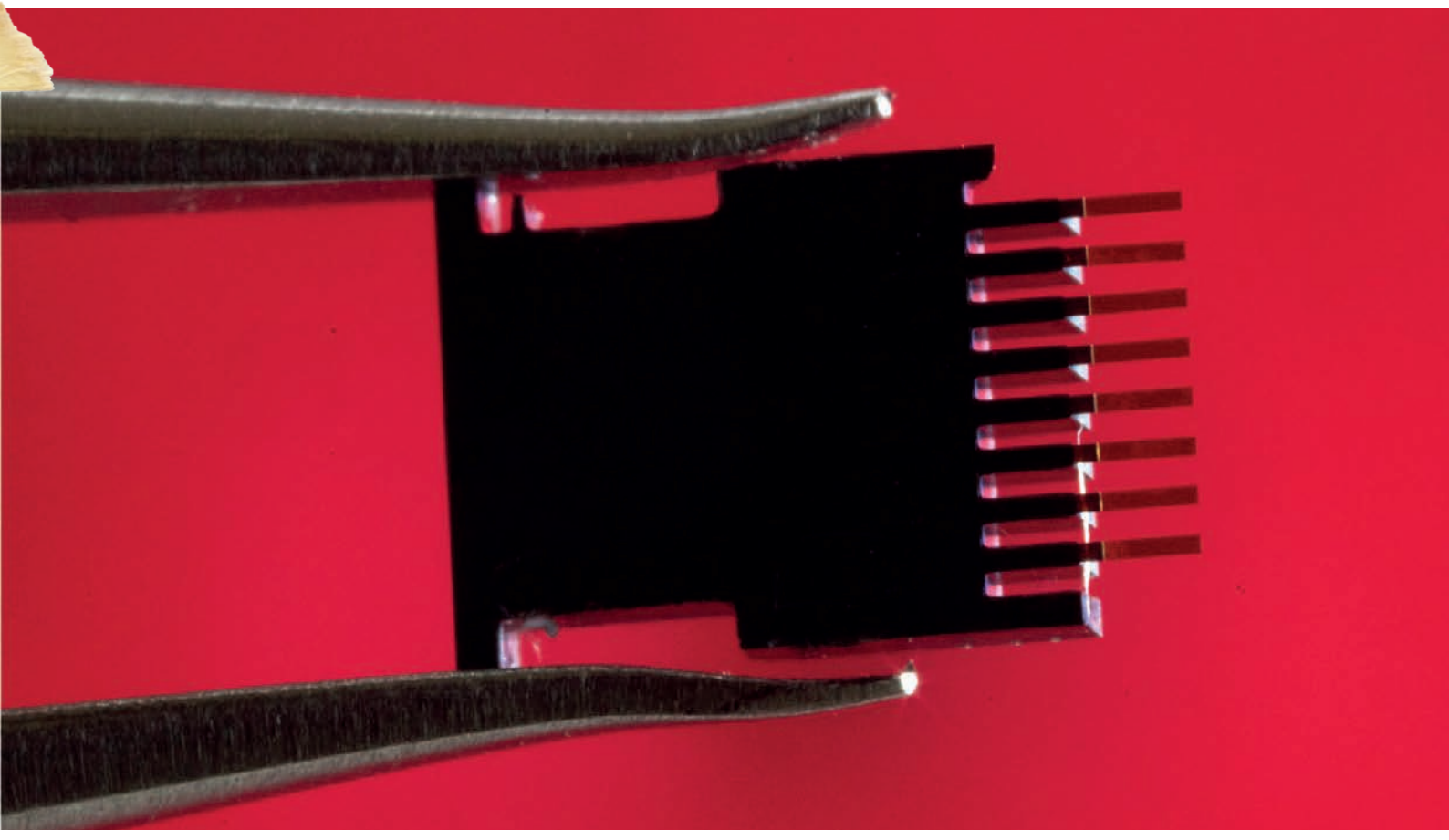
To learn more about the nanosensor and how it helps serve LMICs, we spoke with Priscila Kosaka, a researcher at the CSIC's Bionanomechanics Lab.

Why did you focus on HIV detection?

One of the Bionanomechanics Lab's research goals is to develop ultra-sensitive tools for the early detection of cancer and other fatal diseases – HIV fits into that latter category.

Our HIV sensor's story began some years ago, when we focused on detecting low-abundance biomarkers in the bloodstream. We used cancer biomarkers – carcinoembryonic antigen (CEA) and prostate-specific antigen (PSA) – as our model, spiked into undiluted bovine serum (4). The concentrations we analyzed were at least three orders of magnitude lower than the cutoffs for clinical monitoring, something we hope will be useful as new, low-concentration biomarkers are increasingly discovered by emerging proteomic tools.

In the meantime, we wanted to challenge our nanosensor in human serum – partly to spot problems related to nonspecific interactions and partly to ensure that the device would detect proteins at ultra-low concentrations in human blood. That's when the p24 capsid protein came to our attention. It's an intriguing biomarker because it's only found in the blood of HIV-1 infected people – so we decided to turn our sights toward HIV detection. It wasn't just good for our research, though; prompt identification of HIV-positive individuals during the highly infectious acute or early stage has implications for both patient management and public health interventions.



The microcantilever array used for ultra-sensitive HIV detection. Credit: Joan Costa/CSIC Communication

What are the current challenges in HIV diagnosis?

Identification of individuals in the earliest phases of infection remains a difficult task thanks to the demands of repeat HIV testing and the detection limits of current technologies.

Nucleic acid testing (NAT) is the most accurate and reliable screening platform for HIV. It's theoretically capable of detecting HIV about two weeks after transmission – but the virus' genetic diversity can yield false or discordant results. Moreover, most of the assays used are complex, technically demanding or inappropriate for non-specialist diagnostic laboratories.

Diagnostic platforms like ELISA are in routine use for HIV antibody detection, and the newer assays can spot both antibodies and the p24 antigen. This approach has further shortened the "window period" between infection and detection. p24 immunoassays are simpler and cheaper than NAT and have potential in low-resource settings, but their sensitivity must be improved if we're to use them to detect early-stage infection.

How does your device work?

It's an array of eight silicon microcantilevers that we use as biosensors. They can transform a biological signal into one we can measure. We've recently discovered that the microcantilevers are also good optical cavities; their two opposite surfaces work as semitransparent mirrors that trap light and boost the scattering of metallic nanoparticles. We can use that property to perform a sandwich immunoassay, functionalizing the microcantilevers with capture antibodies and dipping them into serum so that the p24 antigens can bind. Then, we incubate them with gold nanoparticles bound to detection antibodies, rinse, and measure.

Ultimately, we have two detection methods: mass and plasmonic labeling. The microcantilevers act as mechanical resonators that allow us to measure the mass of the captured nanoparticles, and they also work as optical cavities to allow localized surface plasmon resonance – crucial to achieving the ultrasensitivity we need to detect p24 in human serum.

Why is the device viable in regions with limited resources?

The microcantilever arrays and optical cavities are fabricated en masse by well-established semiconductor technology. Similarly, optical components, such as lasers and photodiodes, can be acquired at very low cost. Even microscopy is less of a challenge than ever; smartphones can now be transformed into powerful, economical optical microscopes to be used in field settings. Our nanosensor has the potential to become a cheap and user-friendly technology suitable for resource-limited settings – hopefully, in the very near future. We are working hard to turn that dream into reality!

At the moment, the cost of our sensor is still relatively high. For example, the microcantilever array costs around €20, and each individual analysis can reach €100. But when we begin large-scale production, I predict that the price tag will decrease dramatically – I can envision fabrication costs as low as €1 or less. And when that happens, I'm looking forward to a rollout in the places that could benefit most.

With just a simple two-step process, laboratory medicine professionals can have a result in under five hours, and deliver patient follow-up on the same day. It's our goal that people with HIV will be able to start treatment as early as possible, suppressing viral replication and allowing them to keep their immune systems undamaged – and have a longer, healthier life. It will also substantially reduce the risk of transmission of the virus to uninfected people.

We don't want to stop at HIV. We're also currently working on projects for early cancer detection, and we're interested in a number of other health issues – cardiac disease, Zika, Ebola, and more. We hope that, one day, we may have simple, low-cost point-of-care devices for all sorts of applications – and distribute them to all of the hospitals, clinics and healthcare professionals who need them most.

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Doing More With Less

Research in resource-limited settings means getting the most out of personnel, equipment and supplies – and empowering those who can continue your work

By Raffaella Ravinetto

The concept of conducting clinical trials in resource-limited settings isn't new. In fact, we've been doing it for many decades. What has changed over the last couple of decades is the nature of that work. Until about 25 years ago, most complex multi-center clinical trials were carried out in developed countries by commercial entities. Essentially, pharmaceutical companies funded their own research with the objective of bringing a new intervention to the market. But then, we started to see a shift – even the most complicated trials began to be conducted in LMICs. Why? Three reasons: internal validity, convenience, and neglected conditions.

Internal validity refers to the fact that new interventions must be tested in different populations. Differences in characteristics like ethnicity can change a patient's therapeutic response to a particular drug – and differences in healthcare infrastructure can impact the drug's effectiveness.

Convenience is a less pleasant concept. It refers to the possibility that an unscrupulous sponsor will conduct research in poor countries because it may lower costs, simplify ethical or regulatory review, and make recruitment easier by involving socially vulnerable populations. People with few resources often see clinical trials as a way to access free medical care – and that makes them more likely to involve themselves in research without asking too many questions about the potential risks.

The third reason, *neglected conditions*, deals with our growing awareness that many health problems are mainly or exclusively prevalent in LMICs, and are not yet sufficiently addressed. In the past few years, we've seen a number of positive initiatives, like new Product Development Partnerships (PDP) for research into new antimalarial treatments to compensate for the lack of efficacy of older treatments. Other new public-private partnerships conduct research into neglected tropical diseases that desperately need effective, safe and easy-to-use prevention and treatment tools. So we're really seeing clinical trials go global these days!

Shifting studies

We have always had some trials conducted in academic environments, but nowadays, more and more *big* trials are being carried out by noncommercial entities, which makes a significant difference to both rich and poor countries. There are some research questions that simply won't be addressed by the private sector. An example from my group's work is a comparative study prospectively comparing the safety and efficacy of existing antimalarial treatments in pregnant women. Such a study would hardly be carried out by a pharmaceutical company – after all, what if the company's product proved inferior? That's why we need independent, noncommercial research.

This kind of research also looks at fields that are less likely to turn a profit. Tropical diseases are one such area (and the reason why public-private partnerships like the Drugs for Neglected Diseases Initiative are so vital); pediatric oncology, which traditionally has low patient numbers, is another. With some laudable exceptions, commercial research is by its nature mainly profit-driven, so whenever a research question doesn't offer a significant monetary return on investment, we rely on public funding and noncommercial entities to step up. The role they play is absolutely vital, and the more they take the lead in clinical trials, the more benefit resource-limited countries will gain.

The downside?

For science and medical professionals, the problem with noncommercial trials is that they're often under-resourced in comparison to those self-funded by pharmaceutical companies.

Working in LMICs only exacerbates the problem, which often means stretching your personnel, equipment and supplies as far as they will go. More specifically, as a noncommercial sponsor, you will need to compete for external funding that is always in short supply; work in small teams where individuals may have to play multiple roles; adjust procedures according to local constraints; and maintain the highest quality, reliability and ethical compliance in your work even as you tackle these obstacles.

Let me walk you through an example – the challenge of developing new in vitro diagnostic tests for neglected tropical diseases. You would likely face a number of obstacles along the way:

Funding

To successfully compete for grants, you'll need to convince the funding agencies that your consortium is scientifically sound and can deliver quality results. At this point, you'll also need to start considering benefit-sharing – or, in other words, discovering how you can fully involve your colleagues from the LMICs in which you intend to work. How can you provide those colleagues with an equal partnership, starting from writing the grant application together? How can you ensure that your work will build their capacity to conduct independent research in the future?

Infrastructure

When you discuss working "in Africa," people often envision lifeless deserts, ramshackle buildings, starving people in rags. But in fact, our work contexts can vary widely, from state-of-the-art tertiary hospitals in large cities all the way to remote rural settings with poor medical infrastructure and no research capacity at all. You may need to begin by creating or upgrading the local infrastructure; in particular, labs that can provide routine medical care don't necessarily have the procedures in place to meet research demands. Making them suitable for research requires significant effort and investment – but if you don't do it, you can't move forward.

Recruitment

In clinical research, we consider vulnerable populations to include children, the elderly, the incapacitated, and so on. But vulnerability may be much more widespread, especially (but not exclusively) in LMICs. Often, resource-limited settings lack social security systems and accessible healthcare, which is why many patients view clinical trials as a way to obtain free treatment. It's difficult – but vital – to ensure that you're not unintentionally exploiting that vulnerability when recruiting a patient population. You must also ensure that those who aren't eligible for the trial are not treated as "second-line" patients and still receive some benefit from its presence – for instance, by upgrading local laboratories so that everyone receives better care.

Engagement

Not every researcher is a born communicator – and dialog becomes even more complex when you have to translate into local languages. I've seen many studies regarding patients' capacity to understand research, but very few that closely examine the researchers' ability to explain it. I think we need to ensure that researchers are trained in empathetic communication (see "The Missing Piece of the Puzzle" on page 34), and what's more, I agree that we need to familiarize ourselves with local customs and cultures early on – perhaps with the aid of a social scientist. Unfortunately, there's rarely budget for that type of groundwork – and there isn't always the time. But we need to prioritize it much more than we currently do, and we need to make sure that we're engaging the community throughout our research projects.

The long term

Previously, and in a western context, "post-trial access" referred to ensuring that clinical trial participants could continue to receive the experimental treatment in the window between the trial completion and medicine registration. In LMICs, the problem is more complex: how can the country retain access to the medicine? Many treatments, upon reaching the market, are priced beyond the reach of these countries. There are positive examples of "access strategies," but they're all chosen by the research sponsors themselves. There's currently no system in place to ensure early and continued access at an affordable price to those in the host countries who need it – but, in my opinion, there should be.

Overcoming operational obstacles

In the end, many problems – and their solutions – come back to project management. In small academic groups, when we want to develop the capacity for clinical research, we invest in scientific and clinical practice skills. We often fail to prioritize investment in project management and administration – but those are the skills that make your research more efficient, and even more ethical. Without project management, your budget may be missing essential elements (such as preliminary cultural studies or the resources to upgrade existing facilities or engage the community) – and you can't amend your external budget after the fact, so you need to make sure it's correct from the start. Once your study is underway, you still need administrative skills. If you want to send samples overseas for testing, you'll need fair and transparent material transfer agreements. If you

want to share your data, you'll need contracts that protect your rights, and the rights of your research partners and study population. These are all complicated matters, and they're all too easily overlooked if you don't have administration and legal experts. Never underestimate the value of good management!

And speaking of management, we have to remember that – unfair though it may be – some of us wield more power than others in our collaborations, and it's up to us to fight for those with less. When researchers from highly developed countries work with LMICs, we must not "take charge." It's the local scientists and doctors who have spent their lives getting to know the patients, the diseases, and the available resources – so why aren't we making sure they are the driving force in decision-making? And not just scientists and doctors; if you've spent any time in the field, you'll know that the people on the ground – nurses, community health workers, interpreters, data entry clerks – are all equally important. We can't view them as so many cogs in a machine. We need to support and involve them, and offer access to training and networking, so that they can continue to do their jobs and sustain their fundraising and research capacity, long after we've left.

Raffaella Ravinetto is a senior researcher at the Antwerp Institute of Tropical Medicine (ITM)'s Public Health Department, chairperson of the Médecins Sans Frontières Ethics Review Board, and former head of the ITM's Clinical Trials Unit.

This piece is based on material previously published in international peer-reviewed journals.

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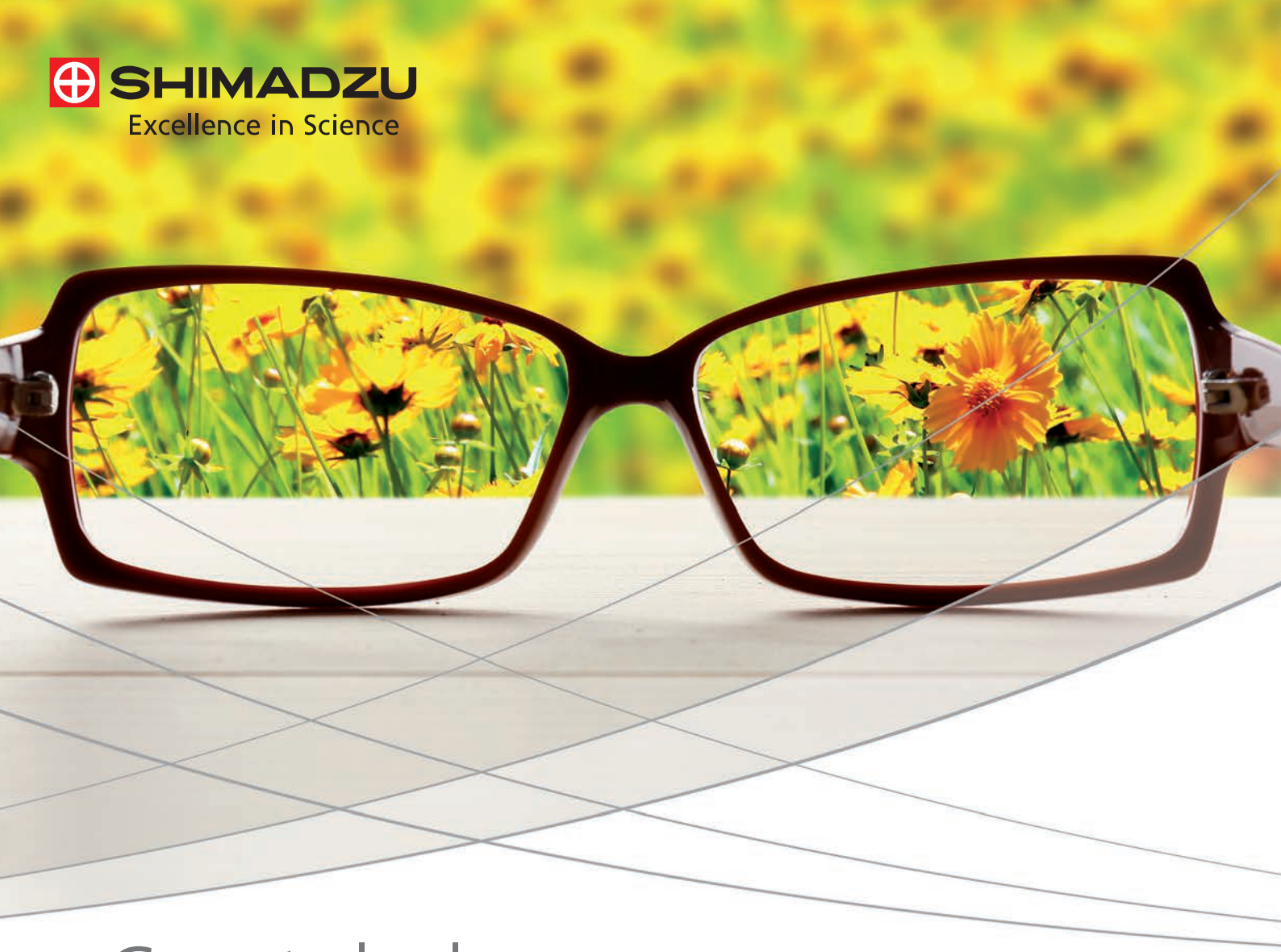

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The Missing Piece of the Puzzle

Patients are a central component of medical research – so why aren't their voices always heard? As a fellow of the European Patients' Academy, I invite you to begin a proper two-way dialog with your research participants – you may be surprised when you both learn something new…

By Marleen Kaatee

A few years ago, medical researchers in many fields began to realize that they faced a significant knowledge gap: they didn't know what patients actually experienced. But how could they find out? Talking to patients was an obvious solution, but most patients don't understand how biomedical science works. There's no common language between the laymen and the laboratory, and it's hard for either group to determine what the other may find useful.

Though it seemed like an insurmountable obstacle at first, the European Union decided to step in. Through the Innovative Medicines Initiative and the European Federation of Pharmaceutical Industries and Associations, the EU launched a massive five-year initiative to train patient advocates in all aspects of medicine research and development. The result? EUPATI – the European Patients' Academy.

EUPATI offers a number of services, but its most recognizable is its "school." The Patient Expert Training Course is a 14-month program that includes both e-learning modules and face-to-face events. After they graduate, students become EUPATI fellows and serve as resources for both patients and researchers.

When I was first diagnosed with primary sclerosing cholangitis (PSC), a rare liver disease, I couldn't find much accessible information in my native language. I knew right away that I wanted to do more to help tackle my disease – and what I figured out is that we needed to change a lot from the patient's perspective. Researchers and medical professionals can access academic papers and contact colleagues, but what can a recently diagnosed patient with no scientific training do? We need to be brought into the fold, so to speak, because we have a lot to learn to really understand our own diseases and the research surrounding them – but we also have a lot to teach healthcare professionals who have never experienced these diseases themselves. Collaboration is key, and if patients are to be equal partners at the negotiation table, we need to understand things at a professional level. With that in mind, I asked around, and someone told me about the Patient Expert Training Course, which was quite new at the time. I applied right away and was accepted. Through my education, I've become a much better participant in my own health care, as well as an advocate for the research and treatment of others.

Expert education

The program kicks off with six online modules that students work through from home – a convenient arrangement, as learning can be scheduled around treatment and other activities! The e-learning system also includes a forum where students can ask questions. When I took the course, there were three specialists assigned to each module, so we had access to researchers, pharmaceutical representatives and patient advocates who could answer our questions 24/7. While working on the e-learning component of the course, students also have two face-to-face sessions that encompass four consecutive full days of training with experts – mine took place in Barcelona. One especially interesting aspect was the role-play sessions; we pretended to be in a situation within the European Medical Agency's Pharmacovigilance Risk Assessment Committee meeting; one person played the patient, another a relative, a third the regulatory representative, and so on. That kind of hands-on training gave us a really good feel for the different positions people hold and their duties within their organizations. It also made me a better participant in research groups, and it gave me the ability to anticipate and address potential areas of miscommunication before problems arise.

Getting started

In the beginning, it was a bit daunting because I wasn't familiar with the vocabulary that the experts use (especially as I wasn't working in my mother tongue). I think the medical field may use more abbreviations than any other! But the e-learning modules really helped me to get a grip on the things I found most difficult. They were so well-organized that I could walk myself through them one step at a time – and for patients who want to know

At a Glance

- *It can be difficult for patients and professionals to connect across language and knowledge barriers*
- *As a result, medical research may not be fully informed – or may not actually be tailored to the needs of the patients dealing with disease*
- *Resources like expert training and online toolboxes can help educate patients to communicate with researchers and healthcare professionals on an equal footing*
- *Professionals also need to reach out to patients, treat them as partners, and make their work accessible*

more, every chapter includes not only a self-test, but also extra reading in case you want to learn about a topic in greater depth.

I think the format of the course really helps students feel like they're part of a group, despite the fact that most of it is held online. Even though I was alone in my room, the modules made learning easy – and I always had the opportunity to ask questions, which was great. The forum was my favorite part of the course; I really appreciated being able to get clarification when I was confused, and I liked the fact that I could sometimes help other students who were struggling with questions of their own. In fact, I had a better experience with the online forum than I did attending university classes in person, because the commitment of the experts was obvious. Whenever I asked anything, I always got an answer within 24 hours!

A toolbox for training

EUPATI offers an excellent online toolbox (eupati.eu), which allows patients to search for any topic – and the resources are all available in seven languages, with more on the way. So even people who can't commit to the whole training course can prepare themselves as a patient representative by going through the toolbox. Of course, for patients who do want the whole package, all of the expert training course modules are available for download – you don't get the "group feeling" or the real-time access to experts if you go through the course yourself, but other than that you can study as much as you like on your own time.

My advice to researchers and laboratory medicine professionals is to be a little more sensitive to patients' needs – whether experts or otherwise. You can point your patients or research participants to the training toolbox and other resources and encourage them to educate themselves. You can also make yourselves accessible to them, so that they feel comfortable coming to you with questions. You never know when you may both learn something new! Another key way to help is by treating patients and patient advocates as equal partners at the negotiation table. Even if they don't have a pile of medical degrees, they're certainly well-versed in their own conditions!

The most important thing is to get patients involved from day one. As a researcher, you might have a brilliant idea for something to study – but you might find that it's not a priority for the patients themselves. By working as a team from the start, you can encourage patients to add their views to your own ideas and learn things that – as a non-patient – you'd have no other way of knowing. For instance, I once had a conversation with 17 other PSC patients; one of them mentioned that he had a milk intolerance... and all the other 16 said they had the same issue! I was telling the story to a researcher and his eyes started to twinkle. He said, "Marleen, I need to know these things. I've been in the lab for 30 years – and I've never met a PSC patient!" For me, that was pretty shocking. But it just goes to show that professionals and patients can actually help one another identify research priorities and get all of the stakeholders involved in the work.

In my experience, if you invest a little time in these kinds of activities, it will come back to you tenfold by making your collaborations and studies much easier – and often much better as well.

The communication challenge

There's also great value in interacting with patients outside the research context. Many organizations have

Do you know a suitable patient for expert training?

Who?
Patients with chronic or lifelong conditions, caregivers of such patients, or employees and volunteers with patient organizations. Participants must live in the European Region, speak English, and have an interest in and a desire to be involved with medical research.

What?
A 14-month training course consisting of six e-learning modules (250 study hours) and two five-day face-to-face meetings. The course is fully funded by IMI and EFPIA.

Where?
The online lessons can be taken in the participant's home. The face-to-face meetings are conducted in Barcelona.

When?
Applications must be received by March 31, 2017. The course itself runs from September 2017 to December 2018, with face-to-face meetings in March and September 2018.

How?
Patients can apply at: eupati.eu/third-cycle-apply-now

Why?
"As a researcher, not having to explain what a Petri dish is, or what pharmacovigilance is, makes communication with patients much easier. It's also more interesting for research and healthcare professionals to talk to informed patients for additional insight into the diseases they're studying."

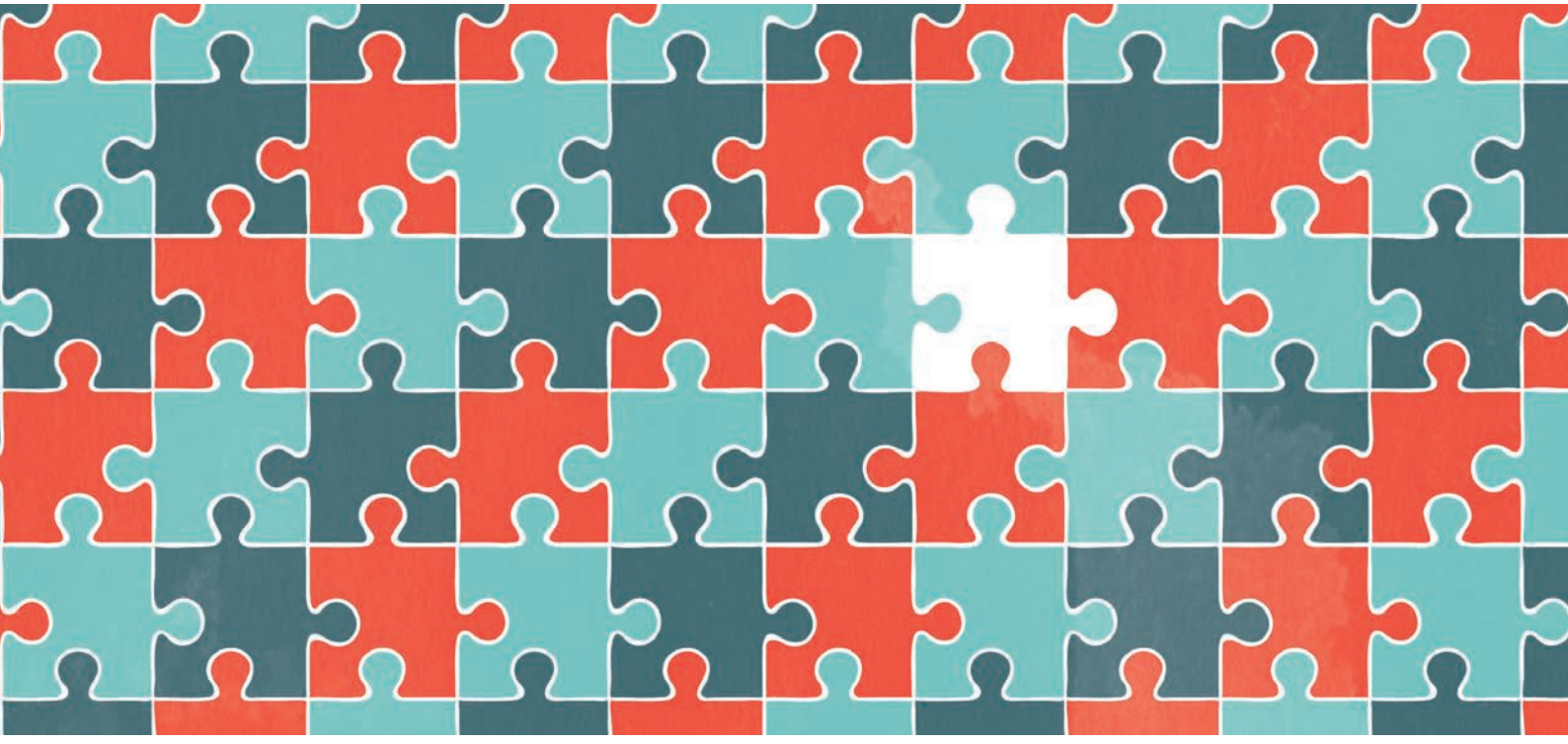
"I think the biggest benefit for me as a patient is that I now know the vocabulary. I understand what the professionals are talking about. And if I have a question, I know how to find an answer."

Facebook pages, which basically means that you have indirect access to those patients and their caregivers 24/7. You can see trends as they happen. For instance, the only possible treatment for PSC is a liver transplant. In the PSC groups on social media, you can read about the difficulties friends and family members face when their loved ones are on the waiting list; you see people deteriorate without having the ability to intervene. But on the other hand, when a patient gets "the call" or has an "anliversary" (marking the anniversary of a transplant), it's a very special experience – and everyone in the group celebrates alongside them.

You also find out about the "little things" by interacting regularly with patients. To give you another PSC example, there is "the itch." Most PSC patients suffer tremendously from itching, but there's no way to cure it. Anti-itching medication exists, of course, but it doesn't significantly affect the cholestatic itch. So if you are a researcher who wants to study the itch, talking to patients first will help you understand exactly which itch they want to have studied and how and why it impacts their lives. Not only will that give you more information for your work and potentially improve your chances of finding funding, but it might also add some motivation from a personal angle.

I think there's a lot of value in talking to patients about your research – but I think there's equal value in making your work accessible to them after it's complete. When you publish the results of your study, you can add a "lay version" so that the participants in your trial, and the disease community at large, can also find out what you discovered. It makes everyone part of a larger community, and I think that's very beneficial.

I would go as far as to say that, if you don't have a patient expert on your team – both to help guide your work and to help you make it accessible to other patients – you're missing a whole array of opportunities to advance medicine.



Finding – and working with – patient experts

The best way to begin your search for a patient expert is to consult with the patient organizations in your country – or, if there aren't any, the international associations. For instance, for liver diseases, we have the European Association for the Study of the Liver. It always starts with finding a patient organization, because then you can contact them to ask for a patient panel; request support with writing a lay version of your research; get assistance seeking funding for your project. The opportunities are almost limitless!

A word of caution: you need to make sure you're actually speaking with the patients themselves; sometimes, patient organizations provide people who claim to know everything about a particular disease, but don't actually have it themselves. In the Netherlands, we call those people "office patients." If you're not a patient yourself, you don't know what it's like to have a chronic illness, no matter how much experience you have.

I always start by asking researchers, "What can I do for you?" They are always very surprised, because the old-school approach is for the patient to dictate what he or she wants, and the researchers to try to cater to it. I turn it around by asking what I can do to help them. The first thing they say most of the time is that they need money – and I say, "That's important, but let's not talk money right now. If we have a good enough plan, the money will come." Then they say, for instance, that they want to do research, but don't know where to find a patient population. That I can help with! "Did you know that I help moderate a Facebook group of 400 patients and caregivers?" Or they'll tell me what they want to research – and it turns out to be something that isn't a high priority for most patients. "Our research priorities are actually X, Y and Z. Here are the results of a pan-European survey we conducted in six languages." When researchers know what's really bothering patients – whether it's something as obvious as transplant success rates or as subtle as needing too much sleep – it enables them to focus their work so that it has the greatest benefit for the patient community.

Of course, patients and professionals are attacking diseases from two very different angles. We can't always expect the two groups to have identical goals, but we can encourage open communication by asking researchers and clinical professionals to make their work accessible to patients, and by asking patients to educate themselves as much as possible in how to be a useful participant in the research. If we can learn to meet in the middle and treat one another as equals, we'll be well on our way to defeating these challenging conditions.

Marleen Kaatee is the founding President of PSC Patients Europe and a fellow of the EUPATI Patient Expert Training Course.

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NextGen

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Three Gurus of Big Data

Big data. Everyone's talking about it, but what exactly is it? How can it be harnessed to advance medical research? And what perils lie within the oceans of data that now surround us? Three experts from different backgrounds go fishing for answers.

Gone are the days of trekking to a library to thumb through research papers or handing out paper questionnaires to collect patient data. Now, we can gather terabytes of data at the click of a button. But are we making the best use of the data we're collecting? Here, data experts Dipak Kalra, Iain Buchan, and Norman Paton join the debate.

Dipak Kalra

Dipak is President of the European Institute for Health Records (EuroRec), and Professor of Health Informatics at University College London, in the UK. As a physician working in London in the early 1990s, he found that the computer systems of the time couldn't give him the insight he needed into his patients' data. He joined a European research project on health records and soon realized that creating truly useful electronic health records was a massive and exciting challenge. Twenty-five years on, Dipak is still working to improve health informatics. He also leads a non-profit institute that aims to promote best practice regarding health data in research and communicate with the public about how their health data is used.

At a Glance

- *Data collection is easier than ever – but with such high volumes at our fingertips, it can be difficult to ensure we're using it well*
- *Before accessing available data, it's important to understand what was collected and how, to ensure that it's fit for your purpose*
- *New kinds of data require new governance, new standards, and new interfaces in order to ensure good quality and comprehensibility*
- *Big data will be increasingly important for a wide range of applications – but only if our technologies, and our methods, keep up*

Iain Buchan

Iain is Director at the Farr Institute of Health Informatics Research, and Professor in Public Health Informatics at the University of Manchester in the UK. As a medical student, Iain Buchan saw the rise of the PC revolution. It was obvious to him that there was a need to fuse pathophysiological and biological reasoning with a statistician's view of analysis and inference. Buchan created a statistical software package (www.statsdirect.com) that quickly attracted tens of thousands of users. Over the years, he became increasingly interested in the interplay between medicine, statistics, and public health data. Buchan's team (www.herc.ac.uk) is addressing what they see as a fundamental flaw in observational medical research – currently, research orbits around data sources, but it should orbit around questions and problems, pulling in data from various sources as necessary.

Norman Paton

Norman is Professor in the School of Computer Science at the University of Manchester in the UK, where he co-leads the Information Management Group. He is a computer scientist by training, with a PhD in object-oriented database systems. His work focuses on data integration, which involves bringing together data from multiple sources in a manner that allows for easy interpretation. Previously, the process has been quite slow and small scale. With the rise of big data, the process needs to be streamlined and made more effective. Paton is currently working in data wrangling – collecting and cleaning up data so that it can be analyzed in an integrated form. Data wrangling is an expensive and time-consuming process, so Paton is working to automate as much of the process as possible.

"I think of big data as more of an era than a specific size or type of data. More and more data is being accumulated from different places, and that creates an opportunity for people to use and exploit it."

What is big data?

Dipak Kalra: This is an interesting question, and one that the healthcare community as a whole has yet to conclusively answer. For me, the characteristics of greatest importance are: a large number (millions) of patients, combining multiple data sources (with various interoperability and linkage

challenges), and data recorded over time to allow trajectories to be determined. I'm interested to see what answers my colleagues will give.

Norman Paton: I think of big data as more of an era than a specific size or type of data. More and more data is being accumulated from different places, and that creates an opportunity for people to use and exploit it. "Big data" has been used as a blanket term to cover numerous cases in different contexts, so it's difficult to find a single definition. However, I believe that it reflects a combination of an increasing number of data sources, an increasing number of domains that have a surplus of data, and the variety that exists within those.

Iain Buchan: There are many possible definitions based around the "four Vs" – volume, velocity, variety and veracity – but ultimately, I define big data as big enough to address the challenge at hand – with sufficient accuracy and timeliness to inform better actions.

"Big data, properly harnessed, gives us bigger science."

What impact is big data having on biomedical research?

DK: Big data allows us to finally have fine-grain, routinely collected clinical data. Soon we will be able to look at large numbers of patients retrospectively and at a much lower cost, which will explode our understanding of diseases, treatments, biomarkers, health service care, pathway patterns, and how to optimize patient outcomes. I cannot imagine a more exciting time than this.

NP: Big data allows more diversity in research opportunities. For example, we might want to better understand the efficacy of a certain cancer treatment; every hospital has records, but pooling together the relevant data from all of them would be an unmanageable task. Computer systems need to be developed that make the process of identifying, integrating, and interpreting diverse data sets more cost-effective. In medical sciences, opportunities are everywhere because information is constantly being produced in hospitals, drug trials, labs, and so on. I don't expect to see one mega project using all the information, but many relatively small-scale, focused projects.

IB: Big data, properly harnessed, gives us bigger science. It allows us to network teams and universities across the world, to collaborate rather than compete. And that collaboration becomes more powerful as the ensemble of data, analytics and experts gets bigger. There are two levels of big data: one is the scale of data and algorithms working machine-to-machine autonomously across locations, and the other is allowing humans to work in a much bigger team. You might think of this as "assisted reasoning for team science."

How can you ensure the quality of your data?

NP: It's extremely difficult to gain a clear understanding of your data set. It's not just a case of "good" or "bad" quality, but knowing whether the data is fit for purpose; what is fit for one purpose may be completely unusable for another. There are many metrics used to measure quality – completeness, accuracy, freshness, and so on, but fitness for purpose may be quite domain-specific.

DK: One has to be careful. When organizations collect data for any purpose (management, tracking, administration, and so on), they select the fields of interest relevant to them

#datasaveslives

The #datasaveslives social media campaign promotes the positive impact that data is having on health. Projects recently highlighted by the campaign include:

- Connected Health Cities: a project that collates health data from multiple cities and uses advanced technology to analyze it. The goal? To use existing resources to connect disparate services and make patient care better than ever. The three-year pilot project involves setting up a "learning healthcare system" that will continually improve care, as well as identifying care pathways for specific needs.
- SPIRE: an information-sharing system that allows doctors in Scotland to share anonymized, encrypted patient data with researchers. Only information for specific purposes will be collected, and after analysis, the data will be destroyed. What's the point? To manage patients with long-term conditions, research specific illnesses, and plan future services.
- Streams: a new app that collects patient data and monitors test results. Health care workers can easily access information and request interventions – but best of all, the app features an instant alert system for potential problems. London's Royal Free Hospital is trialing a version focused on acute kidney injury, and nurses estimate that the app saves them up to two hours every day.

and disregard the rest, which is good practice. Then they filter and select the data to fine-tune it further. The problem starts when somebody else wants to use that data for a different purpose, without being aware of all the previous filtering. It creates a risk of misinterpretation.

IB: I think one of the best ways to improve data quality is to "play back" what you have done to the people closest to the data. As soon as you talk to someone familiar with that data supply chain, they are likely to point out problems that might go undiscovered if you just suck up data. This turns tacit knowledge into explicit metadata – increasing the discovery power per unit of data.

What are the greatest challenges when dealing with big data?

DK: I can see four main issues. The first is in establishing trustworthy practices. This era of big data brings a very different set of governance challenges, which require new codes of practice, as well as winning the trust of society and healthcare providers.

The second is interoperability. I think the adoption of standards is too limited, with many data sets and electronic health records applying different internal data architectures and terminology. There needs to be a range of widely adopted standards so organizations and individuals are able to interface with each other and compare data.

The third is data quality, which we've already discussed.

The fourth is that, as a field, we have been slow to promote the value we get from health data. When we do make great discoveries from health data, we don't always make it clear to society or to funders that it was the result of significant investment in IT, as well as helping patients to be more comfortable with how their data are being used.

IB: I would add that a common mistake is naïve translation of tools from one environment to another. I've seen cases where dashboards designed for business intelligence have been directly translated into healthcare, which means clinicians are faced with a blizzard of dashboards they don't have time to digest. When designing user interfaces, we need to take note of basic learning from avionics, where it is long-established that a pilot cannot focus on more than seven or so dials in his or her field of view.

"This era of big data brings a very different set of governance challenges, which require new codes of practice, as well as winning the trust of society and healthcare providers."

Another common mistake is to apply machine learning to data as if it were an unbiased sample of human health. In medicine, there is so much "missingness" and measurement error in the data, and so many things that can't be measured directly, that data-structure is meaningless without overlaying prior information about the structure that would be in the data if you could observe it. The mistake is looking for patterns

in "buckets" of data when we should be starting with the patterns we know and building more patterns around that. Machine learning requires a very careful approach when dealing with biology and health data.

"I think the biggest misconception is that big data is the answer to everything, and that bigger data will always lead to a better answer."

How important is the public perception of big data?

IB: It's vital. My group has a rule when speaking with those outside the field that we don't talk about data, databases, or information systems in the first part of the conversation. Instead, we talk about problems that the data can be harnessed to address. We need the public on board to help unravel the vast gaps in our knowledge – for example, how best to treat patients with more than one condition. Take a look at twitter.com/hashtag/datasaveslives to see this in action.

DK: Trust and engagement from the public is mission-critical in the growth of big data and its use in research and healthcare. The public have to be confident that the use of their data is in their interest, and in the long-term interest of society. It's also important that the patients feel a sense of personal autonomy about health and wellness. To help foster that, I think we should all be able to access and use our own data, to help us make better decisions about our health.

NP: It's important for the public to have a wider understanding of the opportunities big data presents and how their data is involved with that, but it's difficult when organizations remain relatively opaque in relation to the use they are making of personal data.

DK: I see a lot of news stories focusing on security breaches or data leaks – a missing CD, a stolen laptop, a USB stick found in a waste bin. It leads to a natural distrust about how organizations look after our data. In reality, most data are very well protected – increasingly so, as we implement state-of-the-art security measures. But we need to increase public confidence.

What are the most common misconceptions about big data?

IB: I think the biggest misconception is that big data is the answer to everything, and that bigger data will always lead to a better answer, which is a myth. Indeed, there are some cases where more raw data can reduce discovery power, when the heterogeneity of the data sources increases but there is no metadata to make that heterogeneity useful in analyses. So, it isn't a case of getting as much data as possible, but rather finding

the most powerful analytics possible with the data. It's about bigger science, not just bigger data.

NP: I agree that there is too much focus on size. Although big data is often spoken about in terms of the four Vs, it's easier to get a handle on volume than the others so there is the tendency to associate big data mostly with size.

What are the most important applications for big data?

DK: If I could pick a headline issue for big data to rally behind, it would be that we're an aging society and the number of patients who have multiple long-term conditions is rising. Our historic scientific knowledge of diseases and treatments have usually been based on the study of single diseases, so our knowledge of how multiple diseases interact is fairly limited. Big data will give us the ability to study populations so that if you have a patient with diseases A, B, and C, and you want to find out the effect of treating them with drug X, you'll have a sufficient sample size to get a useful answer.

IB: Multi-morbidity is definitely a key priority. As Dipak says, we're an increasingly aging population with a prevalence of multiple concurrent conditions, and to address that we need actionable analytics – statistical surveillance of primary care and prescription data, with feedback to physicians so they can determine the patient's best care pathway.

Another area of importance to me is infrequent clinical observation giving way to consumer health technologies that can tap into the rhythms of a patient's life via wearables or mobile technologies. If I had arthritis, my patterns of movement might reflect a temporal pattern of symptoms currently invisible to the clinic. That takes me to the third area, which is information behavior. If you're able to use technologies in ways that slot into the rhythms of daily life and don't annoy people, then they will be used more often and so give a less biased sample. The next step is to help influence health behaviors; for example, getting people to exercise more or to persist with preventative medicines that we might otherwise give up on because of a lack of feedback about the benefits we can't easily see. Our bodies are our own laboratories in which we run n=1 experiments, which big data and big analytics may bring to life in new ways.

NP: I think big data is going to be important for almost every application. That doesn't mean it's going to affect every aspect of everything, but big data is going to crop up everywhere so I personally feel like it's difficult to narrow down a few specific important applications.

Where do you think the future of big data lies in five years – or 50 years?

DK: There are many exciting prospects for big data over the next five years. Biomarker discovery, using genetic information, metabolomics and proteomics, will become more efficient. Big data could also make assisted technologies more useful for people with functional difficulties. Then, there are sensors and wearables, which are appearing now but will become much more integrated and useful in the future. In the far future, I think the relationship between healthcare professionals and patients will become more symbiotic. Computer applications will be seen less as tools and more as collaborative agents able to provide insight from large volumes of data – almost like a digital colleague or companion.

NP: In the next five years, I think big data processing is going to become more predictable – we will better understand what we can and can't do with it, and be able to build more mature tools and technologies to support data management and analytics. In 50 years, I believe automation will free up data scientists to focus on how to use data more efficiently, and drive the field forward at a more rapid pace. I don't think we're very far from automated software that, for example, can read through scientific papers and extract key information about a particular protein, pathway, or topic you're interested in. These kinds of applications will make a big difference to a lot of daily life tasks.

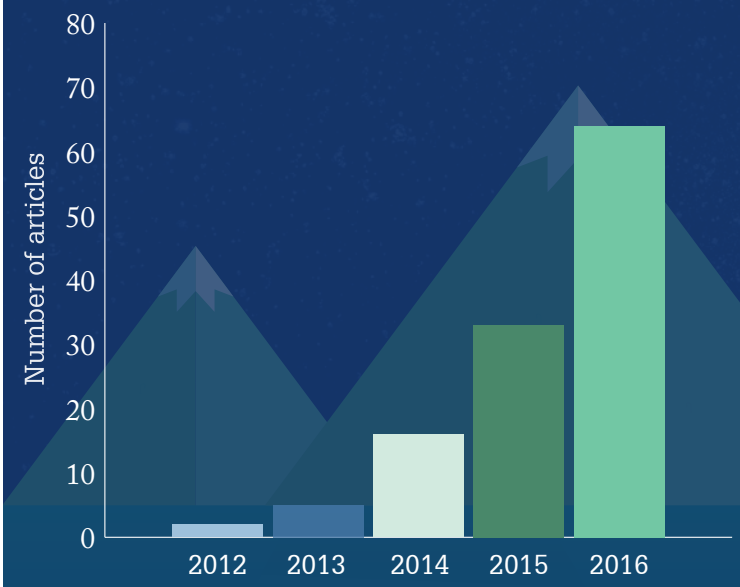
"Our bodies are our own laboratories in which we run n=1 experiments, which big data and big analytics may bring to life in new ways."

IB: Increasingly, we live our lives connected to each other's behaviors through social digital technologies. In 50 years, I think we'll be talking a lot more about how we influence health behavior, as individuals and as societies. Therein lies a "big connectedness" of information – the fusion of biology, behavior, and environmental data, and new understanding of how those three principal components interact – that will push healthcare, consumer health, and public health forward as greater than the sum of their parts.

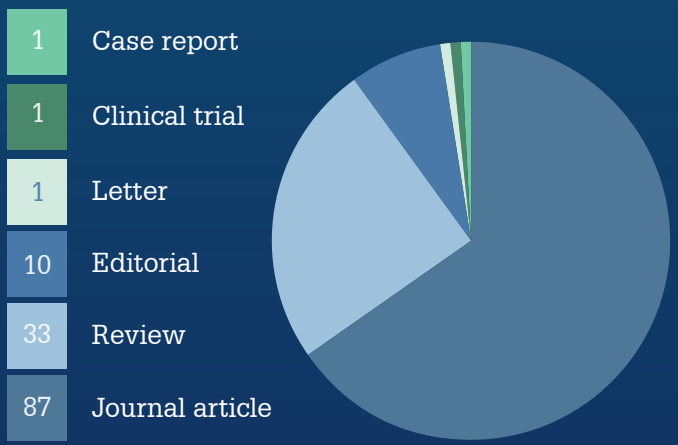
Big Data – And Getting Bigger...

How has the appearance of big data in pathology literature changed over the last five years – and what are the field's priorities?

Articles per year featuring "big data" and pathology



Types of articles published in the last five years



Top ten subjects researched

1. neoplasms
2. brain
3. computational biology
4. factual databases
5. algorithms
6. genomics
7. precision medicine
8. data mining
9. genetic predisposition to disease
10. genome-wide association study

Top ten words and phrases

Words

1. omic	**2.** metagenomics
3. epigenomic	**4.** cardiometabolic
5. actionable	**6.** transcriptomic
7. metabolomic	**6.** personalized
9. metadata	**10.** bioinformatic

Phrases

1. big data	**2.** high throughput
3. digital pathology	**4.** molecular pathology
5. precision medicine	**6.** data set
7. personalized medicine	**6.** data versus big
9. set data	**10.** medicine precision

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Profession

Your career
Your business
Your life

The School of Life

A collaboration between Britain and Bosnia – the Bryan Warren School of Pathology – is bringing education to trainees with limited access

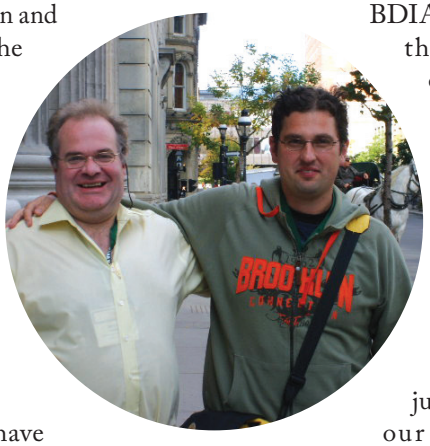
By Semir Vranić

How can pathologists provide the best possible diagnostics in countries with limited resources? The answer to that question is often sought in the development of low-cost equipment and techniques that can offer alternatives to the bulky, expensive options found in many high-tech laboratories. But there are other ways to improve pathology services under difficult conditions. I believe that education is the key. The more our young pathologists know, and the more varied their experiences, the better service they can provide. And what's more, they innovate – translating that knowledge and experience into new ideas.

At a Glance

- *When dealing with limited resources, education can be as valuable for service improvement as money or equipment*
- *The Bryan Warren School of Pathology is providing high-quality diagnostic pathology training that would otherwise be inaccessible*
- *The British Division of the IAP, which sponsors the school, also provides instructor training and bursaries for conference attendance*
- *In the future, we hope not only to improve the school, but to expand to providing even more varied and advanced education*

My colleagues and I asked one another: how can we help young pathologists learn? And the answer that came to us was simple: give them a school. Easier said than done, of course – but once we had the vision, we only needed motivation and hard work to find the resources we needed. Thanks to a few key people in the British chapter of the International Academy of Pathology (IAP), our vision is now a reality.



School's in session

The inspiration to have the British chapter of the IAP sponsor a set of seminars in Bosnia came from Mike Franey, a great friend of mine and a great friend to Bosnia as well. Although he himself is from the UK, Mike has established close relations with the people from northwestern Bosnia – a region devastated during the war from 1992 to 1995. He has always been enormously supportive of my countrymen, delivering all sorts of humanitarian aid to that region through Acorn Aid – an organization he set up himself.

In 2005, Mike met Bryan Warren, who shared his passion for cars and driving – and who also happened to be an outstanding gastrointestinal pathologist from Oxford. He connected me with Bryan in 2006, during the centennial IAP meeting in Montreal. Before the meeting was over, we had made plans to set up the Bosnian-British School of Pathology under the auspices of the British Division of the International Academy of Pathology (BDIAP). The inaugural school was held in Sarajevo in the summer of 2007, and it was a great success! Ever since, we have organized a course every year that covers all aspects of diagnostic pathology. We call it the Bryan Warren School of Pathology (BWSP), and we're very careful to keep it noncommercial; sponsorship comes from the BDIAP and my hospital, the Clinical Center of the University of Sarajevo. The local organizing committee members are all volunteers, and we try to keep the registration fee very low – currently €50 per participant, just enough to cover our costs. Why? It's very important to us to keep this kind of education accessible to all young pathologists in Bosnia and its neighboring countries, so that they face no unnecessary barriers to advancing their knowledge and skills.

I believe there are no other projects like ours in the region, but we'd like to change that! Last year, we started a collaboration with the Turkish Division of the IAP, who initiated a cytopathology course in Bosnia. The inaugural session was held in Sarajevo in June of 2016. Our initial goal was to improve cytopathology service in Bosnia – and our plans are growing ever more detailed. Now, we're planning a series of more in-depth courses in upcoming years to examine various aspects of diagnostic cytopathology. For instance, our next course will have an intensive focus on the cytopathology of the lung and thyroid. We're also currently working with the MD Anderson Cancer Center to plan an advanced surgical pathology course that would be held in Sarajevo in 2018. We may be a small country, but we have big plans for pathology education!

Beyond the basics

The BWSP is more than just a collection of practical courses in diagnostic pathology. I've found that it's also a great platform for participants and lecturers to establish professional relationships. Thanks to the people involved with the school, several of my colleagues and I have had a chance to visit their workplaces in UK and learn from them. We've studied breast pathlogy at Guy's and St Thomas' hospitals and Nottingham City Hospital, lung pathology at the Royal Marsden, gynecopathology at John Radcliffe Hospital, and hematopathology and molecular pathology at the University Hospital of Wales. This detailed on-location training, funded by the BDIAP, has substantially improved the diagnostic skills of all of us fortunate enough to take part, and has undoubtedly increased the overall quality of our pathology service.

In fact, the BDIAP has been very generous in a number of ways. Not only have they provided us with training, but they also support our pathologists biannually so that they can attend the Congress of the International Academy of Pathology (IAP). And in 2012, the BDIAP established a special award called the Nermin Duraković Bursary, in honor of the eponymous translator who supported our collaboration so tirelessly in its early stages. The bursary provides a reduced registration fee and covers travel expenses for any young Bosnian pathologist intending to present at the symposium. Last year, it allowed three pathology trainees to attend the joint IAP and European Society of Pathology meeting in Cologne, Germany. One day, those trainees may come back and teach at the BWSP!

Growing and changing

After each course, we distribute a questionnaire to the participants so that they can tell us what they liked – and how we can improve. Wherever possible, we try to act on those suggestions. The good news is that not only do we have more students every year, but many of them are repeat attendees who keep coming back to continue learning. It seems that the BWSP has become a recognizable annual event with a reputation for quality education and organization – and seeing our numbers increase year on year is the best recognition and reward any of us could possibly have.

We've been asked how long we plan to keep running the school. The answer is: as long as there is a need to improve pathology practice in Bosnia and neighboring countries. Pathologists here work with few resources and limited budgets, which leaves young people who want to study abroad with little to no hope of doing so. For those early-career pathologists, the BWSP is a window to the developed world, and an excellent opportunity for them to receive a high-quality education in modern diagnostics. It may even serve as a springboard to training in other countries or to visiting congresses they had not previously dreamed they might attend!

Last year marked the 10th anniversary of the BWSP. To celebrate the occasion, we conducted a special course in conjunction with the third national pathology congress of Bosnia and Herzegovina. But even a decade after its inception, there are still things we'd like to develop further for the BWSP. For instance, we'd like to improve the practical aspects of the course by using digital slide images, multiheaded scope slide evaluation, and similar tools. We also want to attract more people from countries on the cutting edge of pathology technology – so far, we've had participants from Austria, Slovenia, Great Britain, Germany and the Netherlands, but we'd like to see much more of that.

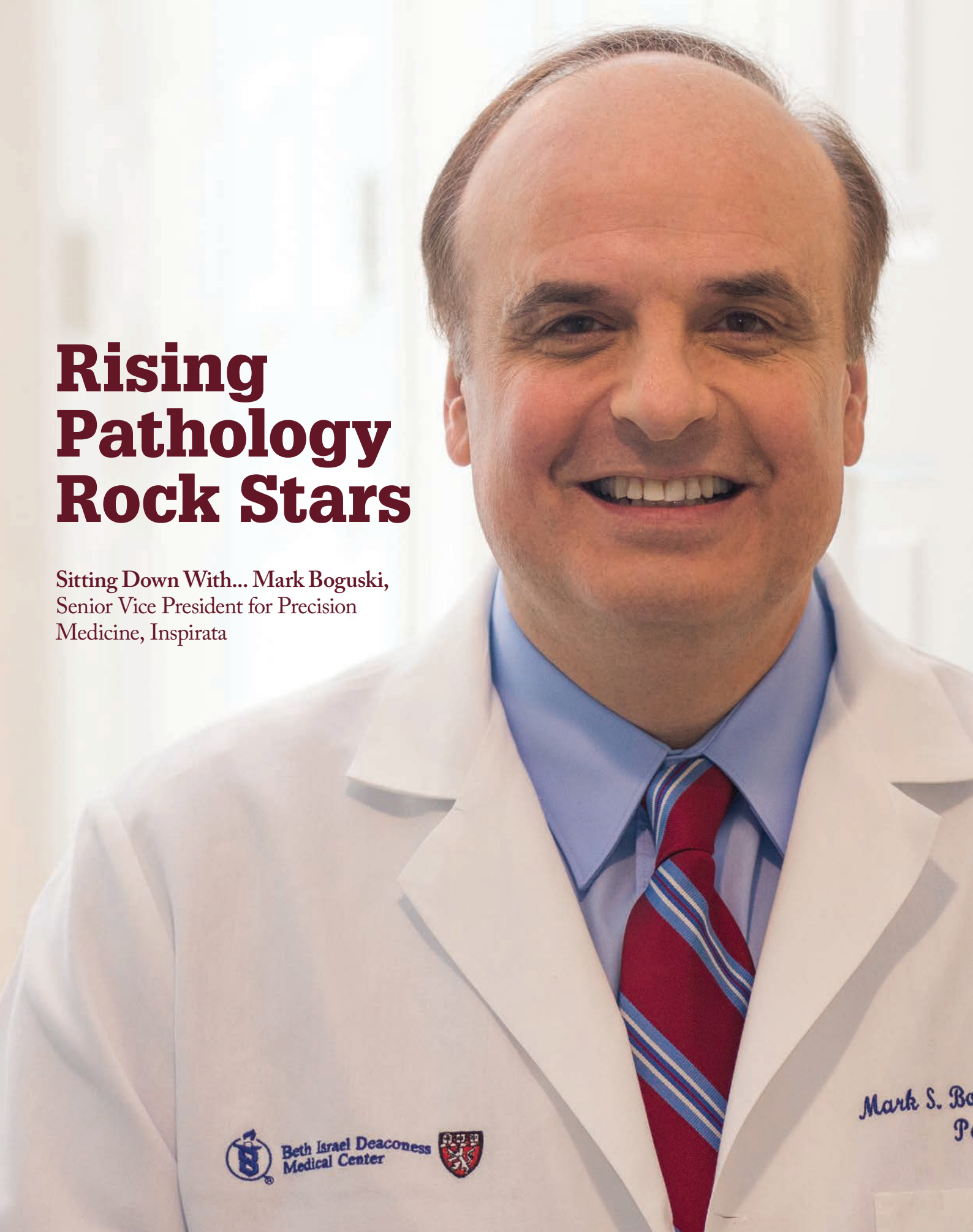
"Seeing our numbers increase year on year is the best recognition and reward any of us could possibly have."

Please consider this an invitation to all you pathologists out there who are interested in teaching – the Bryan Warren School of Pathology welcomes you!

Semir Vranić is an Assistant Professor of Pathology and a Union for International Cancer Control Fellow at the Clinical Center and School of Medicine of the University of Sarajevo, Bosnia and Herzegovina.

Rising Pathology Rock Stars

Sitting Down With... Mark Boguski, Senior Vice President for Precision Medicine, Inspirata



What kick-started your career in pathology, genomics, and bioinformatics?

During my molecular biology PhD, pathology was at a historical turning point – new vistas into understanding diseases at the molecular level were being opened with new tools and technologies, and I wanted to be part of that.

As I was completing my pathology residency in the late '80s/early '90s, the dawn of the human genome project became the great scientific endeavor, and I was immediately drawn to the possibility that we could gain unparalleled insight into the cause of disease by decoding the whole human genome. I soon realized that if the project was going to fulfill its potential, it was going to mean analyzing lots of data with computers. Back then, computers in biology were only used by X-ray crystallographers, as most biologists didn't see the need for them. I considered the future and recognized that biomedical research was going to become a data science – and that's when I made the transition from pathology and molecular biology to bioinformatics and genomics.

You have published books on celebrity diseases – why?

About 10 years ago, my wife (who is also a physician) and I became frustrated when seeing reports in the media that conveyed superficial or incorrect information about the diseases suffered by public figures. We saw a real opportunity to address the health literacy gap by using professional athletes, Hollywood celebrities, and famous politicians as examples in our layman's explanations of disease states. Many public figures are very open about disclosing their health struggles, so we're not violating any medical confidentiality rules or regulations; we're simply taking the conditions they're disclosing and creating "teachable moments" so the average person can understand it in depth.

There's a saying: "Pathologists are the most important doctors that most patients have never met." I believe we should rectify that and spend more time with them. I see many of my colleagues taking the initiative by offering office hours so that patients can gain a better understanding of what's happening; they're almost always grateful for the experience because it enlightens and empowers them.

You've been credited with coining the term "precision medicine" – how do you define it?

To me, precision medicine has three essential attributes: understanding the root mechanistic cause of disease; having the ability to detect those causal factors with a test – biomarker analysis, clinical laboratory tests, and so on; and possessing treatment that can target the root causes.

Personalized medicine, on the other hand, can be done with or without precision medicine and takes into account many other factors, such as patient comorbidities, family history, and their compliance with treatment – drugs don't work if people don't take them correctly (or at all!)

When the term "personalized medicine" became commonly used around a decade ago, many physicians took offense because they felt they had always provided treatment that was individualized to patients. I think it's a good thing that we're now more focused on precision medicine; it's something that we can define by those three attributes, and still incorporate into a personalized approach.

What outstanding moments in your career would you like to relive?

There are two. I was very fortunate to start my professional life when the human genome project began – being part of it was a once-in-a-lifetime opportunity. In terms of a singular moment, I'd say publishing the first comprehensive map of the human genome in 1996 in Science. To me, it was one of the first – if not the first – examples of big data analytics in biomedicine.

I also take a great deal of pride in the invention of comparative genomics (http://tp.txp.to/markboguski) – using the unity of biology across many different levels to study other organisms, such as yeast and fruit flies, and gain insight into the pathophysiology of human disease. In fact, in 1990 we discovered the cause of neurofibromatosis by comparing the human gene to related genes in yeast! This comparative genomics approach accelerated drug discovery tremendously.

What's next?

I'm already right in the thick of my next move! As the head of precision medicine at Inspirata, I'm helping to develop the databases and software tools that will push pathology forward. We're also launching new platforms for knowledge visualization, just-in-time learning and clinical decision support.

A couple of years ago, Forbes magazine predicted that pathologists will be the real big data rock stars of healthcare, and they made that assertion because it's believed that up to 70 percent of clinical decisions are based on laboratory data. Recently, a friend of mine (the Chairman of Pathology at a major Harvard-affiliated hospital) told me that the switch over to a new electronic health record system allowed them to see that 500 million pathology reports (compared with only 14 million radiology reports) were generated in their hospitals over a five-year period. By any definition that's big data – and we're certainly not maximizing its utility in precision medicine.

With that in mind, I'm working towards making Forbes' prediction a reality. I want to empower pathologists to be the big data rock stars of precision medicine – and to use powerful new technologies to improve outcomes and reduce costs for patients and society.

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