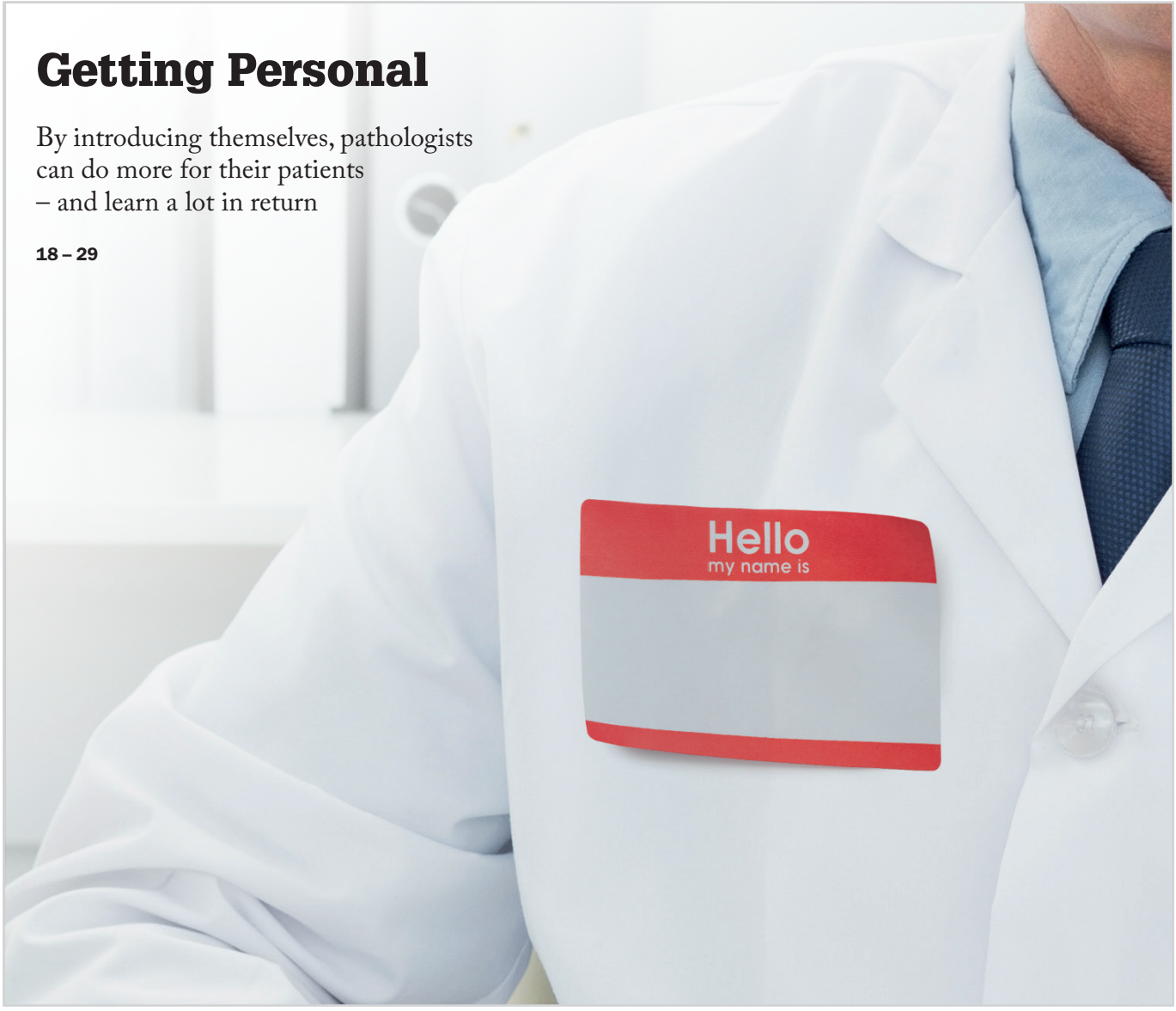
DECEMBER 2017 # 37

the Pathologist™

Getting Personal

By introducing themselves, pathologists can do more for their patients – and learn a lot in return



ion torrent

The future of liquid biopsy is here

From blood sample to variant data, end-to-end workflows for clinical research

Comprehensive, automated solutions using Ion Torrent™ technology help you obtain the answers you need to make the most of noninvasive clinical research samples.

- Detect mutations in cfDNA, CTCs, or both from a single tube of blood
- Maximize accuracy and simplicity with Ion Torrent™ workflows incorporating liquid biopsy and next-generation sequencing
- Choose solutions that adjust to your available sample and throughput needs: analyze from just a few to thousands of biomarkers

Pursue. Pioneer. Prevail.

Prevail with liquid biopsy solutions for oncology research.
See more at **thermofisher.com/liquidbiopsy**

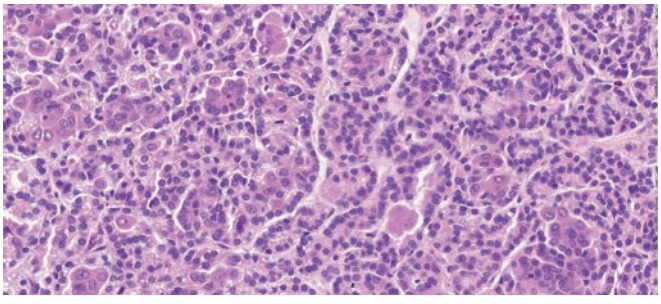
ThermoFisher SCIENTIFIC

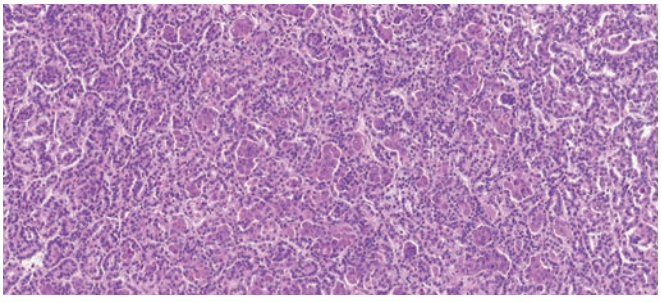
Case of the Month

The pictured kidney tumor is a "rare bird." It has a dual cell population and shows characteristic features of emperipolesis and cyclin D1 positivity in large cells.

What is your diagnosis?

- *A* Papillary renal cell carcinoma type 1
- *B* MiT family translocational renal cell carcinoma
- *C* Urothelial carcinoma with squamous differentiation
- *D* Biphasic papillary renal cell carcinoma
- *E* Chromophobe renal cell carcinoma with quamous differentiation





Answer to last issue's Case of the Month…

A. CDH1

Last month's case was an intramucosal form (pT1a) of hereditary diffuse gastric carcinoma (HDGC). HDGC accounts for 1–3 percent of all gastric carcinomas (1). Most of these tumors are linked to germline mutations of the *CDH1* gene encoding the cell-cell adhesion molecule E-cadherin. Mutations of the *CTNNA1* gene encoding catenin alpha-1 account for a small minority of *HDGC* cases.

The other genes listed are not related to gastric cancer. Germline mutation of *STK11* is typical of Peutz-Jeghers syndrome, whereas *RET* mutations are linked to multiple endocrine adenomatosis syndromes. *FOXL2* mutations are found in granulosa cell tumors of the ovary.

In early stages of HDGC, the tumor presents in the form of small intramucosal foci of signet ring cell carcinoma, or as signet ring cell carcinoma in situ, with or without intraepithelial pagetoid spread into adjacent gastric glands. It is not currently known which intramucosal lesions will progress to highly aggressive, invasive HDGC (2).

References

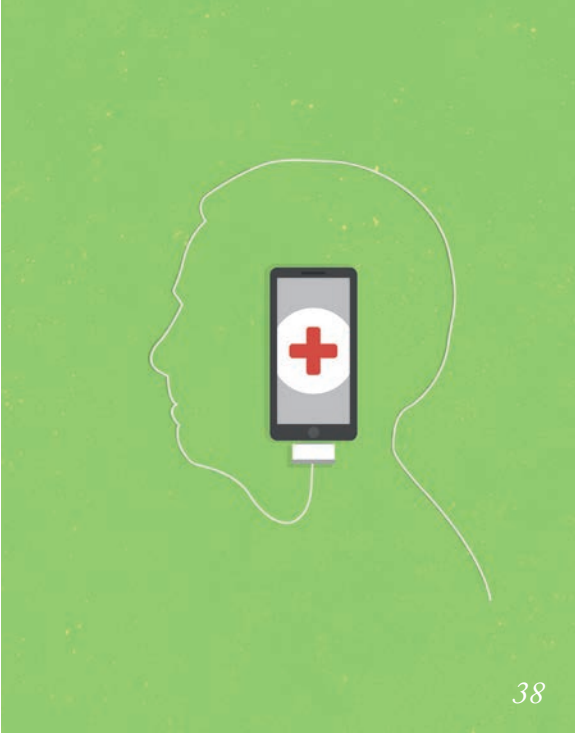
1. *C Oliveira et al., "Familial gastric cancer: genetic susceptibility, pathology, and implications for management", Lancet Oncol, 16, e60–e70 (2015). PMID: 25638682.*
2. *RS van der Post et al., "Histopathological, molecular, and genetic profile of hereditary diffuse gastric cancer: current knowledge and challenges for the future", Adv Exp Med Biol, 908, 371–391 (2016). PMID: 27573781.*

To register your guess for this month's case, please go to http://tp.txp.to/1217/case-of-the-month
We will reveal the answer in next month's issue!

Contents

On The Cover

A nametag on a lab coat, representing the value of pathologists' making themselves and their work known to patients.



Feature

In Practice

Next Gen

Profession

Sitting Down With

the Pathologist

ISSUE 37 – DECEMBER 2017

Change of address:
hayley.atiz@texerepublishing.com
Hayley Atiz, The Pathologist,
Texere Publishing Ltd, Haig House, Haig Road, Knutsford, Cheshire, WA16 8DX, UK

General enquiries:
www.texerepublishing.com
info@texerepublishing.com
+44 (0) 1565 745200
sales@texerepublishing.com

Distribution:
The Pathologist (ISSN 2055-8228) and The Pathologist North America (ISSN 2514-4049), is published monthly by Texere Publishing Ltd and is distributed in the US by UKP Worldwide, 3390 Rand Road, South Plainfield, NJ 07080
Periodicals postage paid at South Plainfield, NJ
POSTMASTER: Send US address changes to The Pathologist C/O 3390 Rand Road, South Plainfield NJ 07080.
Single copy sales £15 (plus postage, cost available on request tracey.nicholls@texerepublishing.com)
Annual subscription for non-qualified recipients £110

texere publishing ltd
Available on the App Store

NanoZoomer

REDEFINED

Introducing the
NanoZoomer S360

Optimized flexibility, speed and image quality for any scanning need.

HAMAMATSU

PHOTON IS OUR BUSINESS

Beyond the Duty of Care

Pathologists' interactions with patients are meaningful – perhaps more so now than ever

The end of a year can bring divided emotions: sadness, excitement, regret, relief… No matter what your views on the events of 2017, there's certainly no denying that it has been a year to remember – and that goes for science and medicine, too.

The year has seen an explosion of new technologies, new recommendations, and new discoveries. It has also seen tectonic shifts in some of the world's largest healthcare systems. In the UK, the National Health Service (NHS) has just seen the announcement of its latest budget – an additional £2.8 billion increase in funding over previous promises, and yet perhaps still not enough to permanently sustain the service. And the US Affordable Care Act might as well be a tennis ball, batted first this way and then back again by the vagaries of politics. All everyday citizens can do is watch to see what might become of the fledgling program.

But even as healthcare systems are in turmoil the world over, one thing is clear to me: that the people on the ground – nurses, clinicians, *you* – are more dedicated than ever to making sure patients receive the best possible care. And it isn't easy. Funding is tight. Grants are disappearing. Pathologists are retiring, with few new faces to replace them. The hours are longer, the work more complex, and often, it may feel like a thankless job.

And so in this month's cover feature (see page XX), I was thrilled to see that it's not just other pathologists who appreciate what you do. Patients are increasingly coming into contact with pathology – for help interpreting genetic test results, for questions about future tests, even for personalized tours of their own biopsies. From what I've heard, it's clear that your input is highly appreciated.

So what's my own personal takeaway from 2017? That medical services, healthcare systems, and even governments are always changing – but that the bond between care provider and patient remains as sacred as ever. That (regardless of billing and contracts and mandatory duties) the people who ultimately hold my care – and that of my seven billion colleagues on Planet Earth – in their hands still have me and my best interests at heart. And that those seven billion other patients are slowly realizing just how big, how complex, and how deeply involved their care teams are in their health.

"Hello, my name is _____ and I'm your pathologist." A simple connection – but one more important than ever to the people on both sides of the bench.

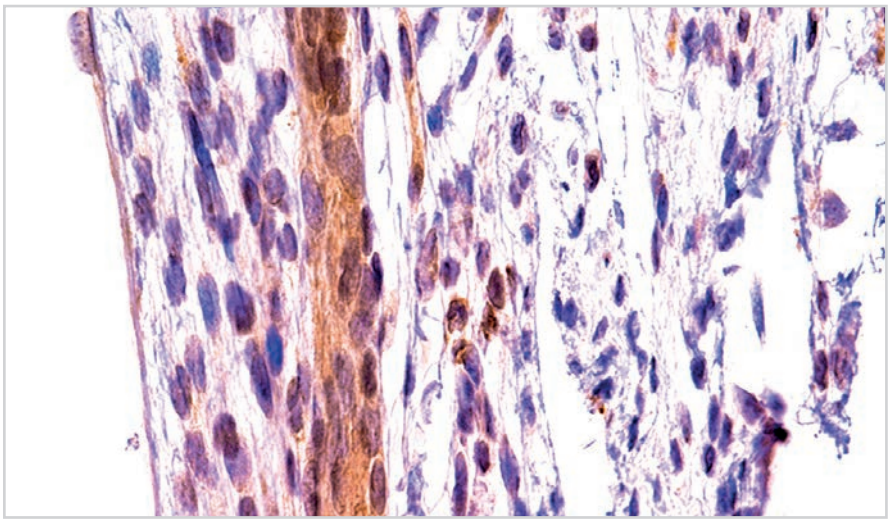
Michael Schubert
Editor

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



Cincinnati Children's

A section of obstructed extrahepatic bile duct in a neonatal mouse that exhibits residual MMP-7 expression (brown).

Biliary Biomarker

Measuring MMP-7 levels could speed up biliary atresia diagnosis

Children born with biliary atresia face a difficult journey. Even the first step – diagnosis – is a challenge many overcome too late. Bile ducts allow bile to flow from the liver to the intestines; biliary atresia blocks that flow and bile accumulates in the liver, causing organ damage and eventually requiring transplantation. If diagnosed early, surgical intervention can restore the flow of bile and prevent complete liver failure – but, unfortunately, that often doesn't happen.

"The current diagnostic algorithms are complex and expensive," says Jorge Bezerra, lead investigator of a study searching for biomarkers of the disease. Because the disease has multiple potential causes, no two cases look the same, which makes diagnosis challenging. "The best biochemical marker, gamma-glutamyltransferase (GGT), has limited specificity," Bezerra explains. "Other investigations include ultrasound and tests to rule out other diseases. This combination takes time and delays surgical treatment. By having a better biochemical marker, one can make the diagnosis more promptly, perform a biopsy, and send the infant to surgical treatment." The liver-sparing procedure, called a Kasai portoenterostomy, has much greater success when performed in early infancy – so an accurate molecular biomarker would be a lifesaver.

And that's exactly what Bezerra's team found – a protein known as matrix metalloproteinase-7 (MMP-7), which is released into the blood after injury of the biliary epithelium (1). "MMP-7 was the protein biomarker with the highest discriminatory value for biliary atresia. Validation was performed in two additional cohorts. Immunostaining showed the highest expression to be limited to gallbladder and extrahepatic bile ducts – the main anatomic sites of injury in biliary atresia." Even alone, MMP-7 proved a useful biomarker for biliary atresia – but its accuracy improved to 95 percent when combined with GGT.

Bezerra and his team are now measuring MMP-7 in neonates to establish normal values and developing an easy-to-perform assay for MMP-7 quantification. Soon, they hope to make the test available to clinicians for prompt inclusion into diagnostic approaches, with the goal of saving livers – and lives.

Reference

1. *C Lertudomphonwanit et al., "Large-scale proteomics identifies MMP-7 as a sentinel of epithelial injury and of biliary atresia", Sci Transl Med, 9, eaan8462 (2017). PMID: 29167395.*

Fostering Better Care

Children entering foster care are receiving extensive screening – but is it cost-effective?

When a child enters foster care, he or she receives a full medical evaluation, including laboratory testing of hemoglobin and lead levels and screening for hepatitis B and C, syphilis, tuberculosis, HIV, and (in sexually active adolescents) gonorrhea and chlamydia. But is all this testing really necessary – and is it worth the cost to the foster care system? New research suggests not (1).

Children entering foster care currently undergo laboratory testing based on recommendations developed by an expert panel in New York, which were last endorsed in 2005 by the American Academy of Pediatrics. "At the time, expert opinion was the highest level of evidence available, as there was very little scientific literature on children in foster care," explains lead author Mary Greiner, who goes on to say that research is paying increasing attention to this underserved population and opinion is shifting.

But if a one-size-fits-all approach to laboratory testing for these children is not cost-effective – what is the alternative? Greiner and her colleagues propose a more targeted approach. "Targeted screening would involve looking at the community and the individual being tested," she says. "Each community may have different prevalence rates of infections and each individual may have their own risk factors, such as exposure to high-risk activities or a history of sexual abuse that would confer increased risk for specific infections."

The study revealed, for instance, that chlamydia screening in sexually active populations provides a good return on investment; 7 percent of adolescents tested positive, meaning that it's more cost-effective to screen everyone than to miss existing infections. For diseases like syphilis or tuberculosis, however, the opposite is true – fewer than 1 percent of children are infected, so screening an almost entirely healthy population is unnecessary and expensive. "In the future, algorithms will likely account for infection prevalence rates in a given community and an individual patient's risk factors for specific infections," says Greiner.

Nonetheless, the researchers were somewhat surprised to find infection rates as low as they were. "Our biggest surprise was that the risk for infectious disease was quite low in this population, at least in our area of the country. Youth in foster care are at high risk of medical problems and come from environments where they are in contact with adults known to be at high risk for infectious disease issues like HIV and hepatitis C." The assumption was that foster youth would also be at high risk – but that is evidently not the case. In the future, then, perhaps they can be spared the extensive testing current guidelines recommend in favor of more optimized screening for the diseases most likely to affect them.

"Despite our article's focus on infectious disease findings, youth in foster care continue to be high risk for other medical problems, including developmental delay and mental health concerns – and they certainly warrant 'early and often' health care surveillance, as recommended by the American Academy of Pediatrics," concludes Greiner.

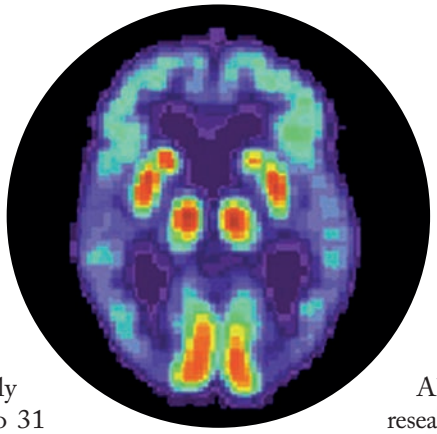
References

1. *MV Greiner et al., "Laboratory screening for children entering foster care", Pediatrics, [Epub ahead of print] (2017). PMID: 29141915.*

The Value of Variants

A new test examines 32 gene variants to make earlier and more accurate predictions of Alzheimer's disease

It's well known that the *APOE-ε4* variant of the *APOE* gene places people at greatly increased risk of late-onset Alzheimer's disease, but only 10 to 15 percent of the population carries the variant, and even some homozygous individuals never develop the disease. It's clear that *APOE-ε4* isn't the only determinant of Alzheimer's disease risk. So, what about the 85 to 90 percent of the population without the high-risk variant?



A new study conducted by researchers at the University of California tackles that question with a polygenic hazard score (PHS) that incorporates not only *APOE-ε4*, but also 31 other genetic variants (1). The test doesn't diagnose Alzheimer's, but it can identify individuals without the disease who are most likely to progress to Alzheimer's dementia as well as determining how steep their cognitive decline is likely to be. Each individual variant alone brings with it only a small risk of disease – but those minor risks are cumulative.

Even in patients who carry no *APOE-ε4* variants, an elevated PHS was correlated with higher levels of amyloid plaques, steeper cognitive declines, and higher incidences of clinically diagnosed Alzheimer's disease. The researchers hope that their new test can be used to identify preclinical disease, so that patients can undergo early or even preventive treatment – while they are still in the best possible neurological health.

References

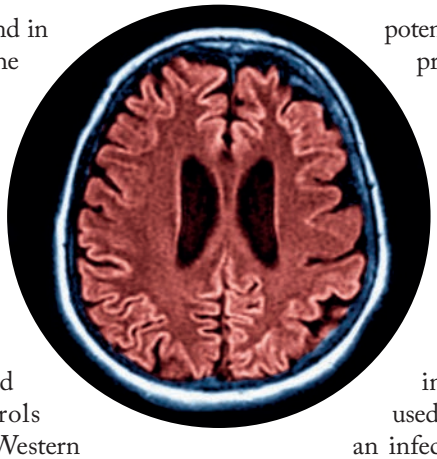
1. *CH Tan et al., "Polygenic hazard scores in preclinical Alzheimer disease", Ann Neurol, 82, 484–488 (2017). PMID: 28940650.*

Beyond the Brain

Skin samples can reveal the presence of infectious prions in Creutzfeldt-Jakob disease, but may also carry the risk of iatrogenic transmission

Creutzfeldt-Jakob disease (CJD) is rare, but difficult to diagnose. At the moment, most conclusive diagnoses require either an invasive brain biopsy or a post-mortem examination – neither of which will be appealing for patients. To avoid causing patients unnecessary distress, a preliminary diagnosis is often made based on symptoms, such as cognitive decline, physical weakness and sensory and functional deficits. Unfortunately, none of these symptoms is exclusive to – or therefore fully diagnostic of – CJD.

Researchers at Case Western Reserve University School of Medicine saw the gap and wondered if the prions that cause the disease could be found in tissues other than the brain. To find out, they applied two laboratory assays – Western blotting and real-time quaking-induced conversion (RT-QuIC) – to skin samples taken from 23 CJD patients and 15 non-CJD controls (1). The first assay, Western blotting, was not sufficiently sensitive; it revealed prions in only two of seven CJD patients. RT-QuIC, however, detected prions in all 23 CJD patients and none of the control samples.



The results are a mixed bag, though. It's great news for diagnosticians seeking an alternative to brain biopsy for their patients – but if infectious prions are present at detectable levels in the skin of CJD patients, then it raises concerns about potential transmission. The prions are notoriously tenacious – well known for their ability to stick to steel and survive many standard disinfection procedures. Is it possible that CJD could be transmitted, for instance via instruments previously used to perform surgery on an infected patient? Directly inoculating the brains of mice with CJD skin extracts did transmit the disease, but more research is required to discern whether or not standard hospital procedures involve the same risk.

References

1. *CD Orrú et al., "Prion seeding activity and infectivity in skin samples from patients with sporadic Creutzfeldt-Jakob disease", Sci Transl Med, 9, eaam7785 (2017). PMID: 29167394.*

Salivary Secrets

Levels of five microRNAs in saliva can hold clues to the length of time concussion symptoms may last

Concussion: an unpleasant diagnosis at best, dangerous at worst – and even more worrying if it's not your diagnosis, but your child's. But concussions vary – sometimes symptoms are mild and fade within a week or so, but they can also linger, causing prolonged difficulty and discomfort. How do we know which is more likely? At the moment, we use a survey of experienced symptoms – but researchers from Penn State College of Medicine believe the levels of five microRNAs (miR-320c-1, miR-133a-5p, miR-769-5p, let-7a-3p, and miR-1307-3p) in saliva may offer a more accurate prediction (1). We spoke to principal investigator Steven Hicks to learn more about the discovery.

What inspired you to investigate prolonged concussion in children?

I was inspired by my experience as a general pediatrician; I often see and treat children with concussions. Currently, there are no objective tools to predict how long a concussion might last. Most are better in two weeks, but up to 33 percent may persist beyond this period, which is frustrating for both parents and doctors. It makes it very difficult to develop accurate prognoses and individualized treatment plans.

Unlike protein biomarkers, which have difficulty crossing the blood-brain barrier, microRNAs are used by the brain as small signaling molecules and can easily cross into other body fluid compartments – and they are extremely concentrated in saliva. Because our previous work had shown that microRNAs are related to other disorders of the brain, including autism, we decided to explore whether they might help us identify and characterize concussions.

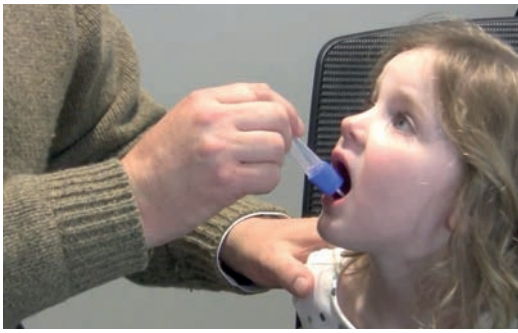
Can you describe the microRNAs you identified?

The microRNAs we identified target gene pathways that are highly related to brain processes. They control axon outgrowth and plasticity – processes that would be extremely important in responding to a brain injury. So unlike protein biomarkers, which generally increase to indicate that a major cellular injury has occurred, microRNAs may actually decrease to allow a protective or adaptive cellular response to neuronal injury. Failure to initiate these molecular pathways (because of underlying genetic reasons or through triage of more immediately important cellular injury or death pathways) might predispose some children to prolonged concussion symptoms.

We also looked at relationships between individual microRNAs and the severity of specific symptoms, such as headache, fatigue, or attention difficulty one month after concussion – and we found several strong correlations. In this manner, levels of specific microRNAs in the first week after an injury might allow us to accurately predict how long symptoms might last, what character those symptoms might take on, and how severe they might be.

How could this translate to a clinical test?

If successful, this approach would give medical professionals an objective way of determining whether a concussion has occurred, how long it might last, and what symptoms might be most problematic. In its current form, this would be an in-office salivary swab processed by a lab within 24 hours – but with advancing technology, point-of-care testing is not far away. This type of knowledge could also help advance research – for instance, by carefully selecting participants for clinical trials to assess the treatment efficacy of certain medications, rather than enrolling any patient with concussion.



Before such a test can enter the clinic, though, it will need to be validated in a larger prospective cohort across a broader age range. The company sponsoring this research has laid a foundation for quick and accurate sample processing and secure return of results. They hope to bring the test to market in one to two years. We are always looking for researchers who are interested in collaborating and I think this type of open, collegial approach will speed the development of the technology.

What are you working on now?

We have some very exciting results, soon to be published, examining the diagnostic potential of salivary RNA profiles in children with autism – a study that currently has over 400 participants and equally promising findings.

In the concussion realm, we are moving forward to validate our work. We are using a longitudinal sample collection design and pairing microRNA profiles with functional measures of concussion symptoms (balance and cognition) as well as subjective symptom reports.

References

1. *JJ Johnson et al., "Association of salivary microRNA changes with prolonged concussion symptoms", JAMA Pediatr, [Epub ahead of print] (2017). PMID: 29159407.*

LITMUS for the Liver

A new project coupling biobanking, research and industry is in search of biomarkers for the evaluation of non-alcoholic fatty liver disease

The LITMUS (Liver Investigation: Testing Marker Utility in Steatohepatitis) project aims to develop, validate and qualify biomarkers to assess patients with non-alcoholic fatty liver disease (NAFLD) and identify those most at risk of developing severe inflammation and liver scarring. A pioneering endeavor funded by the European Innovative Medicines Initiative 2 Joint Undertaking, the project brings together clinicians and scientists from prominent academic centers across Europe with companies from the European Federation of Pharmaceutical Industries and Associations (EFPIA). In total, 47 international research groups based at leading universities and pharmaceutical companies from 17 different countries are participating in the project.

Fay Betsou, Chief Scientific Officer at the Integrated BioBank of Luxembourg (IBBL) explains her organization's role. "IBBL is the central biobank for the LITMUS project. As such, we will gather all of the biological samples that are currently stored at the other partners' sites. We will also serve as the central collection and storage point for the samples that will be freshly collected for the LITMUS project." These samples, obtained from 1,500 or more patients across Europe, will include blood, plasma, serum, DNA, RNA, urine, stool and liver biopsies. IBBL's task? To create a catalog of the samples and their associated data and make it available to the research community.

"Since the beginning, IBBL has focused on establishing and nurturing international partnerships and has been part of a number of consortia within the frameworks of the Innovative Medicines Initiative, Horizon2020 and the Joint Programme in Neurodegenerative Disease Research," says Betsou. The use of a trusted central biobank and optimized, validated protocols is a way for European consortia – especially those that include prospective collection of biospecimens – to ensure standardization. Even in cases where samples have already been collected, a central biobank can be used retrospectively to gather samples and data together, allowing users to check availability and compare samples.

For the LITMUS project, samples will be obtained using standardized collection kits, processed locally according to standard preanalytical operating procedures, and shipped to IBBL for central storage. The samples will be annotated with data on anthropometric, lifestyle, activity, dietary, comorbidity, pharmacotherapy, clinical biochemistry, and histological indices for each patient. The catalog of available samples and data will then be made available to the other consortium partners working on the identification and validation of potential NAFLD biomarkers. But because a collection of samples with extensive clinical data annotation, collected in a standardized manner, holds such tremendous value for research, it won't be reserved for LITMUS project partners alone. Once the project concludes, its catalog will be made publicly available and researchers from across Europe will be able to access the samples and associated data.

References

1. *Integrated BioBank of Luxembourg, "IBBL participates in €34 million EU project on liver disease" (2017). Available at: http://bit.ly/2kaIvAU. Accessed November 29, 2017.*

Good Vibrations

Microelectromechanical resonators could help detect biomarkers in small sample volumes

What?

A "microelectromechanical resonator" – a small, vibrating sensor that may allow the sensitive, specific and affordable detection of biomarkers in even small volumes of blood (1). Senior author Jeffrey Rhoads explains…

Why?

"What made us consider looking into biomarker detection? To be honest, George Chiu, Eric Nauman and I decided upon this research path over a water cooler conversation! George and I have worked together for nearly a decade on various sensing systems, primarily focusing on industrial and national security applications. Eric had been working on research problems related to traumatic brain injury, and he felt that our sensors might be able to have an impact in that space.

The advantage of our method over other existing ones appears to stem from a combination of the high sensitivity of our devices, our statistics-based detection approach, and the fact that we require very small test volumes."

How?

"The system is based on resonant mass sensing. The basic idea is that you have a small-scale vibrating element – in this case, a small plate. The element has a series of frequencies at which it 'likes' to vibrate – natural frequencies, which depend on a number of design parameters, including the mass of the device. If you have a clever way to bind specific masses, like proteins, to your device – for instance, through a functional polymer layer – then you have a sensitive way to detect that biomarker. The challenge is to avoid false positives without using a large sample volume of test fluid. We circumvent this through the use of large sensor arrays, which leverage the power of statistics, and a sensor functionalization and material deposition technique based on small-scale bioprinting.

Generally speaking, the sensing system is agnostic to what it detects. Functionality and selectivity are set solely by the functional layers that we deposit (and, if necessary, develop). For this work we deposited specific antibodies, embedded in a polymer, that have an affinity for the protein of interest. In our earlier work, we used similar techniques to detect analytes ranging from explosive vapors to volatile organic compounds."

Who?

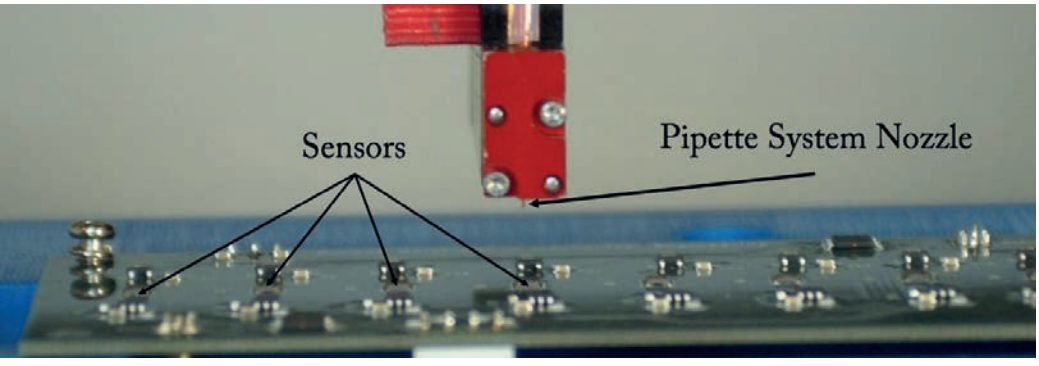
"Given the low-cost nature of our sensor, I think it might be well-suited for lab-based and perhaps even point-of-care diagnostics in the field. Our hope is to provide laboratory medicine professionals with an affordable sensing solution that takes less time to process than current gold-standard methods. Given that the required sample volumes are also low, we may also be able to help reduce the need for large volume fluid withdrawals – for example, enabling the use of finger sticks instead of full blood draws for some applications."

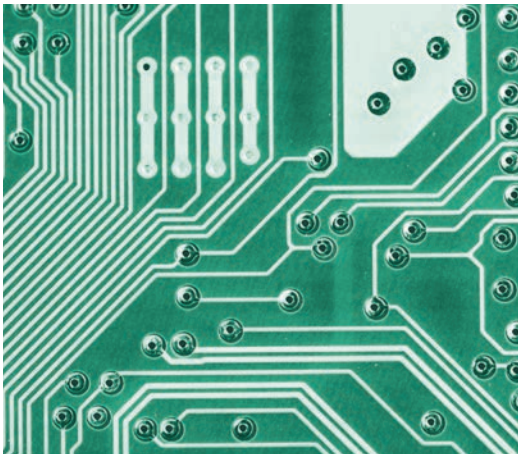
When?

"Before we can bring our biomarker detection sensor to the clinic, I suspect the next logical step is to conduct a small-scale clinical trial. We are currently looking for external partners who work in the clinical medicine space to aid with further testing. At the same time, we are working with the Purdue Research Foundation to identify potential technology transition partners. It's our hope to be able to provide laboratories and field clinics with a better, cheaper biomarker sensor as soon as possible."

References

1. *MJ Wadas et al., "Detection of traumatic brain injury protein biomarkers with resonant microsystems", IEEE Sensors Letters, 1, 2501304 (2017).*





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

Illuminating Renal Pathology

We need to reevaluate our approach to kidney disease

By Anthony Chang, Professor of Pathology at the University of Chicago, and Gladell Paner, Associate Professor of Pathology and Associate Director of the University of Chicago Medlabs, Chicago, USA

Though we're all born with two kidneys, German surgeon Gustav Simon discovered that humans can live a perfectly normal life with just one, performing the first successful nephrectomy in a human in the 18th century (though only after success with animal experimentation). And thus, removal of the entire kidney became the main option for renal cancer treatment over the next century.

In recent years, a paradigm shift towards more conservative nephron-sparing procedures, such as ablation techniques or partial nephrectomy, has occurred for two main reasons. First, not all kidney tumors are bad; some are benign, low-stage or low-grade. Second, and more importantly, there is a greater survival benefit in preserving kidney function. Currently, urologists and oncologists are gaining the upper hand against kidney cancer. For example, in the USA, there are more than 65,000 new diagnoses every year, and earlier detection has resulted in substantial stage migration. Nowadays, over 60 percent of kidney cancers are stage one, with a five-year survival that exceeds 95 percent. Even though the oncologic outcomes are similar, nephron-sparing surgery results in improved outcomes compared with radical nephrectomy because of its superior preservation of renal function.

The classification of renal tumors has also evolved during the last three decades. One major advancement is the emergence of several benign and low-grade neoplastic entities. In 2010, the International Society of Urological Pathology conducted a consensus conference in Vancouver, Canada, to update the 2004 World Health Organization (WHO) renal tumor classification guidelines. This schema became the basis for the new 2016 WHO classification of renal tumors. The nosologic innovations are important for pathologists because some newer entities, which under the old system would have been considered renal cancers, are now excluded due to their favorable outcomes. Some examples include clear cell papillary renal cell carcinoma, multicystic clear cell neoplasm of low malignant potential, and hybrid oncocytic chromophobe tumor. The traditionally known benign kidney tumors, such as renal oncocytoma, metanephric adenoma, and the now unified cystic nephroma-mixed epithelial stromal tumor, remain important for pathologists involved in renal cancer diagnosis.

"Even though the oncologic outcomes are similar, nephron-sparing surgery results in improved outcomes compared with radical nephrectomy."

There is a known association between chronic kidney disease, especially end-stage renal disease, and renal cell carcinoma. Given that hypertension, diabetes, obesity and smoking are all independent risk factors for this cancer, their respective non-neoplastic renal injuries are commonplace in kidney cancer patients. Of the 14 pathologic parameters required by the College of American Pathologists in all synoptic reports for kidney cancer, we can now reasonably argue that the status of the non-neoplastic kidney parenchyma is the most important in T1 tumors – something that is definitely true for patients with benign tumors, which comprise approximately 25 percent of small renal masses.

For example, we recently encountered a pauci-immune crescentic glomerulonephritis in a 60-year-old female with diabetes who underwent radical nephrectomy for a 3.5 cm tumor – a T1a clear cell renal cell carcinoma. Under current American Urological Association guidelines for the management of small renal masses, nephron-sparing surgery is the preferred option. Renal function preservation is especially important for this patient, as most studies of T1a renal cell carcinomas demonstrate a five-year survival rate that approaches 100 percent. The patient is cured of her cancer, but the non-neoplastic kidney disease will result in end-stage kidney disease that will be fatal. This outcome would be the same even if only diabetic nephropathy was present, which occurs in approximately one out of every 12 kidney resection specimens in the US.

In addition, several studies have discovered that non-neoplastic kidney diseases can be observed in at least 15 percent of tumor nephrectomy specimens, and that 60 to 88 percent of these diagnoses are overlooked by practicing surgical pathologists. In fact, at least 65 percent of US pathology residency training programs did not offer formal exposure to renal pathology until the Accreditation Council of the Graduate Medical Education added it as a requirement. Just as in cancer, early detection of non-neoplastic renal diseases is essential for optimal clinical management – and that demands an accurate evaluation from pathologists.

Don't Hold Your Breath

Clinical use of GC-ion mobility spectrometry has great potential – but major hurdles lie ahead

By Wolfgang Vautz, Scientist, Departments of Miniaturisation, Leibniz-Institute für Analytische Wissenschaften – ISAS – e.V., Germany and CEO of ION-GAS GmbH, Germany

Ion mobility spectrometry coupled to rapid gas-chromatographic pre-separation (GC-IMS) has enormous potential for noninvasive, rapid, sensitive and selective analysis of complex gas-phase mixtures. GC-IMS can provide a comprehensive analysis of a gas-phase mixture in a few seconds, after a noninvasive sampling of a small volume (typically 1–8 mL) – even with mobile instruments. Such noninvasive sampling could make the method very useful for the analysis of human breath (1) for (early) diagnosis of diseases, but also for analysis of medication and for the rapid identification of microorganisms.

Several studies have been conducted over the past two decades, demonstrating the potential of GC-IMS for quantification of the anesthetic propofol in breath during surgery (2), for the identification of characteristic patterns for kidney failure with potential for early diagnosis (3), or even for gathering additional information from animal models (4). Furthermore, characteristic patterns of bacteria and fungi cultures can now be identified after 24 hours of incubation, a step forward for the early application of specific antibiotics (5). So why is the method still not in routine operation in hospitals?

One obvious reason is the complex authorization process analytical instruments must undergo before they are approved for clinical use – a necessary but costly and time-consuming undertaking. More specifically to diagnosis, in most cases, explicit characteristic biomarkers are not yet known.

"I believe it will be only a matter of time before the first diagnostic GC-IMS will begin to conquer hospitals and point-of-care facilities."

To develop a diagnostic application using noninvasive GC-IMS, we have to surmount three major hurdles:

First, and most challenging, we must conduct detailed investigations in a large cohort of patients and healthy controls to identify a characteristic pattern of biomarkers. Other stumbling blocks may include inaccurate gold standards for comparison, different states of the disease, comorbid diseases, and all this without having a guarantee of complete success in the development of a characteristic pattern. Regardless, this time-consuming step is most important with regard to method development for medical diagnosis.

Second, once the pattern is defined, all biomarkers must be identified and their causal relation to the disease proven by means of metabolic pathways.

Third, the developed and proven diagnostic method must be validated in a blinded clinical study for specificity and sensitivity.

The first challenge – identifying the valid relevant pattern of biomarkers for a particular disease – is the real key to GC-IMS implementation in the clinic. With the right biomarkers, the conversion of a prototype into a proven medical instrument is, to some degree, a matter of course (although certainly requiring significant time and investment). Despite the challenges, the speed and ease of GC-IMS analysis puts it in an excellent position. And having seen it in action, I believe it will be only a matter of time before the first diagnostic GC-IMS will begin to conquer hospitals and point-of-care facilities.

References

1. *W Vautz et al., "Baumbach: Breath analysis— performance and potential of ion mobility spectrometry", J Breath Res, 3, 036004 (2009). PMID: 21383468.*
2. *T Perl et al., "Determination of serum propofol concentrations by breath analysis using ion mobility spectrometry", British J Anaesthesia, 103, 822–827 (2009). PMID: 19887534.*
3. *N Pagonas et al., "Volatile organic compounds in uremia", PLOS ONE, 7, e46258 (2012). PMID: 23049998.*
4. *S Neuhaus et al. "Comparison of metabolites in exhaled breath and bronchoalveolar lavage fluid samples in a mouse model of asthma", J Appl Physiol, 111, 1088–1095 (2011). PMID: 21778419.*
5. *T Perl et al., "Quintel: Detection of characteristic metabolites of Aspergillus fumigatus and Candida species using ion mobility spectrometry – metabolic profiling by volatile organic compounds", Mycoses, 54, e828–e837 (2011) . PMID: 21668516.*

A Whole New World

There's a need to open up new opportunities for retinoblastoma care. Here's how we're approaching the challenge

By Jesse L. Berry, Associate Director of Ocular Oncology at Children's Hospital Los Angeles (CHLA) and Assistant Professor of Ophthalmology at CHLA and the USC Roski Eye Institute, University of Southern California, USA

We say we are in an era of precision medicine. But what can one do when the very information needed to make these informed, directed, personalized choices cannot be accessed by the clinician? Well, that is the situation we currently face as ocular oncologists for retinoblastoma (Rb).

Despite critical advances in how chemotherapy is delivered, worldwide nearly 50 percent of advanced eyes with Rb are enucleated and many more affected eyes are legally blind – even with treatment (1,2). Why? Because there are no known molecular prognostic features that can predict the response of Rb to treatment and clinical features rely primarily on assessing the size of the tumor or presence of seeding (e.g., Group Classification); however, they still predict with only 50 percent certainty whether an advanced Group D Rb tumor will respond to intravenous chemotherapy or will require subsequent enucleation due to persistent or recurrent tumor. In 2017, for advanced eyes, we have the same predictive value as a coin flip (3).

"There are no known molecular prognostic features that can predict the response of retinoblastoma to treatment."

The vast majority of Rb arises from somatic, germline or mosaic mutations in the *RB1* tumor suppressor gene. And similar to other cancers – such as those found in the breast, lung and prostate – Rb DNA likely harbors specific genetic or

genomic changes that will be informative regarding therapeutic response and/or prognosis. And we need this information because there is currently no targeted treatment or personalized medicine approach for Rb, despite its being one of the first cancers with a known genetic etiology for carcinogenesis. Performing genomic analyses on Rb DNA at the time of diagnosis or during treatment would allow, for the first time, clinical correlations with specific tumor mutations, genomic changes and expression profiles that were only previously available from tumor tissue from eyes that had been already enucleated – and never from those eyes that responded to therapy and were saved. This is because evaluating tumor DNA in Rb is challenging; direct biopsy of the tumors is contraindicated because of the risk of extraocular tumor spread and metastatic disease (4). As a result, the Rb field had a long-standing golden rule: the eye is inviolable during treatment, which means that tumor tissue only becomes available after enucleation.

However, the golden rule changed in 2012 as Francis Munier – an ocular oncologist in Switzerland – introduced a safety-enhanced procedure to inject melphalan into the vitreous cavity of eyes with Rb and seeding (5,6). In this procedure, aqueous humor is withdrawn prior to the injection to lower IOP and prevent reflux of active seeds to the injection site. And it has turned out to be safe: no cases of metastatic disease have been reported with this safety-enhanced technique (7). This method of intravitreal chemotherapy as treatment for vitreous seeding in Rb has been an absolute game-changer for managing the disease, not only by providing a new, highly effective treatment strategy, but also by providing access to the aqueous humor of eyes undergoing treatment. This revolution in one aspect of Rb management has provided a critical opportunity to revolutionize another – the biopsy. We've managed to do just this, and have recently demonstrated that aqueous humor samples can be a "surrogate" biopsy for Rb – a liquid biopsy. In six samples obtained from three children with Rb, we identified cell-free tumor DNA through shallow whole genome sequencing using a next generation protocol, and confirmed that the chromosomal alterations in the aqueous corroborated those found in Rb tumors (8).

"Finally, we can gain access to critical genomic information to help ocular oncologists decide which eyes are likely to be most responsive to therapy."

Our findings provide the proof of concept that, with the aqueous, we have a safe and effective way to derive genetic information from the Rb tumor without enucleation. Finally, we can gain access to critical genomic information to help ocular oncologists decide which eyes are likely to be most responsive to therapy – and can thus be salvaged – and those which are higher risk and should undergo primary enucleation. It could also open up an entirely new research domain for Rb as well as other intraocular diseases, as the aqueous humor doesn't only yield tumor DNA. There is also RNA, microRNA, and possibly other disease markers. In fact, there's a whole new world to explore!

References

1. *JL Berry et al., "Factors predictive of long-term visual outcomes of Group D eyes treated with chemoreduction and low-dose IMRT salvage: the Children's Hospital Los Angeles experience", Br J Ophthalmol, 98, 1061–1065 (2014). PMID: 24671926.*
2. *LS Hall et al., "Visual outcomes in children with bilateral retinoblastoma", J AAPOS, 3, 138–142 (1999). PMID: 10428586.*
3. *JL Berry et al., "Long-term outcomes of Group D eyes in bilateral retinoblastoma patients treated with chemoreduction and low-dose IMRT salvage", Pediatr Blood Cancer, 60, 688–693 (2013). PMID: 22997170.*
4. *ZA Karcioglu. "Fine needle aspiration biopsy (FNAB) for retinoblastoma", Retina, 22, 707–710 (2002). PMID: 12476095.*
5. *Fl Munier et al., "Profiling safety of intravitreal injections for retinoblastoma using an anti-reflux procedure and sterilisation of the needle track", Br J Ophthalmol, 96, 1084–1087 (2012). PMID: 22368262.*
6. *FL Munier et al., "Intravitreal chemotherapy for vitreous disease in retinoblastoma revisited: from prohibition to conditional indications", Br J Ophthalmol, 96, 1078–1083 (2012). PMID: 22694968.*
7. *JH Francis et al., "Risk of extraocular extension in eyes with retinoblastoma receiving intravitreous chemotherapy", JAMA Ophthalmol, [Epub ahead of print] (2017). PMID: 29098285.*
8. *JL Berry et al., "Potential of aqueous humor as a surrogate tumor biopsy for retinoblastoma", JAMA Ophthalmol, 135, 1221–1230 (2017). PMID: 29049475.*


Hello
my name is

Hello, My Name Is...

Patients and pathologists discuss their experiences with patient-centered care and share the value it holds for them

The **Patient Expert**

Pathologists, patients and primary care providers need to communicate openly and enthusiastically with one another

By Marleen Kaatee

MY STORY

As a patient with a rare and incurable disease and a cornucopia of comorbidities, I quickly understood the advantages of learning more about my health issues. I am part of a culture where "discussion and dialog" are considered essential to everyday life, so I knew right from the start that my health care providers would play a huge role in my quest to acquire more knowledge – and that includes the pathologists and laboratory medicine professionals who diagnosed me, and who continue to monitor my health and make sure that my medications are doing their job. I know that I need to educate myself so that I can be an equal partner in discussions about my future treatments and health management. If I want shared decision-making, I had better up my game!

GETTING TO KNOW PATHOLOGY

Before I became a patient (and still in the pre-CSI era), I was only aware of the "pop culture" presentation of pathologists – that they were the doctors who performed autopsies and investigated unexplained deaths. It was only after I became a regular "customer" of the healthcare system that my view expanded.

Patients with autoimmune liver diseases, such as mine, often experience inflammatory bowel symptoms, so when my hospital hosted a patients' open day on the subject, I decided to attend – and I am so glad I did, because it was my first real introduction to pathology. I walked through a huge, inflatable "gut tunnel" to enter the exhibit, and when I emerged, I saw a lady standing in a corner with a microscope, a television screen, and a big bucket of slides.

It was a wonderful way to discover pathology, because that particular pathologist was so enthusiastic about her work that she got everyone else excited as well. She showed us slides of various body parts and disease processes, explaining which parts of the intestine were affected by certain disorders and why. When I told her that my problems were rooted in the liver, she pulled out slides of the liver and began to show them to me, explaining the different colors in the images and what the findings meant in terms of my disease.

THE RIGHTS AND THE WRONGS

All of my medical care is handled through my primary care physician – and I'm happy with that, because he is excellent. He looks at all of my reports, including those from pathology, and translates all of that information into language I understand. I don't feel the need to have one-on-one meetings with my pathologists because they are so good at providing comprehensive information to my doctor, and because my doctor is so good at presenting that information to me.

I consider open communication between patients and physicians absolutely essential. Not all doctors are equally comfortable speaking to patients – and certainly, not all are equally skilled – but both parties are vital to the equation and should be treated as equals. In some instances, pathologists might prefer to relay information to a central contact point (for instance, a primary care provider); in others, they might prefer to speak directly to the patients themselves, rather than go through a middleman. In my opinion, the precise form the communication takes is not nearly as important as the fact that it takes place at all. Doctors should be open to speaking with their patients, and patients should never hesitate to ask questions.

In December of 2016, I co-organized the "Rare Liver Disease Dialog" in the Netherlands, a concept developed by patients and researchers together. During the half-day event, researchers, clinicians and patients from the rare liver disease community met and exchanged ideas. It was a unique opportunity for patients to learn more about both science basics and the ongoing research in their field, and an equally interesting chance for researchers to actually – finally! – interact with the target audience for whom their research aims to make a difference. Topics included unmet needs, why some kinds of research are more difficult than others, and a simple – yet surprising to researchers – request from a patient: could they make their surveys shorter due to disease-related difficulty concentrating? That day, I really feel like we patients were able to put a face to the research in our community – and with the wonderful side effect of mutual understanding.

THE PATIENTS'-EYE VIEW

As a patient, I want pathologists – and, in fact, all doctors – to know that we truly appreciate their sharing information with us. It helps us to visualize our diseases and understand what's going on inside our own bodies. The more friendly and approachable a medical expert is, and the more information they provide

(whether in reports, patient interactions, or educational settings), the more empowered we feel to learn about and manage our own health. As we say in the Netherlands, it's great to have a "peek in the kitchen" to see the secret recipe of our medical care. We really appreciate it when you speak to us! And listening to us, too, might help you to find the missing piece of a medical puzzle…

Of course, not every doctor has the time to interact with every patient – nor is it always necessary. I think there is a lot of merit in community events like the open day where I first encountered a pathologist face-to-face. Any pathologist or "behind the scenes" professional should definitely consider participating in and promoting such an event if they get the chance. However it's accomplished, the key is for professionals to bring their knowledge to the patients and treat them like equals in their own health care.

At the same time, I am a big believer in patients' educating themselves. I think patients should always get involved with their medical care teams – asking questions, studying their medical records, researching and reading as much as possible about their own health issues – and, of course, talking to their doctors about anything they need. The doctor may be the medical expert, but we patients are the experts on our own bodies and symptoms and preferences, and we often have information to share that isn't enshrined in the official medical textbooks. The digestive symptoms I mentioned earlier are one example; they are not all formally considered symptoms of autoimmune liver disease, but most of the liver disease patients I know experience them. If I want my doctor to know that I am uncomfortable and want to explore treatment options for my possible inflammatory bowel, I need to speak up – and my doctor needs to listen! We can only make great progress if we all work together: physicians, pathologists, and patients.

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

BRIDGING THE GAP

Patient-centered pathology from the perspective of someone who has been on both sides of the laboratory bench

By Linda Sejour

Experiencing patient-centered care

I first encountered patient-centered care when I was diagnosed with breast cancer in 2004. I had been working in the histology department at Moffitt Cancer Center for two years when I received the news. I had just had a mammogram at another facility and was given the all-clear, but my supervisor at Moffitt urged me to get another mammogram there, and that second test found cancer. I was shocked. For a brief moment, I thought it might be a false positive – but it wasn't. After further testing, I had all the faith in the world that my diagnosis was accurate, because I know how personally the pathologists at my institution take each slide they review. Every pathologist I know wants to find disease, treat it, and stop it in its tracks. They all want to save their patients' lives.

In my view, patient-centered pathology means looking at each slide or specimen as a patient, rather than just a tissue sample. Moffitt pathologists double-check everything they see to make sure they detect anything that could be wrong – they're like a CSI group! The pathologists really put themselves in the patient's shoes. They make sure the physician has everything they need to share a diagnosis with the patient. Pathologists' work saves and extends lives, and it's important for patients to be aware of that.

As a histotechnologist myself, I know that I feel every part of the patient in the cell tissue cassette. I see the whole picture – the person themselves, rather than just the sample. Sometimes I cry when I know somebody is going to receive a cancer diagnosis, especially if I know it is a young patient. Even if I don't see them, I feel a genuine connection to every one of my patients.

Words to remember

I think it's important to make patients aware that pathologists are the doctors who actually make the diagnoses. We care about the patient; we respect the patient; we want the very best for the patient. And the best way to make sure they know that is to build trust with them. A disease diagnosis – especially one as difficult and emotionally charged as cancer – is something very personal to talk about. By engaging with them and being open and honest, we become a vital link in the chain of patient care and support.

Trust is the lifeline from the patient to the pathologist. In many cases, the patient hasn't met their pathologist personally; they just have a piece of paper bearing a diagnosis. In my case, I was lucky. I worked in the laboratory of my own cancer center, so I could speak with the pathologists directly, but not everyone has that advantage. The laboratory is often a hidden piece of the puzzle, but that doesn't serve anyone's best interests – pathologists should step into the spotlight and speak to patients! Open your doors. Get on social media. Let patients see you. It makes such a difference to us as patients to know the people who have saved our lives and our health.

The **Disease Detective**

Pathologist interactions are vital to help patients understand their diseases and the diagnostic reasoning behind them

By Taylor Schwab

MY STORY

I am a 49-year-old male who used to suffer from interstitial lung disease. I first began to have symptoms about two and a half years ago, and my lung functioning slowly deteriorated. I received excellent care from my pulmonologists, Vincent Valentine and Alexander Duarte, at the University of Texas Medical Branch (UTMB) in Galveston. They prescribed an extensive regimen of tests; I underwent a lung biopsy bronchoscopy, a video-assisted thoracoscopic surgery (VATS) lung biopsy, and several X-rays and CT scans. At first, they thought that I had hypersensitivity pneumonitis – but after various treatments failed to halt the disease progression, additional testing established a new diagnosis: idiopathic pulmonary fibrosis (IPF). My doctors referred me to the lung transplant center at Baylor St. Luke's Hospital in Houston, where I was evaluated and put on the list for a lung transplant.

I received my double lung transplant on March 23, 2017. The procedure went fabulously and I made a remarkable recovery. I owe my life to God, my family, and the exceptional medical providers who saw and continue to treat me. Thanks to them, I feel great!

GETTING TO KNOW PATHOLOGY

Even before I became a patient, I was aware of pathology. I'm an attorney, so I have previously worked with forensic pathologists on cases to evaluate causes of death. But I now know that pathology is much more varied than I had previously seen. I think of a pathologist as a physician who focuses on the causal study of disease and is involved in the microscopic study of cells and cell abnormalities. I primarily think of pathologists as peo**ple who analyze lab specimens under a microscope.**

My first encounter with pathology as a patient was after my interstitial lung disease diagnosis. I have a family history of IPF but, for my doctors, it was difficult to distinguish between that and hypersensitivity pneumonitis. The two diseases have somewhat similar clinical symptoms and radiology findings. To help shed light on my diagnosis, I underwent a bronchoscopy and lung specimens were sent to a pathologist. After the pathology report came back, though, there were still uncertainties as to my diagnosis, so I underwent a VATS lung biopsy. Those results clarified my diagnosis, but did not absolutely rule out the possibility of any other disease.

After my transplant, my former lungs were biopsied. The pathology report confirmed that I had suffered from IPF, rather than hypersensitivity pneumonitis. Knowing that was extremely important to me, because if I had had hypersensitivity pneumonitis, I would have been at continued risk of recurring lung damage in my transplanted lungs if I had not removed myself from the antigen causing the pneumonitis. Because of the difficulties we had experienced in pinpointing the offending antigen – in retrospect, an obvious challenge as none existed – I was pleased to have a confirmed diagnosis of IPF.

All of my care providers made sure I understood the nature of my disease from a pathology perspective. My pulmonologist shared and explained my pathology reports with me after my biopsies. Later, I also met my pathologist, Tim Allen, during an online conference call with my pulmonologist and radiologist. During this conference, my three doctors briefly reviewed my case and went over the pertinent radiology and pathology findings. I had questions about my pathology reports and my diagnosis, and Allen explained the reports and the reasons behind the differential and my diagnosis in terms I understood.

After my conference with the multidisciplinary team, I felt I had a better understanding of my disease and greater

"I think patients often feel out of touch with pathologists' work because there is little, if any, interaction between patient and pathologist."

peace of mind. It was – and still is – important for me as a patient to know as much as I can about my disease, its causes, treatment, and prognosis. My pathologist answered several perplexing questions I had about the findings from the two biopsies I underwent. Without this contact, I would still have lingering doubts as to my diagnosis and the differences in the biopsy reports.

THE RIGHTS AND THE WRONGS

I really appreciated being included in the multidisciplinary conference between my pulmonologist, radiologist and pathologist. It was the first and only time I was able to speak with a pathologist. That time was very valuable to me, because my pathologist provided me with insight into my disease by using my own biopsy slides to point out to me some of the basis for his diagnosis. I was able to visualize what we were discussing, and to directly see the impact of the disease on my lungs. For those suffering from interstitial lung disease, pathology plays a big role in diagnosis, so I feel that all patients should be able to meet with a pathologist to review their biopsy reports and findings. Meeting with a pathologist should be part of the patient management protocol for these types of diseases.

One thing I would have appreciated was easier access to my pathology reports. UTMB uses an electric medical record system that allows patients access to test results and some reports. My pathology reports were unfortunately not accessible, though I was eventually able to obtain them by other means. As a patient, I want easy access to my medical records – including pathology reports. That's something I would like pathologists and hospital administrators to know, so that perhaps in the future patients will have access to their complete records.

THE PATIENTS'-EYE VIEW

I think patients often feel out of touch with pathologists' work because there is little, if any, interaction between patient and pathologist. I would appreciate having an office visit or phone call with a pathologist after undergoing procedures to review and explain the findings in the reports. I want to be fully informed of my disease and the foundation behind its diagnosis.

I would also encourage patients to educate themselves as best they can about their disease and the various methods used in diagnosing it. That way, they can have a basic understanding of what's wrong, how the doctors go about learning more, and what can be done to address the issue. All patients deserve a basic understanding of what the tests and procedures can and can't reveal about their disease. I think patients should consider obtaining copies of their pathology reports, and seeking out a visit with their pathologist to discuss the reports if they have questions.

From a layman's perspective, one often thinks that medicine is black and white – that there is an absolute certainty or concrete answer to every medical condition. I thought that the results from my VATS lung biopsy would provide me with an absolutely certain diagnosis – but, of course, that wasn't true. The report left open the possibility of a differential diagnosis; it was still possible that I had a different form of interstitial lung disease. I was somewhat disappointed, but I came to the realization that medicine can be an inexact science and that patients should be aware that diagnoses are rarely made with 100 percent conviction.

I realize that medicine, and in particular histopathology, is complicated. It can be difficult to explain pathology results to patients in terms they understand. Being able to translate medical terminology into laymen's terms is a talent that I suspect is often overlooked and undervalued in the medical profession. For patients who do want that explanation, I feel it is critical to the doctor/patient relationship to be able to meet with each doctor providing specialty care. I feel more involved and informed in my care when I have an understanding of my disease and the reasoning behind its diagnosis. Even if it is not part of the standard protocol, I feel that a meeting with the pathologist should be an option offered to any patient who wants to discuss reports. Getting that expert viewpoint first-hand can be a valuable part of a patient's journey through care.

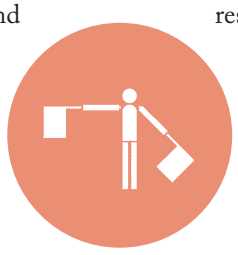
Taylor Schwab is proudly married to his wife of 25 years, Kelly. They have two children, Ashley and Austin, in college. He is an attorney who concentrates his practice in estate planning, probate and real estate law.

The **Holistic Healer**

Interacting with our patients can empower them to become leaders in their own medical management

By Marilyn Bui

I believe that the patient is the ultimate driver of their own medical care and well-being. It's important that they have the best possible understanding of their diagnosis and disease process, so that they can determine how they will face their medical challenges – in mind, body and spirit. We as physicians are facilitators in this process, and I consider it our duty to be compassionate, competent, and provide the best possible care.



As a pathologist, practicing "patient-centered pathology" means I need to be mindful that, behind each case, there is a patient who deserves my best effort. I am in the unique position to serve as a leader in multidisciplinary patient care in the era of precision medicine. It's often said that 70 percent of medical decisions made by clinicians are based on a pathology or laboratory report, which shows the great responsibility with which we are entrusted. It's my goal to live up to that responsibility. I will serve as the custodian of the patient's tissue to ensure that it is used appropriately to generate accurate and timely diagnostic, prognostic and therapy selection information. I will be the manager of the patient's laboratory data to help clinicians make sound medical decisions and provide effective care. I welcome the opportunity to interact with patients – to explain their pathology results, to perform fine needle aspiration biopsies, and more. When I practice pathology, my priority is the needs of the patient and the clinician.

PUTTING THE PATIENT FIRST

Moffitt Cancer Center is a team of oncology experts that includes physicians, advanced practice professionals, nurses, and a variety of support staff, whose goal is to ensure that patients at the Center receive superior, patient-centered care. We also recently celebrated the first anniversary of our "Patients First" program, which is a collaborative effort to ensure that all patients receive timely, compassionate, innovative and personalized care. Patients First also incorporates our "Moffitt Promise," which integrates the four core concepts of patient- and family-centered care: respect and dignity, information sharing, participation, and collaboration.

We've made a number of recent user-friendliness changes to improve the patient experience. First, the Patient Access and Clinic teams have created new scheduling and express check-in processes that have been progressively rolled out over the past year in several clinic locations to improve new patient access. Simplified algorithms make it easier for patients to be quickly scheduled with an appropriate provider. As patients arrive for their appointments, they are greeted by a patient access representative who immediately checks them in, bypassing full registration as long as the account details are current. The result is increased patient satisfaction, improved team member efficiency, reduced pre-visit wait times, and a reduced need for patients to wait in line. Second, we've changed how our care coordinator assistants (CCAs), who gather important patient information before the visit, perform their work. In the past, CCAs reported to individual clinics, even though information often needed to be shared throughout the clinic operation. Under the new design, they report to one manager as they reach out to patients and outside organizations to obtain records – which allows them to better coordinate resources and ensure consistent care.

There's a well-known story about President John F. Kennedy's visit to NASA in 1962. He noticed a janitor carrying a broom, introduced himself, and asked what the man was doing. The man responded by saying, "Well, Mr. President, I'm helping put a man on the moon." To most people, the janitor was just cleaning the building – but he knew he was part of a larger story that was about to make history. Moffitt's Chief Medical Officer and Vice President of Quality, Robert Keenan, shared this story in our first Patients First Meet and Greet of 2017 to inspire all Moffitt team members to look at the big picture and understand that we all play a role in Patients First – and that includes pathologists as much as anyone else.

PATIENT-CENTERED CARE IN PRACTICE

From a cytopathology point of view, when I am called to perform a fine needle aspiration biopsy, I immediately put down whatever I am doing and go straight to the clinic. Why? Because I realize that, if I make even one patient wait in the clinic unnecessarily, it will delay not only that patient's care, but also the care of all subsequent patients – and I don't mind having to work late to catch up with non-patient-facing work. I also enjoy interacting with patients and clinical teams; I feel inspired and empowered by being closer to the patient, my clinical colleagues, and the opportunity to make a tangible difference by providing valuable pathology information.

From a sarcoma pathologist's point of view, our multidisciplinary clinic format is really cool. Imagine – a

patient comes to Moffitt Cancer Center and gets to see all of the subspecialties related to their care, all on the same visit. Not only that, but the physicians from different subspecialties communicate in real time to create a management plan. It's like a personalized mini-tumor board on demand!

Of course, not every institution has these things in place or has the resources to implement them. I still think there's a lot pathologists can do for their patients even without a strong, patient-centered infrastructure. For instance, a separate, patient-friendly pathology report in addition to the traditional ones for medical professionals would be well-received, and would help patients feel informed and empowered. It's also wonderful when pathologists are able to make themselves available to explain their findings to patients. The benefits are threefold – patients learn about their disease and treatment; clinicians have more educated patients who become active participants in the treatment process; and pathologists become more visible to those who rely on (and, in some cases, fund) our services. Finally, there's great value in active social media involvement. It's yet another way to provide patient education, and you may capture an audience online that you would never see in your office!

WORDS TO THE WISE

I consider it our job as pathologists to help our patients understand what we do. Importantly, though, they need to know that education isn't a one-way street. We don't just provide patients with information; we can also learn from and be inspired by them. I learned this from one of my own patients, Ray Paul, a sarcoma patient at Moffitt whose approach to his pathologic findings – and the beautiful artwork he created to help him understand and cope with his disease (1,2) – taught me a lot about interacting with patients, and about the value of such non-traditional interactions. It's my hope that, as we work hard to connect with patients, increasing numbers of them will get to know their pathologists – and that, in doing so, both they and we gain valuable partners in the disease-fighting journey.

Marilyn Bui is a Senior Member of the Department of Anatomic Pathology, Section Head of Bone and Soft Tissue Pathology, and Scientific Director of the Analytic Microscopy Core at Moffitt Cancer Center. She is also a Professor and Director of the Cytopathology Fellowship Program at the University of South Florida Morsani College of Medicine Tampa, USA.

Reference

1. *M Bui, K Galagan, "Art From the Heart", The Pathologist, 23, 46–49 (2016). Available at: http://bit.ly/2is7BXN.*
2. *M Bui, K Galagan, The Healing Art of Pathology. College of American Pathologists: 2016.*

The **Involved Interpreter**

Helping patients understand their own disease not only offers peace of mind, but also allows them to see the ongoing value of pathology

By Timothy Craig Allen

"Patient-centered pathology," to me, has a very broad definition; it can mean any interaction between a patient (or family member) and a pathologist. A pathologist who speaks with a patient on the phone to describe the pathophysiology of a disease is practicing patient-centered pathology. A pathologist who sits at the microscope with a patient, describing the characteristics of a tissue, is practicing patient-centered pathology. And a pathologist using telemedicine to show and describe a tumor to a patient, explaining its molecular features and how they influence treatment choices, is an excellent example of practicing patient-centered pathology.

I practice patient-centered care in several ways. On some of my pathology reports, I put a comment describing the patient's situation in layperson's terms. I explain briefly what a pathologist is, and invite the patient to speak with me on the phone about their case – or even to come by and look at their slides with me and discuss the disease pathophysiology. Sometimes, I use telemedicine to discuss and clarify the details of the patient's diagnosis with them and their family. In an anatomic pathology diagnostic management team (DMT) conference, I work with my colleagues in radiology, oncology, surgery, and radiation oncology to speak with patients and families about disease presentation, diagnosis, therapy, expectations, and follow-up. It sounds like a lot when written down – so imagine how much it must be for patients to handle without our help! This "real-time tumor board" actually only takes about 10 minutes most of the time, and it provides our patients and their families with facts, clarity, understanding, and a plan. Ultimately, it provides them with a very important peace of mind.

WHAT DIFFERENCE DOES IT MAKE?

In my opinion, it is too early to make definitive statements about the difference this type of pathology practice makes to our patients' outcomes. As we evolve a more patient-centered approach to the pathology we provide our patients, we will be able to generate and assess much more data – and then we'll be able to make robust determinations regarding patient value. Such information is going to be extremely important, because outcome changes, cost savings and patient satisfaction are quickly becoming the indicators that drive payment for the new patient-centered behaviors we are developing.

That said, some things are intuitive, and we certainly can't deny that there are plenty of anecdotes that indicate increased value. It sounds counterintuitive, but patient-centered care – especially using telemedicine – does not require the patient's physical presence at every doctor's appointment like our traditional methods of medical practice do. With a "real-time tumor board" or anatomic pathology DMT conference, the patient and family can sit in the comfort of their own home and speak with a pathologist, either alone or with other members of the healthcare management team.

Anecdotally, patients with whom I've spoken have enthusiastically expressed that they value an approach to pathology that prioritizes them. A pathologist who speaks with a patient can often provide the patient with a sense of clarity and comfort that – although impossible to label with a dollar amount – is nonetheless extraordinarily valuable at a time of heightened anxiety, fear, and stress. With a telepathology conference, a patient can essentially combine four or five doctor appointments into one 10-minute telemedicine experience, saving days or weeks of time and avoiding travel and scheduling delays. Finally, there is a strong sense that direct pathologist interaction reinforces the patient's understanding of the pathologist's role – and thus, their understanding of the value of pathology.

"Pathologists can no longer afford to be in the shadows, ignored, or misunderstood."

STORIES FROM THE FRONT LINES

Let me share three anecdotes that I think truly illustrate the importance of patient-centered care. The first concerns a patient who lives out of state, and who was thrilled to be able to speak with the pathologist and radiologist about his tumor and the proposed therapy for the specific diagnosis. He was delighted to be able to speak with his healthcare team from his home, hundreds of miles away from his diagnosing and treating physicians. To him, it was an office visit with the pathologist in his own living room.

In another example, a cancer patient was very worried about receiving treatment, but after discussing her options – chemotherapy, molecular, and immunotherapies – she understood why it was best for her to receive the specific therapy that had been suggested. She was extremely thankful to the team, including the pathologist who described the cancer in detail, for having the telepathology discussion that provided her with better insight and peace of mind.

My third example regards a patient who had received a transplant and was concerned about whether or not his children had a genetic predisposition to the same disease. He had tried for some time to ask about the likelihood of such a predisposition, but had been unable to get a clear answer to his question. After some discussion with the pathologist and another subspecialist physician, the patient was relieved to learn that his children were at no increased risk. He made sure we knew how extremely grateful he was that he could sleep better with the knowledge that his children were safe.

OUT OF THE SHADOWS

I would strongly advise other pathologists to consider patient-centered discussions. It's easy to start; why not put on your report who you are, explain what a pathologist is, and let your patients know that you are available to speak with them about the diagnosis or show them their slides? Telemedicine is another arena where even small changes can make a big difference – but when becoming involved in that, you must be careful to work with a knowledgeable IT person who can help you to quickly develop a thorough understanding of the technology needed for a seamless conference.

Particularly in today's world of changing healthcare payment models, an increasing regulatory and governmental presence in payment decisions, and increased patient confusion around new therapies (especially molecular therapies and immunotherapies for cancer), it is necessary to clarify who we are and what value we provide to our patients. Direct discussions with patients will not only provide them with a better understanding of their diagnoses, but also emphasize our value – which, in turn, improves the likelihood of appropriate payment for the vital services we provide as part of the healthcare team. Pathologists can no longer afford to be in the shadows, ignored, or misunderstood.

To me, the future of medicine is not merely the development of better diagnostic tools, a better understanding of disease processes, or better therapies. The future of medicine will also require our ability to deliver these new and evolving therapies quickly and efficiently to our patients, while educating them about the new tests and treatments. If a patient cannot travel to the hospital, or does not clearly understand the diagnosis or the need for a specific treatment and so does not make the effort to adhere to it, then the best therapy in the world is useless to that patient. Yes, it presents a challenge and, in my opinion, it is also a powerful reason to develop patient-centered approaches to diagnosis and treatment. As curators of diagnoses and guides to treatment and recovery, we pathologists should – or rather must – play a central role in patient-centered care models.

Timothy Craig Allen is Professor in the Department of Pathology, Director of Anatomic and Surgical Pathology, and Laboratory Director in the Department of Laboratory Services at the University of Texas Medical Branch, Galveston. From 1 January 2018, he is Professor of Pathology and Chair of the Department of Pathology in the School of Medicine at the University of Mississippi Medical Center, Jackson, USA.

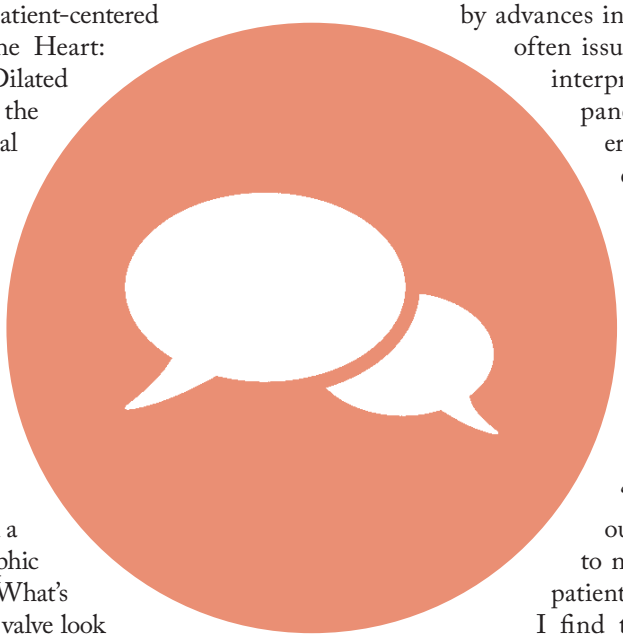
The **Pathology Promoter**

Teaching patients about their diagnoses, either one-on-one or in group settings, is good for all involved – and for the future of our profession

By Gustaaf de Ridder

As we make increasing amounts of information in medical charts directly available to patients, we pathologists must be prepared to offer explanations. Often, the clinicians who request pathology services don't have the time to explain the results – and that's where patient-centered pathology comes in. To me, the term denotes the involvement of the pathologist in explaining their findings – and the implications for medical care – to patients. And that can happen one-on-one or in a group setting.

I was recently involved in a patient-centered symposium called "Affairs of the Heart: Living with Hypertrophic and Dilated Cardiomyopathy" (1). The aim of the one-day, multidisciplinary educational event was to teach heart failure patients a little about the anatomic changes and the genetics of cardiomyopathy. I was lucky enough to have been invited by the cardiologists at my institution, and I – the cardiothoracic pathology fellow – jumped at the chance. I brought along a few specimens from our collections, which allowed me to show the patients exactly what it means, from a tissue standpoint, to have a hypertrophic or dilated heart. What's enlarged? What's abnormal? What does an artificial valve look like? It was amazing to see how meaningful such information was to those people directly affected by heart disease. It was a first for me – I've never done anything like that with patients – and a first for those there to learn; many of them had no idea what a dilated or hypertrophic heart actually looked like, despite living with one day in and day out. I was touched to witness their reactions as they suddenly understood what their disease physically meant.



HOW PATHOLOGISTS CAN SERVE PATIENTS – AND VICE VERSA

I would highly recommend that pathologists participate in this kind of focused, organized event, if you get the opportunity. You'll be amazed at the difference a little education makes to your patients. And, of course, such forums aren't limited to affairs of the heart. Take colon cancer as an example; do patients understand what their disease looks like or what the terminology signifies from a pathologist's point of view? What's microinvasive disease? What does it mean to have a T1 or a T3 tumor? Most patients have no idea – but with a disease as common as colon cancer, a patient symposium would be an efficient platform to provide welcome education, and an easy way to make patients feel more comfortable and at ease with their care.

Events aren't the only way to communicate with patients, though. Now that patients frequently see their own pathology reports (and the names of the pathologists who wrote them), they sometimes reach out to the pathologists themselves to ask questions. The trend may have been prompted somewhat by advances in molecular pathology, where we often issue complex reports – results and interpretations of targeted sequencing panels for different tumors, inborn errors of metabolism, mitochondrial disorders, and so on – that even the clinicians can't always fully understand or act upon. Sometimes, there simply isn't any action to be taken. Nevertheless, the patients are still curious – after all, they're trying to observe and comprehend their own genome! When they come to us and ask, "What does this mean?" I think it's our responsibility to answer – and to make sure we do so in a way our patients can understand.

I find that talking with patients and teaching them about their disease processes

"I find that talking with patients and teaching them about their disease processes brings me closer to the art of practicing medicine."

"With a simple introduction to pathology, we can have a knock-on effect on population health."

brings me closer to the art of practicing medicine. Some of that depends on where you practice; in the current for-profit healthcare system in the US, for instance, I find that production is sometimes emphasized over quality of delivery. Pathologists and radiologists – those of us who don't often see patients directly – can easily lose sight of why we're practicing medicine in the first place. It's a little like we become abstracted from our mission. If you interact with patients – ideally in person, but at least over the phone or by email – I think it helps restore some balance to what should be an altruistic profession. In my opinion, that's the greatest benefit we pathologists can get from patient-centered pathology.

FROM PATHOLOGY TO PRIMARY CARE

Clinicians generate the biopsies; we interpret them. At my institution, we have discussed the possibility of a more targeted approach to biopsying various disease processes to yield better results. Often, biopsies aren't taken exactly where we need them – they might come from next to the lesion, or from the middle instead of the edge – so we are unable to get as much information as we'd like. We are working with clinical staff to improve that. The other thing we need is better utilization management; we should not do biopsies when they're not needed. Sometimes, things that don't need to be sent for pathology get sent anyway. Then, of course, we have to take the biopsy through to the reporting stage, which means the patient has not only undergone an unnecessary procedure, but that they are also facing unnecessary costs. My goal is to establish a continuous, two-way conversation between primary care and pathology, so that we can reduce unnecessary testing and improve necessary testing.

If the idea of patient-centered pathology intrigues you, I suggest that you take up the practice early. If you don't, then it may be forced upon you later in your career, once you've grown used to your own way of doing things. Seek it out as early as possible – during training, if possible – and explore what different avenues are available. That said, if you're already 40 years into practice, it doesn't mean you can't or shouldn't go and ask your clinical group about opportunities for patient interaction. It's never too late to start!

The one factor that isn't up to us as pathologists is time. In my experience, physicians of every specialty are pressed for time, and the topic comes up frequently when discussing the idea of patient interactions. Pathologists tell me that they're concerned about the amount of time it takes, and – in the United States, at least – it's unfortunately not billable time. I do think, though, that it is time well spent. I think people should try to take a step back and consider what it might mean to the patient to be educated about a new diagnosis by an expert they can trust. Better knowledge won't only reassure them; it might also encourage them to modify their behaviors, adhere to medication regimens, and overall improve the health of the group. With a simple introduction to pathology, we can have a knock-on effect on population health.

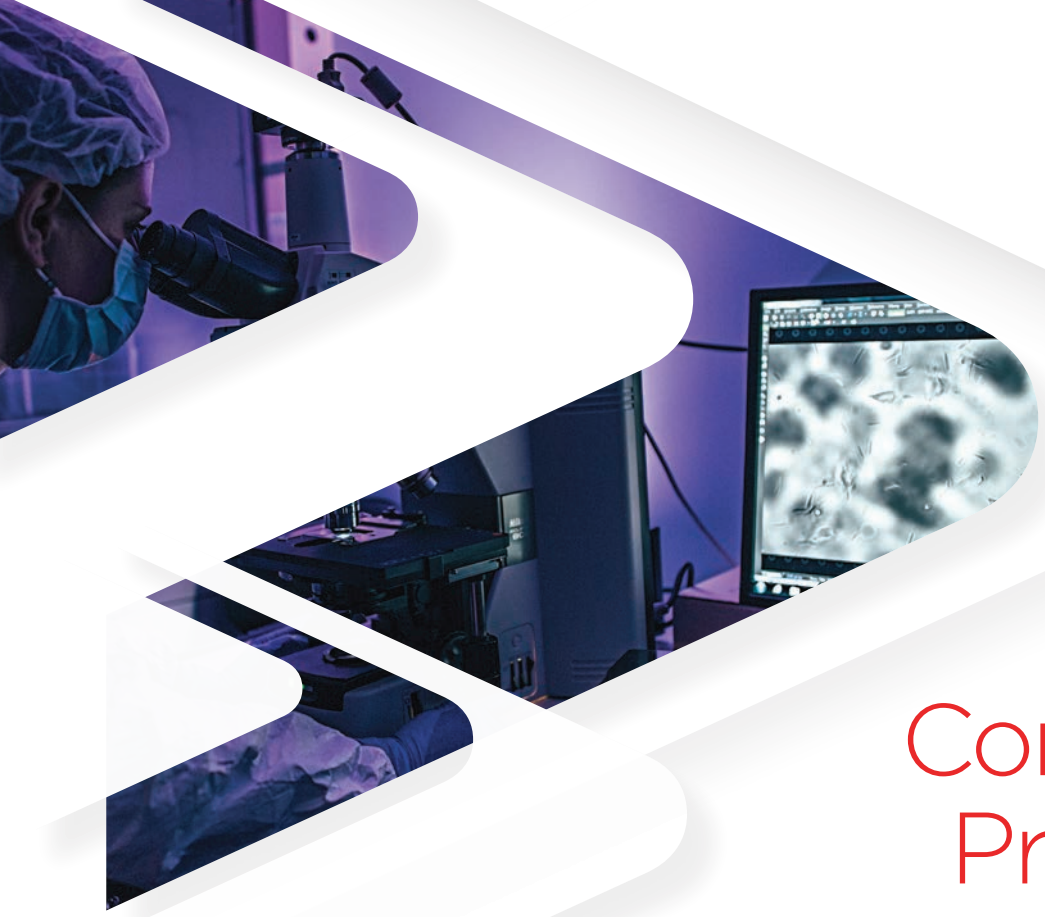
SHIFTING THE STEREOTYPE

There is a common misperception that pathologists don't have any patient contact. I've heard many medical students repeating this false impression: "Pathology is a pretty good gig, except that you don't get to interact with patients anymore." Well, I'm a pathologist, and I find patient contact incredibly rewarding. And I firmly believe that there would be many more people interested in practicing pathology, if people realized that it can be just as much of a person-to-person discipline as any other specialty. Shining the spotlight on patient-centered pathology is great for both healthcare in general and the future of our field.

Gustaaf de Ridder is a Clinical Associate in the Department of Pathology at Duke University, Durham, USA.

Reference

1. *Duke Pathology, "de Ridder presents patient-centered pathology sessions" (2017). Available at: http://bit.ly/2jVoMVG. Accessed November 24, 2017.*



TACONIC
Models For **Life.**

Only Commercial Provider of Germ-Free Mice

AVAILABLE GERM-FREE ANIMALS

C57BL/6
Swiss Webster
BALB/c

MICROBIOME SERVICES

Generation of germ-free Genetically Engineered Models (GEMs) colonies
Association of germ-free animals with specific flora
Germ-free derivation and husbandry
Fecal microbiota transplantation and custom associations

APPLICABLE TO ALMOST ANY THERAPEUTIC AREA

MICROBIOME EXPERTISE

Taconic Biosciences has decades of germ-free experience, with the highest number of health standards, germ-free options, and microbiome services. Demonstrated expertise available via protocols and videos such as *Veterinary Care of Germ-Free Mice* and *Microbial Monitoring of GF Isolators* available online at **www.taconic.com/microbiome**

PA1047-EN-1711

In Practice

Technologies and techniques
Quality and compliance
Workflow

A Guiding Light for Sequencing

New recommendations for NGS bioinformatics pipelines aim to standardize sequencing workflows to reduce variability between clinical laboratories

By Somak Roy and Alexis Carter

More than ever, pathologists and laboratory medicine professionals are turning to next generation sequencing (NGS) to provide patients with diagnostic and prognostic information. But not every laboratory performs sequencing and analysis the same way, and variability in clinical laboratory practice can lead to problems. To tackle this, the Association of Molecular Pathology (AMP) has released several sets of guidelines for sequencing and panel validation, culminating in a new set of consensus recommendations for NGS bioinformatics pipelines (1). With this latest release, the association hopes to provide guidance throughout the NGS workflow, so that patients in need of genetic analysis can receive the best possible care.

At a Glance

- *Next generation sequencing (NGS) is being increasingly adopted, but variability between clinical laboratories remains high*
- *New guidelines from the Association for Molecular Pathology hope to improve and standardize the NGS bioinformatics pipeline*
- *The recommendations emphasize the crucial role of a properly trained and qualified molecular laboratory professional*
- *They also provide practical guidance for NGS design, development and operation*

What prior guidelines were used for NGS?

Guidelines for the analytical validation, interpretation and reporting of NGS tests were published in the medical literature earlier this year (2,3), and the molecular community is progressively adapting them into practice. However, prior guidelines did not specifically address requirements for validating NGS bioinformatics pipelines. The limited number of NGS pipeline validation studies, and the high degree of variability between studies, certainly reinforced the need for guidance in NGS bioinformatics pipeline validation.

Why was it so important to plug the guideline gap?

NGS technologies are being rapidly adopted in the clinic, but the constant evolution of technology and the absence of clear recommendations for analytical validation of NGS bioinformatics pipelines are contributing to variabilities in clinical laboratory practice. With the lack of clear guidelines, each laboratory must figure out its own best practices, effectively reinventing the wheel. Good guidelines work on a couple of levels. Firstly, they help laboratories reduce the time it takes to implement NGS bioinformatics by giving them a checklist of requirements; moreover, an established, trustworthy list allows them to plan adequately for time, labor and resources. Secondly, peer-reviewed and approved guidelines – if properly followed – can help laboratories improve quality, by setting minimum thresholds for good practice.

Of course, laboratories may certainly exceed minimum thresholds to their own comfort level – or as appropriate to the nuances of their own testing.

AMP believes it is the responsibility of professional organizations to establish guidelines for professional practice and, as such, we routinely engage with other professional associations to publish evidence-based practice guidelines. Our members are among the early adopters and users of NGS technology in a clinical setting and have accumulated substantial knowledge and expertise as it relates to this novel and powerful technology. The 17 consensus recommendations in our latest report (see Table 1) are designed to help clinical laboratory professionals achieve high-quality sequencing results, with the ultimate end result of delivering better patient care.

How were the new guidelines determined?

AMP convened and led a multidisciplinary subject matter expert working group with representation from the College of American Pathologists and the American Medical Informatics Association to summarize current knowledge, expose challenges, and provide guidance on how to develop, implement and validate high-quality bioinformatics pipelines to ensure better overall patient care. The guidelines are based on evidence from a review of published literature, empirical data, current laboratory practice surveys, and expert professional experiences. Because these recommendations represent current best practice in a rapidly developing field, AMP anticipates the need for ongoing updates.

What are the key take-home messages from the new guidelines?

First and foremost, the new recommendations emphasize the critical role of the properly trained and qualified molecular laboratory professional to achieve optimal NGS test quality.

As noted, the new guidelines represent a set of minimum standards for NGS bioinformatics pipelines, which we anticipate will help not only clinical laboratories, but also NGS instrument manufacturers, software companies and researchers to advance medical technology in a safe and responsible way.

These recommendations were developed to optimize patient care and,

	Recommendation
1	Clinical labs offering NGS should validate their bioinformatics pipelines themselves
2	Appropriately qualified staff must oversee the validation process
3	Validation should be performed once the bioinformatics pipeline is completed and established
4	Validation should take place under real-world conditions
5	Each component of the bioinformatics pipeline should be individually validated
6	Bioinformatics pipelines should comply with patient privacy and security laws
7	Validation should suit the intended clinical use, specimen, and variant types tested
8	Bioinformatics pipelines should comply with laboratory accreditation standards and regulations
9	Bioinformatics pipeline documentation should comply with laboratory accreditation standards and regulations
10	Samples in the bioinformatics pipeline must have at least four unique identifiers (including a location identifier)
11	Quality control and quality assurance parameters should be evaluated and used during validation
12	The methods used to alter or filter sequence reads should be validated and fully documented according to laboratory accreditation standards and regulations
13	Laboratories must maintain the integrity of each data file generated in the bioinformatics pipeline
14	In silico bioinformatics pipeline validation can be used with, but not instead of, end-to-end validation using human samples
15	Validation should include confirmation of a representative set of variants with high-quality independent data
16	Clinical laboratories must ensure the accuracy of software-generated HGVS variant nomenclature and annotations and document any corrections
17	Significant changes to any part of the bioinformatics pipeline require supplemental validation

Table 1. A summary of the 17 consensus recommendations for the development, implementation and validation of NGS bioinformatics pipelines (adapted from 1).

as a result, many clinical laboratories may find that they are already compliant with many of them. Laboratories should focus their efforts on determining what, if any, changes are needed to their existing pipelines and processes, and then appropriately plan to implement those changes in a stepwise manner. Not every change will be a simple one; some of the guideline recommendations, for instance, may require certain laboratories to make fundamental changes to sequence file content to standardize sample identification. These processes must be implemented carefully and with an appropriate amount of validation prior to being put into clinical use.

Some of the guidelines address the inner workings of the pipeline itself to ensure the safety, accuracy and security of the data as it flows through the process; those recommendations aim to reduce the likelihood of errors reaching the laboratory medicine professional for interpretation.

The NGS bioinformatics pipeline validation guidelines include a number of recommendations intended to help pathologists and laboratory medicine professionals communicate with bioinformaticians and technology professionals to ensure that they understand the limitations of their pipelines, appropriately interpret NGS data, and adopt best practices when developing or updating pipelines

The full reports provide a thorough explanation of each recommendation to assist in comprehension and implementation into clinical molecular diagnostic laboratory practice.

How can pathologists who use NGS promote the new guidelines?

All of the guideline documents are freely available for download, so pathologists can easily share this information with their colleagues. After all, understanding and communicating the importance of adhering to published guidelines – and following the guidelines to the best of your ability yourself – are great ways to help promote best practices in laboratories around the world.

Somak Roy is Assistant Professor of Pathology at the University of Pittsburgh Medical Center, Working Group Chair and Member of the Association for Molecular Pathology, USA.
Alexis Carter is Physician Informaticist at Children's Healthcare of Atlanta, Working Group Member, 2017 AMP Informatics Subdivision Chair, and Board Member of the Association for Molecular Pathology, USA.

References

1. *S Roy et al., "Standards and guidelines for validating next-generation sequencing bioinformatics pipelines", J Mol Diagn, [Epub ahead of print] (2017). PMID: 29154853.*
2. *MM Li et al., "Standards and guidelines for the interpretation and reporting of sequence variants in cancer", J Mol Diagn, 19, 4–23 (2017). PMID: 27993330.*
3. *LJ Jennings et al., "Guidelines for validation of next-generation sequencing-based oncology panels", J Mol Diagn, 19, 341–365 (2017). PMID: 28341590.*

The Need for (Sequencing) Speed

Rapid whole genome sequencing of NICU patients can save costs and improve health and quality of life

By Shimul Chowdhury and David Dimmock

When your newborn baby is in intensive care, nothing matters except finding the reason for the illness and treating it. No parent given a choice would consider sparing any effort or expense that seemed likely to provide an answer. And yet, diseases in newborns often go undiagnosed, or are diagnosed only later in life. Why? In many cases, it's because they have a genetic disorder – a problem often missed in the neonatal intensive care unit (NICU). And those that are less common are more difficult to spot. For some patients, the diagnostic delay can mean the difference between life and death – and for others, it can have an immeasurable impact on future health or quality of life. What can be done to help them?

Rapid whole genome sequencing (rWGS) is a rapidly emerging methodology that can aid in providing timely diagnoses for children in the NICU. However, due to concerns regarding the cost and accessibility of the testing, as well as the lack of reimbursement, the approach has not been widely adopted. Genetic disease is thought to be the leading cause of death in the NICU – but all too often, children (especially those who don't exhibit the classic symptoms of genetic disorders) remain without a genetic diagnosis. Newborn babies often fall into this category, and so doctors don't necessarily consider sequencing – even in the event of an undiagnosed illness. But it can be a costly mistake. Rapid whole genome sequencing (rWGS) can save weeks of diagnostic uncertainty, enable early and effective treatment, prevent unnecessary interventions, and discharge infants earlier – and in better health.

At a Glance

- *Genetic disorders are difficult to diagnose in newborn babies – but spotting these diseases is critical*
- *Early diagnosis of genetic diseases can help target treatment, reduce costs, and improve patients' health and quality of life*
- *We recommend rapid whole genome sequencing (rWGS) for as many NICU patients without clear diagnoses as possible*
- *To make sure rWGS reaches every patient who might benefit, we aim to make it a first-tier reimbursable test*

A pressing need

There are approximately 8,000 genetic diseases that can affect patients in the NICU. And in acutely ill babies, conventional testing is often too slow to help guide prompt and appropriate disease management. rWGS provides a powerful approach to help diagnose children in the NICU quickly, guide their medical management, and ultimately yield better outcomes.

Neonates can be extremely difficult to diagnose and treat in comparison with older infants and children. Because these children are so young, many of the classic signs and symptoms by which we commonly identify genetic syndromes have not yet presented. Moreover, with acutely ill newborns in the ICU, medical decision-making often happens in seconds – whereas in other settings, fast action may not be as critical. Overall, there are thousands of neonates in the United States who are not being sequenced, but could benefit significantly from the testing.

How do we test?

The pipeline at Rady Children's Institute for Genomic Medicine is calibrated to process genomes as fast as possible. Our bioinformatics pipeline allows us to process a genome in 45 minutes, followed by rapid analysis, interpretation and reporting. In routine genome-wide sequencing, on the other hand, price is a more significant factor than speed (and immediate answers may not be as critical) – so patients often wait for some time before receiving results. In our Clinical Genome Center, we process samples for acutely ill babies as soon as they reach the laboratory. It's exciting that we recently validated our new Illumina NovaSeq 6000 high-throughput sequencing system, which will allow us to process up to 12 genomes in 24 hours.

This builds on our previously validated HiSeq2500 and HiSeq4000 instruments. We continue to build our infrastructure to scale our ability to provide as many rWGS tests as we can.

The optimal use of sequencing is to provide rapid results that allow us to take better care of children with a suspected genetic disorder. We continue to push the boundaries of this testing and expand the criteria for the kids we sequence. I think that we honestly do not know how many of these kids have genetic diseases – and we have had multiple instances in which we have found diagnoses in children after initially thinking that the chances of discovering something genetic were very small. Now, there are certain exclusion criteria in our studies – isolated prematurity, for instance – but we are really trying to broaden our approach and not select only cases we think have a high likelihood of being genetic. We are focused on the clinical utility and medical management of these children.

We enrolled our first Rady Children's patient in July of 2016 and have been fortunate enough to have gathered multiple success stories in the short time since. We made a recent diagnosis in a child with uncontrolled seizures within 39 hours of receiving a blood sample. This guided the therapeutic path for the child, who received a radical change in diet along with vitamin B6 and other supporting therapies that are not first-line seizure medications. With the help of genomic information, the physicians were able to control the seizures.

In another case, outlined in TIME magazine (1), we made a molecular diagnosis within 96 hours in a newborn with uncontrolled seizures. That diagnosis allowed us to provide targeted medication that stopped the seizures and allowed the baby to rapidly improve. She was discharged from the NICU in 18 days. Almost a year later, the child continues to develop normally; in fact, she is exceeding all expectations! This story starkly contrasts with that of a Rady Children's Hospital patient who was born a year before we started performing WGS. That child had an extended stay in the NICU, did not receive the same molecular diagnosis for six weeks, and is now seriously neurologically compromised.

The overall snapshot of our results is that we are able to provide a diagnosis for 30 to 40 percent of children. But the number we are most proud of is that 70 percent of the children we diagnose receive a change in medical management while they are still in the hospital – it really shows the medical benefit of this testing. We can customize treatment quickly and effectively, and work toward better outcomes for our youngest, sickest patients.

"For children in whom we never suspected a genetic disease, not only did the diagnosis come as a surprise, but it supported dramatic improvements in their care."

Spreading the word

We have been really impressed with the responses of the physicians we have spoken to regarding WGS, and with their willingness to adopt it. It's never easy to bring such a disruptive technology into a unit as specialized and critical as the NICU, but the physicians and nurses we've worked with have been great advocates for our mission. And it's a winning situation for everyone – especially the patients. For children in whom we never suspected a genetic disease, not only did the diagnosis come as a surprise, but it supported dramatic improvements in their care.

How do we share this revolution with a broader audience? Our immediate goal is to provide insurance companies with data supporting the clinical utility and cost-effectiveness of rWGS so that it can become a first-tier reimbursed test; we must partner with various companies and institutions to make this happen, so we're hoping to work with increasing numbers of children's hospitals. The more patients we can reach with rWGS testing now, the faster we'll be able to make it an accessible test for every patient.

We envision a day when the medical team can order and secure this testing for any child in intensive care who needs it. Insurance coverage without preauthorization will reduce the lag time in recognizing the value of rapid implementation of precision medicine. We also hope to keep working to bring the costs and time down for rWGS. We believe the advent of this technology in the clinic will require dedication and resources – and we'll need to establish genomics education across all specialties of medicine. Our hope is that, in the future, we'll see enthusiastic adoption of all of these steps – and the life-saving value of genomics will be widely recognized.

Shimul Chowdhury is Clinical Laboratory Director at Rady Children's Institute for Genomic Medicine, San Diego, USA. David Dimmock is Senior Medical Director at Rady Children's Institute for Genomic Medicine, San Diego, USA.

Reference

1. *A Park, "Genetic testing is providing new hope for babies born with mysterious ailments" (2017). Available at: http://ti.me/2fkRSM6. Accessed November 21, 2017.*

ion torrent

Ion Torrent™ Oncomine™ Dx Target Test—new paradigm in testing for NSCLC-targeted therapies

With this first *in vitro* diagnostic (IVD) test for NSCLC-targeted therapy using next-generation sequencing (NGS), you can fully utilize the power of NGS while relying on a validated IVD solution.

- Complete validated workflow of reagents and instruments
- Software-generated results with associated therapy indications
- Superior level of service and support

Find out more at **thermofisher.com/oncomine-dxtarget**

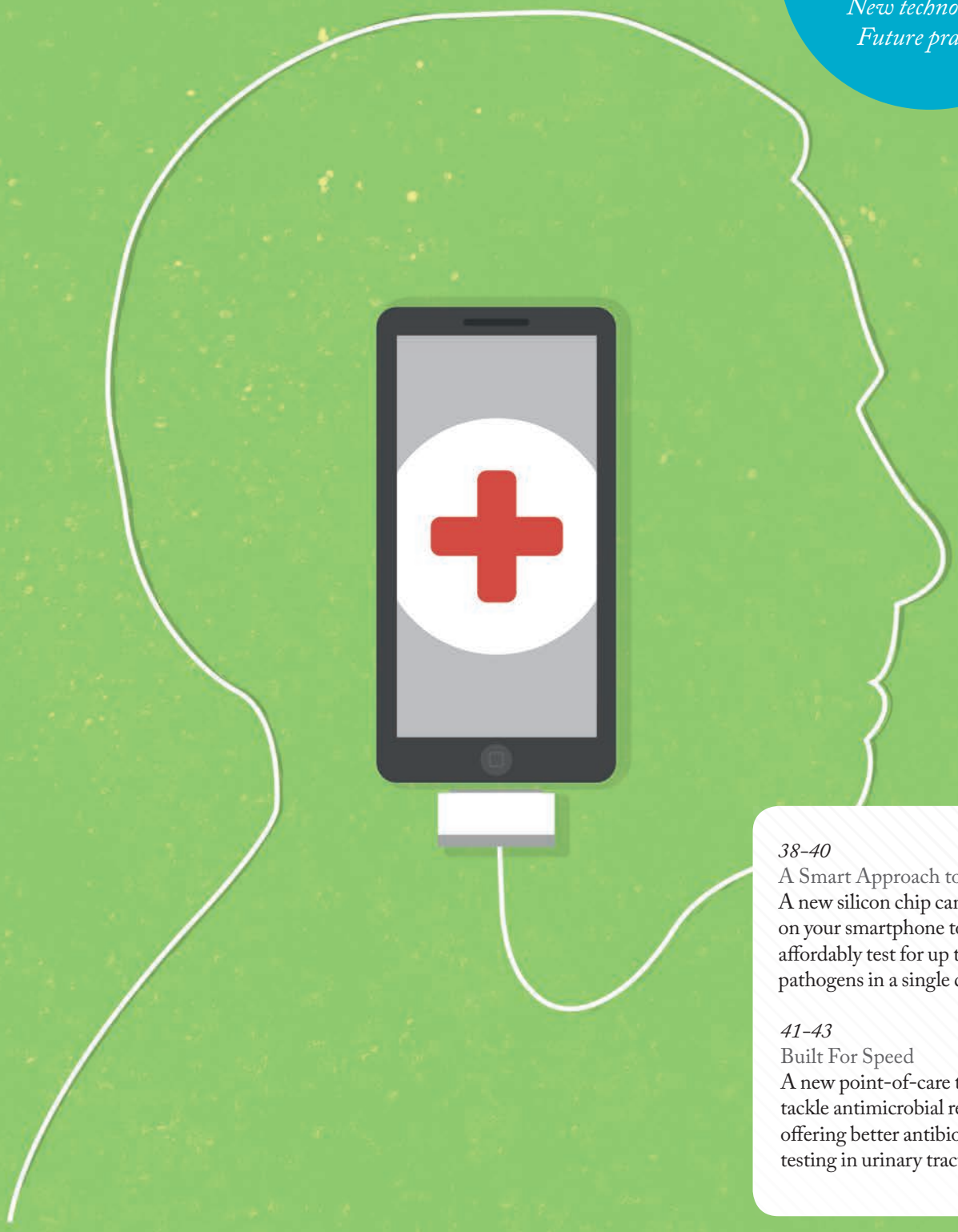
ThermoFisher SCIENTIFIC

Available currently in US only.

The test reports fusion/translocation variants for *ROS1* only. The test only reports *ALK*, *MET*, and *RET* mutations and does not report *ALK*, *MET*, and *RET* fusion/translocation variants.

NextGen

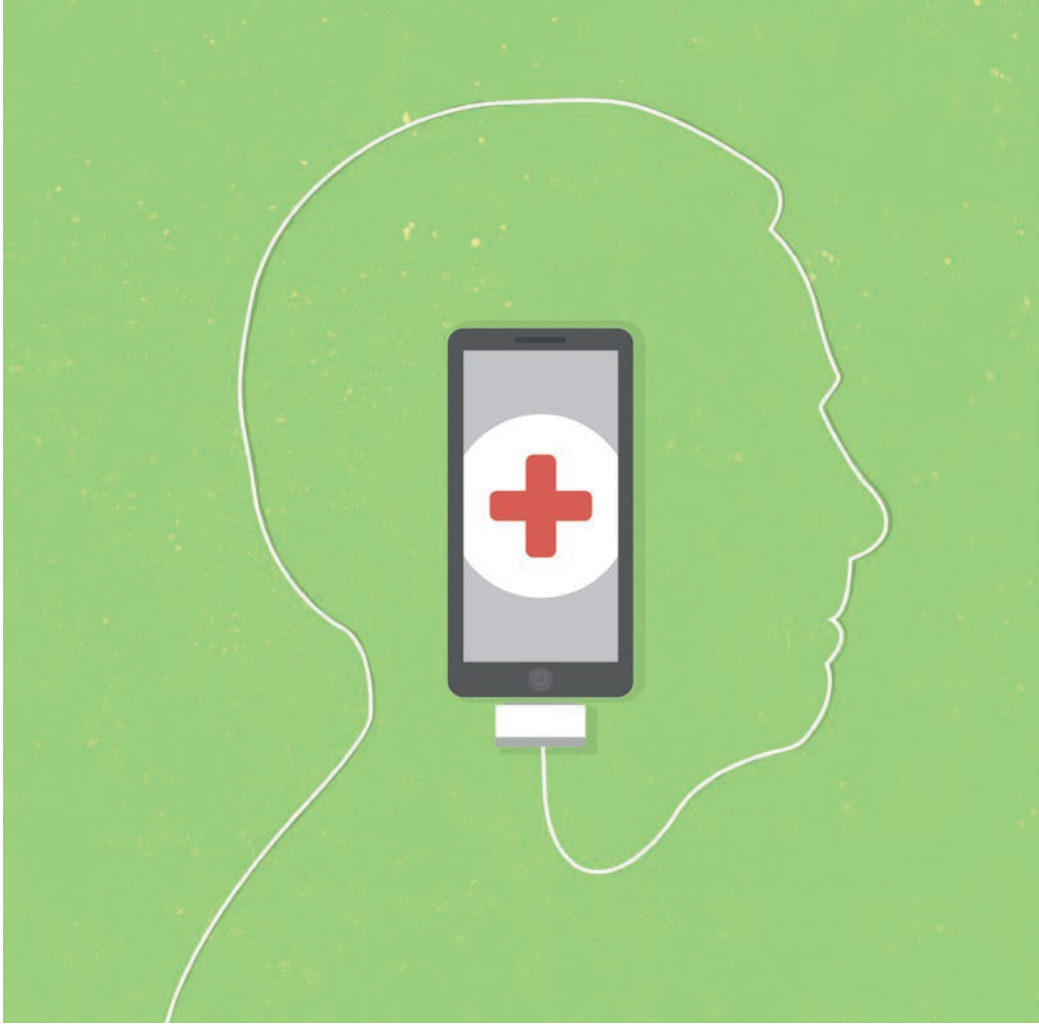
Research advances
New technologies
Future practice



A Smart Approach to Testing

A new lab-on-a-chip for nucleic acid analysis works with your smartphone to offer a broad range of potential diagnostic applications

By Brian Cunningham



Did you know that the average person spends over four hours per day on their mobile phone (1)? And although smartphones are becoming indispensable tools for business and entertainment, they also have the potential to transform the way we interact with the health system. With computers in our pockets, it should be easy to get more immediate, more convenient, and lower-cost access to doctors. Infectious diseases are one application where getting immediate results from a test, rather than waiting several days for samples to be sent to a lab and cultured, is very important. Speed can limit the spread of a virus among animal or human populations. It can identify a dangerous bacterial species in food preparation or in the hospital before it causes an epidemic. Infectious diseases also represent one of the leading causes of death in resource-limited parts of the world. In those places more than anywhere else, an inexpensive point-of-care test can have an enormous impact.

At a Glance

- *Smartphones are ubiquitous – and they offer a cheaper, quicker way to access doctors and medical tests*
- *We have devised a new silicon chip that amplifies pathogenic DNA and RNA; results can be read by a smartphone*
- *The aim is to offer faster, more affordable diagnostics at the point of care, which will be especially valuable in resource-limited settings*
- *The current device is a prototype – but, when scaled up, it will offer a range of human, veterinary and environmental tests*

The chip and the cloud

Nucleic acid (DNA and RNA) testing is the key to rapid detection and identification of pathogens. We no longer have to culture each microbe and wait for it to grow to a point at which we can make a morphologic diagnosis; now, we simply take a look at its sequence to deduce both what it is and – in some cases – the best way to treat it. In our research, we showed that the conventional laboratory test for nucleic acid amplification of pathogenic DNA (or RNA) can be performed in a silicon chip – and that a single chip can perform tests for up to eight separate pathogens in a single droplet of fluid without severely compromising the detection limits of the test. Our system uses the phone's internal camera to gather a fluorescent image of the chip and its internal microprocessor to interpret the image and give a validated result using integrated experimental controls (see Figure 1). It also integrates a local smartphone app with a cloud-based service system that combines the results of the test with the patient's other medical records. And that carries an added benefit: it enables epidemiological interpretation when results are gathered from a distributed network of users taking the same test.

We began our work by developing an endpoint (yes/no) test for a set of equine respiratory diseases (2). Our goal was to demonstrate how the system could be used for racing animals, food animals, and companion animals before moving to human applications – partly for safety reasons, and partly because veterinary medicine represents a market with fewer

regulatory hurdles than human diagnostic testing. We also wanted to contribute to that field because, through collaboration with a practicing equine vet, we learned that there is a substantial unmet need. The test was successful enough that a company has now licensed the patents and pending applications and is planning development of a commercial product for both animal and human applications.

Meanwhile, we developed a subsequent assay for four human viral pathogens (Zika, dengue 1, dengue 3, and chikungunya) using a single droplet of whole blood as the test sample (3), which enabled us to integrate sample handling with our test. We also incorporated kinetic monitoring of the chip so that we could estimate the concentration of the virus, rather than simply provide a yes/no output. One vital member of our team, a molecular biologist, has helped us develop and validate a set of selective primers for all the target pathogens, and is now advising us on the performance criteria that our test must meet to be equivalent to conventional laboratory methods.

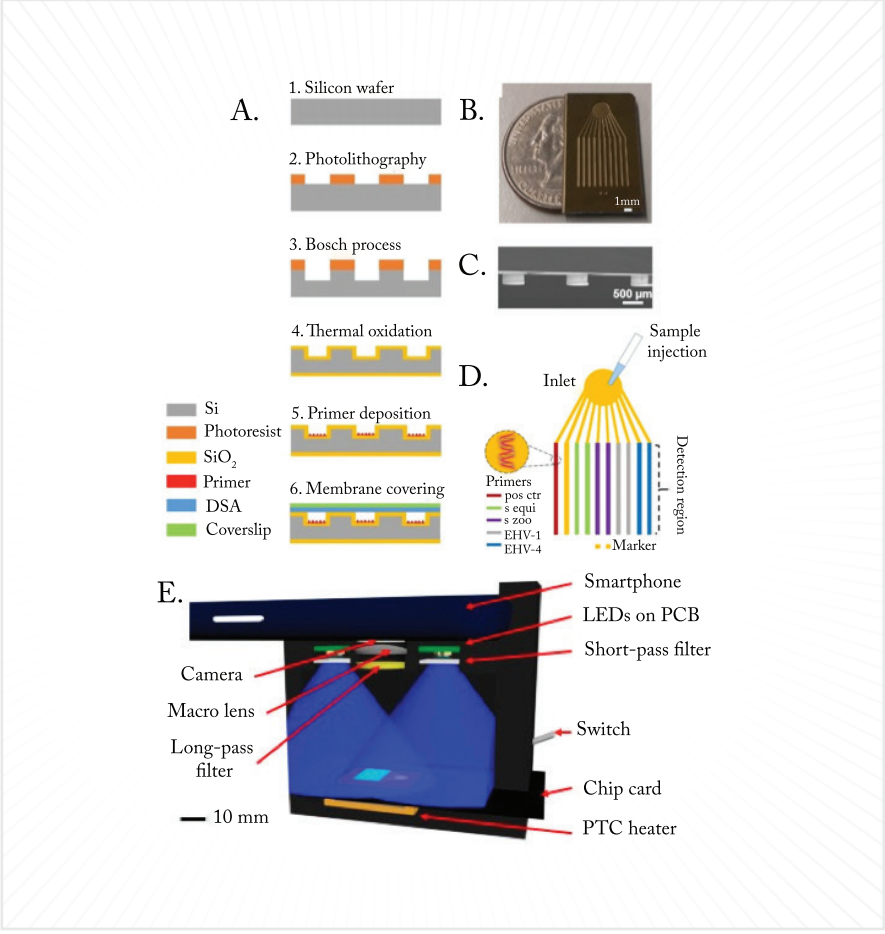
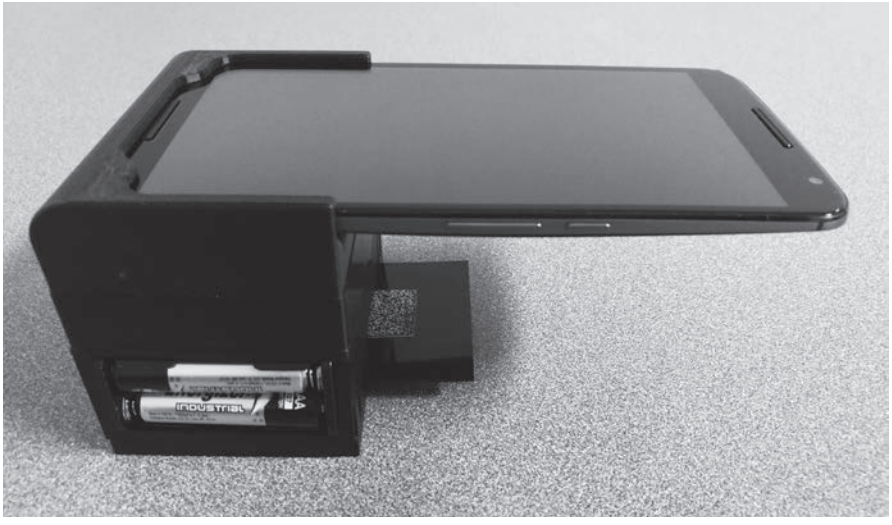


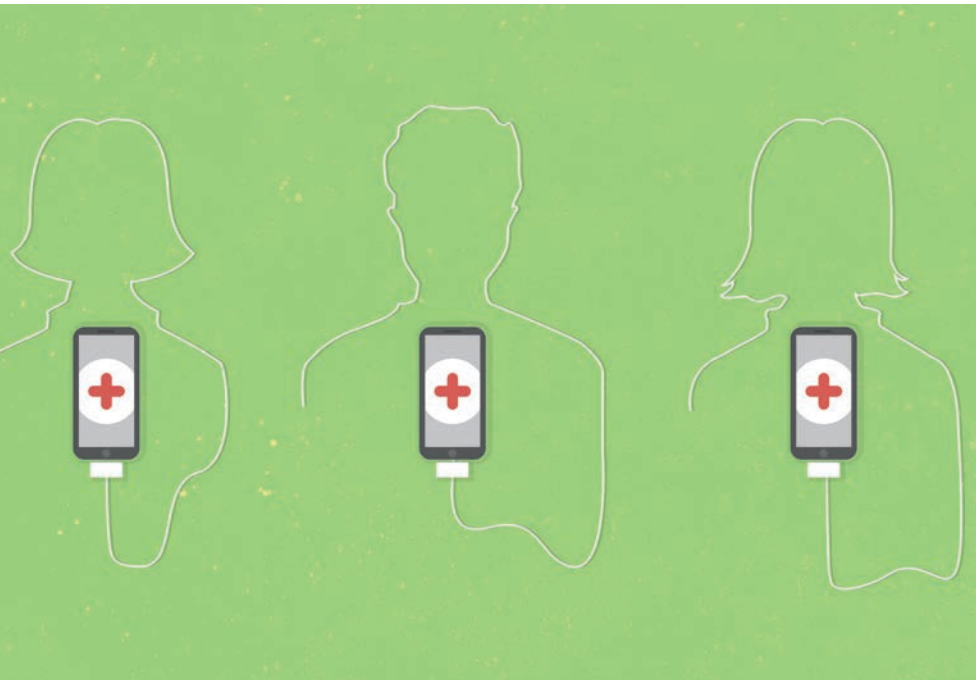
Figure 1. A diagram of the new lab-on-a-chip device. A. Preparation of the chip; B. Size comparison; C. Micrograph of the chip itself; D. Diagram of the chip's function; E. The device assembled with a smartphone.

Practical purposes

When might a test like ours come in handy? One example might be when an animal appears to be sick, but the cause is not known. Our test could diagnose whether the animal has one of the eight most common respiratory diseases – and, if it did, it could be immediately quarantined to reduce the opportunity for the infection to spread. Consider the case of food animals being raised in a facility with thousands of others; if one falls ill, it's unfortunate, but if they all fall ill, it's catastrophic. Imagine the housing of racehorses before a big event – even a single animal's illness is a costly event, but it's staggering when multiplied.

Eventually, we can envision tests like this being available in the drugstore, so that when you feel lousy, you can perform a test on yourself and have the results communicated immediately to your





doctor. The doctor could then prescribe medication or another course of treatment based on your results, along with a video interview, your medical records, and other symptoms. You could avoid ever going to a clinic, waiting in long lines, or coming into contact with other people's germs. That's a nice thought for anyone – but even more of one for people who have difficulty attending clinics in person, such as those with limited mobility or those who are immunocompromised.

And, of course, the test's benefits to humans aren't limited to the doctor's office. Other scenarios could include validation that food preparation surfaces and facilities are free of listeria or salmonella at fast food restaurants, testing for the presence of antibiotic-resistant bacteria on surfaces in the intensive care unit of a hospital, testing water at the beach for *E. coli*, or making certain that norovirus is not present on a cruise ship. There are even defense-related applications, such as the detection of biological warfare agents. What started as a simple test for respiratory diseases in horses has the potential to offer a whole new world of health and safety applications for everyday life.

The move to the clinic

We expect our chip to become a supplement to current laboratory methods, rather than replacing them completely. For instance, it could be used in rapid-response situations that might still require follow-up validation by a conventional laboratory test. Pathologists will be able to devise tests for common sets of pathogens in specific scenarios, and will be able to continually adapt and deploy modified tests as new strains of pathogens are identified. Our test is basically equivalent to the laboratory methods used now, but implemented in a lower volume format and using a smartphone camera as the detection instrument. I expect that pathologists will want to contribute to developing more sophisticated experimental controls and image processing methods to improve the validity of test results, and they will certainly be involved in interpreting the results that will be delivered by a distributed network of instruments. Overall, by lowering the cost and convenience barriers for performing a test, pathologists will likely become busier as the populations they can serve expand.

At the moment, the chip is not yet ready for clinical deployment. We have a working laboratory prototype developed by a team of professors, graduate students, and a veterinarian. We are licensing our patents and pending patent applications to enable the device to be commercialized and mass-produced. In the meantime, we're also working on two more aspects of development: ways to integrate more of the sample handling, so that the test can be more fully automated, and image processing approaches and engineering designs that will hopefully enable us to surpass the detection limits of conventional methods.

Brian Cunningham is Willett Professor of Engineering and Director of the Micro and Nanotechnology Laboratory in the Department of Electrical and Computer Engineering, Department of Bioengineering, at the University of Illinois at Urbana-Champaign, USA.

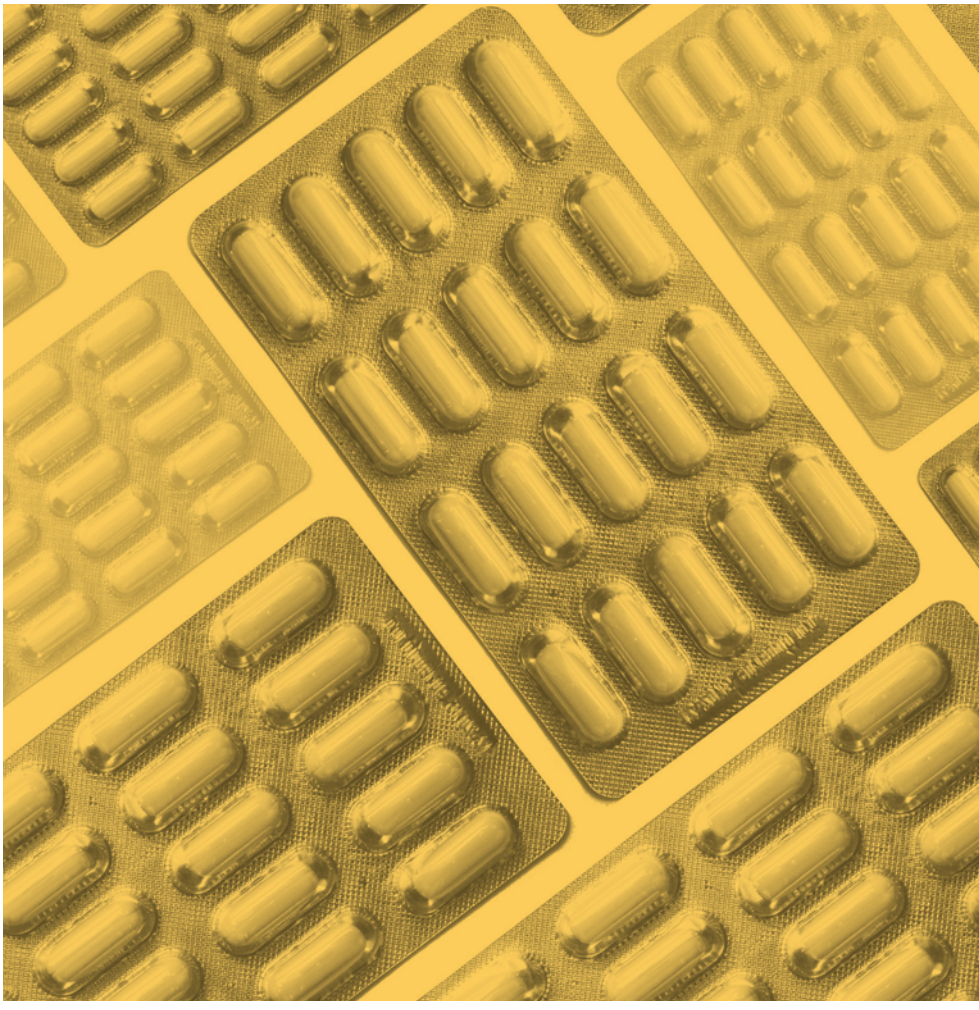
References

1. *Hackernoon, "How much time do people spend on their mobile phones in 2017?" (2017). Available at: http://bit.ly/2qXgA98. Accessed November 23, 2017.*
2. *W Chen et al., "Mobile platform for multiplexed detection and differentiation of disease-specific nucleic acid sequences, using microfluidic loop-mediated isothermal amplification and smartphone detection", Anal Chem, 89, 11219–11226 (2017). PMID: 28819973.*
3. *A Ganguli et al., "Hands-free smartphone-based diagnostics for simultaneous detection of Zika, Chikungunya and Dengue at point-of-care", Biomed Microdevices, 19, 73 (2017). PMID: 28831630.*

Built for Speed

Urinary tract infections account for a large portion of antibiotic prescriptions – but could a new point-of-care test help doctors prescribe more selectively?

Roisin McGuigan and Michael Schubert interview Johan Elf



The threat of antibiotic resistance needs no introduction, and yet antibiotics are still being incorrectly prescribed around the globe. New and improved approaches to diagnosing bacterial infection are needed, and many research groups are working on the problem. But once diagnosed, which antibiotic to prescribe? Current tests used to determine antibiotic susceptibility can take several days, which could prevent the right antibiotic from being prescribed right away.

Now, a team from the University of Uppsala, Sweden, has developed a rapid point-of-care (POC) test to determine the susceptibility of bacteria to antibiotics in urinary tract infections (UTIs), with a turnaround time of just 30 minutes. We spoke to Johan Elf, Professor of Physical Biology and Chair of Molecular Systems Biology at Uppsala University to find out more…

At a Glance

- *Despite the ever-growing threat of antibiotic resistance, incorrect prescribing is still a huge problem – better diagnostic approaches are needed*
- *A team from Sweden have produced a rapid POC test that can determine susceptibility of bacteria to antibiotics in urinary tract infections*
- *If the test is easy to use, automatic and the size of a shoebox, it has the potential to bring susceptibility testing closer to patients*
- *The start-up company that has now taken over development hopes the test will hit the clinic within the next few years*

How did you come to focus on a POC test for antibiotic susceptibility?

My lab was working on the basic science of cell-to-cell variation and we had developed very sensitive tools to measure growth rate at the single molecule level. When we started looking at cell-to-cell variation in antibiotic response to understand the origins of bacterial resistance, we realized that we could tell if the bacteria responded to the antibiotic in just a few minutes. The next step – envisioning a POC test for antibiotic susceptibility – was a small one.

And why focus on UTIs in particular?

A hundred million women suffer from UTIs every year, and this accounts for a very large fraction of antibiotic use. At the same time, there is widespread antibiotic resistance. Doctors stop using the first-line antibiotics when the local resistance is higher than 20 percent. But they could still be used in 80 percent of cases if we could only determine the antibiotic resistance profile before prescribing the drug. It would allow us to both extend

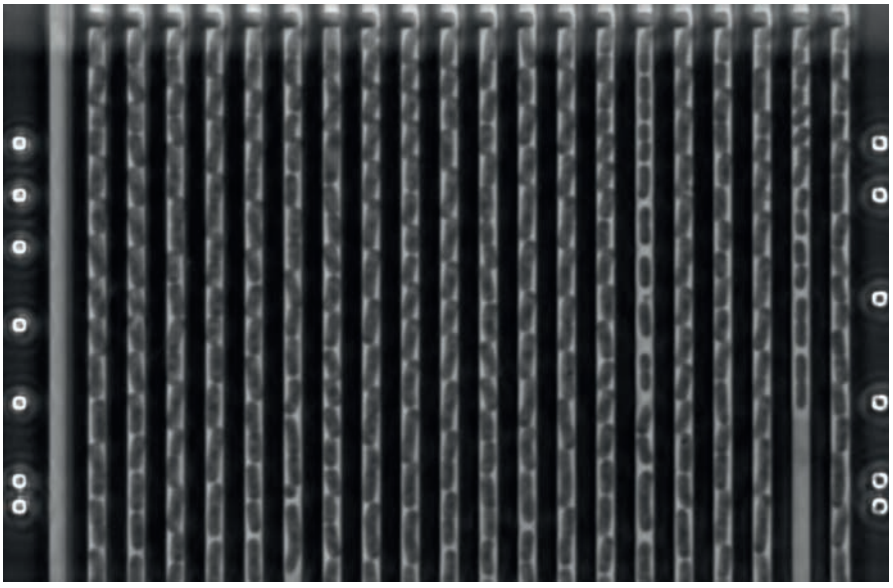


Figure 1. *Klebsiella pneumoniae* growing in the microfluidic chip imaged in phase contrast. The bacteria are 0.003 mm long and divide every 30 min. Credit: Özden Baltekin

"We need to stop using antibiotics when there is no bacterial infection, and we need to save broad-spectrum antibiotics and new drugs for when they are truly needed."

the lifetime of the existing antibiotics, and at the same time ensure we are always prescribing an effective antibiotic for that particular patient. It would also allow us to identify patients who don't have a bacterial infection at all.

How does the fast antibiotic susceptibility test (fASTest) work?

It's based on a microfluidic chip with structures small enough to allow us to selectively capture one bacterium in each of the 4,000 channels. Some of the channels are exposed to the test antibiotic, and we monitor the growth rate response by direct single-cell imaging (see Figures 1 and 2). Because we can detect the volume extensions of individual cells and average over a few hundred cells, the average growth rates can be determined in just a few minutes (1). The principle is very similar to a standard plating assay, but miniaturized – which makes it much faster, because we do not need to wait for the bacteria to multiply.

What equipment and training will be necessary to administer the test?

For use in primary care, I expect that the test will have to be very simple and automatic. Ideally it should involve simply opening the lid of a shoebox-sized device and placing a urine sample and a plastic consumable inside. A 10-minute wait and you'll have a result of a bacterial count, and within a maximum of another 20 minutes, you should have an antibiotic susceptibility response for a few relevant antibiotics. As we couldn't achieve this next stage in a university setting, a company in Uppsala has taken over the development.

Could fASTest be adapted for use in other types of infection?

Sepsis obviously comes to mind because of the sensitivity and speed, and because we only need a few hundred bacteria. But other diseases, such as meningitis or mastitis, could also be considered.

How important is POC testing in trying to curb resistance?

It definitely has its role to play. We need to stop using antibiotics when there is no bacterial infection, and we need to save broad-spectrum antibiotics and new drugs for when they are truly needed. However, right now, there are no actual POC susceptibility tests and doctors have to base the first treatment on statistics alone. Using POC susceptibility testing, we can keep using old antibiotics in the cases where they are effective, even if the average resistance is very high.

When will fASTest likely hit the clinic?

The method needs to be made user-friendly, and the consumable chip and reader device need to be produced at a large scale to become inexpensive. This task is now in the hands of the start-up company – Astrego Diagnostics. If they work with a bigger company for production and to reach the clinics, I would hope that it could be done in about three years.

What's next for your laboratory?

We will continue with our fundamental science projects related to intracellular biophysics and methods development for single molecule tracking in live cells. We will also do some work on the molecular mechanisms for cell-to-cell variation in antibiotic response, which underlie the

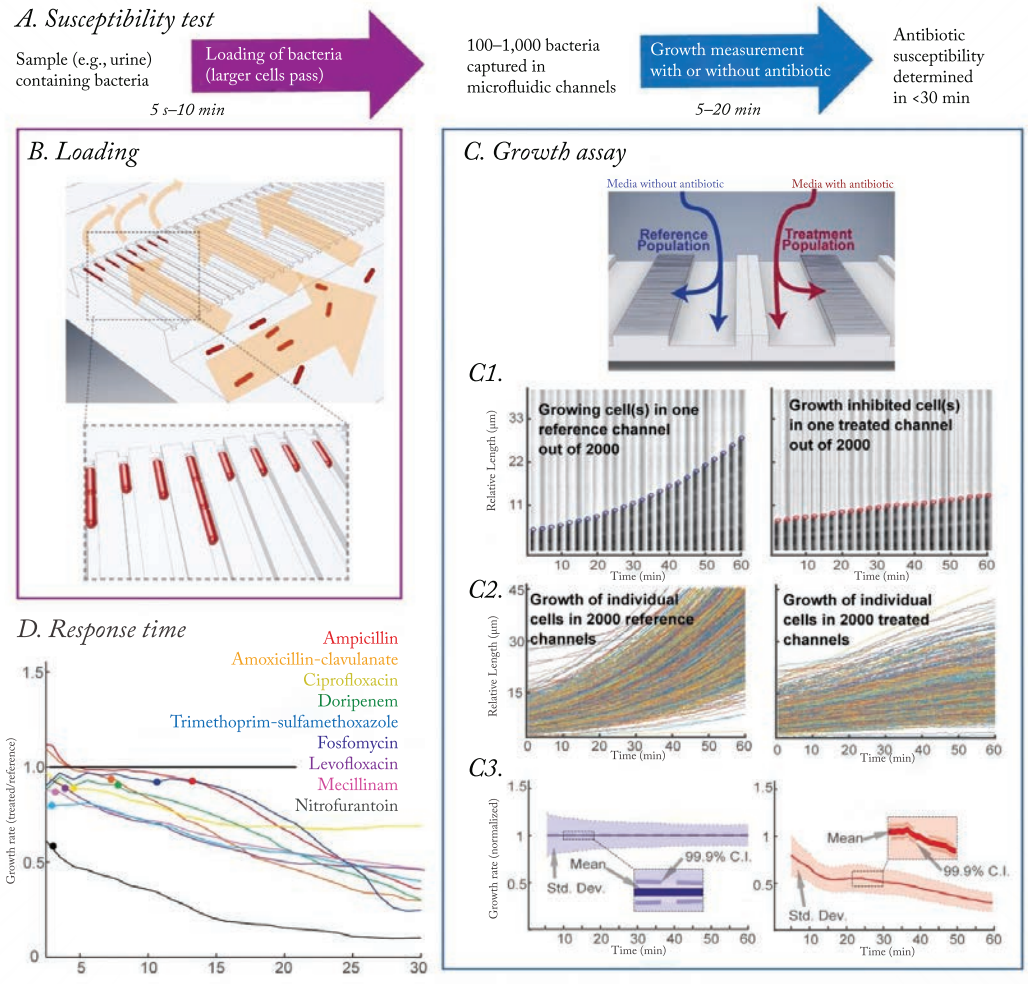


Figure 2. A. Overall workflow for the fASTest test. B. Individual cells are sucked into the cell channels where they get stuck at the 300 nm constriction at the end (inset). C1. One row of 2,000 cell channels is treated with an antibiotic and the other row is used as a reference. C2. Growth in one individual cell channel without antibiotic (left) and one with antibiotic (right) monitored over time (x-axis) as observed with phase contrast microscopy. C3. Length extension over time as determined for cells in 1,600 individual cell channels without antibiotic (left) and with antibiotic (right). C4 Average growth rates for the bacteria in C3 together with 99.9% SEM and population standard deviation D. The average growth rate and 99.9% SEM for susceptible bacteria exposed to one of nine different antibiotics (colors), normalized to the growth rate in the non-treated reference channels. Only data from one typical reference channel is displayed (gray). Dots indicate when the growth rate has dropped below untreated reference with 99.9% probability. Credit: Johan Elf

development of resistance.

fASTest is a great example of the importance of basic research. If we had not pushed the measurement technology to answer our basic science questions, we would not have the microfluidics and image analysis tools we needed to create this test.

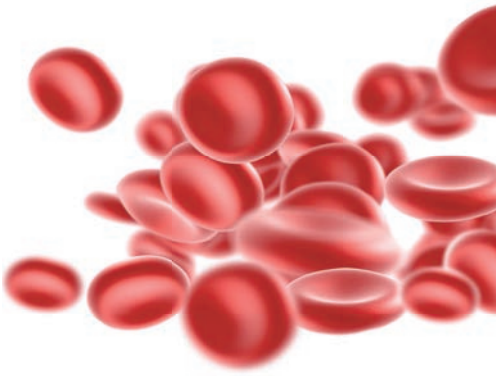
We believe the method could also be used in other types of infection in which quickly choosing the correct treatment is important.

Reference

1. *Ö Baltekin et al., "Antibiotic susceptibility testing in less than 30 min using direct single-cell imaging", Proc Natl Acad Sci, 114, 9170–9175 (2017). PMID: 28790187.*

Idylla™ RAS
Liquid Biopsy Testing

CE mark expected soon



Fast Treatment Initiation
within hours instead of days

Idylla™ RAS Liquid Biopsy Testing

Demonstrates high concordance to tissue testing in mCRC patients

ctKRAS – detecting 21 clinically relevant mutations

ctNRAS-BRAF – detecting 23 clinically relevant mutations

Fully Automated
Molecular Diagnostics

FAST · ACCURATE · EASY · 24/7 ACCESSIBLE

At the advanced edge of Oncology,
rapid access to accurate data on disease state is vital.

The revolutionary, fully automated Idylla™ System in combination with the Idylla™ Tests, is the future of diagnosis and monitoring.

BIOCARTIS

For more information: www.biocartis.com

Profession

Your career
Your business
Your life

A Lever and a Place to Stand

Overuse of unnecessary or even harmful medical services is a serious healthcare problem. Boosting awareness may not be enough to change doctors' ordering habits – the drivers behind overtesting must also be addressed

By Michael Schubert

"Choosing wisely" – a simple phrase, covering all manner of situations. Nowhere is carefully considered decision-making more important than in medical care, where even the smallest error can have grave consequences. But not every "unwise decision" in healthcare is an error; sometimes, it's a question of less-than-optimal resource use, which itself feeds downstream consequences like hospital blood draw-induced anemia, false positive results, or incidental findings that may never have affected a patient's health if not discovered and pursued during other investigations. Such is the dilemma of unnecessary testing. An extra complete blood count here or erythrocyte sedimentation rate there is unlikely to prove severely damaging, but each test comes with a cost, both to patient comfort and to the laboratory's resources.

Such considerations gave rise to the eponymous "Choosing Wisely" campaign – a movement intended to encourage better decisions about medical services by primary care physicians, specialists, and patients, who together

At a Glance

- *Over the past five years, the Choosing Wisely campaign has highlighted the extent of test overutilization in healthcare*
- *Awareness isn't necessarily enough – even with this knowledge, many doctors continue to order unnecessary tests*
- *To change behavior, we need to discover what drives overuse and target interventions to those specific obstacles*
- *Pathologists can help by interacting with ordering specialists, and by developing reasonable testing rules and policies*

are best positioned to change the status quo. In 2010, an article in the New England Journal of Medicine outlined medical professionals' ethical responsibility to contribute to reducing unnecessary testing and proposed a "Top Five" list of the most expensive and overused tests in each specialty (1). A year later, another paper estimated that – even using the most conservative estimates – waste in just six categories amounted to at least US$558 billion per year, more than one-fifth of total healthcare expenditures (2). In the same year, the Choosing Wisely campaign was launched. Featuring Top Five lists from nine specialties, the goal was to raise awareness about overutilization and encourage medical professionals to take steps to prevent it. In medicine, more is not always better – and Choosing Wisely places the lever for change firmly in doctors' hands and encourages patients and physicians to discuss when tests and treatments may not be needed.

A shift in perspective

Since its launch, the movement has grown to include a wide range of specialties, and a correspondingly wide range of testing recommendations. The American Society for Clinical Pathology, for instance, has a "Top 20" list of "things physicians and patients should question." Their recommendations include aspects such as not ordering population-based vitamin D screening, avoiding routine preoperative testing for low-risk surgeries, and not using the bleeding time test to guide patient management (3). To some physicians, some of these may seem obvious. After all, one-third or more of the UK's population exhibits vitamin D deficiency in the winter (4), but not all require immediate medical intervention – so why subject them to testing? Others may be less intuitive; for instance, doctors may hesitate to perform even low-risk surgery without first establishing a patient's complete blood count, clotting times and general health. But when these tests influence care in fewer than three of every 100 patients, neither the stress nor the cost may be worthwhile.

These are the kinds of changes to patient care that Choosing Wisely has spent the past five years working to normalize. What began as an idea in 2011, with just a few societies and recommendations, has now grown into a movement with over 80 societies issuing over 500 recommendations about services that may not be necessary in every instance. One factor that has really helped drive the success of the campaign among doctors is the support of the American Board of Internal Medicine (ABIM) Foundation in establishing relationships with professional societies, health systems, researchers, and funders. And although Choosing Wisely and the ABIM Foundation might not be well-known names among the general public, the campaign has another powerful partner – Consumer Reports. Their involvement has helped to bring the campaign to patients by producing reports, brochures and videos to educate patients on utilization management and how to discuss it with their doctors. Furthermore, the campaign has spread to nearly 20 countries – so despite its United States origins, it's now a truly global phenomenon. In just five years, Choosing Wisely is becoming a household name – and, as a result, the need to decrease unnecessary medical services has become an accepted imperative.

"The need to decrease unnecessary medical services has become an accepted imperative."

Proving itself in patient care

Choosing Wisely recommendations have been tested in, and incorporated into, many health systems. The increase in traction is due to the guidelines' success on the ground; most health systems that have promoted Choosing Wisely have found that utilization of unneeded services has decreased and conversations about those services has increased. One study showed that, among primary care physicians, those familiar with the campaign tended to be more cost-conscious than colleagues unfamiliar with it, and tended to make less use of low-value services (5). Individual health systems have seen great success in implementing the guidelines. California's Cedars-Sinai Health System, for instance, reduced multiple metrics (including inappropriate blood transfusions, vitamin D testing and human papillomavirus testing) by at least 20 percent over a year of adherence to Choosing Wisely guidelines (6). The University of Utah decreased its lab cost per patient per day from US$138 to $123 with no increase in readmission

"We need to understand what drives inappropriate ordering and try to design our interventions to address those issues."

Source: Choosing Wisely®: A Special Report on the First Five Years.

rates, and the University of Vermont Medical Center reduced lab tests on patients with end-stage renal disease by 72 percent and the ordering of complete blood counts and basal metabolic panels on adult inpatients by 48 percent.

There's little doubt, then, that the Choosing Wisely recommendations are helping to optimize patient care. The challenge now is how to spread effective interventions to other health systems. Changing routine behaviors and practices is difficult in any profession – and that can keep physicians ordering unnecessary tests and procedures, and prevent the transition to newer, more streamlined approaches to patient care. Even when physicians agree with the campaign's recommendations, they may think their patients expect certain tests, or they may be uncertain about when to order them for specific patient indications. And that's why a new paper, which takes a look at the movement's history and the promise it sets up for the next five years (7), acknowledges that we need to continue to develop and test innovative behavior change strategies for both physicians and patients. According to lead author Eve Kerr, Professor of Internal Medicine at the University of Michigan and Director of the VA Center for Clinical Management Research, Ann Arbor, USA, there is no single best way to disseminate Choosing Wisely recommendations to physicians – or to educate them about better test utilization. Instead of seeking a Holy Grail answer, Kerr believes we need to understand what drives inappropriate ordering and try to design our interventions and educational approaches to address those issues. Is it uncertainty about the best course of action? Concern about patient expectations? Worries about financial losses? Simply not agreeing

with a recommendation? Perhaps it is something else altogether.

How you can help

Pathologists can work within their institutions to spread the Choosing Wisely recommendations they endorse. How? Kerr says one way is to develop rules and policies about when not to perform certain tests, even when ordered. Pathologists can take steps toward implementing such rules by working with health system leadership to explain the need for them and outline how they can improve overall patient outcomes and cost savings. Another recommendation is to provide ordering clinicians with feedback about when and why tests might not be indicated for particular patients or populations. In some fields, doctors can order a full battery of tests without thinking about whether or not they are all necessary – thyroid panels, for instance, or workups for coagulopathy. Partnering with the primary care doctors and specialists who do the bulk of ordering is a great path for reducing this kind of overutilization.

The tremendous growth in medical societies, health systems, and even states espousing the Choosing Wisely campaign in just these first five years has laid a solid foundation for next steps. Pathologists can help move the campaign forward by working within their own institutions and partnering with researchers to trial innovative approaches to decreasing unnecessary testing. It's this kind of collaborative work – involving pathologists, primary care physicians and researchers – that can ultimately lead to less expense, less testing, and a better healthcare experience for our patients.

Reference

1. *H Brody, "Medicine's ethical responsibility for health care reform – the Top Five list", N Engl J Med, 362, 283–285 (2010). PMID: 20032315.*
2. *DM Berwick, AD Hackbarth, "Eliminating waste in US health care", JAMA, 307, 1513–1516 (2012). PMID: 22419800.*
3. *American Society for Clinical Pathology, "Twenty things physicians and patients should question" (2017). Available at: http://bit.ly/2iWd1ec. Accessed November 27, 2017.*
4. *Scientific Advisory Committee on Nutrition, "Vitamin D and health" (2016). Available at: http://bit.ly/2acOT5x. Accessed November 27, 2017.*
5. *M Grover et al., "Physician cost consciousness and use of low-value clinical services", J Am Board Fam Med, 29, 785–792 (2016). PMID: 28076262.*
6. *Choosing Wisely, "Choosing Wisely®: A special report on the first five years" (2017). Available at: http://bit.ly/2Ae03QC. Accessed November 27, 2017.*
7. *EA Kerr et al., "Choosing Wisely: how to fulfull the promise in the next 5 years", Health Aff, 36, 2012–2018 (2017). PMID: 29137505.*

Leader of the North

Sitting Down With… Victor Tron, Past President of the Canadian Association of Pathologists, Chief and Medical Director of Laboratory Medicine at St. Michael's/St. Joseph's Hospital, and Professor of Laboratory Medicine and Pathobiology at the University of Toronto, Canada

How did you discover pathology as a career?

I attended medical school at the University of Alberta in Edmonton, where pathology was – and still is – a prominent faculty. I found pathology to be highly logical; it had a scientific bent, which I've always valued. We had excellent teachers and, as a result, I was not the only one of my classmates who went on to a successful career in pathology. And none of us have any regrets about the decision we made!

What makes a good pathology leader?

The answer is complicated! I think a good leader in pathology is no different to a good leader anywhere else. You need to have an interesting vision, work toward it, and engage others to work with you. As pathologists, we have to show people that we're not hidden in our offices looking down our microscopes – we're part of the larger world of medicine. I also think it's important for people in any profession to give back. I owe my current position to the many pathologists who went before me, and I consider it my duty to support those who will come after. And that's why it was such a great honor to serve as President of the Canadian Association of Pathologists (CAP-ACP). We may not be as large as some other pathology organizations, but we work hard to be innovative, and we certainly have things to contribute to the community. I really cherished my time as President, and I think CAP-ACP is in good hands for continued growth.

What's next for you?

I've rededicated myself to my hospital work. At the moment, I'm busy leading the integration of two laboratories in two separate teaching hospitals, which is going well. I enjoy my clinical work more than ever and, even though I've been a dermatopathologist for many years now, there's always more to learn. I continue to see things I've never seen before, and there are always new diagnostic aids to apply, which I find extremely exciting. And, of course, I still try to foster the careers of others as much as I can, both on my own and as Past President of CAP-ACP. I get a lot of enjoyment out of helping others succeed.

My goal is to continue practicing pathology for quite some time. I don't see retirement on the horizon anytime soon – there are too many exciting things to do!

What's your take on pathology education?

I like to engage my students and encourage them to think. When I get a group of students around me, they immediately open up their laptops. I make them close all but one (they're allowed to have a scribe), because I want them talking with each other and drawing on personal experiences to problem-solve.

I also mentor junior faculty, which is not so much teaching as it is coaching – and, as a chief of service and a medical director, trying to provide them with the resources they need to be successful. I think mentoring is about connecting with people in a way that makes them feel valued and supported. For instance, I don't set up meetings with people in my office; instead, I drop into their offices, sit down, and have a chat with them there. I think that makes people feel much more relaxed. They don't have scary formal appointments; it's a lower-key and more natural way of engaging with and supporting them. I liked it when people took that approach with me in the past, so I give my faculty the same courtesy.

Do you have advice for others following in your footsteps?

One of our greatest challenges is leading a group of leaders. All medical professionals are leaders – each one of us has special interests and expertise – and developing the skills to help and manage people like that is essential. We parachute people into leadership roles because they're strong researchers or great teachers or superb diagnosticians, but we don't necessarily give them the skills and resources they need to do a good job unassisted.

"It's a real honor to open up the tray and wonder, 'Who am I going to help today?'"

In pathology, we struggle with encouraging candidates to enter our field. We're trying to find new ways of engaging with medical students, and one way to do that is to support and encourage our trainees and junior doctors. Often, medical students will connect with registrars or residents to ask about their work, so we're trying to ensure that they have the resources they need to enjoy and promote pathology. And it's working; they've been great participants at our annual meeting – they're doing an awesome job. Value your early-career pathologists, because they will encourage the next generation.

A number of years ago I led a CAP-ACP campaign, MyPathologist.ca, to reinforce the idea that pathologists stand with patients throughout their medical journey. Our patients are at home, anxiously awaiting their results, and it's truly rewarding when we can help them on their medical journey. For the most part, the results are good news – but even when they aren't, we provide the most up-to-date, accurate diagnosis to guide therapy. I want aspiring pathologists to know that I look forward to my cases – my patients – every day. It's a real honor to open up the tray and wonder, "Who am I going to help today?"

Advancing Cancer Diagnostics
Improving Lives

Leica
BIOSYSTEMS

Connect to Workflow Optimization

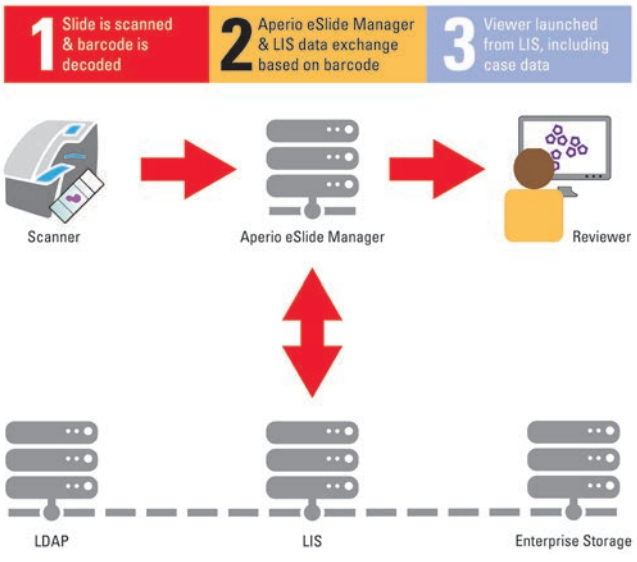
With Aperio Digital Pathology and Seamless IT Integration

The open architecture and standards of Aperio Digital Pathology ensure maximum interoperability with different LIS, LDAP, storage and other IT systems.

Now, pathologists can easily retrieve and view digital slides from their LIS; exchanging data seamlessly via bi-directional communication.

With over 2,000 scanner implementations and 150 LIS integrations, Aperio Digital Pathology offers customized LIS integration, as well as turnkey integration with existing commercial LIS solutions.

LeicaBiosystems.com/IT



For Research Use Only. Not for Use in Diagnostic Procedures.

17578 Rev A · IMC-3021-REV-A 12/2017