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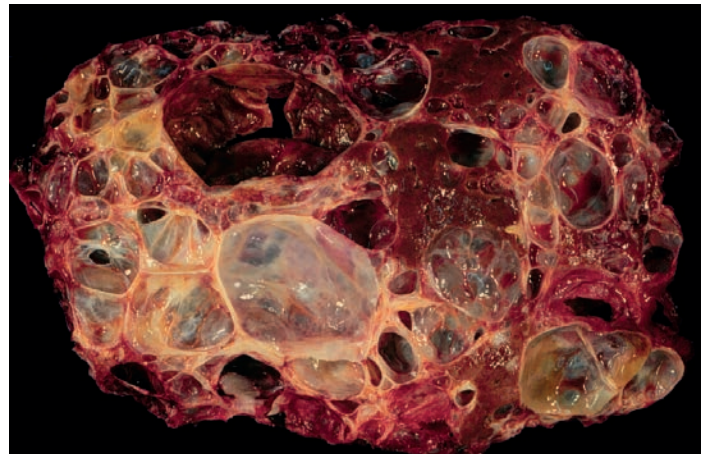
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Case of the Month



This liver disease is most often associated with the mutation of which gene?

- a PKD1
- b PKD2
- c PRKCSH (hepatocystin)
- d SEC63
- e LRP5



Answer to last issue's Case of the Month...

Solitary fibrous tumor

Solitary fibrous tumor (SFT) was originally described as a pleural tumor by Klemperer (1). Less commonly, it presents as an intrapulmonary neoplasm (2). In both locations, it is positive for CD34, Bcl-2 and CD99. STAT6 is currently used as the most reliable marker for SFTs (3).

References

1. P Klemperer, CB Rabin, "Primary neoplasms of the pleura", *Arch Pathol*; 11, 386–411 (1931).
2. N Rao et al., "Intrapulmonary solitary fibrous tumors: clinicopathologic and immunohistochemical study of 24 cases", *Am J Surg Pathol*, 37, 155–166 (2013). PMID: 23108019.
3. JM Kim et al., "Comparison and evaluation of risk factors for meningeal, pleural, and extrapleural solitary fibrous tumors: a clinicopathological study of 92 cases confirmed by STAT6 immunohistochemical staining", *Pathol Res Pract*, 213, 619–625 (2017). PMID: 28552537.



To register your guess, please go to <http://tp.txp.to/0917/case-of-the-month>
We will reveal the answer in next month's issue!



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The Sound of One Hand Clapping

*Speaking up for yourself is valuable
– but only if you have an audience*

Editorial



Recently, in an interview for Vox’s “The Weeds (1),” well-known American surgeon and public health researcher Atul Gawande was asked, “What do you think is particularly important for individuals working in the medical field to know about communication and people skills?”

I agreed with the start of his response – “It’s all about communication” – but was taken aback as he continued, “There are corners in medicine where you don’t really have to be good at communication. You can work in laboratory medicine; you can work in a basic science lab; you can work in pathology, where your life is under a microscope. That did not appeal to me, because I like talking and connecting with people.”

How can someone so visible – the author of four books, a MacArthur Fellow, a director in the World Health Organization – be so wrong about pathology, and share those views so publicly? And, more importantly, what impression are Gawande’s many followers getting of pathologists? Antisocial. Isolated. Unfriendly... No wonder such stereotypes persist (2)! We encourage pathologists to speak up for themselves and their profession, but communication is a two-way street, and it’s hard to carry on a conversation when the people you’re talking to simply aren’t listening.

What can you do? First and foremost: be seen. Invite clinicians and patients into your office, or into the laboratory. Speak to them about the diagnoses you make. Demystify what lies between sending a sample to the laboratory and receiving a diagnosis – and how to proceed from that point onward. As you’ll see in this month’s feature article, you might be surprised at just how unfamiliar your clinical colleagues are with your work.

Have you experienced similar attitudes toward your choice of specialty? Do you have any suggestions for surmounting those stereotypes – not just by finding your voice, but by making sure it’s heard? If so, I’d love to hear about it (edit@thepathologist.com).

More than anything in my time with *The Pathologist*, I’ve enjoyed learning from the pathology community – and I’ve found that pathologists are enthusiastic about sharing their expertise. As diagnostic technologies advance, precision medicine expands, and the laboratory becomes an ever-larger piece of the healthcare pie, I hope we can work together to set the stage for open dialog between pathologists who are eager to talk and clinicians who are excited to listen.

References

1. S Kliff, “Weeds Live: Atul Gawande on opioids, end of life care, and rock and roll” (2017). Available at: <http://bit.ly/2xYXuzz>. Accessed September 13, 2017.
2. M Schubert, “The Last Respite of the Socially Inept?”, *The Pathologist*, 3, 18–25 (2014). Available at: <http://bit.ly/1Fs4FSH>.

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

Paper Trails

A cheap and disposable test powered by your fingertips could bring a range of useful diagnostic test options to low-resource settings

Paper: cheap, manufactured almost everywhere, and easily disposed of. These characteristics make it a highly useful substrate with which to develop low-cost diagnostic devices. Now, a research team have taken this useful material one step further, by developing a paper-based test powered through touch. The self-powered, paper-based electrochemical device, or SPED, requires no electricity, clean water, or equipment. It can be safely disposed of by incineration (a bonus when dealing with viral infections like HIV), and provide accurate electrochemical sensing.

“Other low-cost devices, like test strips, can only provide colorimetric information, and lose accuracy in places with high relative humidity,” says Ramses Martinez, assistant professor of industrial and biomedical engineering, Purdue University, USA. “SPEDs are fully self-powered, can provide accurate sensing independently of the environmental humidity, and can be used by untrained personnel.”

To use the device, the user first taps the triboelectric generator

on the bottom of the SPED for two or three minutes to allow electricity from the tips of the fingers to be harvested; this is accumulated in a small portable circuit called a “potentiostat” (see Figure 1). Next, the user takes a fingerprick blood sample and places it on top of the testing region of the device, and an accurate

measurement of different analytes,

such as glucose or lactic acid, is provided in under 30 seconds. Some of the tests can also be performed with other substances, such as testing urine for malnutrition problems, or testing if water is potable.

The team behind the test hope to extend the testing abilities of the device, in order to create one capable of quickly performing a whole blood panel. “To facilitate the reading of so much information coming from a small device, we created a machine-vision algorithm that can take a digital image of the SPED, find the test areas, and read the results in real time,” explains Martinez. “While we have this algorithm currently working as a cell phone app, we plan to implement this in see-through devices like the HoloLens, so the user can “see” the results on glasses as soon as they are looking at the SPED.”

Martinez envisions the tests being used in resource-limited settings, or by military personnel deployed in remote locations. “We hope the low cost of SPEDs can make this technology easily accessible to a large number of pathologists, especially those working at the point of care. We also hope ‘paper tests’ could aid in testing people who fear needles, and in getting large populations tested quickly using the minimum amount of resources.”

Expanding the tests available is now the aim – by focusing on multiplexing, the team are working to provide as much relevant medical information as possible within a single cheap test. *RM*

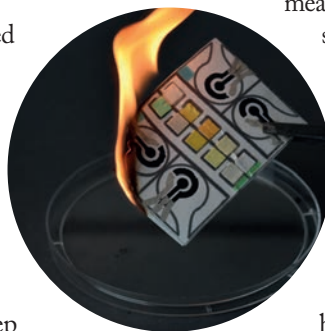


Figure 1. The SPEDs devices can perform electrochemical analyses using energy accumulated by the potentiostat (left).

Delving into the Dark Code

Genome exploration tool Orion digs into non-coding regions for disease-causing mutations. Developer Ayal Gussow explains...

What inspired you to develop Orion?

A large part of our research focuses on detecting disease-causing mutations in patients. As the non-coding regions of the genome are so poorly understood, mutations within those regions are generally ignored, even though they may be causing the disease. There was a clear need for a method that can assess whether a non-coding mutation is pathogenic.

Prior to Orion, we developed similar methods for localizing disease-causing mutations within protein subunits (1) and untranslated regions (2). Tackling the whole genome was a natural next step (3).

The process of developing the tool was quite enjoyable. Given the challenge posed by the vast size of whole genome – three billion bases! – and the dearth of knowledge of the non-coding genome, we needed to properly harness computational resources and population genetics theory to develop Orion. Our team consisted of talented programmers and computational biologists, and working together to resolve these challenges was both interesting and exciting.

How does Orion work?

Orion is based on a cohort of 1,662 control genomes. We scanned this cohort's genomes for regions that comparatively appear to have fewer mutations than we would expect. The underlying assumption of this approach is that regions with fewer observed mutations than expected are biologically important and therefore would likely cause disease if mutated.

Thus far, we have demonstrated that the Orion regions are significantly enriched for previously discovered pathogenic mutations. We anticipate that researchers can immediately implement Orion to detect new pathogenic mutations in patients.

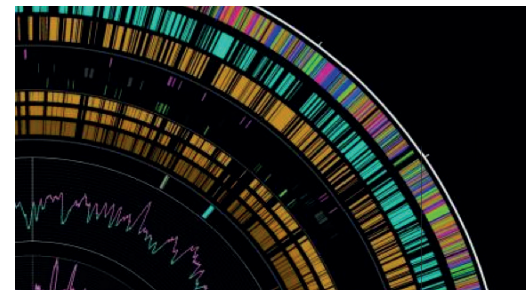
In my view, our most striking finding was the comparison between conservation and intolerance. Conservation (as measured by GERP++) evaluates purifying selection across the mammalian lineage, whereas intolerance (as measured by Orion) evaluates purifying selection within humans. By comparing the two scores, we found that a subset of regulatory regions are very intolerant, but not very conserved – that is, these regions appear to be undergoing purifying selection in the human, but not the mammalian, lineage. What does that mean? That those regions are uniquely important to humans. It would be interesting to follow up by exploring their biological functions. And of course, from a clinical perspective, these results illustrate Orion's value in detecting important, disease-relevant regions that cannot be spotted via conservation-based methods.

How can pathologists use Orion?

We anticipate that Orion will point researchers to interesting portions of the genome that have unclear function, but are clearly under purifying selection. It would be interesting to explore these regions to better understand the biology of the non-coding genome.

We have created a web tool (www.genomic-orion.org) that allows researchers to view and extract scores, along with links to download the full set of scores and regions. Orion can easily be implemented into a mutation analysis pipeline, either by analyzing the scores of potential disease-causing mutations or by flagging mutations that fall in Orion intolerant regions. We have a great team and are always happy to help researchers who want to work with Orion, so feel free to email us with questions.

In the clinic, Orion can already help



assess the likelihood that a mutation is pathogenic. That said, we are currently working on applying Orion to a much larger cohort, which should vastly improve our resolution. And as more researchers and laboratory medicine professionals use Orion with their data, we will learn more about how best to deploy it and what type of improvements we may want to implement.

What are the next steps for Orion?

The other intolerance methodologies we previously developed for the exonic portion of the genome are based on several thousand to tens of thousands of samples – but because there are far fewer whole-genome samples publicly available, Orion is based on fewer than 2,000 samples. Adding more will greatly improve our resolution and the tool's overall utility.

We are also analyzing the effects of mutations in Orion regions on gene expression, and using Orion to explore other features of the non-coding genome, such as lncRNAs.

References

1. AB Gussow et al., "The intolerance to functional genetic variation of protein domains predicts the localization of pathogenic mutations within genes", *Genome Biol*, 17, 9 (2016). PMID: 26781712.
2. S Petrovski et al., "The intolerance of regulatory sequence to genetic variation predicts gene dosage sensitivity", *PLoS Genet*, 11, e1005492 (2015). PMID: 26332131.
3. AB Gussow et al., "Orion: Detecting regions of the human noncoding genome that are intolerant to variation using population genetics", *PLoS One*, 12, e0181604 (2017). PMID: 28797091.

TRI a New Kind of Spectrometer

An inexpensive, smartphone-based device could offer a wide range of point-of-care tests

What

Everyone's vision of the "laboratory of the future" is different – but most agree that it should be reliable, versatile and efficient. And if those attributes don't come with huge costs or space requirements – even better. Enter the US\$550 spectral transmission-reflectance-intensity (TRI)-Analyzer (1), which can perform an array of tests on the spot by harnessing clever optics and the power of a smartphone. But is it the future?

"Several years ago, we completed an early demonstration of a smartphone as a spectrometer. The spectrometer itself was handheld, but to interface with any sort of meaningful biological sample, it needed to be attached to some benchtop optics. The next step was to produce a truly handheld device with everything inside, including the light source and sample interface." To that end, the research team condensed three general optical techniques – transmission, reflection and intensity, each of which uses a different optical path – into a compact package to minimize size and cost. Best of all, the system wasn't designed for a specific test. "So many recent advances in the point-of-care testing realm focus on miniaturizing a test for a single condition. The TRI-Analyzer is a handheld instrument capable of measuring thousands of commercial tests."

How

The TRI-Analyzer was developed from the ground up. "We wanted to design a device that maximized spectral resolution (and therefore sensitivity) and versatility,"

explains Long. He and his colleagues began with optical simulations to develop the ideal light path, and then substituted in commercial optical components. First, they designed the custom fiber-optic assembly and the 3D-printed cradle in which the optics are mounted; then, they built a prototype and tested each of the three modalities with basic samples, such as food coloring. "We also wanted to run some proof-of-concept experiments using biological samples from a context where a portable device would be beneficial," says Long. To that end, the team assessed the TRI-Analyzer's performance with an ELISA assay to detect an indicator of pre-term birth (fetal fibronectin protein) and a fluorescent assay to measure phenylalanine, an indicator for phenylketonuria.

Who

The regulation of new medical technologies is stringent, so it will be some time before the TRI-Analyzer is approved for routine clinical use. In the meantime, though, veterinary pathologists take note: "The best patient right now would be a cow or horse. Just like people, they catch diseases and are highly mobile. 'Clinic access' is often challenging, and getting results back to patients after laboratory analysis can be difficult when they're out in the pasture. Having a device that could perform a test on-site would obviously be beneficial."

Personally, though, Long says he is incredibly interested in global health applications. "I'd love to see the TRI-

Analyzer used by clinicians in rural or remote places where there might be clinics, but not clinical laboratories. Perhaps a doctor who travels to a dozen clinics on a regular basis could take the TRI-Analyzer with them as a portable lab system instead of collecting clinical samples, sending them off to a lab, and then trying to reconnect with a patient a couple of days later."

Why

Long and his colleagues hope that the TRI-Analyzer will help free many diagnostic tests from the centralized laboratory. Their ultimate goal? A tool that researchers and clinicians can use to quickly translate both existing and novel biomedical tests from the benchtop to the bedside. Better yet, they anticipate that the decreased logistics of sample collection, shipping, tracking, and follow-up will save time for physicians and laboratory professionals alike.

"I'd hope that we move away from having a separate gadget for each test we want to perform and toward a future where a single device can serve as a more universal portable laboratory capable of measuring many different types of tests," concludes Long. "I hope our work helps nudge the field in that direction." *MS*

Reference

1. KD Long et al., "Multimode smartphone biosensing: the transmission, reflection, and intensity spectral (TRI)-analyzer", *Lab Chip*, [Epub ahead of print] (2017). PMID: 28752875.



The Trials of Mesothelioma

The International Mesothelioma Interest Group has issued updated guidelines for diagnosis

Famously linked to asbestos exposure, malignant mesothelioma (MM) is an uncommon cancer that can prove difficult to accurately diagnose. But as testing methods advance, methods for distinguishing subtypes of MM are improving – with newer antibodies becoming available for immunohistochemistry (IHC) panels, and molecular testing methods

displacing IHC in some cases as the preferred method for separating benign and malignant proliferations.

To provide guidance for pathologists and address the latest advances, the International Mesothelioma Interest Group has issued updated guidelines, covering a range of practical topics for pathologists looking to accurately diagnose MM (see Table 1), while also covering some of the latest advances, including predictors of prognosis and therapy response (1).

The authors caution that pathologists should not consider asbestos exposure when diagnosing the disease, but offer a notable reminder: “MM, although a rare tumor, has a grave prognosis and invariably has medicolegal implications.” *RM*

What do the 2017 guidelines cover?

Benign versus malignant mesothelial proliferations
Cytologic diagnosis
Key histologic features of pleural and peritoneal MM
Histochemical and IHC stains in diagnosis and differential diagnosis
Distinguishing epithelioid MM from other cancers
Molecular markers in diagnosing MM
Electron microscopy in diagnosing MM
Caveats and pitfalls

Table 1. The topics covered by the 2017 malignant mesothelioma guidelines.

Reference

1. *AN Husain et al., “Guidelines for pathologic diagnosis of malignant mesothelioma: 2017 update of the consensus statement from the international mesothelioma interest group”, Arch Pathol Lab Med, [Epub ahead of print] (2017). PMID: 28686500.*

Random Acts of Kinase

A newly validated clinical assay can detect gene fusions that lead to cancer

Gene fusions – genomic events where parts of two separate genes are connected to form a single hybrid gene – have been found in almost every type of human cancer. With over 10,000 different fusions identified to date (1), it’s unsurprising that they play a role in so many different forms of the disease. In particular, gene fusions involving kinases, such as *ALK*, *RET*, *ROS1*, *FGFR*, and *NTRK*, are known to be involved in multiple cancers. The discoveries of those fusions meant new opportunities for patients to receive therapy in clinical trials – but before those treatments could be offered, laboratories needed a clinical-grade test

that could detect multiple types of gene fusions, including novel ones. And that’s why Sameek Roychowdhury’s group at the Ohio State Cancer Center developed OSU-SpARKFuse (2) – a new type of gene fusion assay.

“OSU-SpARKFuse involves focused sequencing of tumor RNA through hybridization-based enrichment of a selected panel of transcripts,” explains Roychowdhury. “Because it is not an amplicon-based approach, the assay is not limited to select exons and directionality of gene fusions, and has the capacity to discover fusions involving new gene partners, breakpoints, and orientations.” Why is the test so valuable? Gene fusions can happen in any type of cancer (though they’re more common in certain types, such as thyroid, lung, and cholangiocarcinoma) – which means that the test could hold value for any patient diagnosed with the disease. Currently, a clinical trial at James Cancer Hospital at the Ohio State University offers OSU-SpARKFuse to

patients with metastatic or advanced stage cancer of any type.

Such RNA sequencing has value even beyond gene fusions, though. The assay can also detect other transcriptome events, such as splicing or exon skipping. Roychowdhury emphasizes the power of clinical-grade RNA sequencing to detect splicing and gene expression, and to enable immune cell profiling, giving just one example from his own experience: “A young woman with metastatic lung cancer was found to have MET exon skipping and benefited from a MET inhibitor in a clinical trial.” MS

References

1. *National Cancer Institute, “Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer” (2017). Available at: <http://bit.ly/2h7mtKa>. Accessed September 15, 2017.*
2. *JW Reeser et al., “Validation of a targeted RNA sequencing assay for kinase fusion detection in solid tumors”, J Mol Diagn, 19, 682–696 (2017). PMID: 28802831.*

No Lens, No Problem

Holographic lens-free microscopy can image thick tissue samples simply and inexpensively

Although technological advances have taken telepathology forward by leaps and bounds, allowing physicians to remotely access medical data and make diagnoses, there is still an urgent need for a reliable, inexpensive means of imaging and identifying disease. Standard optical microscopy tools unfortunately don't fit the bill; they are expensive, relatively bulky, and many laboratories – especially in resource-limited settings – have no access to such equipment.

According to Aydogan Ozcan and his research colleagues at the University of California, Los Angeles, the solution may be holographic lens-free microscopy (1). The group's unique method provides high-throughput imaging of samples with diffraction-limited resolution over large fields of view – but most importantly, it does so without compromising on cost-effectiveness or portability.

Ozcan explains, “We prepare tissue samples using a technique called CLARITY, which makes tissue transparent using a chemical process that removes fat and leaves behind proteins and DNA.” The method typically requires tissue staining via fluorescent dyes, which carry several drawbacks; not only can they be costly, but the staining tends to degrade over time, making it harder for microscopists to gather information from samples. Instead of fluorescent dyes, Ozcan's team used colorimetric dyes that can be used with regular bright-field microscopy tools without any noticeable signal loss over time.

To image the samples, the team

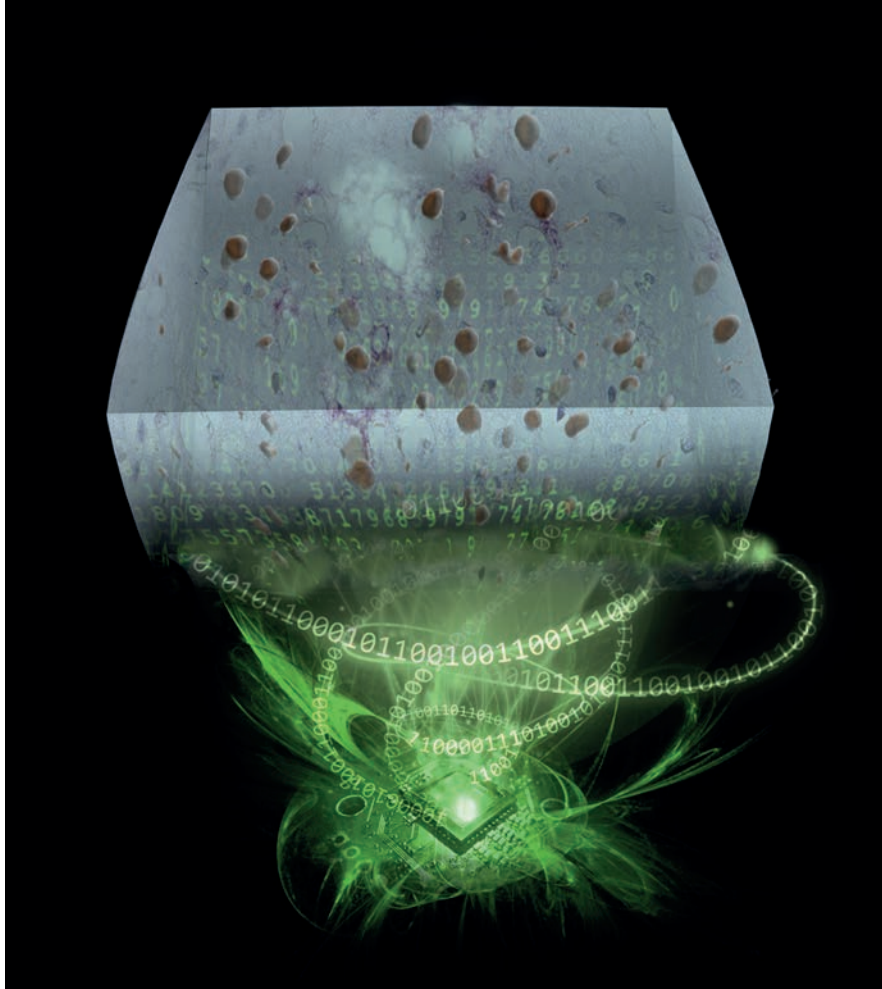
developed a computational imaging device made of components that collectively cost just a few hundred dollars: a holographic lens-free microscope capable of producing 3D pictures with one-tenth of the image data that conventional scanning optical microscopes need. Ozcan talks through the process: “In this computational microscope, the cleared tissue is placed in a small container on a silicon chip that contains millions of photodetectors – the same type of chip found in mobile phone cameras. When we shine light on the sample, low-resolution shadows from the tissue fall on the chip. Those shadows, created by the interference of light scattered by the sample, form holograms of the cleared tissue sample.” Next, the researchers enhance the resolution and enable 3D imaging by shifting the sample relative to the image sensor and capturing holographic shadow again. That allows them to digitally view different cross-sections, or digital slices, of the tissue sample. “To put it simply, through computation- and holography-

based algorithms, we converted a standard 10-megapixel imager into a several-hundred-megapixel microscope that can digitally image through different slices of a thick tissue sample.”

Now, Ozcan and his colleagues can image tissue samples up to 0.2 mm thick – over 20 times thicker than a typical sample. It's especially important for such a device to handle thick samples because, in laboratories without sophisticated equipment, producing thinner tissue slices is difficult. But even well-resourced labs can benefit: “It enables us to study larger sample volumes, which could help us to detect abnormalities earlier than we otherwise would.” In fact, they're already aiming higher, hoping eventually to develop a version of the microscope that can image even thicker tissue samples. *MS*

Reference

1. Y Zhang et al., “3D imaging of optically cleared tissue using a simplified CLARITY method and on-chip microscopy”, *Sci Adv*, 3, e1700553 (2017). PMID: 28819645.





Writing Off Cancer

When it comes to identifying cancerous tissue, is the “MasSpec Pen” mightier than the sword?

Meet the MasSpec Pen, a handheld mass spectrometry device with the potential to speed up accurate and intraoperative diagnosis of human cancer. The pen – which releases a single water droplet onto suspected cancer tissue before drawing it back up for chemical analysis – was able to predict cancer with high sensitivity (96.4 percent), specificity (96.2 percent), and an overall accuracy of 96.3 percent (1).

Finding and removing the edges of cancerous tissue by sight alone is a particular challenge for surgeons, and successful resection of all the cancerous tissue clearly has huge health implications for the patient. The resulting demand for precise, accurate and rapid detection has already inspired one similar device: the electro-surgical iKnife, which uses rapid evaporative ionization mass spectrometry (2). Both approaches use mass spectrometry, but the MasSpec Pen has one major difference: unlike the iKnife, which burns the target tissue and uses the smoke for analysis, it doesn't destroy tissue as it analyzes it.

The MasSpec Pen was conceived by Livia Schiavinato Eberlin, Assistant Professor, Department of Chemistry, University of Texas at Austin – but for this small, yet seemingly mighty technology, it is only the beginning.

“We are going to further validate the technology with larger sample sets and expand to other cancer types – then we'll start testing in surgeries with our colleagues in the Texas Medical Center to compare our results with current results from clinical practice,” says Eberlin. “Next, we should expand to larger clinical trials to properly evaluate if the technology can improve surgical treatment and patient care.” Eberlin and team hope to be able to trial the device during operations within the next 12 months.

Eberlin says it is very rewarding to work on a project with such high potential impact. “I am very passionate about the field, and specifically about developing mass spectrometry technology that can make a real difference in clinical practice,” she says. “We hope pathologists will be excited to have one more tool in their tool-set. If we are successful, we will hopefully be helping surgeons and pathologists by expediting the process of surgical margin evaluation during surgery, meaning less time in the frozen room for surgical pathologists. My amazing

research team and I have been working extremely hard on this project. It is amazing to see what they have accomplished so quickly!” *JC*

Reference

1. J Zhang et al., “Nondestructive tissue analysis for ex vivo and in vivo cancer diagnosis using a handheld mass spectrometry system”, *Sci Transl Med*, 9, eaan3968 (2017).
2. J Nicholson, RMA Heeren, “Pioneers of Precision”, *The Pathologist*, 6, 18–27 (2015). Available at: <http://bit.ly/1G6PTjQ>.

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In My View

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

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

Contact the editor at edit@thepathologist.com

The Transformed Pathologist

Patients benefit when all physicians, including pathologists, improve their clinical knowledge and communication skills



By Byron Barksdale, Pathologist, North Platte, USA

“Control your destiny or others will.”
– Jack Welch

The “transformation” of pathology has increasingly become a buzzword in the field’s literature over the last five years. Transformation suggestions run the gamut from pathologists’ embracing precision medicine to their participation in diagnostic management teams (see “Curing Our Diagnostic Disorder,” 18). All of these suggestions have merit in the quest to further emphasize the value of being a pathologist – both in the view of others (such as our colleagues, medical students, administrators, regulators, and payers) and for ourselves.

Yo Yo Ma, when he was seven years old, performed before the great cellist Pablo Casals. Casals was impressed with

the young prodigy, but nevertheless told him: “You should also play baseball.” In other words, stretch your interests and limits, regardless of your age. Casals also told Ma that he was a human being first, a musician second, and a cellist third – specifically in that order. In my opinion, a transformed pathologist should be a human being first, a physician second, and a pathologist third – again, specifically in that order.

Why? My view of pathologists as physicians first involves face-to-face interaction with patients regarding their medical care. Historically, many famous physicians worldwide were pathologists first, then further trained to be surgeons, internists and pediatricians. Clinicians through the ages have gone back into training, completing pathology residencies to augment their understanding of the concepts of disease (1) – knowledge that is useful both in the research laboratory and at the patient’s bedside.

“A transformed pathologist should be a human being first, a physician second, and a pathologist third.”

Healthcare professionals talk about the absolute necessity for clinical-pathological-radiological correlation

to increase the likelihood of correctly diagnosing the “problems” affecting patients, especially in regard to skin disorders, bone tumors and chest nodules. How better to be of value than to be very clinically oriented – if not clinically trained – in these subspecialties of medicine?

Instead of merely “talking the talk,” I have borrowed two concepts from other healthcare professional groups to actually “walk the walk.” First, I have set up a melanoma clinic in the underserved region of western Nebraska, where skin cancers (including melanoma) are often diagnosed at later stages. And second, I have set up an interventional

pathologist practice where I personally perform bone marrow aspirations, fine needle aspirations, shave and punch biopsies, and more. In that practice, I personally perform the procedures (bone marrow aspirations and biopsies, skin biopsies, soft tissue fine needle biopsies, and so on), then immediately examine the material to either provide a quick diagnosis or repeat the biopsy immediately if the sample is inadequate.

Are you, like me, a pathologist who enjoys interacting with patients? Do you, like me, believe that wholesome patient interactions primarily improve patient care and outcomes, and secondarily improve your status as a

valued member of the healthcare team? If so, then I encourage you to transform yourself into a clinician-pathologist. Remember, the word “art” occurs four times in the Hippocratic Oath. Expand your practice of the “art of medicine.” Yes, transforming into a clinician-pathologist will feel awkward for a few weeks – but once that passes, you will gain credibility and confidence, as well as the respect and admiration of others – including me.

Reference

1. JC Brunson, EA Gall, *Concepts of Disease: A Textbook of Human Pathology*. The Macmillan Company: 1971.

Stepping Stones to Retirement

There is more than one way to conclude a long and rewarding career



By Charles van Heyningen, International Advisor and Fellow, Royal College of Pathologists, United Kingdom

In my early sixties, I developed a serious illness and had to take several months off from work. When I was able to return, my colleagues encouraged me to work part-time, with flexible hours, before resuming full-time employment.

I took their advice, and it soon became apparent that I could actually retire from full-time work and continue on a fixed-term, part-time basis. Not only was this financially attractive (ensuring an optimum long-term pension), but it was also in keeping with my wish to step down towards retirement, rather than opt for a sudden cessation of full-time work.

When I made my wishes known, the medical director at my hospital was very supportive and made arrangements for the necessary change of contract; we agreed that I would sign a two-year, part-time contract. One of my consultant scientist colleagues made a similar arrangement at a similar time – and, in practice, the outcome was equivalent to us sharing a single full-time job.

One result of my part-time appointment was that I was no longer head of department or clinical director, meaning that the remaining work was shared by other staff members. As a result, when my colleague and I reached the ends of our contracts and chose to fully retire from National Health

Service (NHS) employment, our posts were not replaced in the newly formed network between Aintree and the Royal Liverpool Hospital pathology services, now called Liverpool Clinical Laboratories. Instead, our duties were divided between other staff members in the department.

“Retirement is often no longer a single event, but a gradual process over years or even decades.”

After retiring from NHS employment, I have not only continued volunteering for activities and organizations that interest me, but

even taken on new part-time volunteering challenges. These includes work for the Royal College of Pathologists, the Association for Clinical Biochemistry and Laboratory Medicine, the mental health charity Mind, Rare Disease UK, and the local hospital public and patient involvement panel. I can participate in these organizations on a flexible, part-time basis – and I have the freedom to choose only what interests me the most. And that keeps me motivated, so I can continue to be mentally active and engaged to prevent the onset of dementia.

Lately, I have learned that I am unwittingly following a new trend towards “pre-tirement,” a term that arises from the fact that retirement is often no longer a single event, but a gradual process over years or even decades. “Pre-tirees” in their fifth, sixth and even seventh decades of life ease themselves gradually into retirement by reducing working hours in favor of other interests, such as volunteering, childcare, studying or exercise. A change of career and traveling more frequently are hallmarks of those in pre-tirement, although many also continue to work (whether paid or unpaid) well beyond the state retirement age. Retirement in the United Kingdom has become a process, not an event.

“Making longer lives financially viable requires a fundamental rethink of life trajectories.”

When asked about retirement, John Dean, director for quality improvement at the Royal College of Physicians, said (1), “I think that the concept is outmoded. If we’re lucky enough to spend each part of our lives doing a mix of what we enjoy, what rewards us, and what we’re best placed to do, then we should.” A recent leading article in *The Economist* magazine states that, as life becomes longer, the word retirement – which literally means “withdrawal to a place of seclusion” – has become misleading (2). At 65 you are not clapped out, but pre-tired. In a further special report, the author notes

that making longer lives financially more viable requires a fundamental rethink of life trajectories (3).

I believe that those approaching the traditional retirement age might benefit from increased flexibility in working arrangements. Reduced hours, flexible part-time work and reduced on-call commitments might all contribute to wellbeing. After 40 years of doing out-of-hours, from a one-in-two rota as a junior doctor to one in 10 nights in my later career as a pathologist, coming off the on-call rota was a great relief even though it was not that demanding in the later stages. It’s my opinion that similar arrangements could help many pathologists live longer, happier working lives – and perhaps even help alleviate the “retirement cliff” that threatens pathology as a whole.

References

1. *John Dean: Committed to quality improvement*, *BMJ*, 357, j3049 (2017). PMID: 28659314.
2. *The Economist*, “Retirement is out, new portfolio careers are in” (2017). Available at: <http://econ.st/2u6Zac7>. Accessed August 24, 2017.
3. *The Economist*, “Getting to grips with longevity” (2017). Available at: <http://econ.st/2sYHm2W>. Accessed August 25, 2017.

Good on Paper

As we develop new point-of-care diagnostics for resource-limited settings, the humble sheet of paper has a lot to offer...

By Andres Martinez, Associate Professor of Chemistry, California Polytechnic State University, San Luis Obispo, USA.



Approximately 70 percent of all clinical decisions and therapeutic treatments are based on the results of a diagnostic assay, but they account for only 2.3 percent of the total medical costs of treating a patient in the United States (1). Diagnostic assays play an even more critical role in remote, resource-limited settings where doctors or other trained medical personnel are not available (2). In these settings, a reliable diagnostic could mean the difference between

life and death; millions of people in developing countries die every year from preventable or treatable diseases, at least in part because appropriate assays are not available (3). In resource-limited environments, most existing technologies are either too expensive or not compatible with the extreme conditions encountered (4). Low-cost, point-of-care tests (POCTs) have the potential to overcome both of these challenges if developed appropriately – and some, such as the rapid test for malaria, have already had an impact, leading to a significant reduction in the burden of disease around the globe (3). With appropriate design, next generation POCTs could lead to further improvements in global health.

A POCT is the combination of assay chemistry and a platform (i.e., a device) to support that chemistry. To be useful in resource-limited environments, the device must be cheap, small and portable; the reagents must be stable at room temperature; the results of the assay chemistry need to be accurate and easy to interpret; the assay should have

“The potential benefits of new diagnostic technologies easily justify the investment in time and resources required to develop them.”

minimal power requirements (ideally, the assay should not require electrical power, but battery-powered assays are an option); and the assay should be relatively simple to perform – ideally, the user must only apply the sample to the device and then read the results. The WHO released the “ASSURED” criteria to describe the perfect assay: affordable, sensitive, specific, user-friendly, rapid, equipment-free and deliverable to end-users. Paper-based platforms were developed specifically to meet the demands of resource-limited settings.

Paper has many inherent characteristics that make it well-suited as a platform for POCTs – it is cheap and widely available, it wicks fluids by capillary action, it has a large surface-to-volume ratio, and it provides a white background that makes color changes easy to see. The first examples of paper-based devices were simple dipstick assays (like litmus paper) that monitored the concentrations of certain analytes using color changes. Then came lateral-flow immunoassays, such as the rapid diagnostic test for malaria and the home pregnancy test, which vastly expanded the range of analytes that could be detected on paper by relying on antibodies for detection. A global community of researchers is now working on the next generation of paper-based devices known as microfluidic paper-based analytical devices, or microPADs.

MicroPADs are devices made from paper or other porous membranes, patterned with hydrophobic inks to create hydrophilic channels. Like conventional microfluidic devices made from glass or plastic, microPADs comprise a network of channels that can be used to process small volumes of sample and perform multiplexed assays. Unlike conventional microfluidic devices, microPADs wick fluids by

“A reliable diagnostic could mean the difference between life and death.”

capillary action, so they don’t rely on pumps or other supporting equipment. The combination of microPADs with new assay chemistries is leading to more sensitive and quantitative assays that should expand the applications and utility of paper-based tests (4).

Though POCTs for use in resource-limited settings must be cheap, rapid and simple, the process of developing these devices is challenging, expensive and time-consuming. However, the potential benefits of new diagnostic technologies easily justify the investment in time and resources required to develop them. And who knows – the device originally developed to use in rural villages could one day end up serving the populations of major cities too.

References

1. UP Robr et al., “The value of in vitro diagnostic testing in medical practice: a status report”, *PLoS One*, 11, e0149856 (2016). PMID: 26942417.
2. D Mabey et al., “Diagnostics for the developing world”, *Nat Rev Microbiol*, 2, 231–240 (2004). PMID: 15083158.
3. AN Abou Tayoun et al., “Democratizing molecular diagnostics for the developing world”, *Am J Clin Pathol*, 141, 17–24 (2014). PMID: 24343733.
4. AK Yetisen et al., “Paper-based microfluidic point-of-care diagnostic devices”, *Lab Chip*, 13, 2210–2251 (2013). PMID: 23652632.

CURING OUR DIAGNOSTIC DISORDER

The disease has a variety of symptoms: medical errors, poor utilization management, professional misunderstandings. Could the diagnostic management team prove to be a panacea?

By Michael Laposata



We are all aware of the key issues that pathology faces in patient care – diagnostic errors, failures to communicate, poor test utilization, and even miscommunications and misunderstandings between the bench and the bedside. And, of course, we are also all in agreement that these issues need to be fixed. Unfortunately, that’s where the consensus ends. How do we address these overarching problems? How can we improve communication, education and patient management across disciplines and specialties?

We already have a tool that allows us to discuss cases with clinicians, review treatment decisions, and reconcile them with existing test results and patient outcomes – the case conference. But those meetings take place long after the relevant decisions have been made. Why? Perhaps it was necessary in the past, when specialists had to travel to consult with one another, or wait for days while test results were mailed from one site to the next. But nowadays, we have the technology to assemble a team of experts from various specialties, either in person or remotely, and discuss a patient’s treatment not after, but as a part of, the decision-making process. I call this the “diagnostic management team,” or DMT.

Three key features make the DMT unique:

- It takes place in real time.
- All of the information is written into the patient’s medical record.
- It results in clinically valuable information.

What exactly is “clinically valuable information?” To provide an example, let’s say I spot a band of abnormal hemoglobin on a patient’s capillary electrophoresis. To get paid, the only notation I need to make is, “abnormal band seen.” But that’s not informative; it won’t help with the patient’s care. Instead, I should say, “There was an abnormal band of hemoglobin; it was in this region of the gel; it was later identified as hemoglobin Köln; and the patient is (or is not) likely to require transfusions.” The DMT gives us the opportunity to provide value-added data – and because we’re doing it in real time, the clinicians get that information in time for it to be reflected in their treatment decisions. All too often, the pathologist has information that could be useful, but because he or she is never asked, the doctors never hear it. That’s what I want to change.

“DO IT MY WAY!”

There has been one barrier after another to implementing the DMT in hospitals – and most of those barriers can be explained by the incentive that all doctors have at this particular time and times in the past: money.

My startling first experience with colleagues who didn’t know how to evaluate partial thromboplastin time (PTT) – a blood clotting test – was in 1984. I was a resident in clinical pathology, and I received a call over my pager from an internal medicine resident who was particularly smart, and I admired him for seeming to know everything. He asked me a simple lab test selection question: what subsequent tests should he order for a prolonged PTT? I would have assumed he knew the answer – but when I discovered that he didn’t, I realized that I had a body of knowledge about making a diagnosis that he and most residents in other specialties did not have. I asked him what he had done to evaluate prolonged PTT prior to our conversation, and he said, “I did what every other doctor did – I guessed which test to pick and then guessed what the results meant.” His response reminded me that there was very little teaching about test selection or result interpretation in medical school, even though doctors do it every day.

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I went straight to my professor, who dealt with coagulation, and said, “We have to develop an interpretive service similar to the one offered by radiology.” They don’t just hand back a film and say, “You figure it out; call me if you have any questions.” They automatically interpret their results, so I recommended that we do the same in pathology. His answer to me was, “I have to become an associate professor or I’ll lose my job. And you don’t become an associate professor by taking care of patients – you do it by publishing papers!” As a trainee, it was



a shocking revelation to hear my mentor admit that patient care was not the primary responsibility of a hospital physician. But at that stage of my career, what could I do?

Well, I got my first job: director of the coagulation laboratory at the University of Pennsylvania. Now that I was on the faculty at a major medical institution, I designed and implemented a new diagnostic test result form: a page to be inserted into a patient's chart that had not only blanks for the lab test results, but also a box at the bottom in which to write a patient-specific narrative. It was incredibly well received – so much so, in fact, that the hematology fellows were no longer receiving as many consults.

Unfortunately, the response to the new service also prompted the Chief of Hematology to come and ask me to stop providing interpretations. Of course, I asked why; after all, the information had obvious benefits, especially for clinicians.

His answer was, “My hematology fellows aren't seeing as many patients anymore, so my revenue is down.” Naïvely, I asked if that wasn't less important than an immediate diagnosis – I didn't want to delay treatment. Nevertheless, he said, “Do it my way!” That was the end of it. He was a full professor and I was only an assistant professor, so I knew I couldn't win.

“I DON'T NEED THIS!”

The only solution I could devise was to keep moving up the ladder. Eventually, I joined Massachusetts General Hospital as director of clinical laboratories and associate professor at Harvard Medical School. Another step upward; another attempt to implement diagnostic interpretation. I initiated an interpretation program for complex coagulation cases; it was an even bigger success this time around, because the field was becoming rapidly more challenging with the introduction of



new anticoagulants and other coagulation-related therapies. Not everyone cottoned on right away, though. There was one hematologist in particular (subsequently my best professional friend, I have to add!) who came in with an interpretation I had created and said, “I don’t need this!” I said, “Yes, I know, but most of the doctors in this hospital do need it,” and he crumpled the paper up, threw it at me, and left my office. Yet again, I could have backed down – but I didn’t. It was becoming obvious that the few hours of education medical students receive in lab test interpretation was never going to be enough. Somebody was going to get hurt.

So we persisted with the interpretive service, and eventually created a program that became a source of national and international attention because of its clinical value in establishing a rapid, accurate diagnosis. In fact, the interpretations in the chart – attributed to us as pathologists – actually led to patient referrals to our pathology service from other doctors in the area, and we developed a widely respected clinical practice for patients with bleeding and clotting disorders.

The patients themselves were very confused to be referred to a pathologist, though, with some even asking if they had been referred in preparation for an autopsy! I assumed they were joking, but I’m afraid that just highlights the need for us to educate our patients and the public about what exactly it is that we do. Every pathologist should be enthusiastic about spreading the word – and we should all embody the three ‘As’: affable, accurate and available.

A TECHNOLOGICAL LEG UP

In 1996, I gave a talk to my colleagues about the DMT and what I hoped to accomplish. I happened to mention that I used a Dictaphone to record my cases; then I sent them out to be typed, and when they returned, I edited them. A time-consuming process, especially with 20 or so cases per day! But that day, for some reason, there was a software developer in the audience. He took me aside after the talk and said, “There’s no need for all those steps. I can make this much easier for you.”

We ended up working together to develop software that provided a customized bank of pre-written comments. That way, I could just select the comments I needed for any individual case, and then add any unique information afterward. We still had to individualize it for each patient, but the software gave us a head start. In fact, it made us fast enough to sign out 30 or even 40 cases in a single session, enabling many more interpretations of patient records.

Our ultimate goal is now to complete what we call a “what’s in the box?” project. We’d like even the smallest community hospital to be able to contact us and say, “We’re interested in

THE DIAGNOSTIC AND MANAGEMENT AUTOPSY

What is the diagnostic and management autopsy (DMA)?

The “diagnostic and management autopsy” involves an expert review of the diagnostic decisions made before death. The review is conducted by specialists in the patient’s conditions – possibly pathologists, but also physicians from other departments (1) – and can often provide additional information on the cause of death and any potential diagnostic errors that were made prior to death. It is especially useful in situations where a complete diagnostic autopsy is not possible. It’s important to note, however, that the DMA is not a replacement for the traditional autopsy; rather, it can be considered another option to gain critical information to improve clinical performance.

For example, a DMA of a patient death from a coronary stent thrombosis would involve a review of medical decisions in the days leading up to that death by a group of experts in coagulation and vascular disorders. Those experts will be more familiar with the tests, treatments, and decision-making related to the patient’s cause of death than a single pathologist who is unlikely to have expert knowledge about blood clotting.

How did the DMA come into existence?

The idea grew organically out of a particular case. The patient in question had a coronary stent thrombosis, but was told he could wait a few months before having coronary bypass surgery. The next day, he died. Obviously, our

first question – and the family’s – was, “Who said you could wait three months, and why?” But that’s not a question you answer by cutting open a body in a case of obvious stent thrombosis. That’s a question you answer by reviewing the records.

Eventually, the hospital began to send us cases to review. The clinical leaders said, “If you can review these cases and make recommendations, we can begin to improve.” And as a result, the safety ratings at the University of Texas in Galveston have dramatically increased! I think that when recommendations come from a team of experts, it’s easier to push through the necessary changes. Often, they’re just simple points of education – things that have changed since the clinicians were in medical school. So there’s a lot of improvement to be had simply by implementing these DMAs.

Why do we need the DMA?

The number of complete diagnostic autopsies performed has declined dramatically over the last few decades (2). Why? Families may object to traditional autopsies because of cultural, religious, or even aesthetic preferences – it’s an invasive procedure that many prefer not to permit for their deceased relatives. Not every hospital has the time and resources to conduct autopsies – some don’t even have autopsy suites anymore. Additionally, we’re now able to glean more information than ever without the need for a full autopsy: laboratory tests are more sensitive, imaging has improved, and genetic and genomic studies have exploded.

When discussing uncommon diseases, community hospitals often tell us, “We

don’t have patients with that disease here.” But these patients are scattered all over the world – so it’s reasonably likely that they do, in fact, have patients with the disease; they’re just not being diagnosed. And without a DMA, you might never know that.

The DMA allows us to offer a different kind of autopsy to those for whom the traditional autopsy is inaccessible or unpalatable: an expert review, focused on the patient’s medical records, that can reveal more information about the cause of death and flag up any possible errors without the need to “disturb” the body further. It can be performed at any time after death, as long as the patient’s medical record is still available. Thus, it is possible for us to perform DMAs even on cases that are decades old – without the need to exhume a body. This both pleases family members seeking answers and simultaneously allows practitioners to perform quality control checks and improve the standard of care for future patients.

References

1. *M Laposata, “A new kind of autopsy for 21st century medicine”, Arch Pathol Lab Med, 141, 887–888 (2017). PMID: 28661212.*
2. *“Death of the Autopsy?”, The Pathologist, 33, 18–27 (2017). Available at: <http://bit.ly/2escu4Q>*

setting up or connecting to a DMT.” And then we’d send them a box. What’s in the box? For one thing, the software I’ve just described – something to allow them to enter comments, connect with other experts, address billing and payments, and anything else they need. If we could assemble a DMT starter kit like that, then anyone could set up a team. That’s our goal – and I think it’s well within reach.

“HEALTH ECONOMISTS HAVE REFERRED TO DMTs AS ‘THE MISSING LINK.’”

FROM CONCEPT TO REALITY

I joined the faculty at Vanderbilt University as pathologist-in-chief in charge of both anatomic and clinical pathology. The role came with a wide range of opportunities, but most importantly, the opportunity to truly begin building a diagnostic management solution. That’s when we came up with the name – “diagnostic management team” – and it’s when we began implementing them in microbiology, hematopathology, coagulation, and transfusion medicine. Each of these areas claimed a triumph in improved patient care and decreased cost. It became abundantly clear that, with thousands of increasingly complex laboratory tests available, diagnostic expert consultations were necessary to help our bright and well-intentioned physician colleagues.

About five years ago, there was an unidentified epidemic in the United States. We had a patient fall victim to it in Nashville; she presented with symptoms of meningitis and was transferred to Vanderbilt. The infectious disease doctor referred it to the microbiology DMT because she had no idea what the causative agent might be. It took the DMT about a week, but they figured it out – *Aspergillus fumigatus*, a common disease-causing fungus in immune-deficient patients. But our patient wasn’t immune-deficient. We eventually discovered that she had been caring for her invalid husband, injured her back, and had an injection of prednisone – and it turned out that the injection was to blame. There were birds flying around in the facility that manufactured the prefilled prednisone syringes,

and the syringes had become contaminated with *Aspergillus*. Thanks to the DMT’s identification of the problem, the company stopped production of the syringes and the epidemic ended (2).

THE ECONOMIC ANGLE

After we started the DMT program at Vanderbilt, they brought in a business expert who knew nothing about medicine to determine whether or not it provided an economic advantage. Specifically, they wanted to know whether the DMT process reduced length of stay – because it costs about US\$2,000 a day to keep a patient in the hospital. So if an extra \$20 lab test can discharge a patient even one day earlier, the overall cost is massively decreased.

It’s amazing how many people say, “I think I’ll just see the results of the first lab test, make a decision, and then order the second test if necessary.” By doing that, they’ve just added another day to the patient’s stay – and another \$2,000 to the bill! So why not have a set of relevant tests and order them all at once? Not every doctor feels confident enough in his or her laboratory knowledge to do that – and that’s why you have an expert team to help!

So the hospital asked the business expert to check every one of the codes for a diagnosis-related group and see if the length of stay changed for any of them between August and December of 2011, immediately after we started the coagulation DMT. He said, “There’s a significant reduction in the length of stay for two things – but because I’m not a medical expert, I don’t know if either one is related to coagulation.” I sat there thinking, there are thousands of codes – please say something coagulation-related. And it turned out that the two things were pulmonary embolism and intracranial hemorrhage – our bread and butter!

We then realized just how much impact the DMT was having, not just on patient outcomes, but on the hospital’s bottom line as well. But unfortunately, the gains weren’t coming directly from the laboratory budget, and hospital managers think of budget success or failure by department. They’ll look at the laboratory budget and say, “What? Ten percent more tests?!” and ask us to reduce that number. It doesn’t always matter that those relatively inexpensive tests save thousands of dollars, if the managers don’t make the connection. You have to look at the budgets globally to see the difference, but too many managers don’t understand that a little extra in one budget can result in saving a fortune on another. Clearly, resources like clinically effective DMTs can play a significant role.

PILOTING PROGRESS

I’m currently Chairman of the Department of Pathology at the University of Texas Medical Branch (UTMB). That was

TONSILLECTOMY TRANSFUSIONS

A friend of mine was an ear, nose and throat surgeon at the Massachusetts Eye and Ear Infirmary while I worked at Mass General. He performed a lot of tonsillectomies on eight- to ten-year-old boys and would often request coagulation tests to ensure that they would not have bleeding issues after the procedure. He said that he often found a prolonged PTT.

When he received an abnormal PTT result, he had two choices: i) call a hematology consult, which would usually take two days, or ii) transfuse two units of plasma. Most of the time, he opted to transfuse so that he could complete the procedure and discharge the child. Unfortunately, he was doing this between 1981 and 1984 – a time when one in every 20 bags of fresh frozen plasma was infected with either HIV or hepatitis C.

We didn't know that at the time, of course – but these children were put at risk because their surgeon didn't know what test to order.

My friend admitted to me that he was overjoyed when, in 1995, we began providing interpretations along with our test results. But then he considered how many people he had unnecessarily transfused. His “error” didn't come to light when his patients were eight years old, but many years later – when these children had become young adults and needed liver transplants or received diagnoses that would change and abbreviate their lives.

And yet, nobody (until now) has pointed out the root cause of this problem – the fact that somebody didn't know what laboratory test to pick because of an inability to interpret a prolonged PTT. In short, a major diagnostic error led to patient deaths.

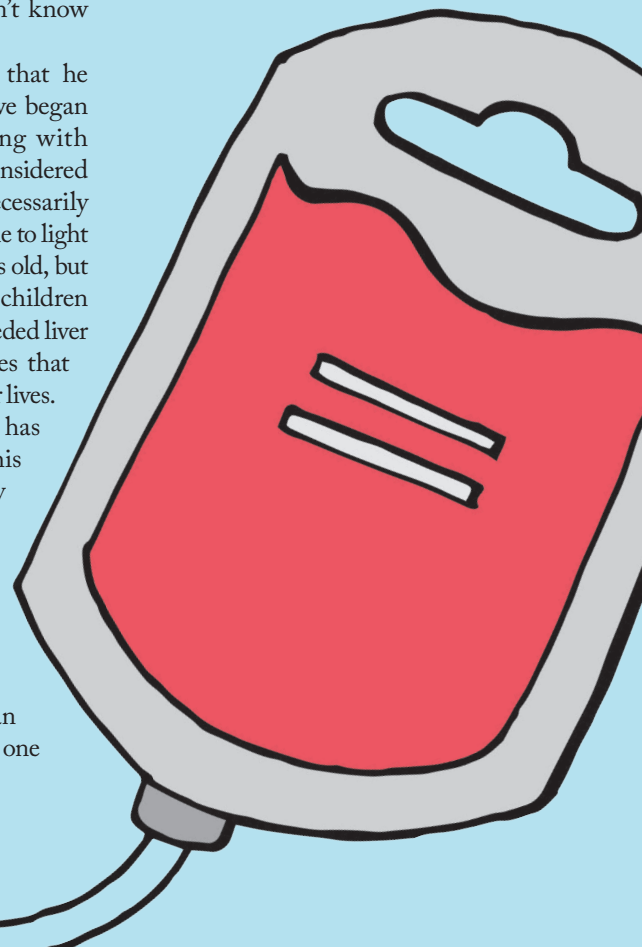
I wish I could say that this was the only example of such an error but, unfortunately, it's just one of many.

a calculated move – Texas was once its own country and still believes in itself as the strongest state in the union. It has a strong sense of “can-do”, which is exactly what we need to fully realize the potential of the DMT. We also have a powerful medical system – eight campuses, for which we can share diagnostic experts to ensure that each campus has access to every possible area of expertise while working remotely. We have four DMTs in place right now, but if we can get all of the campuses linked via telemedicine, we'll have dozens!

We're piloting the telemedicine approach at the moment. We have a designated DMT room with screens and cameras so that we can see our long-distance collaborators and they can

see us. If we gather all of the experts from all of the medical schools involved, we can cover almost the entirety of diagnostic pathology in a single team. We'll have experts in virtually everything! How do we help a patient in a town without a university hospital? We may offer a subscription service or a “pay for what you use” model as we move forward – so if a clinician is uncertain of the correct diagnosis, or in some cases is unsure how to treat the patient, they can dial a number and reach the DMT.

We're lucky that we have people here in Texas who are willing to put enough money behind the project to get us through testing and put the full system into operation. It

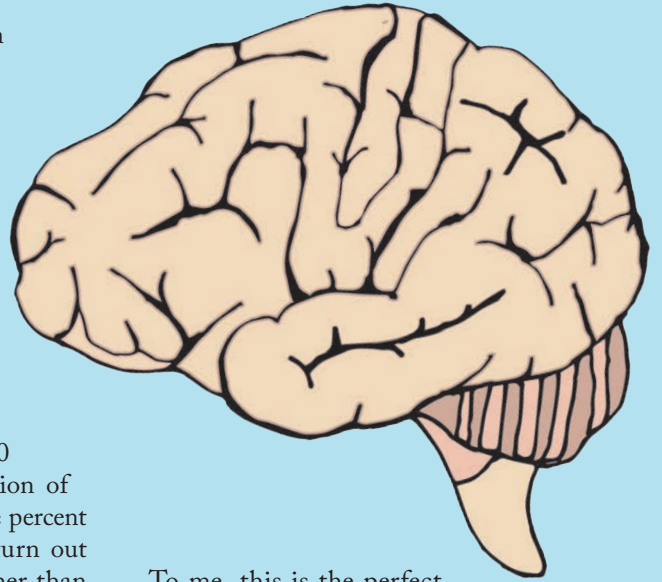


A DANGEROUS DIFFERENTIAL

At a diagnostic management team meeting in the late 1990s, I was presented with the case of an infant who developed a subdural hematoma. Her father was accused of shaking her to produce the hematoma; despite his defense that a minor fall had caused the observed bleeding, he was convicted of child abuse and imprisoned. Later, the same patient came to my institution – this time with meningitis. Our expert DMT clearly showed that she suffered from a common bleeding disorder known as von Willebrand disease, a diagnosis that had been missed during the previous evaluation because of a flawed interpretation of the lab test results. The fall the father had described in his defense could indeed have produced the subdural hematoma in a child with an underlying bleeding disorder. After two years in prison because of a diagnostic error, he was finally released.

A subsequent case arose when an attorney read about the first story and contacted me about his client. Again, a child had suffered a subdural hematoma – and, as in the previous case, our DMT found that he and both of his siblings had severe, previously undiagnosed von Willebrand disease.

Since that time, I have been involved in more than 30 cases associated with a question of child abuse. Approximately five percent of cases of bruised children turn out to be child abuse mimics, rather than true child abuse. Such patients require a thorough coagulation evaluation to determine whether a bleeding disorder is present. I am pleased to say that, in all but two cases in which I have explained a bleeding disorder to a judge or jury in support of falsely accused caregivers, the child has been returned to a loving home.



To me, this is the perfect illustration of the need for DMTs – a team of diagnostic professionals can look at something like suspected child abuse, find evidence of a bleeding disorder that might otherwise have been missed, and realize, “Holy cow! This was not child abuse at all. It was an underlying disease.”

doesn't cost a lot, at least on a healthcare scale (maybe a few hundred thousand). Health economists have referred to DMTs as “the missing link.” Texas is a great proving ground; with a population of nearly 30 million, you can imagine how many hospitals and primary care clinics need diagnostic support on a regular basis. The endgame is to provide accessible services to all of those institutions to obtain better patient outcomes. We should never allow our patients to die because there is no expert in their immediate environment.

Once we have developed DMTs for dozens of clinical areas and can bring diagnostic experts electronically to the bedsides of patients all over the world, we will have achieved a goal that started with a simple query from one resident to another in 1984.

BUILDING ROME

I've been invited to speak at more than 50 different medical schools and over 20 different major societies about the DMT.

Recently, the Institute of Medicine convened a panel of 21 experts to put together a report on improving diagnosis in healthcare (1); it's a summary of all of the literature on diagnostic error, and it speaks loudly that there is a major safety problem in healthcare that must be addressed. So, with everybody saying that the DMT is a great idea and highlighting how badly our patients need it, why has nothing changed?

The biggest reason, in my opinion, is the lack of incentives for pathologists in the United States. Right now, we are paid handsomely for anatomic pathology work – recent statistics from the College of American Pathologists state that the average pathologist works about 48 hours a week and makes US\$250–400,000. If you're interrupted to answer diagnostic questions that don't involve a microscopic diagnosis, you lose money, because those events are only worth about \$25 each. If you go to the emergency room and stop a patient from losing

a unit of blood an hour through a chest tube, it's worth \$25. So obviously, pathologists here are incentivized to focus on anatomic pathology.

I recently visited a prestigious university to give Grand Rounds. They had a Department of Laboratory Medicine with experts from many specialties. I asked, "Why aren't you taking an interpretive approach to report development?" and they said, "We don't have the right IT infrastructure to do it." I was astounded! But here's something that surprises me even more: to this day, nothing has changed. The department is just throwing the test results over the wall like they've been doing for the last century, even though they have all the necessary people power to get it done properly!

Despite obstacles like these, I haven't lost any of my enthusiasm. It may take a while for the idea of the DMT to become commonplace, and even longer for it to be widely implemented – but after all, Rome wasn't built in a day. I'm going to keep working on this until I can't work anymore.

The external environment in the United States is changing. The pay-per-click model is going away, and different methods of payment for healthcare delivery are taking its place – and that's good news for the DMT, and good news for patients. Why? If anatomic pathology alone isn't as lucrative as it was before, and you as the diagnostic pathologist are responsible for getting involved in microbiology, transfusion, endocrinology, coagulation, and other areas, then you'll have to adapt quickly. If you can't, you will be ill-prepared for this new environment. I'm looking forward to that day, because I truly believe – and the Institute of Medicine agrees – that DMTs can solve many of our existing issues with diagnostic error and improve outcomes for all of our patients.

WILL PATHOLOGISTS GO FOR IT?

Not the old school, no.

And I'll admit that it's not an easy change for a pathologist to make. Instantly, you're being put into the firing line. You are now accountable for a much greater medical challenge – integrating large amounts of diagnostic data. Not only that, but it's a big change to your day-to-day routine as well. For example, I have to take phone calls to discuss my recommendations and interpretations. I have to attend team meetings. It all adds hours to my day. My medical liability has changed now that I'm in the middle of this team sport called "making a diagnosis." It's far easier to sit on the sideline and do what you've done for years.

I think new trainees are the key to real change. The residents at my hospital have never worked in the "old" way. They have responsibility for providing a diagnosis – and not only that; a recommendation as well. One told me, "During my training,

"WE SHOULD NEVER ALLOW OUR PATIENTS TO DIE BECAUSE THERE IS NO EXPERT IN THEIR IMMEDIATE ENVIRONMENT."

I've seen and been involved in hundreds of cases. I've learned how to do my job and how to help patients. If you had just lectured at me for 14 hours over the month of my coagulation rotation, how would I have learned anything?!"

You can't just put all of the responsibility for change onto the shoulders of the next generation, though. Yes, it has to fall on fertile soil, but somebody has to provide an example. The residents who come through our program realize that this is the only way to practice pathology – you must make real-time contributions and learn from real-life situations. Classroom lectures alone are not enough. And that's why our teaching programs are successful: one domino tips another. The residents go to the laboratory in the morning and ask the technologist, "What do you have for coagulation cases?" and the technologist gives them the day's cases. Then, they have the rest of the day – from about 8:00 AM to 4:00 PM – to call the doctors, find out more information, and stop tests that aren't needed. At the end of the day, they show up with an interpretive paragraph on each of those cases. It gives me great pride to know that they can walk out the door and have that kind of impact on all of their patients.

Michael Laposata is Chairman of the Department of Pathology at the University of Texas Medical Branch at Galveston, USA.

References

1. EP Balogh et al., "Improving diagnosis in healthcare", *Institute of Medicine* (2015). Available at: <http://bit.ly/1KxJPO4>. Accessed September 1, 2017.
2. AC Pettit et al., "The index case for the fungal meningitis outbreak in the United States", *N Engl J Med*, 367, 2119–2125 (2012). PMID: 23083311.



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30-35

Keeping Up With Precision Medicine
The oft-overlooked field of ocular cancer gets a next generation update to provide patients with better diagnosis and targeted treatment.

Keeping up with Precision Medicine

How a specialized next-generation sequencing panel is giving ocular cancer patients access to new targeted therapies

Ruth Steer interviews Rajesh C. Rao

Advances in common cancers – breast, lung, prostate, colorectal and more – are in the news every day. But while those fields are blazing new trails in cancer treatment, ocular oncology is falling behind. For the most part, the treatment of ocular and orbital (abbreviated as “ocular”) tumors have not yet benefited from many of the emerging and established technologies in oncology and other disciplines to personalize medicine – and there has been no exploitation of cancer-causing genetic and epigenetic changes for diagnostics and treatment. For instance, some types of breast cancers can be treated by epidermal

At a Glance

- *Although precision medicine for cancer is a rapidly rising field, its application to ocular cancers is often overlooked*
- *Epigenetic modifiers like histone methyltransferase EZH2 can be good biomarkers for tumor cells in the eye*
- *A special sequencing panel identifies actionable genetic alterations in ocular cancers*
- *By collaborating with oncologists, ophthalmologists and researchers, pathologists can help improve the diagnosis and treatment of these diseases*



growth factor receptor (EGFR) inhibitors, and patients with certain lung cancers can receive anaplastic lymphoma kinase (ALK) inhibitors. These therapies are based on knowing the gene mutations in oncogenes and tumor suppressors, or copy number alterations that drive the growth of the cancer. Epigenetics – modifications to DNA or histones that aberrantly switch tumor-promoting or cancer-preventing genes on or off, without changing the genetic sequence – is an emerging field that has deepened our understanding of how tumors form. No epigenetic-based therapies currently exist for ocular cancers because epigenetic regulation of those cancers remains poorly understood. We’re working to help change that. Here’s our story so far...

Expanding the horizon with epigenetics
When my colleagues in ophthalmology

and I first started paying attention to epigenetics in 2008, the focus was on histone methylation – the addition of methyl groups to histone tails – and how that affects gene expression. Though a “hot” area, no one had really examined it in the developing mammalian retina. So we decided to investigate, and published a paper showing how the histone and methyl marks change during retinal development in the mouse (1). We discovered some interesting trends: a lot of these histone marks were upregulated in the inner retina, and some of the enzymes involved were developmentally regulated. One of these, the histone methyl-transferase EZH2, was expressed only during the growth phase of the retina, and then switched off when the retina was formed. Interestingly EZH2 was emerging as a major target for cancer therapies because it appears to be

enriched in cells that grow quickly, such as fetal cells as well as cancer cells.

From studying the developing human retinae, we found that EZH2 was highly expressed in fetal retinae, but not postnatally (2). Because embryonic proteins can be expressed in cancer cells (3), we studied retinoblastoma samples, and found that EZH2 was highly expressed in the tumor cells from this childhood cancer. We also found it to be a good biomarker; immunohistochemistry on these tumor samples for EZH2 was almost a black and white indication of where tumor cells are... and where they are not. Histopathologic detection of EZH2 expression allowed identification of single tumor cells that were invading into the optic nerve or adjacent tissues. Because the decision to use systemic chemotherapy is linked to whether retinoblastoma cells have spread to the optic nerve – and beyond – staining these specific markers could help provide better indications of whether further treatment beyond surgery is actually warranted.

EZH2 was already under scrutiny by several companies, and small molecule inhibitors against it were in trials for other tumor types, such as lymphoma. We tested some of those inhibitors and found that they selectively killed the retinoblastoma cells, sparing the normal retinal cells. This was our entry point and, since then, we've published papers showing high levels of EZH2 in different tumors including vitreoretinal and orbital lymphomas, medulloepithelioma, and basal cell skin cancer, which can occur on the eyelid and the orbit, where it is difficult to treat (4–6). Right now, we are looking at some of the pathways downstream of EZH2, including DNA methylation.

A precise approach

An important part of our studies is to help patients with ocular cancers gain access to more targeted treatments. A close collaborator, Scott Tomlins, helped

Why “Sexy” Needs Substance

By Rajesh C. Rao

We all like to hear things in soundbites but, in my view, we should also explain what we mean when we use terms such as epigenetics, stem cells and precision medicine.

I've been in the stem cell field since 1999, and in epigenetics since 2008, and I think the term epigenetics is becoming like “stem cell” in that it means many different things to different people. Scientists and clinicians have been expressing their concerns about how the term epigenetics can get misused in the media (13) – and we need to be more cautious with it. Why? Epigenetics could essentially mean anything; some of the influences are outside genetics. My concern is that using epigenetics as a “grab bag” term is not helpful for science, patients or clinicians.

Whenever I talk about epigenetics, I quickly provide the context of how I intend to use the term, stating that I am using it to refer to chemical modifications that occur to DNA and histones, and how these changes link to gene expression. Doing so brings me to a relatively focused area, so I can talk about some of the mechanisms driving the changes.

Going back to the stem cell analogy, some clinics state they are using stem cells – but don't truly know if the “stem cells” they purport to use share defining characteristics of these cells such as self-renewal

and tissue-specific differentiation (14). And in some cases, these clinics are putting patients in danger; take, for instance, the widely reported case of three female patients in Florida who suffered blindness as a result of an untested “stem cell therapy” (15).

Precision medicine is another grab-bag term. But haven't we always been doing precision medicine? I am a retina specialist, and when I see a patient with macular degeneration or diabetic retinopathy, I routinely take into account their medical history such as whether they smoke and what medications they take, their A1C, and the findings from the retinal exam. One could (truthfully) say, “I'm practicing precision medicine!” – after all, the treatments are being tailored to the patient based on the unique characteristics of their disease. So again, rather than using “precision medicine” as a grab bag term, I try to contextualize my usage: “By precision medicine, I mean that the patient has particular germline or somatic genetic changes (mutations or copy number alterations) or epigenetic changes (over expression or under expression of specific genes) – and based on those genetic or epigenetic alterations, I can now link the patient's disease to a more tailored diagnosis, treatment, or experimental intervention being tested in a clinical trial.”

The bottom line? The moment we start using specialized terms, such as epigenetics, stem cells and precision medicine, we should also define them and include the context of how we are using them to describe our patients or their treatments.

develop the panel for the National Cancer Institute MATCH trial (see “The NCI-MATCH Trial”). Together, we’ve been using the same technology to study eye and orbit tumors. But because ocular cancers are quite rare – there are only about 5,000 cases per year in the United States (7) – acquiring tissue for study can be challenging. I use the analogy that studying cancer and human tissues is like studying freshwater; just like most freshwater is “locked up” in ice at the poles, most human tissues are embedded in wax and archived in hospitals and medical

centers. But this fixation process and the wax can make downstream research applications more difficult, especially when trying to study the epigenetics. It’s why we’ve had to take a unique approach.

Using a scalpel, we “shave” off sections of samples to collect DNA, which we then put on a next-generation sequencing (NGS) panel (similar to NCI-MATCH, see p25) to find mutations, gene alterations or copy number changes in those tumors. The panel is enriched for gene targets for which drugs have already been approved by the FDA (or in trial) for other cancer

indications. So far, we’ve discovered many actionable alterations in genes, including *MYD88*, *ARID1A*, *EZH2*, *PTEN*, *TP53*, *HRAS* and *NRAS* (2, 4–6, 8). We’ve also found that eye lymphomas have a certain “flavor” and abundance of mutations that are not present elsewhere; *MYD88* was commonly mutated in orbital marginal zone lymphomas, but uncommonly in marginal zone lymphomas elsewhere in the body (6). As there is already a drug in trial against the mutation we identified, we hope that our orbital lymphoma patients might be attractive candidates.

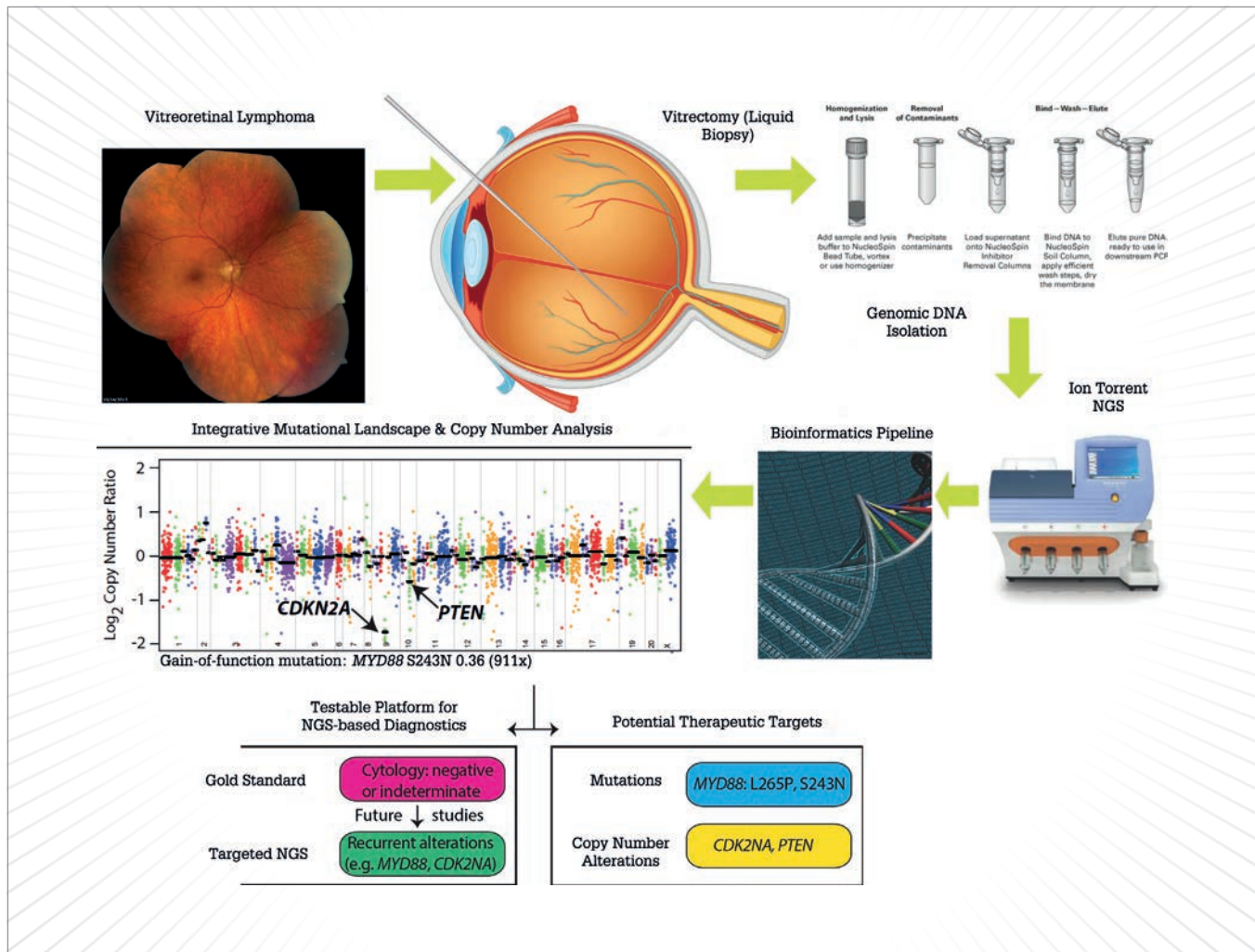
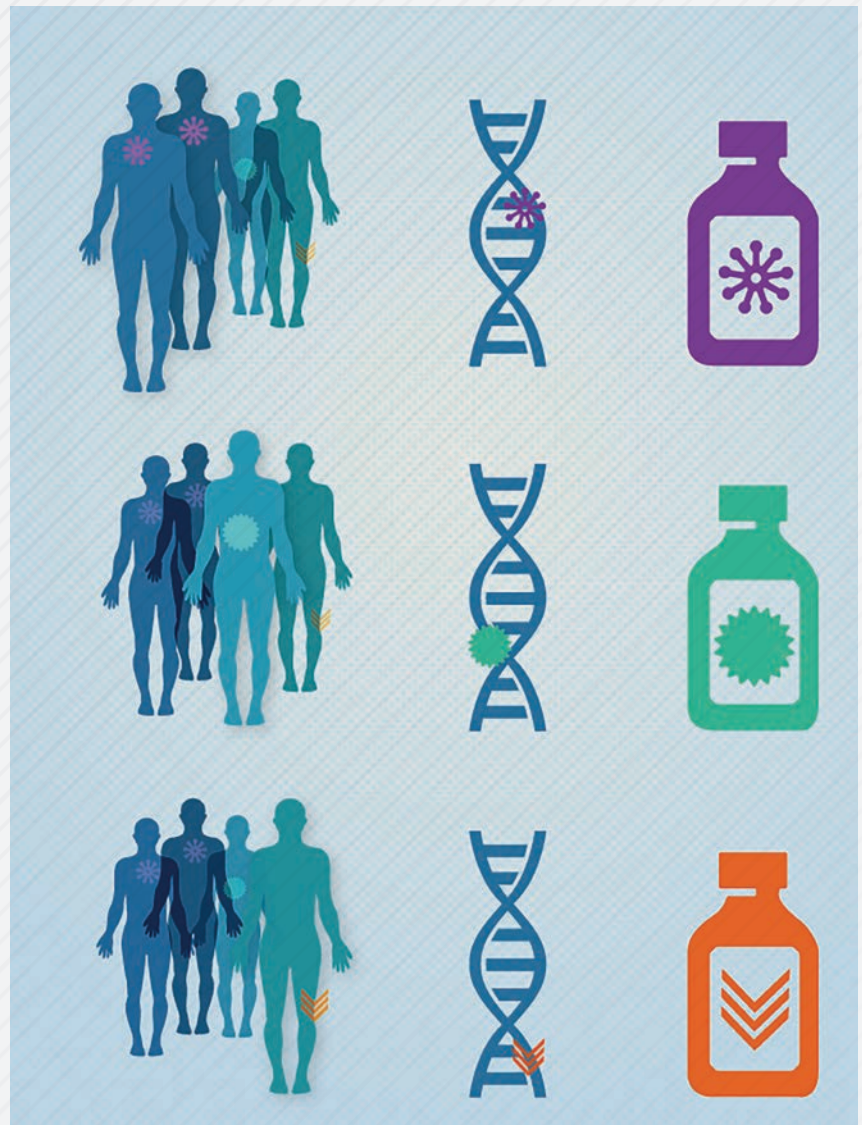


Figure 1. Workflow of determining driver and potentially actionable genomic alterations in vitreoretinal lymphoma. Adapted from (8).

The NCI-MATCH Trial

The NCI-MATCH Trial (NCT02465060) is an ongoing precision medicine cancer treatment trial (11). In this study, biopsies from patients are analyzed using an NGS-based panel to identify actionable genomic alterations for precision medicine-based treatment strategies. Patients with advanced solid tumors, lymphomas, or myeloma who have progressed on standard treatment for their cancer, or patients with a rare cancer for which there is no standard treatment, are eligible for MATCH. Currently, there are 19 treatment arms open to patients, including genetic changes in *EGFR*, *ALK* and *mTOR* (11). In the NCI-MATCH “basket trial,” patients can be enrolled in a trial no matter what kind of cancer they have, provided they have the same mutation that the trial drug is targeting. The trial utilizes the OncoPrint Comprehensive Panel (OCP) to detect genomic variants in patient samples (12). The OCP was developed from analysis of over 700,000 tumor samples, and combination of genomic alterations with available therapeutics and ongoing clinical trials.



Study locations around the world involved in the INSPPIRE pediatric pancreatitis project.

We’re basically looking for the “low-hanging fruit” – tumors that haven’t yet been sequenced. And with orbit and eye tumors being so much rarer compared with other cancers, we have had to dig deep into our archives or collaborate with other centers to find tumor samples for study; in some cases we are analyzing samples that are 30 years old! But science

and sequencing technologies have moved so fast that, for relatively little money, we can use small amounts (as little as 5 ng of tumor DNA) of these archived samples – including those that we thought were “locked up in ice” – and still retrieve usable information. Our initial goal is for patients with eye cancer to have the same options and treatments as patients who have other

cancers through basket trials (clinical trials that target cancers based only on whether they contain specific genetic alterations, rather than the part of the body they come from). We hope to exploit drugs in our armamentarium that may be more specific than chemotherapy because they target genetic alterations present in the tumor, but not in normal tissue. In the future,

“Ophthalmology can learn from other fields, like pathology, that are leading in precision medicine, and then apply it to ocular oncology.”

we want to help other ophthalmologists, ocular oncologists and pathologists who see patients diagnosed with eye cancer by using these precision medicine strategies to identify diagnostic or druggable targets in their patients’ ocular cancers – and thus which clinical trials a patient may be eligible for. And if the drug receives approval, we’ll have made an important link in bridging a drug from other types of cancer or diseases to the field of eye cancer, and helped our patients access more targeted therapies.

A call for collaboration

We’re also hoping to improve diagnosis. Vitreoretinal lymphoma is rare – there are only around 400 cases per year in the US (9). Because of its link to CNS (brain) lymphoma, it’s a deadly disease, with only a quarter of patients surviving more than five years after diagnosis (10). It represents a crucial unmet need, not only because there is no standardized treatment – but also because it is very difficult to diagnose. In small-volume vitreous samples taken from four patients with confirmed or suspected vitreoretinal lymphoma, we identified alterations in *MYD88*, *CDKN2A* and *PTEN*, showing

that it is feasible to perform targeted NGS on intraocular liquid biopsies (as small as 500 µl or 5 ng of DNA) and identify the presence of tumor-causing mutations or copy number alterations (8) (see Figure 1).

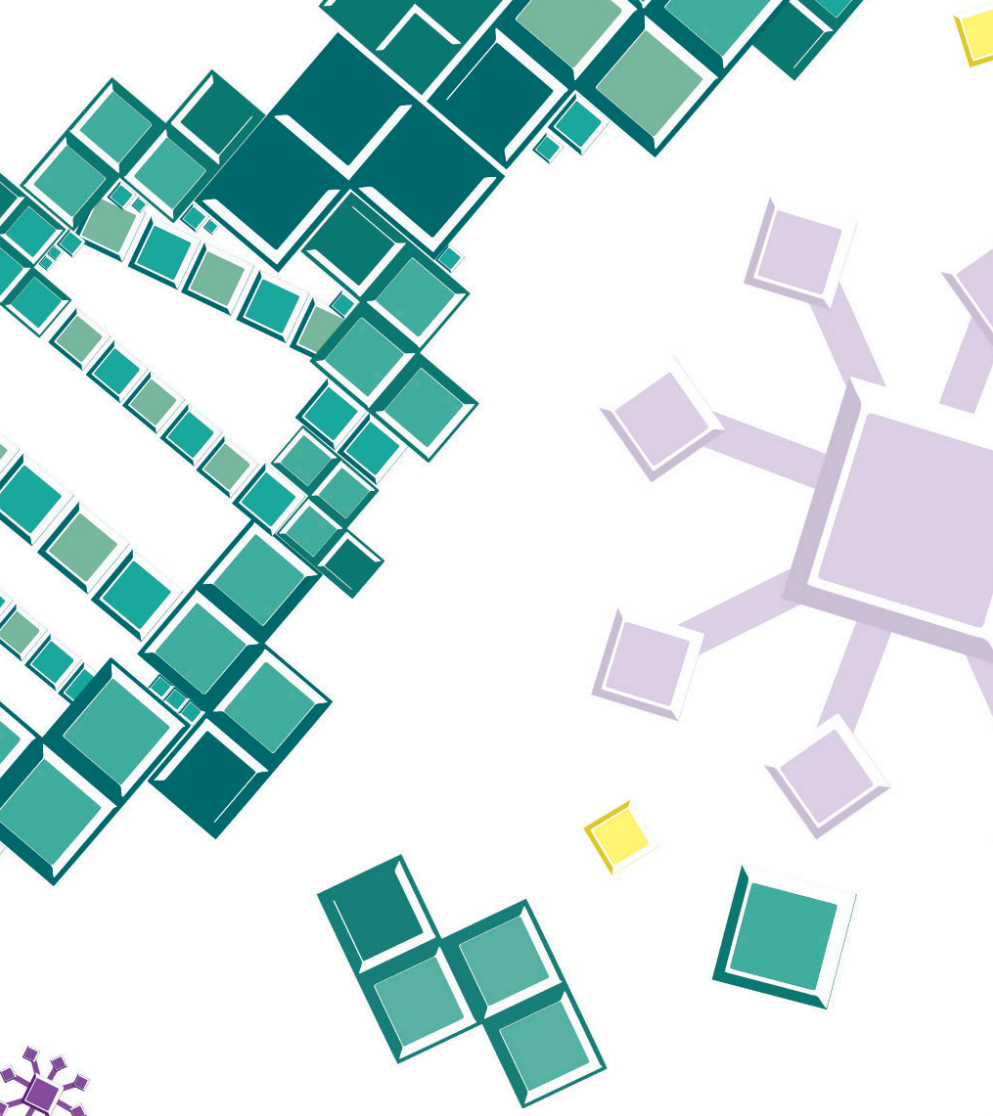
This approach could potentially enhance vitreoretinal lymphoma diagnosis and influence patient care. For instance, prior vitreous biopsies from one of the study cases had all been read as cytologically negative, with neither eye showing the presence of cancer cells. Two years after initial consultation, the patient presented with vision loss and right hemianopia; he had a brain lymphoma mass that was pressing on his visual centers. When we analyzed his original vitreous samples which had been stored in the freezer when collected two years prior to the brain lymphoma, we found tumor DNA confirming what later showed up in the brain: diffuse large B cell

lymphoma. Vitreoretinal lymphoma can be difficult to diagnose through standard cytology approaches, but because our test is so sensitive, as little as 5 or 6 ng of DNA is needed – which can come from just a few tumor cells in the eye. In the near future, we’d like to develop a diagnostic test that can be used by anybody. We already have the basis for the test, but because our research was only based on four samples – about one percent of all cases in the US – we want to collaborate with others; we need more samples to show that diagnosis using this precision medicine approach could be accurate and beneficial.

Making strides forwards

The key take home message is this: the technology we need is there, but to make more progress in the field, different teams need to talk. Just as





ophthalmology has led the way in stem cells and gene therapy, we can learn from other fields, like pathology, that are leading in precision medicine, and then apply it to ocular oncology. We can use today's technologies to make powerful advances to improve both diagnosis and treatment for our patients. Because ocular tumors are so rare, collaboration is really the key – it helps us bring the power of NGS, “big data” bioinformatics, precision medicine and epigenetic technologies to bear on this intractable problem.

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References

1. RC Rao et al., “Dynamic patterns of histone lysine methylation in the developing retina”, *Invest Ophthalmol Vis Sci*, 51, 6784–6792 (2010). PMID: 20671280.
2. M Khan et al., “Characterization and pharmacologic targeting of EZH2, a fetal retinal protein and epigenetic regulator, in human retinoblastoma”, *Lab Invest*, 95, 1278–1290 (2015). PMID: 26280220.
3. M Monk and C Holding. “Human embryonic genes re-expressed in cancer cells”, *Oncogene*, 20, 8085–8091 (2001). PMID: 1178182.
4. RC Rao et al., “EZH2, proliferation rate, and aggressive tumor subtypes in cutaneous basal cell carcinoma”, *JAMA Oncol*, 2, 962–963 (2016).

PMID: 27054919.

5. SE Avedschmidt et al., “The targetable epigenetic tumor protein EZH2 is enriched in intraocular medulloepithelioma”, *Invest Ophthalmol Vis Sci*, 57, 6242–6246 (2016). PMID: 27842164.
6. AK Cani et al., “Comprehensive genomic profiling of orbital and ocular adnexal lymphomas identifies frequent alterations in MYD88 and chromatin modifiers: new routes to targeted therapies”, *Mod Pathol*, 29, 685–697 (2016). PMID: 27102345.
7. Cancer.org, “What are the key statistics for eye cancer?” (2017). Available at: <http://bit.ly/EyeStats>. Accessed June 13, 2017.
8. AK Cani et al., “Next generation sequencing of vitreoretinal lymphomas from small volume intraocular liquid biopsies: new routes to targeted therapies”, *Oncotarget*, 8, 7989–7998 (2017). PMID: 28002793.
9. CC Chan et al., “Primary vitreoretinal lymphoma: a report from an International Primary Central Nervous System Lymphoma Collaborative Group Symposium”, *Oncologist*, 16, 1589–1599 (2011). PMID: 22045784.
10. University of Michigan Research, “Out of sight”, (2016). Available at: <http://bit.ly/UMichigan>. Accessed June 13, 2017.
11. National Cancer Institute, “NCI-MATCH Trial (Molecular Analysis for Therapy Choice)”, (2015). Available at: <http://bit.ly/MatchTrial>. Accessed June 13, 2017.
12. DH Hovelson et al., “Development and validation of a scalable next-generation sequencing system for assessing relevant somatic variants in solid tumors”, *Neoplasia*, 17, 385–399 (2015). PMID: 25925381.
13. Chris Woolston. “Researcher under fire for New Yorker epigenetics article”, *Nature* (2016). Available at: <http://bit.ly/Woolston>. Accessed July 19, 2017.
14. RC Rao et al., “Stem cells for retinal disease: a perspective on the promise and perils”, *Am J Ophthalmol*, 179, 32–38 (2017). PMID: 28428049.
15. E Kuriyan et al., “Vision loss after intravitreal injection of autologous ‘stem cells’ for AMD”, *N Engl J Med*, 376, 1047–1053 (2017). PMID: 28296617.

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38-39
Lost in Post-Translation
Lithium is effective in less than half of patients with bipolar disorder – but can studying its effect help us better understand and treat the disease?

40-43
HRD Times
It's time to look beyond the role of homologous recombination deficiency in ovarian and breast tumours, and ask what role it plays in other cancers.

specific molecular underpinnings of a complex polygenic disorder rather than simply describing its phenotype and phenomenology.) We used what we dubbed a “molecular can-opener” strategy to identify the underlying molecular pathogenic mechanism of BPD. In this case, lithium was our “can-opener”, which we used to “pry” into the pathophysiology of the disorder. We reasoned that, if we could find lithium’s target specifically in BPD neurons, we could then define the “lithium response pathway” – which would likely be uniquely abnormal in BPD. We also reasoned that examining proteomics may be more informative than looking at genes and transcriptomics, because the proteome is the ultimate integrator for the cell of multiple inputs at the genetic and epigenetic level, and determines the neuron’s actual behavior.

Targeting CRMP2

Using unbiased proteomic techniques to study the protein interactions of BDP-hiPSC-derived neurons we identified the target: collapsin response mediator protein-2 (CRMP2). We then mapped upstream and downstream from that node to complete a picture of the lithium response molecular pathway, and validated it in human neurons, mouse models (both histologically and behaviorally), and in actual bipolar human patient brain specimens.

We found that lithium alters the activity state of CRMP2, which is a central modulator of cytoskeleton (1). When CRMP2 is active, it binds cytoskeletal elements; and when it is inactive – by being phosphorylated – it releases cytoskeletal elements. This toggling back and forth between an active and inactive state is a normal adaptive mechanism, and there is a certain ratio of inactive-to-active CRMP2 (~0.5 in hiPSC-derived neurons, but we are still in the process of defining the normal ratio in patients). In particular, the molecule appears to dictate the form

and function of dendritic spines – the key to neural network assembly and function. When CRMP2 is active, dendritic spines are active; when it is inactive (or, in the extreme, missing), dendritic spines are inactive and even diminished in number. The set-point for the ratio of inactive:active CRMP2 is simply set too high in lithium-responsive bipolar patients; lithium “resets the thermostat” to a normal level, and neural networks function more normally.

It came as a surprise that an inherited and developmentally-based disease like BPD was not caused by an abnormal gene, but rather by the aberrant post-translational regulation of a normal gene. We have now described the first disease caused by an abnormal post-translational modification (PTM) in psychiatry (and perhaps in any non-neoplastic medical condition). It was also surprising that the pathogenesis came down to something as structurally fundamental as cytoskeleton.

Better diagnoses – and new drugs?

Assessing the CRMP2 ratio for a given patient could confirm the diagnosis of BPD, indicate whether or not the patient should be started on lithium, and allow the progress of the patient to be followed. We envisage a test that determines the phosphorylated:unphosphorylated CRMP2 ratio in blood samples from patients. What we now need to find out is whether the ratio can be seen in lymphocytes alone or whether we need to convert the lymphocytes to neural progenitor cells or neurons first and then determine the ratio. Even though the conversion process could take up to 8–12 weeks at this stage, it would still be faster and cheaper than the typical management of bipolar patients, which entails a trial-and-error prescribing of drugs (and often more than one) over years before the right treatment is found. Intriguingly, we would be using a highly accessible means (a blood draw) for predicting and characterizing the complex circuitry of a highly inaccessible

organ (the brain).

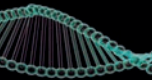
Ultimately, finding compounds that alter this pathway would allow us to discover drugs that are much more effective, selective, and less toxic than lithium. We also believe that the pathway plays a role in other neurological conditions (including some neurodegenerative diseases); therefore, effective drugs might be even more widely applicable. Another take-home message is a reinforcement of the critical nature of cytoskeleton to the function of neurons. Furthermore, although the neural stem cell and regenerative medicine fields have tended to focus on neuron replacement and neurogenesis, it is probably more accurate – and fruitful – to address neural network preservation and reconstruction as the key to the reversal of disease symptomatology.

The technique we used could be thought of as “reverse drug discovery” – rather than first discovering a mechanism, pathway, or target and devising a drug against it (the traditional route of drug discovery), we started with an agent that is already known to be bioactive, and then worked backwards to find a pathogenic mechanism or pathway. With that knowledge in hand, we can now go forward and seek better pharmacotherapeutics, which could potentially benefit many more patients.

Ervan Y. Snyder is a practicing pediatrician, neonatologist, and child neurologist who serves on many advisory committees and editorial boards in the public and private sectors. Regarded as one of the fathers of the stem cell field, he is also often viewed as a “bridge” between the basic science, clinical, and industrial communities.

Reference

1. BTD Tobe et al., “Probing the lithium-response pathway in hiPSCs implicates the phosphoregulatory set-point for a cytoskeletal modulator in bipolar pathogenesis”, *Proc Natl Acad Sci*, 114, E4462–E4471 (2017). PMID: 28500272.



HRD Times

We already know that homologous recombination deficiency plays a role in many ovarian and breast tumors – so why hasn’t it been explored further?

When DNA double-strand breaks occur in a healthy individual, the homologous recombination (HR) pathway generates a new strand of DNA and inserts it into the previously damaged area. It’s a complicated process that involves multiple different proteins that first bind to the loose ends of DNA, then initiate DNA excision of the damaged area, exposing the single-strand. If one or more of these proteins malfunctions, then the pathway is disturbed and DNA repair cannot take place. There are other repair pathways that can compensate but, all too often, DNA damage accumulates, which can lead to the worst-case scenario: cancer.

At a Glance

- *Repairing double-strand breaks in DNA is a complicated process, and when it goes wrong, it can result in cancer*
- *Some proteins, such as BRCA, play a role in the DNA repair pathway and are known to be common in certain cancers*
- *Data on which tumors are affected by these mutations is limited, and more research is needed to identify patients who could benefit from treatments such as PARP inhibitors*
- *Working to identify which tumors harbor DNA repair mutations, and what impact these have on treatment response, could help achieve better results for patients*

It’s already known that mutations in *BRCA1* and *BRCA2* – genes whose resultant proteins play a prominent role in the HR repair pathway – are relatively common in ovarian and breast tumors. Otherwise, data regarding which tumors are more commonly affected by HR deficiency (HRD) are quite limited, and not large scale – which means some patients could be missing out on the best treatment.

Beyond BRCA

As a clinical fellow at the Lombardi Comprehensive Cancer Center at Georgetown University in Washington, DC, I have been taking care of patients who are *BRCA1/2* and *PALB2* mutation carriers. During my two years of oncology training so far, I have witnessed the implementation of exciting new therapies (for example, PARP inhibitors) and unique drug combinations for these patients, and watched them respond remarkably well. I have also seen some of the negative impacts related to these mutations, including recurrent cancers and the need for prophylactic surgeries to minimize future cancer risk.

My work gave me a special interest in these patients, and so I participated

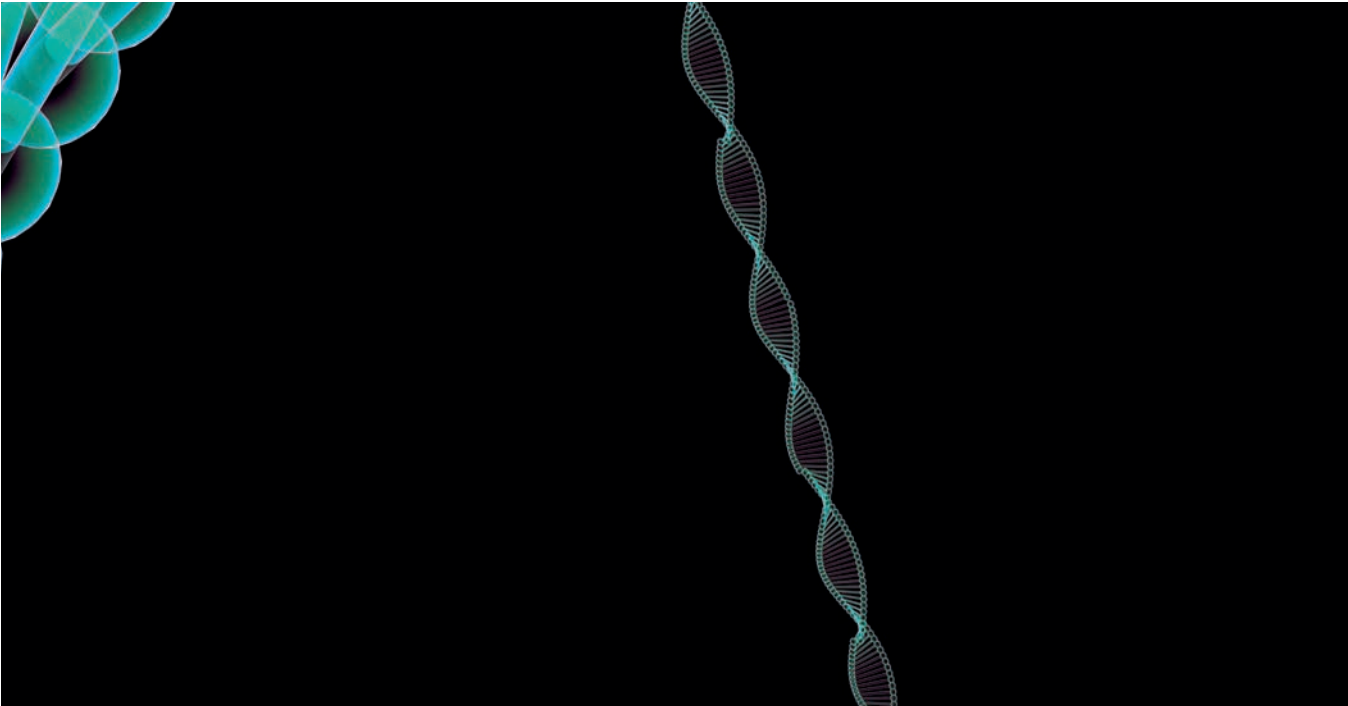
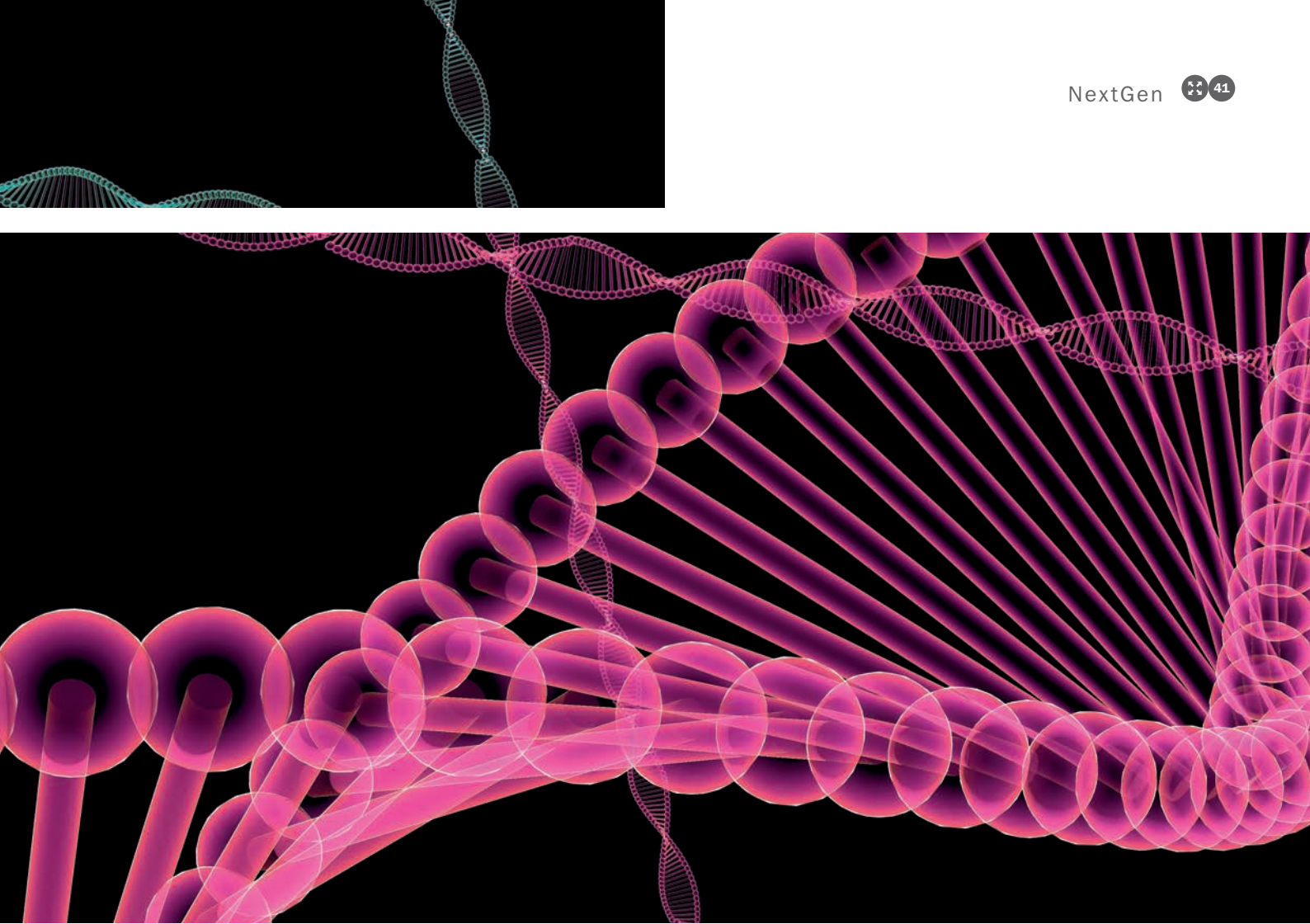
“If one or more of these proteins malfunctions, then the pathway is disturbed and DNA repair cannot take place.”

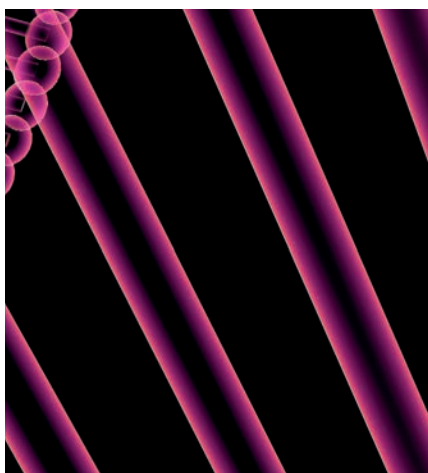
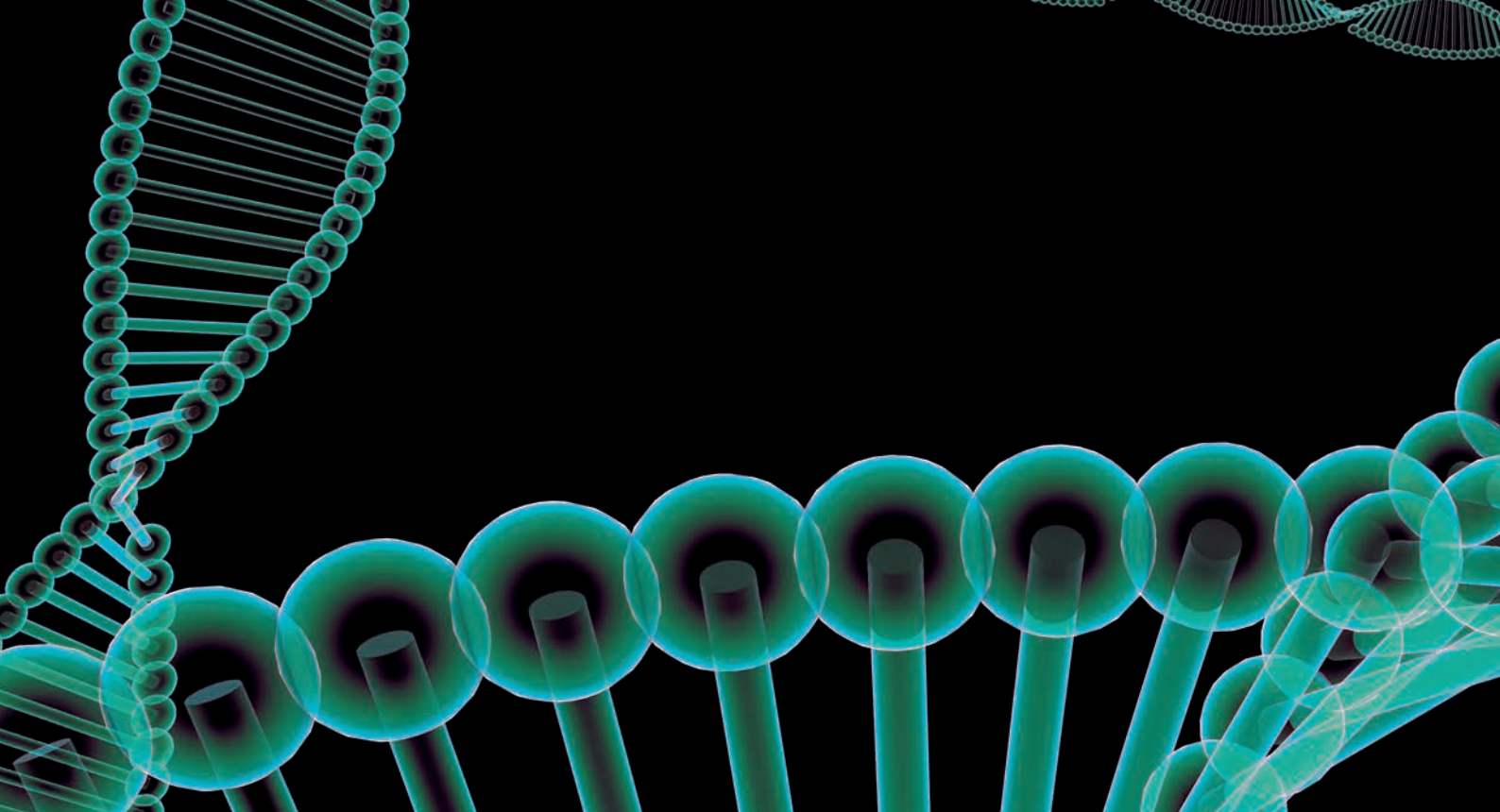
in the design of a clinical trial looking more broadly at genetic mutations in the HR repair pathway. In the trial, which will be opening this fall, a PARP inhibitor will be combined with platinum chemotherapy for patients with advanced solid tumors and a somatic or germline mutation in one of the genes involved in the HR pathway.

Being involved in designing this trial opened my mind to the potential treatment possibilities for a larger group of patients than just *BRCA* mutation carriers. I wanted to find out how large the group of patients that could benefit

	Cancer lineage	Frequency of HR mutation (%)
High frequency	Endometrial	35.5
	Ovarian	16.9
	Glioma	14.6
	Prostate	12.8
	Breast	12.3
Low frequency	Gastrointestinal stromal tumor	1.3
	Sarcoma	3.3
	Head/neck	4.9
	Hepatobiliary	6.4

Figure 1. Frequency of HR mutations in different cancer lineages.





“A better understanding of HRD’s role in cancer has the potential to lead to many advances for patients.”

from more tailored therapies truly might be. Although several groups have begun to define the prevalence of HRD within specific tumor lineages (1, 2) my colleagues and I decided to perform a study evaluating all tumor lineages – to our knowledge, the largest study evaluating the prevalence of HRD so far (3).

HRD definitions

To gain a better understanding of the prevalence of HRD, we reviewed molecular profiles from 53,619 solid

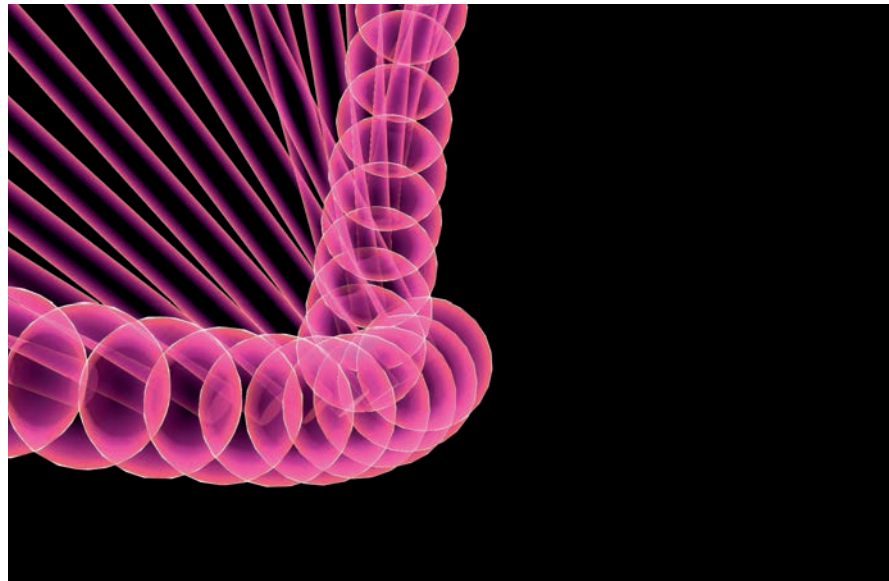
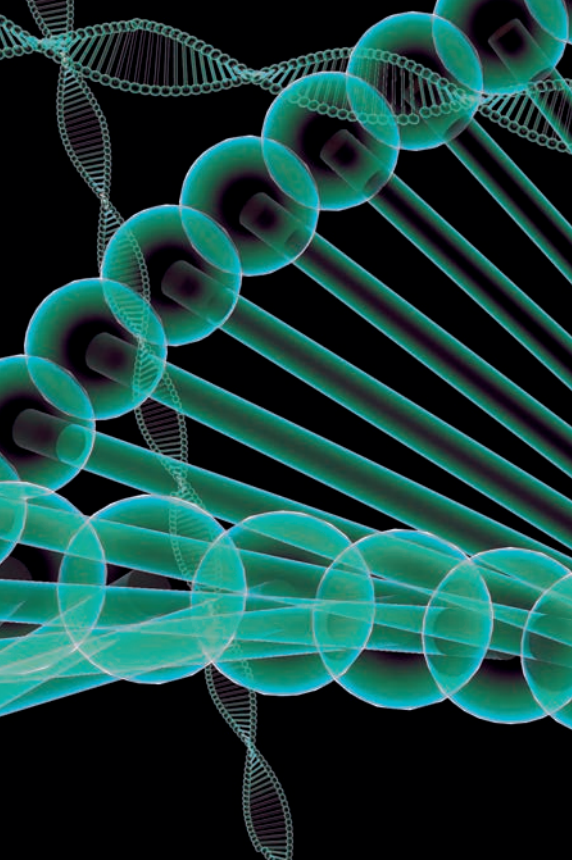
tumor samples using several methods, including next generation sequencing. The tumors were taken from patients with a range of cancers, including breast, ovarian, pancreatic, lung, as well as unknown cancers. The aim was to identify somatic pathogenic mutations in HR genes, including *BRCA1/2*, *ATM*, *PTEN* and *PALB2* (4). Overall, the frequency of HR mutations amongst all tested tumors was 13 percent, with

some lineages having a much higher frequency than others (see Figure 1).

One of the main challenges we faced was deciding exactly how to define HRD, and therefore which mutations we thought would be impactful and should be included. We decided to include most genes involved in the HR pathway, but it’s important to bear in mind that some may not confer as much clinical significance as *BRCA*, for example. We were surprised to see the number of tumor lineages that were impacted by these mutations – with *BRCA*, *PTEN*, and *ATM* mutations seen quite widely. It could certainly expand treatment options for patients with, for example, lung cancer with a *BRCA* mutation.

Understanding the mutation landscape

One appealing feature of our study is that we were able to use commercially available technology to generate our results. The molecular profiling techniques we used can be performed on any solid tumor tissue, and are often covered by insurance. However, there



is still work to be done. We don't yet know how these results affect clinical outcomes – we would assume that patients with mutations in other genes involved in the HR pathway, beyond *BRCA*, will respond favorably to PARP inhibitors and platinum chemotherapy. Although this is just now starting to prove true in the literature (2, 5, 6), we have some way to go to ensure each mutation within the HR pathway carries a similarly weighted impact. Additionally, this testing evaluates for a mutation within the tumor itself, but not germline mutations. We also don't know how this affects outcome; most of the previous work with *BRCA*, for example, was done using “*BRCA* mutation carriers” – patients with germline *BRCA* mutations. You could argue that knowing the somatic mutation landscape is actually more meaningful when it comes to predicting therapy response, but only time will tell.

To clinical trials, and beyond
When the planned multi-institutional trial valuating the use of PARP inhibitors with platinum chemotherapy

in patients with both germline and somatic evidence of HRD is completed, we hope to couple this with our assessment of clinical outcomes to address the questions our study has raised. Doing so should help us to discover what the HRD response to PARP inhibitors and platinum chemotherapy will be, and to see which HRD mutations seem to cause the most striking effects in relation to therapy response – and mortality. Another exciting avenue is the potential to exploit the accumulation of DNA damage in tumors with HRD to achieve responses to immunotherapy via increased neoantigens and potentially increased tumor lymphocytes. A better understanding of HRD's role in cancer has the potential to lead to many advances for patients, so it warrants much more exploration.

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References

1. *N Matsuda et al.*, “Identification of frequent

somatic mutations in inflammatory breast cancer”, *Breast Cancer Res Treat*, 163, 263–272 (2017). PMID: 28243898.

2. *J Mateo et al.*, “DNA-repair defects and olaparib in metastatic prostate cancer”, *N Engl J Med*, 373, 1697–1708 (2015). PMID: 26510020.
3. *ClinicalTrials.gov*, “Niraparib plus carboplatin in patients with homologous recombination deficient advanced solid tumor malignancies”, (2017). Available at: <http://bit.ly/2wAGVN1>. Accessed August 22, 2017.
4. *LK Heeke et al.*, “Prevalence of homologous recombination deficiency (HRD) among all tumor types”. Abstract presented at the American Society of Clinical Oncology Annual Meeting; June 5 2017; Chicago, USA. Abstract #1502.
5. *ML Telli et al.*, “Homologous recombination deficiency (HRD) score predicts response to platinum-containing neoadjuvant chemotherapy in patients with triple-negative breast cancer”, *Clin Cancer Res*, 22, 3764–3773 (2016). PMID: 26957554.
6. *Mirza MR, Monk BJ, Herrstedt J, et al.* Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. *N Engl J Med* 2016;375(22):2154–2164. PMID: 27717299.

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Leading the Way

As diagnostic technology continues to improve, how can pathologists ensure they are still leading the diagnostic pack?

Leading the Way

Pathologists need to take on the challenge of leadership or risk losing their value

By Sandip SenGupta

Why should pathologists become leaders? The very future of our profession hangs in the balance. Pathology's future is brighter than ever, thanks to exciting new advances in biomarker discovery that let us deliver better healthcare outcomes for our patients through effective and timely laboratory tests and services. But as precision medicine grows increasingly popular, strong leadership from pathologists is paramount to ensuring that we – and not other specialists – are the ones actually performing and interpreting these new tests. We can't afford to have internists or oncologists "eat our lunch!" Given hospital administrators' relentless attention to the financial bottom line, nothing less than the viability and sustainability of

At a Glance

- *As testing technology advances, pathologists need to make sure that they are the ones performing and interpreting tests*
- *A pathologist's place goes beyond diagnostic tests to include improving bioinformatics, advocating for patients and educating clinicians*
- *Pathologists also have the expertise to ease the transition from volume-based to value-based care and improve utilization management*
- *Given the wide remit of their skills and knowledge, it's vital for pathologists to take on leadership roles*



our clinical laboratories is at risk. If we as pathologists do not lead the way and demonstrate our value to patients, to our clinical colleagues, and to hospital and regional health system administrators, it will also become increasingly difficult to encourage a new generation of physicians to enter our specialty.

The value of a pathologist

First and foremost, a pathologist's job is to make a timely, accurate, clinically useful diagnosis based on the examination of a patient's tissue or fluid samples. But our role does not end there. Every day, we provide guidance in terms of the effect of our diagnosis on patient care – possible genetic implications for the patient's family; the need for further diagnostic testing or other investigations; guidance on clinical management and therapeutic decision-making (for instance, precision medicine based on the results of cancer biomarker testing); and much more. Clinical pathologists, in particular, guide clinicians on critical matters in

transfusion medicine, infection control, and antibiotic stewardship, to name just a few of their key roles.

Certified pathologists are skilled in making accurate diagnoses and interpreting complex test results from ancillary techniques such as molecular diagnostics and flow cytometry. As physicians with special expertise in laboratory medicine, we are uniquely placed to combine information from laboratory test results and basic sciences with clinical medicine (for instance, the patient's clinical presentation, diagnostic imaging, and intra-operative findings). Although many of our activities in patient-centered care are currently focused on personalized cancer treatment, our value is truly much broader than any specific disease group. Patient-specific blood product transfusion needs are a great example of this. Laboratory medical directors can ensure that patients have privacy when providing specimens for testing, followed by access to their test results



via easy-to-read, plain-language reports through hospital patient portals. Pathologists can use their knowledge of medical informatics to advocate for interoperability of laboratory information systems across regional healthcare systems, so that patients' results are available seamlessly across a continuum of care – for instance, from a community-based primary care setting to an academic tertiary or quaternary care hospital. Similarly, the adoption of digital pathology is enabling pathologists to provide more timely diagnostic information to patients in remote or rural communities. Examples that come to mind include interpretation of abnormal blood smears, Gram stains, or frozen sections.

Pathologists also play a vital part in educating clinicians, particularly in the realm of appropriate test utilization. For example, with the convergence of technologies in artificial intelligence, digital medicine, and medical informatics, there are tremendous

opportunities for pathologists to create new value for their healthcare ecosystems through enhanced clinical decision support and appropriate test utilization. With new medical information arriving on a daily basis, our knowledge around laboratory tests increases – and clinicians are scrambling to keep up to date. Add to this the risk avoidance that our medical expertise offers to both clinicians and to hospital administrators, and it becomes increasingly apparent how much value an experienced, locally available pathologist brings tremendous value to the table. It is, quite frankly, indispensable!

Patient-centered care

The concept of “patient-centered” care seems self-evident; after all, haven't physicians have always focused on the patient and advocated on the patient's behalf? Of course they have! But the definition of patient-centered care has evolved. Its modern meaning deals with developing systems, processes and pathways that keep the patient at the center of the planning, rather than traditional healthcare models that place the physicians' and hospitals' needs first. Long wait times, poorly coordinated care amongst a variety of healthcare providers, and multiple specialists all duplicating their efforts in history-taking and documentation are all too evident in the existing model of care. Perhaps the greatest value that pathologists bring to the new model is their interest and expertise in the information in patient data repositories (laboratory information systems and electronic medical records), and their efforts toward making this critically important patient information quickly and easily transferrable from one health care provider to another. It is often stated that over 70 percent of clinical decisions are driven by laboratory results (1), but more work is required to ensure that this information can be accessed more readily by a wider array

of healthcare professionals, including those working in medical data registries, pharmacies, and at the point of care. Pathologists, by the very nature of their generally broad practice, tend to work in teams more often than other physicians – and, counter to common stereotypes, are more likely to have strong team-building skills and experience with collegial and collaborative approaches to problem-solving.

“Modern-day technological, healthcare, and economic realities are such that volume-based care will likely not be sustainable beyond the next five years.”

As we move from a volume-based to a value-based care model, these skills and attributes are becoming more important than ever. Modern-day technological, healthcare, and economic realities are such that volume-based care will likely not be sustainable beyond the next five years. Governments and payors are increasingly seeking innovative ways to fund healthcare, and I expect that we will see continued evolution of models of health funding reform (especially those based on the bundling of services that were once paid for individually). Efforts focused on healthcare outcomes



for patients and institutions, rather than episodic care, will be rewarded for meeting predetermined favorable criteria – and punished for adverse events. This value concept can be neatly summarized in a mathematical expression:

$$\frac{\text{patient outcomes} \times \text{patient satisfaction} \times \text{timely access to care}}{\text{cost}}$$

In such an environment, laboratories can demonstrate value – or even create new value – by focusing on clinical

deliverables and helping to ensure that their organization performs well in external benchmarking with peer group institutions. For example, availability of point-of-care lactate testing in the emergency department for patients suspected of having sepsis can save lives through prompt triaging and timely care. The ready availability of critical test results – and thus, the ability to make rapid clinical decisions – lead not only to favorable patient outcomes, but also to better performance against other hospitals. And who better than pathologists to evaluate which tests to

offer, which platforms to use, where to conduct tests, and which provide the best cost-benefit ratio and risk mitigation?

Value-based care will impact every pathologist differently. Those who currently practice primarily in fee-for-service environments (like high-volume dermatopathology or gastrointestinal pathology) may see a negative effect, as value-based care may result in fewer biopsies. In my hospital, for example, our gastroenterologists have a laboratory where they review images from tiny cameras that their patients ingest. Fewer endoscopic biopsies are required – which is better for the patient and saves resources within the healthcare system, but it also means that fewer GI biopsies are coming to the pathology department. On the other hand, pathologists working on salary may feel less impacted and more liberated to advocate for changes that make sense for their patients from a holistic perspective. The pathologist can have a greater role in tumor boards and in developing patient care pathways. In my hospital, as Laboratory Director, I am routinely asked to review and approve all medical directives (acts delegated by physicians to nurses) that involve ordering certain lab test panels and standardized “order sets” (comprehensive sets of orders on a patient’s chart based on their condition or intervention). Regardless of its effect on pathologists, though, patients undoubtedly stand to benefit from greater integration of their care.

Utilization management

With the advent of sophisticated computerized data analytics, utilization management is entering a new phase. Now we can focus our attention on physician outliers. Instead of expending a tremendous amount of time, energy and resources on educating and managing the behaviors of all physicians, the emerging trend is to channel resources into identifying the 20 or so percent of physicians

who are responsible for 80 percent of the laboratory's activity and cost. This is especially true for expensive send-out tests. A study from the 1980s demonstrated that there was very little value in getting physicians to reduce automated core lab testing, as the net savings was amazingly small. Manual tests are a different matter – so creating algorithms to reduce, for example, unnecessary manual differential cell counts is a useful approach. So is reducing send-out tests, which are often focused on molecular diagnostics and tend to be costly. Our laboratory, like many across North America, focuses on reducing send-out test costs – which can easily run into six or seven figures annually. Clinician education remains a mainstay of utilization management, especially now that so many diverse groups of healthcare professionals (midwives, physician assistants, nurse practitioners) can order laboratory tests. But with residents and fellows rotating through clinical services every four to six weeks in teaching hospitals, it is impossible to keep up solely by providing education. That is where pathologists can help: by working collaboratively with their clinical colleagues to develop testing algorithms that are, whenever possible, evidence-based.

But these “soft rules” for lab utilization need to be accompanied by “hard rules” – logic rules built into order-entry software programs that stop access to tests that are expensive, not indicated, or require prior consultation with a pathologist. Those with a special interest in medical informatics can create additional value by developing rules frameworks for their systems, in concert with bioinformaticians and computer technology experts. As artificial intelligence and neural network technology continues to advance, pathologists who are

comfortable working in those realms can develop algorithms to decide the most appropriate test-ordering strategies for their clinicians or consolidate information from multiple databases to create new knowledge. The possibilities are almost endless!

“Pathologists begin taking on leadership roles far earlier than many of their clinical counterparts.”

The dyad leadership model
Most organizations, especially larger hospitals, still seem to have dual reporting structures. The laboratory administrative director (or equivalent) reports directly to his or her supervisor, often a vice president, whereas the pathologist reports to the chief medical officer. Yet it is the laboratory medical director who legally bears responsibility for quality and patient safety. Administrative and medical directors who are not able to work closely on all aspects of laboratory operations (even if only to provide oversight or gain awareness of the decision-making that takes place) create serious interpersonal conflict – or worse, jeopardize the mission of the organization. By working closely together, the administrative and medical directors – like two sides of the same coin – can foster unity and advocate more strongly and effectively for the laboratory. That is the essence of the dyad leadership model: equal input from both

administrative and medical experts, along with an acknowledgment of the roles and limitations of each.

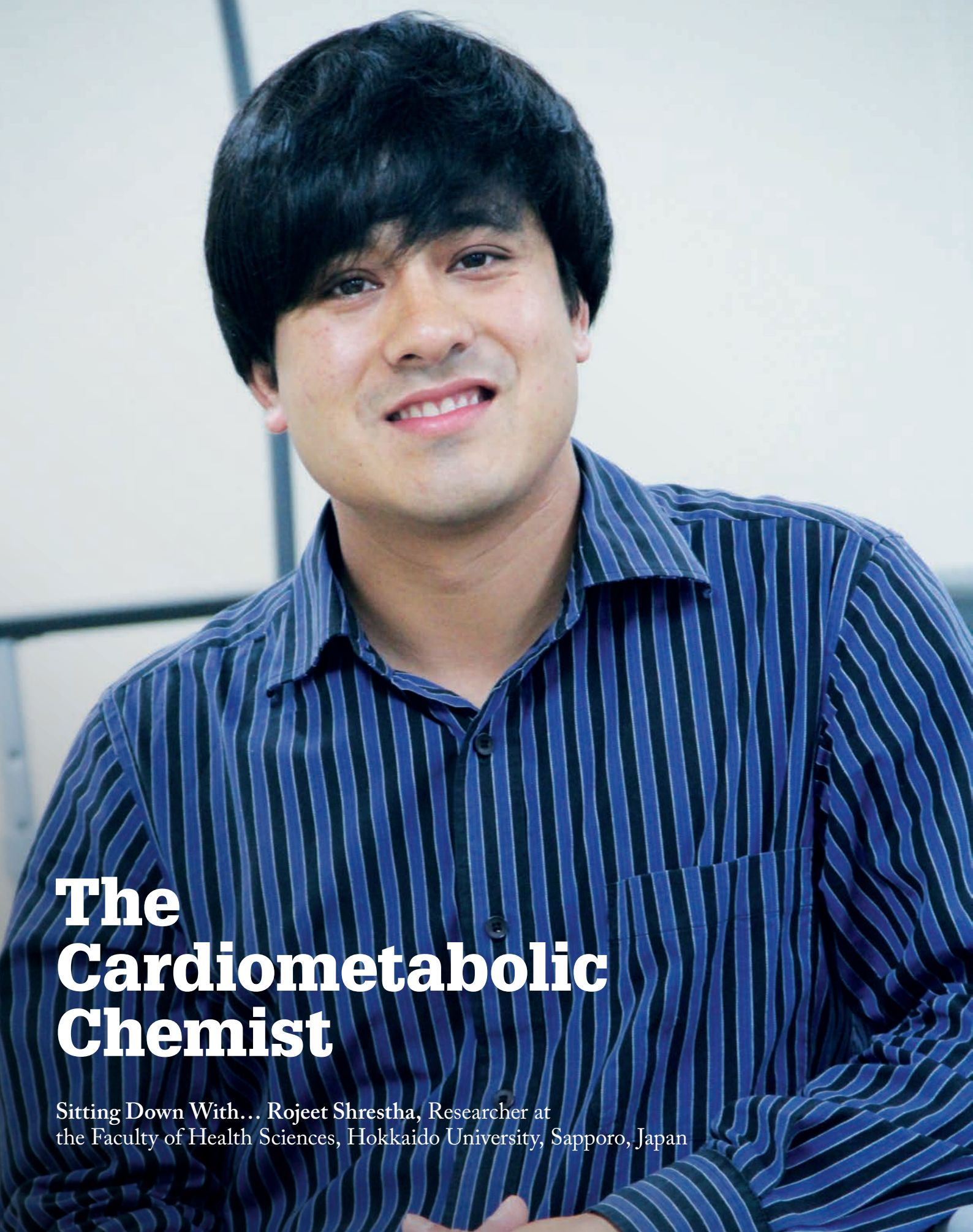
In my experience, the combined strength of these two arms of the traditional organizational chart is far greater than the sum of its parts. This dyad model also builds greater transparency and trust with the senior hospital leadership to whom the duo report, and reduces strife and conflict. Each role is a necessary part of decision-making, so meetings are cancelled if both are not available to attend. Every pathologist who is concerned about a good working environment should be interested in ensuring a strong dyad leadership model in their organization.

Fortunately, it seems to me that more physicians are becoming interested in medical leadership. Witness, for instance, the interest and growth in America of combined MD/MBA degree programs and in leadership education. Check out the American Association for Physician Leadership (physicianleaders.org) or, in Canada, the Canadian Society of Physician Leaders (physicianleaders.ca). Pathologists began taking on leadership roles far earlier than many of their clinical counterparts, largely by virtue of the need to have management structure in the laboratory – but we're still in the early stages. More pathologists need to get out of their comfort zones and mingle with other physicians. Find a role that crosses specialty borders and take it on as a challenge. In short, be involved or be outsourced!

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References

1. C Naugler, “Laboratory Utilization Management in Canada”, *Utilization Management in the Clinical Laboratory and Other Ancillary Services*, 279–285. Springer Nature: 2017.



The Cardiometabolic Chemist

Sitting Down With... Rojeet Shrestha, Researcher at
the Faculty of Health Sciences, Hokkaido University, Sapporo, Japan

Why did you choose laboratory medicine? My years as a postgraduate student at Nepal's Tribhuvan University were challenging. I should have expected that – the program accepts only two students each year – but we were also the first batch of students to spend a considerable amount of time on clinical laboratory practice, medical laboratory education, and research. Most people emphasize diagnosis and prognosis in laboratory medicine, but I was interested in predictive biomarkers. Early identification of individuals at risk of disease will have a profound impact on socio-medico-economic problems. Cardiovascular disease and metabolic syndromes will soon be a global health crisis – and because lipids and lipoproteins are strongly associated with cardiometabolic disease pathophysiology, I chose that field for my research career.

Tell us about the ups and downs of your career...

I represent a phase of rapid advancement in Nepalese laboratory services. In my early career, automation in the clinical laboratory was something we could only read about. We did all of our laboratory investigations manually, and quality management was very difficult. Now, though, we have shifted toward automation, and toward a greater focus on quality control and accreditation.

One thing I have learned is that we laboratory professionals cannot just stay in the lab; we must interact with clinicians and patients. Proper instructions for specimen collection are crucial for reliable, accurate diagnosis. I remember reporting azoospermia in a patient, but then discovering that we had received a nasal discharge sample (“segan” in the local language) instead of the requested sample (semen)! Because the clinical staff had not explained how to collect the specimen, the patient never realized his error...

In early 2013, I hit a speed bump: stage

II diffuse large B-cell lymphoma. I was devastated. Not only was I living and working in a foreign country, but now I also had to juggle cancer treatment! But I couldn't let cancer stop me, so I revised my day-to-day schedule, with chemotherapy in the mornings and work in the afternoons. It was a dark moment in my life, but it taught me the importance of seizing the moment. Whatever you can do, do it today – because who knows what will happen tomorrow?

How did the new outlook affect your career?

I think that attitude, along with my interest, eagerness and enthusiasm, has played a significant role in my achievements to date. I strongly believe in the maxim, “Where there's a will, there's a way.” Throughout my career, I have always been keen to learn, and every day's experience has taught me new things. Hard work and consistent devotion are the keys to success – and each new achievement inspires and motivates me further.

What's your biggest highlight so far?

During the AACC annual meeting in 2016, Carl Burtis – editor of Tietz' Fundamentals of Clinical Chemistry – invited me to the Clinical Chemistry editorial dinner. It was so special for me to spend time with the person whose textbook I had used for decades. I was presented with a recent edition of the textbook autographed by all the editors of Clinical Chemistry. To this day, it remains the most precious gift I have ever received.

What advice could you offer colleagues?

Today's young laboratory professionals are the pillars of future lab medicine. Providing them with appropriate training is key for success. I always try to inspire my students, and I get as much joy from their achievements as from my own. I always enjoy communicating with students and early-career professionals in laboratory

medicine; I use social media to stay in touch with hundreds of colleagues, and I am always happy to provide advice and suggestions when asked.

For those considering a career in laboratory medicine, I would like them to know that the field has a bright future! It will always occupy a central role in medicine, and its practitioners are true behind-the-scenes heroes in patient care. Of course, not every laboratory medicine professional works in a healthcare setting; many pursue research instead – and both are equally valuable contributions to science and society.

The world of laboratory medicine has expanded its focus beyond the lab walls, though. Professional networking – both in person and online – is an integral part of any science career. I am heavily involved myself: I created the Nepal Association of Medical Laboratory Sciences' Facebook group (3,000 members); I am the elected secretary of the AACC's Lipoprotein and Vascular Disease Division; I contribute to the Clinical Chemistry Trainee Council's online educational resources; and, recently, I was appointed as both an executive member of the IFCC's Committee on Internet & eLearning and social media coordinator of the IFCC as a whole. It is a huge responsibility for me, but also a great way to contribute to our academic society – and I hope it encourages other laboratory medicine professionals to do the same.

What most inspires you?

Meeting eminent scientists in person is a great source of inspiration. I remember when I first attended an international meeting, I had the wonderful opportunity to meet and talk with prestigious figures in the field of clinical chemistry – people I had only known from the bylines on scientific papers and textbook chapters. Even brief talks with scientific heroes are motivating!

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