AUGUST 2018 # 45

# the Pathologist™

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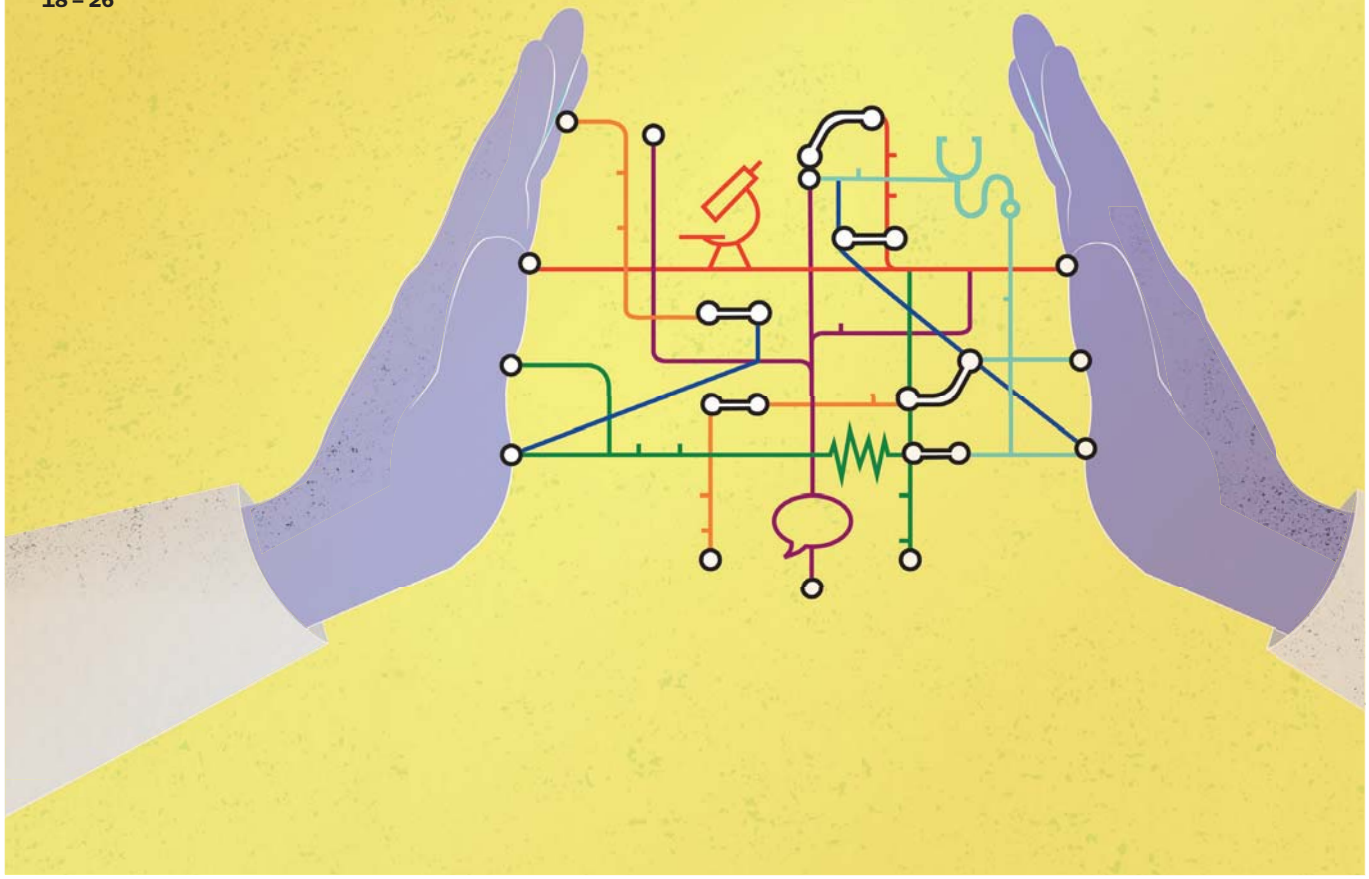
## Tell Me, Doctor…

Are you communicating adequately with your non-pathologist physician colleagues?





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# Case of the Month


A 48-year-old woman presented with a left ventricular mass, diagnosed by CT scan, approximately 20 years prior to resection. Over the previous few months, she complained of worsening tinnitus in the left ear, headaches, and increasing ddizziness. After resection, the tumor was grossly described as multiple fragments of calcified red/black tissue and was submitted after decalcification.

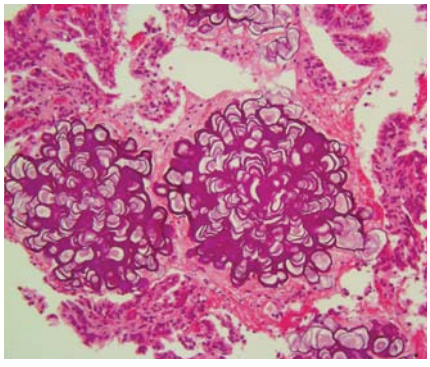
*What is your diagnosis?*

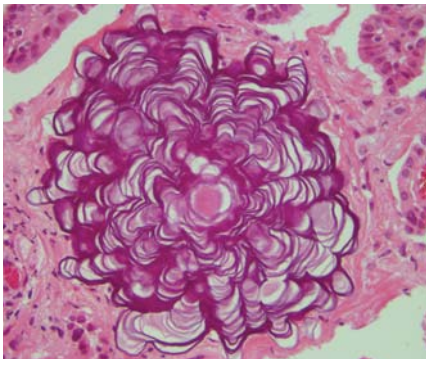
*a* Papillary meningioma

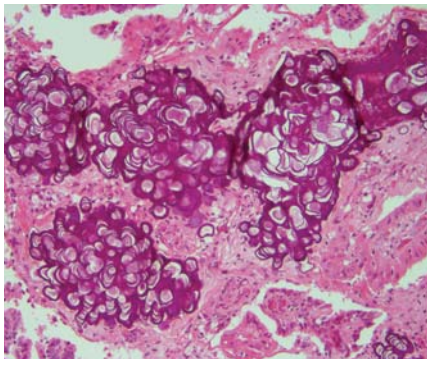
*b* Choroid plexus papilloma

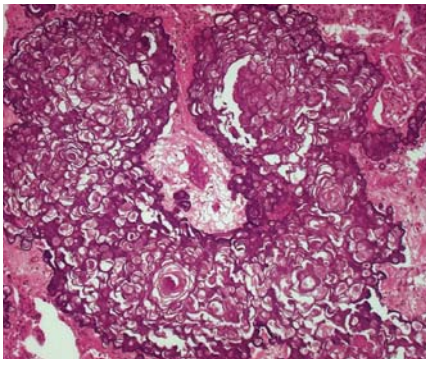
*c* Choroid plexus carcinoma

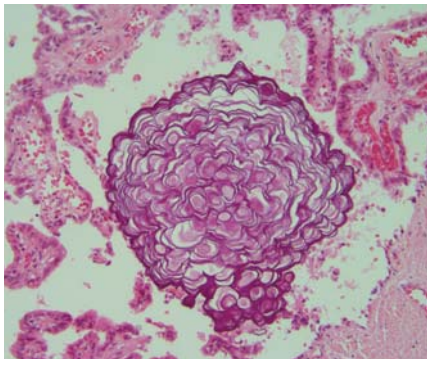
*d* Metastatic carcinoma

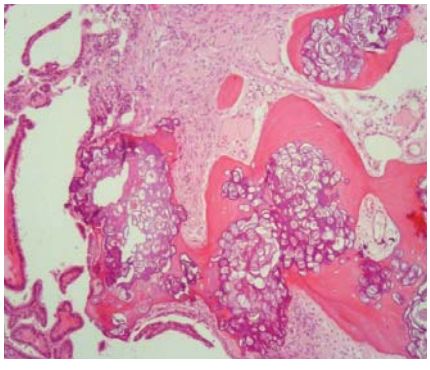












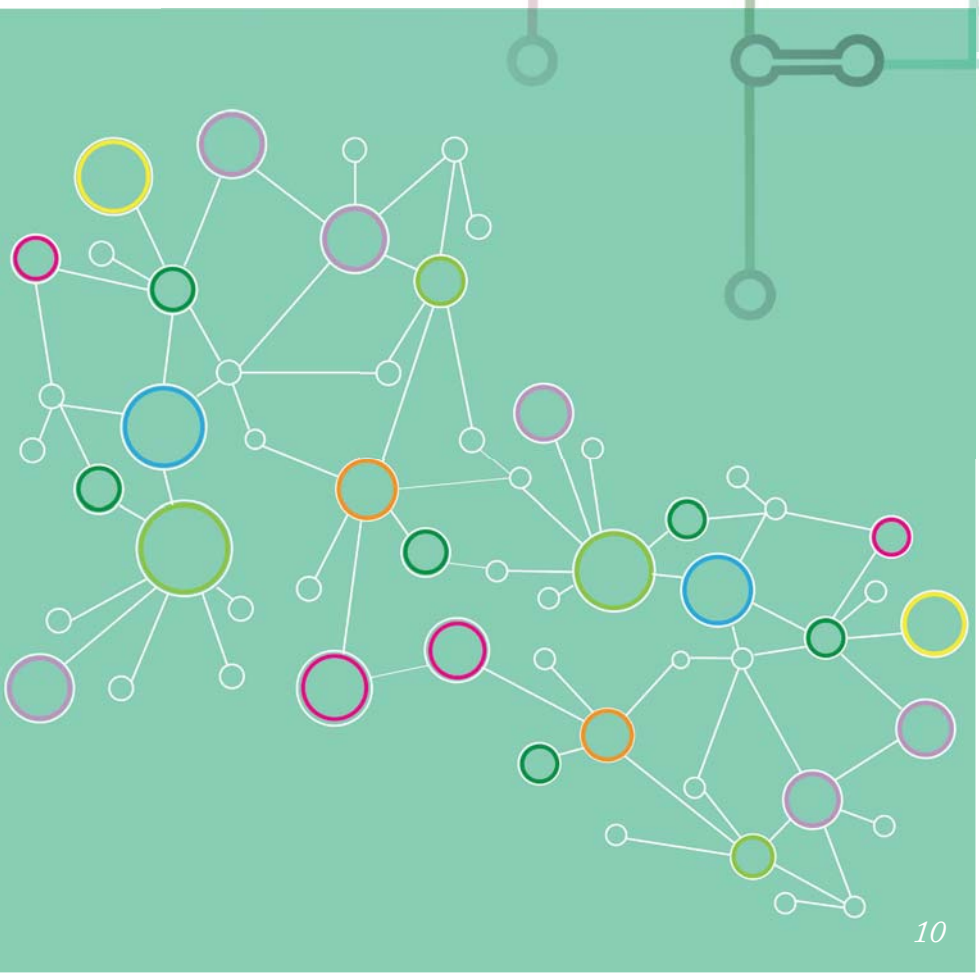
## Answer to last issue's Case of the Month…

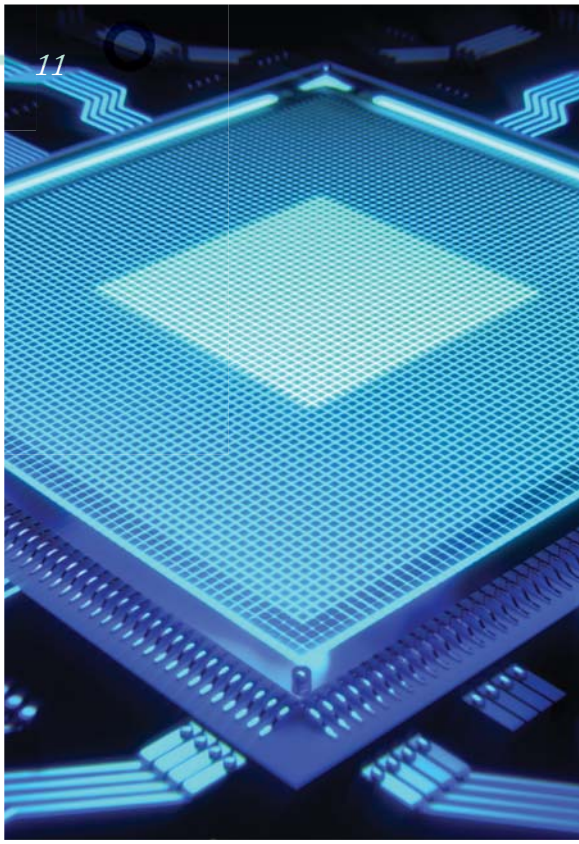
*A. Androgen*

This is a salivary duct carcinoma, a highly aggressive malignant tumor resembling high-grade ductal carcinoma of the breast. Approximately 70 percent of all salivary duct carcinomas express androgen receptors, which can be demonstrated immunohistochemically in the nuclei of this tumor.

**To register your guess, please go to http://tp.txp.to/0818/case-of-the-month**
**We will reveal the answer in next month's issue!**

# Contents






## On The Cover

*Inter-specialty collaboration represented by a stylized subway map of specialties connecting two hands.*

## Upfront



## In My View

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**ISSUE 45 – AUGUST 2018**





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Since the American Society for Clinical Pathology's inception in 1922, our organization has worked to provide excellence in education, certification, and advocacy on behalf of patients, pathologists, and medical laboratory professionals. All of our activities are designed to feed into ASCP's four pillars – knowledge, advancement, global community, and collaboration. The National Pathology Quality Registry helps pathologists improve quality and patient care; the ASCP Foundation raises money to provide scholarships and increase laboratory visibility; and the Center for Global Health's work with the President's Emergency Plan for AIDS Relief and our Partners for Cancer Diagnosis and Treatment in Africa initiative improve the diagnosis, care, and treatment of people all around the globe. Our portfolio of publications addresses the educational and academic research needs of our members, but what about the application of that research? And how do we explore the increasingly global aspect of pathology in ways that are relevant to our members today?.

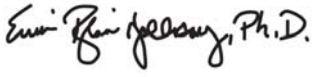
That's where The Pathologist comes in. By bringing the magazine to our members, we're increasing their access to world-class material while satisfying all four of our tent pole values. An interview with Richard M. Linnehan, a veterinarian who also happens to be an astronaut, provides insight into the importance of comparative pathology. Articles such as "Stromal Secrets" and "Instant Raman" examine non-invasive tests for diseases such as endometriosis and inflammatory bowel disease, respectively. The Case of the Month represents a bite-sized way to test your knowledge. And when you're having a bad day, articles such as Kamran Mirza's "Our Secret Language" provide the inspiration you need to persevere.

The Pathologist is committed to publishing informed opinion pieces and articles covering cutting-edge technology that facilitate conversation among the world's leaders in pathology and laboratory medicine. It seemed only natural to bring this resource to our members, so that they are better equipped to meet the demands of today, while paving the way for the future.

As we approach our 100th anniversary, we must continue to evolve to maintain our place as the world's largest organization for pathologists and laboratory professionals. As the authority on education, certification, and advocacy for the field, we must act as a guardian for the profession. This partnership with The Pathologist accomplishes all of that – and more.

My best to you all.

**E. Blair Holladay**
*CEO, American Society for Clinical Pathology*



# 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*

# Recognizing and Reacting to PID

**On its 10th anniversary, the UK Primary Immunodeficiency (UKPID) registry aims to raise awareness and improve care**

Where can you find almost 10 years' worth of data collection on primary immune deficiency (PID), representing 97 percent of immunology centers across the UK and nearly 4,800 patients? Answer: the UK Primary Immunodeficiency (UKPID) registry's second report on the rare syndrome (1). The new report includes data from more than twice as many cases as their first publication in 2014 (2). "It was more than four years since our last report," says Matthew Buckland from the University College London's Centre for Immunodeficiency. "In that time, there has been a change of platform, re-validation of original data, and improved diagnostic criteria applied. With a significant increase in patient numbers approaching UK prevalence, we felt it was time to re-analyze the data."

PID affects only one in 16,000–50,000 people, and with more than 300 types of PID (3) – some of which have been diagnosed in fewer than 10 patients – the condition can be difficult to spot. Consequently, patients often experience significant delays in having symptoms recognized and receiving the correct treatment.

The national registry for structured data on PID syndromes aims to combat that diagnostic challenge by providing and collating trustworthy information for both doctors and patients. "It's a unique data resource of patients with primary immune deficiency – a true collaborative effort from clinicians across the four nations," said Buckland. "For rare diseases, this is the only way that we can collect reliable information that informs standard and novel approaches to treatment or cure."

As awareness of PID has increased, so has the number of patients diagnosed, which is why the UKPID team emphasize the importance of a valid authority on primary immunodeficiency. Thanks to our growing understanding of PIDs, screening for one type of the disorder (severe combined immunodeficiency, or SCID) on newborn blood spots will be trialed this year, hopefully allowing healthcare teams to support patients from a much earlier stage.

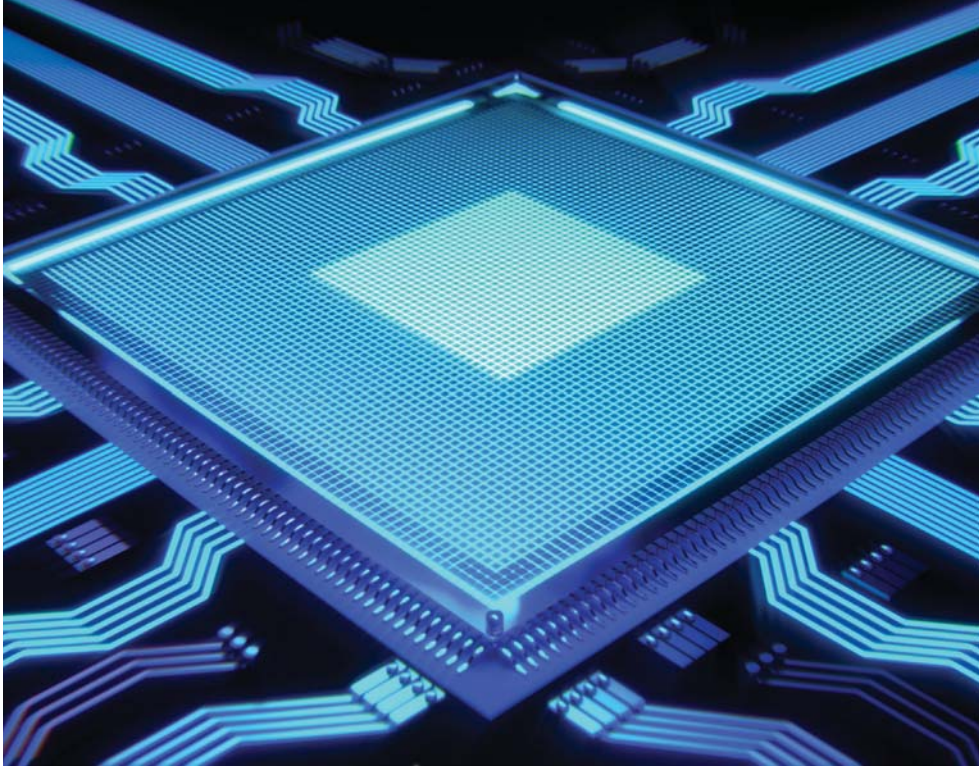
Data in the new report covers disease prevalence, delays in diagnosis, age of onset, and different treatments, such as hematopoietic stem cell transplantation (HSCT) and gene therapy, all of which can help doctors faced with unfamiliar symptoms or a rare diagnosis. "Contributing centers now have new tools for the self-interrogation of data, which helps feasibility assessment for specific studies on patient subpopulations," says Buckland. "The next stage is to implement new 'level 3' projects – studies that answer questions on specific diseases or their traits, such as inflammatory lung disease in common variable immune deficiency."

*References*


1. *B Shillitoe et al., "The United Kingdom Primary Immune Deficiency (UKPID) registry 2012 to 2017", Clin Exp Immunol, 192, 284–291 (2018). PMID: 29878323.*
2. *JD Edgar et al., "The United Kingdom Primary Immune Deficiency (UKPID) Registry: report of the first 4 years' activity 2008-2012", Clin Exp Immunol, 175, 68–78 (2014). PMID: 23841717.*
3. *PIDUK, "Types of PID" (2017). Available at: https://bit.ly/2zcxK8l. Accessed July 5, 2*

# The Gentle Fetal Genome

## Can lab-on-a-chip technology enable extensive – yet noninvasive – prenatal screening?



Invasive testing on a fetus is never desirable but can be unavoidable, which is why so many researchers are working on new and improved noninvasive prenatal tests (NIPT). One such research team is using inertial microfluidics within a lab-on-a-chip device to collect circulating fetal trophoblasts in maternal peripheral blood (1). Here, we speak with Marnie Winter, first author and research associate at the University of South Australia, to find out how the method differs from existing NIPT.

### What is the origin of your work?

We have been working in the field of rare cell isolation for a number of years, with a particular interest in the isolation of circulating tumor cells, which poses a similar technical challenge to the isolation of circulating fetal cells from pregnant women's blood. Recently, the field of prenatal screening has been revolutionized by the introduction of NIPT based on circulating cell-free fetal DNA. The technique has now gained broad clinical acceptance for the detection of a number of common genetic disorders; however, the technology is limited. By relying on fragments of DNA in the maternal blood stream, such tests are unable to provide information on the full range of potential genetic abnormalities.

Our experience in rare cell isolation and the great diagnostic potential of circulating fetal cells, which provide a whole intact genome, prompted us to refocus our efforts towards the isolation of those cells. From our perspective, that is a more elusive goal – but one that could have a huge impact on prenatal screening.

### How far are you from having such an impact?

Our work thus far demonstrates the potential for inertial microfluidics to enrich circulating fetal cells. The isolation of these cells from blood has been attempted many times in the past, but is extremely challenging, so the field has stagnated. However, modern technologies (ours included) give us hope that we can reliably isolate these cells from all pregnancies. By combining our cell isolation (and the whole fetal genome contained within) with cutting-edge genomic technology, we can offer much more comprehensive prenatal screening. We believe that cell-based NIPT will form a part of the prenatal screening landscape in the near future.

### How do you see your lab-on-a-chip technology fitting into the pathologist's workflow?

In general, lab-on-a-chip concepts enable the manipulation of clinical specimens with very high accuracy and efficiency – and can often be completely automated. As a result, these technologies have a high potential to simplify and facilitate a pathologist's workflow. In our specific case, inertial microfluidics is an extremely gentle, rapid, and cost-effective way to enrich rare cells. None of the standard enrichment approaches have been clinically useful in circulating fetal cells because to their extreme rarity and stringent sample requirements.

### What's next?

For the test to be clinically viable, we need fully integrated technology that requires minimal user input. We are currently working on creating technology to address this. At the same time, we are working with industry partners and geneticists to develop genetic analysis techniques specifically for low-number or single circulating fetal cells.

Our research is supported by the Australian Research Council Centre of Excellence in Convergent Bio-Nano Science and Technology, and also by the National Health and Medical Research Council (Australia). There are a number of key collaborators for this project, including Majid Warkiani from the University of Technology Sydney, Tristan Hardy from SA Pathology, and Dierdre Zander-Fox from Monash IVF group.

*Reference*

1. *M Winter at al., "Isolation of circulating fetal trophoblasts using inertial microfluidics for noninvasive prenatal testing", Adv Mater Technol, 3 (2018).*

# A Change of Heart (Genetics)

## A new model system may help personalize cardiac channelopathy diagnosis and treatment

As genetic testing gets faster and cheaper, people are increasingly having their own genomes examined for all manner of variation. Much of this scrutiny is focused on disease risk. "Could I be in danger of a heart attack? Will I suffer the same problems as my grandmother? How long am I likely to live a healthy life?" But not every gene variant affects disease risk – and even for those that do, the increase could be statistically meaningless.

Joseph Wu and his research team at Stanford Medicine set out to dispel the mystery of variants of unknown significance (VUS) in patients at potential risk of heart problems. In particular, they focused on a family of disorders known as cardiac channelopathies (1). "About 30 percent of negative autopsies in young individuals could possibly be explained by genetic mutations in channelopathy-related genes," says Wu. "However, clinical management is still hindered for most of these disorders because of insufficient knowledge of the functional consequences of genetic mutations."

Wu blames the problem on inadequate model systems for research – but there is a solution. "The recent emergence of induced pluripotent stem cell (iPSC) technology has provided an unprecedented opportunity for generating and studying iPSC-derived cardiomyocytes from channelopathy patients," says Wu. "These cells can accurately recapitulate human disease electrophysiology in vitro, allowing investigation of patient- and mutation-specific disease mechanisms." iPSCs can be used to study the pathogenicity of not only channelopathies, but other cardiac disorders as well. And the story doesn't end there; Wu is optimistic that his group's investigations could lead to precision diagnosis and treatment. "Future studies based on human iPSCs and genome editing could provide a personalized approach to drug therapy for patients with congenital long QT syndrome and other inherited conditions associated with cardiac arrhythmias."

For the time being, the Wu lab will continue to establish and validate the potential of iPSCs as a model for accurately decrypting the pathogenicity of unknown variants in cardiac disorders. In the future, their approach, which combines genome editing and iPSC techniques, may be used to accelerate progress toward precision medicine in cardiology. "We are very excited about our data," Wu says. "With the increasing usage of next generation sequencing, many unknown functional variants will undoubtedly appear. We believe this approach will be a common method to decipher VUS in the future."

*Reference*

1. *P Garg et al., "Genome editing of induced pluripotent stem cells to decipher cardiac channelopathy variant", J Am Coll Cardiol, 72, 62–75 (2018). PMID: 29957233.*

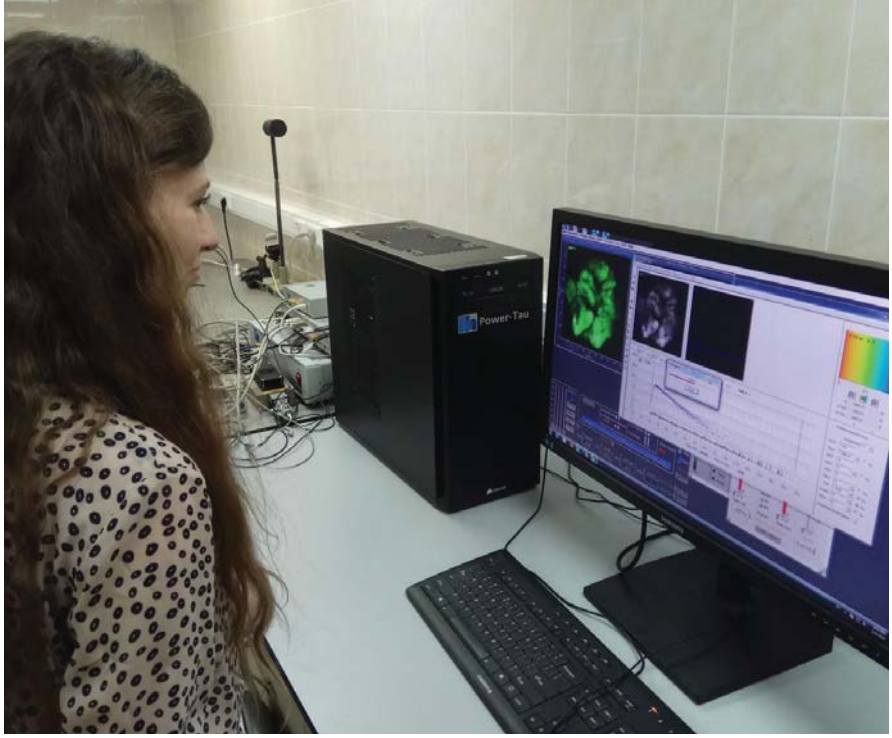
# Fluorescence Macroscopy

## Using a macro-scanner to image larger samples with the detail of fluorescence microscopy

"Fluorescence microscopy is considered a minimally invasive optical technique to address a number of biological questions that cannot be answered by other means in a fast and relatively inexpensive way," says Vladislav Shcheslavskiy, a senior research scientist at Becker & Hickl. "Although there are a lot of powerful methods to interrogate biological systems in vitro, there are a limited number of ways to explore samples in vivo, especially when they're large."

To overcome this difficulty, Shcheslavskiy and colleagues from Russia developed a system that allows users to boost fluorescence laser scanning microscopy to image samples as large as 18 $mm^2$ – where the previous limit was less than 1 $mm^2$. But what separates this technology from mainstream imaging techniques for large samples?

"Currently, there are systems on the market that allow you to do whole-body imaging, but they lack molecular sensitivity," explains Shcheslavskiy. "We believe our macro-scanner can find applications in profiling tumors and in determining surgical margins. We should also note that the exploration of the tumors in this case is based on the observation of intrinsic fluorophores that are present in it, so it is a virtually label-free approach to the monitoring of samples." Their "macroscopic" technique can also examine tumor response to different therapeutics, and can be combined with other imaging systems to expand its scope of use. Shcheslavskiy adds, "Of course, before they can enter routine use in clinics, all results obtained by optical methods have to go through independent checks



by biochemical and other common methods for clinical labs." As well, his group's next steps include making the system more user-friendly and updating the software and hardware to increase its flexibility and compactness.

Shcheslavskiy concludes by highlighting the collaborative scope of the project, saying, "This work would be impossible without our collaboration with biologists. I would like to take the opportunity to express my appreciation to my colleagues from Privolzhsky Research Medical University, Nizhniy Novgorod, especially Elena Zagaynova and Marina Shirmanova. who were the main driving forces in the experiments carried out with the developed system."

*Reference*

1. *VI Shcheslavskiy et al., "Fluorescence time-resolved microimaging", Opt Lett, 43, 3152–3155 (2018). PMID: 29957804.*

# Quick Hits

## Pre-emptive Liver Protection

One in 50 patients who take an interferon-β (IFN-β) biologic to treat multiple sclerosis have adverse side effects that cause liver injury; up to 60 percent present with abnormal biochemical liver tests. Although the treatment benefits many, the detriment to these patients cannot be overlooked – so a group of researchers hope to help with new biomarkers for liver injury caused by IFN-β (1). These biomarkers may make it possible to predict whether a patient is susceptible to liver injury.

## Just a Breath Away

A new diagnostic for pancreatic cancer may come from an unlikely source: your breath! A study of volatile organic compounds in breath has found that they act as novel biomarkers to detect the disease (2). GC/MS analysis of exhaled air can allow diagnosticians to identify patients with pancreatic cancer with 81 percent sensitivity.

## A Swallowable Substitute

The standard protocol for diagnosing small intestinal bacterial overgrowth and similar gastrointestinal tract disorders requires a breath test that evaluates intestinal gases – but the test often lacks accuracy. A swallowable capsule measured hydrogen concentration – associated with GI diseases – over 3,000 times higher than a breath test, resulting in a higher signal-to-noise ratio and subsequently a more precise diagnosis (3).

## Familial Heart Care

A review of existing scientific literature on non-syndromic thoracic aortic disease (NS-TAD) has shown that familial screening may benefit populations. The findings showed that associated gene mutations were found in 33 percent of first-degree relatives and 24 percent of second-degree relatives (4), meaning that relatives of patients diagnosed with sporadic NS-TAD would benefit from genetic screening.

*References*

1. *K Kowalec et al., "Common variation near IRF6 is associated with IFN-β-induced liver injury in multiple sclerosis", Nat Genet, 50, 1081–1085 (2018). PMID: 30013178.*
2. *SR Markar et al., "Profile of exhaled-breath volatile organic compounds to diagnose pancreatic cancer", Br J Surg, [Epub ahead of print] (2018). PMID: 30019405.*
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4. *G Mariscalco et al., "Systemic review of studies that evaluated screening tests in relatives of patients affected by nonsyndromic thoracic aortic disease", J Am Heart Assoc, 7, e009302 (2018).*

# In My View

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

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

*Contact the editors at edit@thepathologist.com*

## Changing the Perception of Pathology

**Pathologists need to reach out to the general public – and the earlier, the better**

*By Hayley Pincott, Associate Practitioner in Oral Pathology at University Dental Hospital, Cardiff, UK*

I'm fortunate enough to have found a career that I completely love and feel respected in. As a department, my colleagues in oral pathology and I are very rare. Why? Firstly because oral pathology is so specialized that the services we provide make us the only one of our kind in Wales; secondly, I feel, because our extreme specialization has led to a great working relationship with other healthcare professionals. However, there is still a large pathology workforce whose situation is vastly different, and I know that not everybody in laboratory medicine feels that they are recognized in the service they provide to patients and the impact they have on patient care. The question we need to ask ourselves is, "Are we doing enough to change this?" We are relatively unknown to the public – and, in some cases, even misunderstood by other healthcare professionals – but are we to blame for this? Are we taking part in public engagement or career talks in schools to change that perception? With the concern of a shortfall in workforce in the future, I feel we need to act to engage young people in pathology and biomedical science. I'm an avid watcher of the BBC2 fly-on-the-wall documentary Hospital. On the show, "the lab" is referenced quite often, but the term "pathology" is never used. Why not? And could a small change like using the word "pathology" start the ball rolling in making others aware of how much we are involved in healthcare?

About 18 months ago, I became a STEM ambassador because I really wanted to showcase my job and make students aware of pathology as a possible career choice. I also wanted to highlight our role in patient care to the public. I've visited a few schools to demonstrate pathology as much as I can; with students, I've stained cheek cells to view in a microscope, grown bacterial cultures, and demonstrated infection control. As part of British Science Week, I spent the day at a primary school where the theme was "exploration and discovery." I had the opportunity to teach different classes about body maps, including the circulatory system, which let me talk about the structure of blood

*"I feel we need to act to engage young people in pathology and biomedical science."*

and why it's important to us in pathology. The students were really excited about extracting DNA from their cheek cells, which opened up a channel to talk about the role of genetics. Another visit to a primary school was about healthy lifestyles, and that allowed me to talk about hemoglobin and the importance of iron in carrying oxygen. I showed the students how iron was found in a healthy diet by chasing bran flakes around a petri dish of water with a magnet! It was a really fun way to introduce them to hematology. One child even told me that they thought science was meant to be boring, but what we were doing was really fun. I think that if you engage children at a young age, their interest in science can potentially follow them through their education.

I've also recently competed in an online project called I'm a Scientist, Get Me Out of Here, which connected students with scientists. It was an incredible experience and I can't recommend it highly enough – you don't even need to leave the lab or office, so it's great for those who lack time or work in remote areas.

In general, I really enjoy public engagement, showcasing and discussing what we do as clinical scientists, anatomical pathology technicians, biomedical scientists, medical lab assistants, associate practitioners, and the many other roles involved in pathology. I have organized events for Biomedical Science Day (in which we'll place a stand in the concourse of University Hospital of Wales to raise awareness of laboratory medicine, as well as visit schools) and National Pathology Week (November 5–11), when we'll be inviting primary schools to visit on Friday and offering drop-in educational sessions to the public on Saturday.

Not sure where to begin with public engagement? Organizations like the Royal College of Pathologists, IBMS, and STEM Learning have amazing ideas and resources online for activities. Taking part is great fun and has the potential to change lives. If each institution committed to just one science event a year, it would be a huge but achievable way to promote laboratory medicine.

# The Economics of Personalized Medicine

## Can companies investing in innovative liquid biopsy technologies continue to ignore healthcare economics?

*By Ilan Danieli, Chief Executive Officer of Precipio, New Haven, USA*

As an economics-trained executive of a cancer diagnostics company, I often struggle to rationalize the business model and economic considerations of our healthcare environment. Most people are familiar with the statistic (ostensibly) stating that 90 percent of a patient's healthcare costs are incurred during the last six months of their life. We also know that the value derived from that spend – as measured by patient quality of life during that period – is often questionable. Yet companies continue to develop products and services that feed into and worsen that statistic, rather than attempting to improve it. We routinely hear of a new "miraculous" chemotherapy drug that costs US$100,000 per regimen and extends patients' lives by an average of about three months. This leads us to a complex question: How do we balance clinical, emotional, moral, and economic considerations? Are we, as a society, directing our resources in a sensible manner?

The field of liquid biopsy is one of the most exciting and promising areas in cancer diagnostics. As we have learned, the biology of malignant tumors is constantly evolving – but they give us one easy way to keep an eye on those changes: they shed DNA "breadcrumbs" into the bloodstream. The ability to detect tumor-based genetic changes via a simple, noninvasive blood test (a liquid biopsy) provides critical insight

*"Much like diabetes patients constantly monitor their blood sugar levels [...], cancer patients should constantly be on the lookout for genetic changes in their disease."*

into the patient's current clinical state. Companies have seized on this concept, raising hundreds of millions of dollars to develop sophisticated technologies that identify these changes and aid clinicians in treating patients. Some of the leading players have spent millions to develop broad panels with hundreds of genes, running on sophisticated next generation sequencers with complex bioinformatics platforms. As a result, these tests are expensive – $5,000–8,000 per test.

There are two key applications of liquid biopsies, each with very different target audiences, clinical needs, usage patterns, and related economics.

The first application is screening. One of the key factors in a successful battle against cancer is early detection. Just as in other areas where preventative medicine plays a prominent role, the ability to identify genetic abnormalities that may cause cancer – before the disease ever arises – is an attractive concept. As a once-in-a-lifetime test, clinicians treating patients may recommend that they and their family members get screened using large panel tests to identify potential risk. Payers may agree to cover the cost, balancing the high price against the potential benefit of early detection; indeed, it's likely that patients who can afford such prices themselves will want to "purchase" this insight into their future health risks.

The second application is monitoring. Science has taught us that cancer constantly evolves – whether based on genetics, outside factors (such as smoking or sunshine), or the very chemotherapy intended to battle it. A treatment that works today may become ineffective tomorrow. And even patients fortunate enough to achieve remission still face the terrifying possibility of the cancer's return. The good news is that, in either scenario, those genetic changes may present in the blood stream for "early warning" detection via liquid biopsy.

Timing is everything. Catching these changes early is critical, so it is imperative to constantly monitor the patient – both during treatment to quickly spot genetic changes that might render chemo ineffective and after remission in case the cancer returns. Much like diabetes patients constantly monitor their blood sugar levels to identify spikes and drops, cancer patients should constantly be on the lookout for genetic changes in their disease so that doctors can respond before it's too late.

*"Every piece of diagnostic information is useless if it doesn't drive a clinical decision."*

The problem is, these sophisticated tests are very expensive. A clinician, payer, or even a patient may be able to stomach a one-time $5,000 screening test. But there is no doctor, and certainly no payer, who, in the current economic environment (which is unlikely to improve in the near future), will agree to pay for this test more than once. And so, although this technology is sustainable for screening, it's far outside the realms of economic reality as a tool for ongoing cancer monitoring. In that sense, there is a major disconnect between the technology's ability and its applicability. Payers realize this and are reluctant to reimburse for these large panel tests; this is part of the reason many of these companies raise such vast sums of money, with investors essentially subsidizing the payment of these tests because the market will not.

The other disconnect revolves around the actionability of the tests' results. Every piece of diagnostic information is useless if it doesn't drive a clinical decision. A panel of hundreds of genes may be relevant as a "catch-all, fire in all directions" tool for patients seeking to turn over every stone in their genetic footprint. But for specific cancer patients with a diagnosed disease, the universe of genetics-driven treatments available – and thus, the actual number of relevant, actionable genes to be interrogated – is limited. So, for monitoring, large panels present a tremendous overkill.

Therefore, for the purpose of patient monitoring, we need targeted liquid biopsy solutions with panels that deliver focused, clinically actionable information at a cost that enables regular monitoring. Panels consisting of a small subset of clinically actionable genes relevant to the specific patient's type of cancer, using less complex and costly technologies, result in tests at a fraction of the price point of other broad NGS panels. As in many areas, there is no one-size-fits-all technology. Though some players focus on broad panels that provide exciting tools for patient screening, others take into consideration economic factors, creating low-cost tests that are economically feasible for repeat testing.

With the skyrocketing costs of healthcare, I believe solutions that embrace, rather than ignore, economic considerations will play a prominent role in patient monitoring through liquid biopsies.

# Coming Soon: Third-Wave Diagnostics

**The need for continuous and contextual biochemical data is clearer than ever – and enabling technology may be just around the corner.**

*By Jason Heikenfeld, Professor at the University of Cincinnati and Chief Science Officer at Eccrine Systems Inc., Cincinnati, USA*

When is it appropriate to attach the moniker "stone age" to a previous era of science and medicine? You could easily argue that pathology was in just such a stone age before biofluid- and tissue-based diagnostics came of age. So when will our present-day capabilities be similarly relegated?

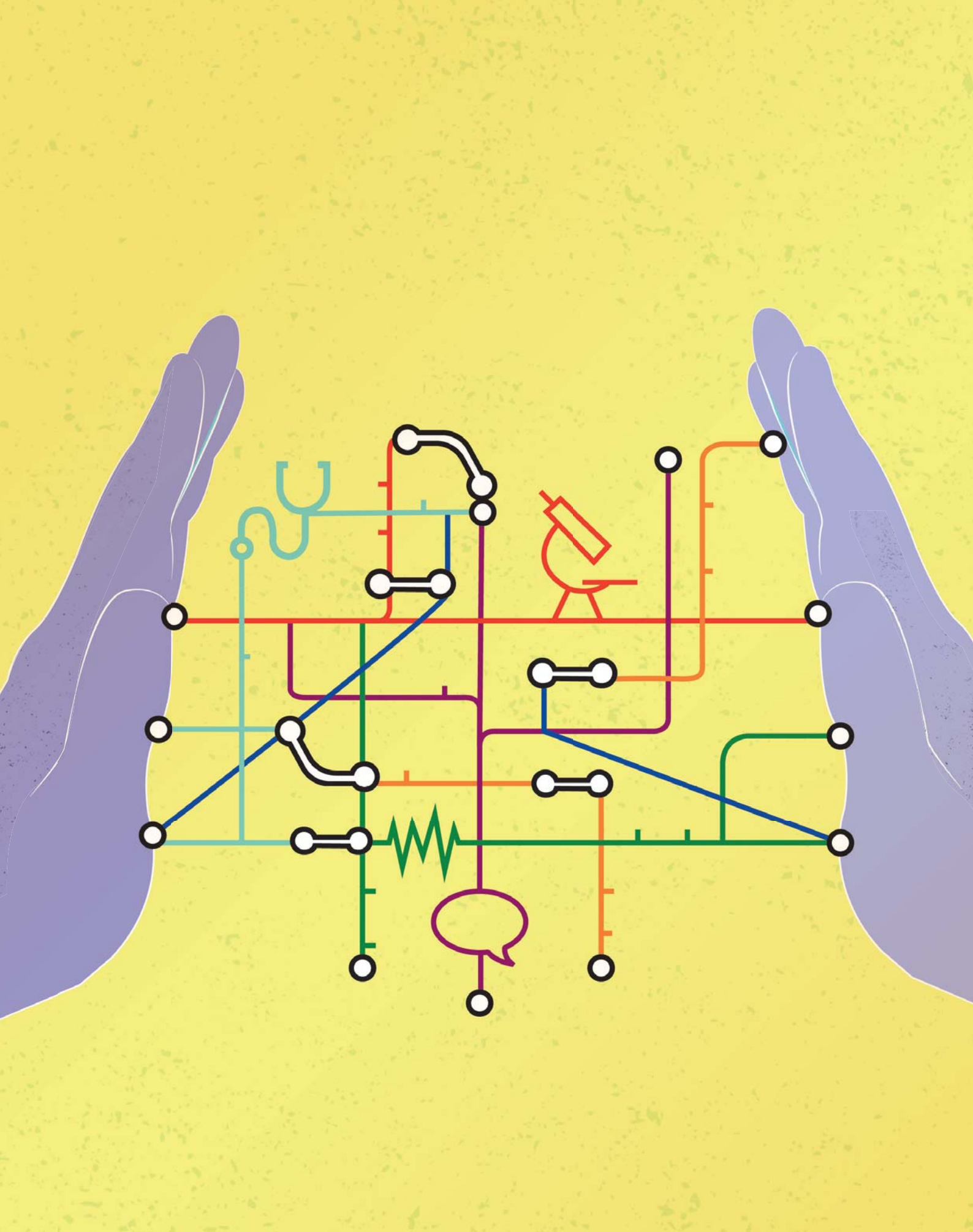
The last century produced the first wave of modern diagnostics based on collected biosamples that had to be sent to a laboratory for analysis. More recently, we have seen a second technological wave of point of care diagnostics that put the lab right in the hands of the doctor. This second wave brings added convenience and can even allow the doctor to validate a diagnosis while in the presence of the patient. Despite these advances, the remaining gaps in patient care are so significant that – one day not too far in the future – we may agree that pathologists in 2018 were in the "stone age" of medical diagnostics. To visualize the gaps, it may help to start thinking about what might soon be possible…

Imagine personalized therapeutics, where the dosing is adjusted in real time based on each individual's unique rates of absorption and metabolism and their treatment responsiveness. Or something even simpler: knowing for certain that the patient is actually taking the drug at all. Imagine a complete, continuous biochemical view of lifestyle choices for a cardiac patient, measuring potassium and brain natriuretic peptide continuously on both good and bad days. Imagine mental or stress disorders without the need for biased self-reporting, with treatment based instead on quantitative cortisol responses to daily stressors. Or imagine a workforce safety system in which chemical toxin exposure is reliably recorded as internal exposure and organ loading, not just in terms of what volume of toxin may have breached protective clothing.

Imagination may soon become reality with the third wave of diagnostics – one that allows patients to take the laboratory with them in the form of wearable biochemical monitoring systems. That's what prompted our research group (in partnership with Air Force Research Labs) to seek not a technological solution, but rather to first uncover the fundamental questions and challenges that would face such diagnostics. It led us to a biofluid that was at the time underused, but arguably had the highest upside potential: eccrine sweat. Seven years after that first inspiration, we have now demonstrated a wearable device that can locally stimulate sweat for multiple days, wick a tiny sweat sample up off the skin surface, and transport it within minutes to a Bluetooth-connected array of sensors that can continuously report analyte concentrations. In essence, we are extracting blood-level information continuously and noninvasively, with less than five-minute time stamps. And it works exceptionally well for small, hydrophobic analytes that partition readily through the tissue layers between blood and the sweat glands (such as steroid hormones or small-molecule drugs). Proteins and antibodies are larger and therefore more challenging because they are highly diluted in sweat, but we can now pre-concentrate such analytes by several orders of magnitude – also continuously and within minutes.

> *"Our goal is something even more powerful than continuous biochemical data for a patient; we want that data to be contextual."*

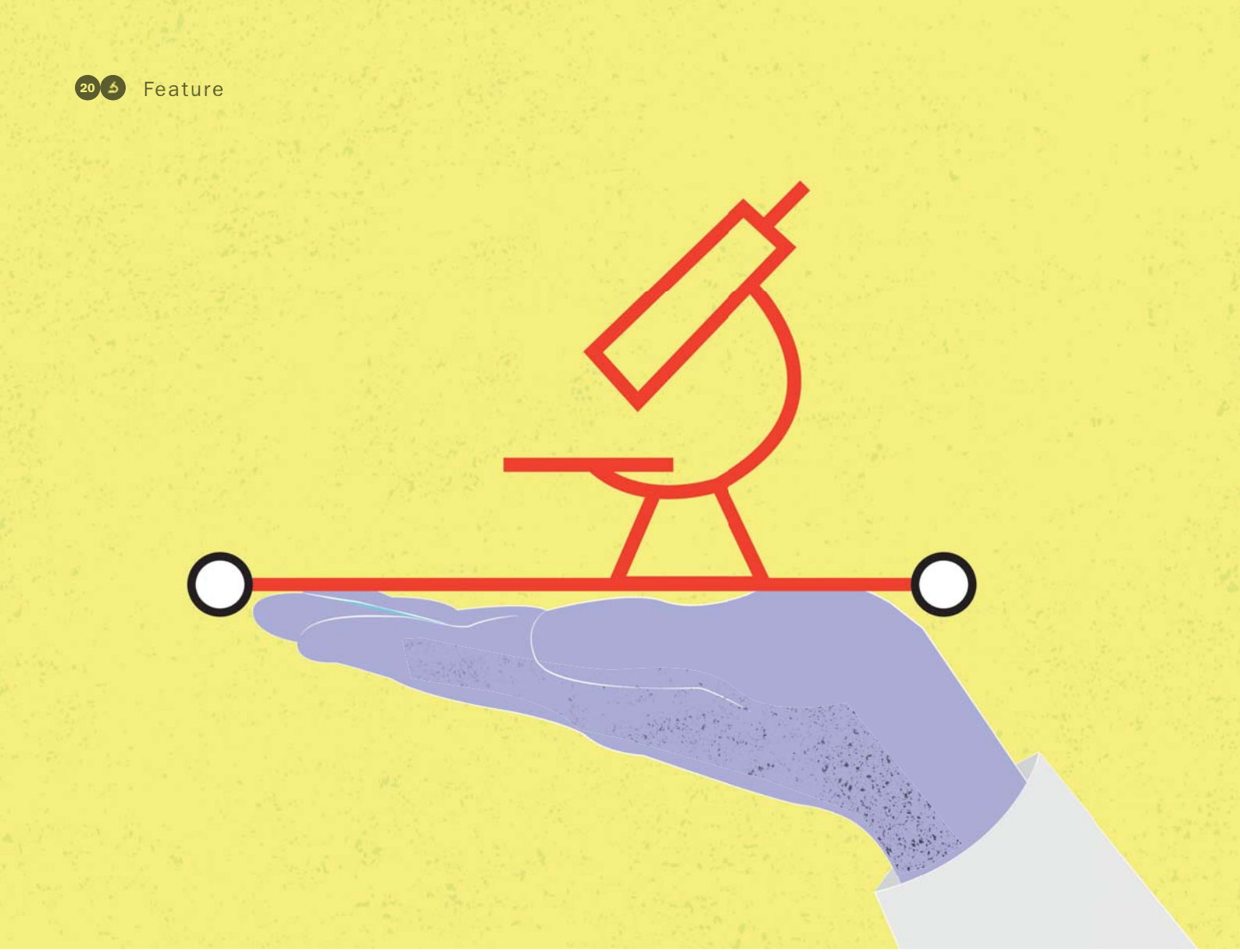
With this device, we hope to ride the crest of that third wave. Our goal is something even more powerful than continuous biochemical data for a patient; we want that data to be contextual. As doctors, you know just how limited a single data point can be – and you know that, in many cases, you would find it more powerful to trade absolute concentration accuracy for the ability to closely monitor relative changes in chemical analytes. Measuring such changes can be particularly powerful when they are placed into context. Coming back to the cardiac patient from earlier – was the spike in blood pressure due to eating a cheesesteak sandwich or because of a daily stress event? Or did the patient simply stop taking their statins? For many diseases, the coming wave will make current diagnostics look like interpreting a connect-the-dots picture before the connecting lines have been drawn.



# Tell Me, Doctor...

To keep pace with medicine's future, pathologists need to develop much better communication skills – with great urgency

*By Timothy Craig Allen*



"OUR INABILITY TO INTERACT EFFECTIVELY AND EFFICIENTLY WITH OUR PATIENTS, ADMINISTRATORS, AND NON-PATHOLOGIST PHYSICIAN COLLEAGUES IS TODAY'S GREATEST RISK TO OUR PROFESSION."

"The single biggest problem in communication is the illusion that it has taken place."
—*George Bernard Shaw*

"It is not what you say that matters but the manner in which you say it; there lies the secret of the ages."
—*William Carlos Williams*

Communication is everything – whether via a pathology report, a test result, a phone call or email to a colleague, a chance meeting with an administrator in the hall, or a conference room discussion. Communication is written words, eye contact, tone of voice, body language, dress and appearance, and much more – and it's something all physicians should strive to improve. For pathologists – traditionally office-bound, glass slide-reading diagnostic physicians – improved communication is unquestionably the key to our future success in today's evolving world of molecular medicine, team-focused patient

care, and payment for quality.

We pathologists must become better communicators to meet our new responsibilities as more engaged medical team players. Indeed, it's becoming increasingly obvious that our traditional approach to communication (primarily sitting in our offices generating electronic pathology reports and making the occasional phone call) is our likely path to failure as a profession.

Yet we resist even discussing how we might become better communicators. We seem to poke our heads out every now and then to point out the need to improve our professional communication skills, before sticking our heads back into the sand and hoping it will all just go away.

The issue won't go away. But we might disappear. Right now, we are the physicians who hold intimate knowledge of the details of molecular diagnostics and immunotherapy testing; we are the experts in cancer staging; we are the authorities on the pathophysiologies of diseases. But our industry colleagues have become so frustrated with our reluctance – or even refusal – to engage with them that they are beginning to bypass us altogether. Instead, they take their testing questions and needs to interventional radiologists and treating physicians. According to other professionals with whom I've personally spoken, bypassing pathologists is quickly becoming a trend – a chilling circumstance that we need to begin changing right away.

## Conversations with colleagues

Our resistance to fully addressing communication comes, I think, from a widespread sense of discomfort about the issue. Nobody wants to be considered a deficient or inferior communicator, and the idea brings about a vague sense of shame. Many of us even fear that we could become the subject of mockery if we openly confess to the elephant in the room: that we are not as skilled at communication as we ought to be. Professional communication is difficult, and it is hard to admit that it is difficult. And yet, our inability to interact effectively and efficiently with our patients, administrators, and non-pathologist physician colleagues is today's greatest risk to our profession.

What do we need to do?

- Actively engage with the healthcare team and get a seat at the table with them when decisions are being made.
- Routinely and collegially interact with our non-pathologist physician colleagues and our administrators.
- Involve ourselves in patient decision-making.

If we don't do these things, we will not be part of the future of medicine. It's a strong assertion to make, but it's one I truly believe – and we need to take equally strong action to remedy the situation. I don't think it will be of any surprise to the majority of pathologists that communication is a problem, and yet we have not even begun to grasp the solution. Let's use these concerns not to stoke fear, but to energize ourselves and other pathologists. The time for discussion is now.

Pathologists often talk about what we think our non-pathologist colleagues want but, all too often, we don't hear what they actually need. Why? Because we are not talking to them. We interpret or divine among ourselves what we believe they need, often leaving them unsatisfied when we are wrong. These are our professional colleagues – people who want good relationships with pathologists – and they are frustrated when those relationships don't happen. They fall all over themselves trying to communicate with us until, eventually, they give up, discouraged that they are not getting what they need. There's only one way to fix this problem: we must speak to them. We need them to tell us what they want, what they expect, how well we are delivering our services to our patients, and what we can do to improve. Strong, focused conversations with our colleagues will help guide us in providing better patient care. We must develop better, necessary, expected, and appreciated communication skills; we really have no choice.

"IMPROVING COMMUNICATION SKILLS DOESN'T JUST MEAN 'TALKING MORE.'"

## Finding time for culture change

Changing the way pathologists communicate will require no less than a cultural shift for all of us. Why? Because improving communication skills doesn't just mean "talking more." It isn't limited to specific situations, such as when working intraoperatively with a surgeon. We are endeavoring to be efficient and effective professional communicators in any situation that may arise as we conduct our professional responsibilities. It's not something pathologists are incapable of doing; a few days spent at any pathology conference will demonstrate just how communicative we can be in the right circumstances. Critically, what we need is more of our most precious resource – time.

Communicating successfully while still managing to allocate enough of our time to signing out cases or managing the laboratory is a significant, and often underestimated, challenge. To overcome it, we will have to change the way we spend our days – doubly hard given that we are currently paid for the behaviors and actions that have guided us into our traditional world of inefficient and infrequent communication. It's a factor we can't ignore as we step up our efforts to communicate in ways that don't directly lead to payment. But it's also a factor we must learn to overcome.

"WE NEED TO UNDERSTAND THAT FOCUSED MENTORING OR EDUCATION IN COMMUNICATION IS NOTHING TO BE ASHAMED OR EMBARRASSED ABOUT – AND CERTAINLY NOTHING TO SHY AWAY FROM."

The problem cannot be solved by a couple of classes on how to talk to others. We need our best minds working on ways to achieve the necessary culture change – taking us out of our comfort zones without impacting our ability to get the (paid) work done. The balance can be achieved – some pathologists are succeeding exceptionally well. Now, we need them to share their secrets and act as role models to the rest of us.

## Physicians first

In discussions with my pathologist colleagues, I've discovered that many of us see ourselves as just that – pathologists, rather than physicians. It's vital for us to realize that, just like other medical professionals, we need to constantly work to be better communicators. In our non-pathologist physician colleagues' world, it's simply unheard-of not to speak with a patient – and that's the mindset we pathologists need to adopt. If the expectation for other physicians is robust, direct, timely, and clear communication, then why shouldn't it be the same for us? If other physicians are taught to communicate effectively during residency and beyond, then why shouldn't we do the same?

Our jobs have changed significantly in recent years as science and technology have advanced by leaps and bounds. More and more, we practice "team medicine," which means we need to interact with other doctors, nurses, bioinformaticians, geneticists, researchers… the list goes on. This brave new world into which we have been thrust can be disorienting,

but it's also given us the need – and the opportunity – to develop communication skills of the same professional level as our non-pathologist colleagues. Practice makes perfect; if we pay consistent attention to developing those skills, we will quickly become much more comfortable speaking with not only our professional counterparts, but with administrators, patients, and families as well. Soon, we'll be having these interactions on a daily basis or even more often, just as our non-pathologist colleagues do.

We can no longer envision ourselves solely as laboratory dwellers, examining slides. Our prior communication training (or lack thereof, especially for older pathologists) did not prepare us for today's communication needs. But let me repeat: those pathologists who cannot communicate and collaborate effectively will find it increasingly difficult – eventually even impossible – to be a meaningfully contributing member of the increasingly broad medical teams responsible for patient care.

### The introversion myth

There is a widespread belief that many pathologists are introverted – one perpetuated through assumptions and jokes, some even told by pathologists themselves. We need to see this stereotype for what it is – a corrosive generalization that arose at least in part because of our discipline's longtime lack of focus on our communication skills. The time is ripe now to step out of our comfort zones and erase that myth – for our patients' sake and for our own. We must work together to teach our residents better communication skills, building upon what they learn as medical students; at the same time, we must assist our practicing pathologist colleagues who struggle to enter the new world of medicine. We must help those pathologists who have generally not spoken with patients nor actively and routinely communicated with non-pathologist physician colleagues and administrators – while remaining sensitive to their needs, experiences, and priorities.

"PATHOLOGISTS ARE NOT POOR COMMUNICATORS BY NATURE; WE ARE SIMPLY OUT OF PRACTICE IN THE PROFESSIONAL SENSE."

## A COMMUNICATION PROFESSIONAL'S PERSPECTIVE

Patrick Smith is Professor of Family Medicine, Chief Faculty Affairs Officer, and School of Medicine Associate Dean of Faculty Affairs at the University of Mississippi Medical Center, Jackson, USA. He has a PhD in psychology with expertise in communication.

I propose that the discipline should reduce variability in communication patterns to ensure that all communication is precise, clear, concise, and timely. To improve, pathology needs to create curricula that focus on communication. Other disciplines have extensive experience in creating a curriculum as an infrastructure for the communication competency dimension within graduate medical education. Perhaps adapting curricula from other disciplines for application to pathology would be a way forward. It may sound daunting, but help is available; many family medicine and primary care departments hire behavioral science faculty to do (or at least assist with) this work. Good training leads to good communication, and good communication leads to good patient care!

Perhaps most importantly, we need to understand that focused mentoring or education in communication is nothing to be ashamed or embarrassed about – and certainly nothing to shy away from. We cannot let the introversion myth stop us or impact our participation in multidisciplinary medical care. In fact, we should embrace continuous communication training as a team. Even our role models – those pathologists who are already visible and interactive – could benefit from continuing education. Strong communication skills are taught in medical school, but in my experience, pathology residents have traditionally let those skills fall into disuse, as they have not been necessary for us to practice successfully as physicians. Forging communicative relationships and getting out of our comfort zones as pathologists means we must rethink who we are.

## No shame, no blame

We must recognize that pathologists are not poor communicators by nature; we are simply out of practice in the professional sense. I expect that pathologists communicate as well as anyone else in everyday situations – with family and friends, while running errands, or even as patients! And I suspect that most pathologists were reasonably skilled communicators in medical school. Despite the stereotypes, most of us didn't choose pathology because we lacked the ability or inclination to interact with others! Unfortunately, many of us have passively allowed our professional communication skills to wither from lack of use. If we make a point of starting to use them regularly, I anticipate that they will rapidly return and improve.

One thing I want to make extremely clear is that pathologists shouldn't consider less-than-perfect communication a failing. Instead, we should acknowledge that it's not a skill with which we are all equally comfortable – and when we hear other pathologists say things like, "I don't want to talk to patients," or, "I don't feel comfortable speaking to colleagues," we should encourage them to find ways of overcoming their discomfort. Risk managers will readily tell us that the biggest risk for medical malpractice among physicians is poor communication. We need to jump feet-first into the challenge of getting out of our offices and meeting our colleagues' and our patients' needs.

## Our challenge is greater

Our non-pathologist physician colleagues communicate many times a day, often moment to moment, so even those less comfortable with it rapidly develop and maintain a good set of skills. As a result, improvement typically involves little more than "brushing up" on those skills. We, in contrast, must develop ours almost from the ground up. Our challenge is greater, but the principle remains the same: we are simply joining our colleagues on their quest for better communication.

To fully develop and maintain superior professional communication skills, we must use them frequently.

"PATHOLOGISTS HAVE TRADITIONALLY MET EVERY CHALLENGE THAT HAS ARISEN IN OUR PROFESSION; THIS IS MERELY THE NEXT IN LINE."

Communicating well once every six weeks misses the mark. We must habitually communicate efficiently and effectively with the administrators in the C-suite, the surgeon in the operating theater, the nurse in the hospital room, and the patient in the clinic. We should build frequent practice into our communication goals – not every six weeks, but every six hours or even every six minutes.

Our charge is clear, and the risks of not heeding the call are just as clear. Pathologists have traditionally met every challenge that has arisen in our profession; this is merely the next in line. We should have every confidence that we can develop and maintain excellent professional communication skills – and we can start by talking amongst ourselves about it. We all know the names of pathologists who are strong advocates and advertisers of the discipline – so we should be asking them: how do you do it? What is your advice? How should we be talking to one another, to other health care professionals, to patients? In this way, we can progress in the brave new medical world from the "doctor's doctor" to the "patient's doctor."

Who knows? One day soon, we could be the doctors whom others consider role models for professional communication!

*Timothy Craig Allen is Professor and Chair of the Department of Pathology, The University of Mississippi Medical Center, Jackson, USA.*

# From the Horse's Mouth

## Non-pathologist medical professionals give us their thoughts on communicating with pathology

Inter-specialty communication is vital – that's a given. But it's not enough to simply be aware of its importance; pathologists, like all other disciplines, must play an active role in ensuring that the lines of communication are open. Too often, pathologists guess at the needs of other specialties instead of asking directly, which could lead to better information and, ultimately, more productive conversations. So what do surgeons, radiologists, and other non-pathologist physicians need? Two other medical professionals share their views…

### The surgeon

*Christopher Anderson is Professor and James D. Hardy Chair of Surgery, Chief of the Division of Transplant and Hepatobiliary Surgery, and Medical Director of Abdominal Transplant at the University of Mississippi Medical Center.*

*What is the current state of pathologist communication?*

Highly variable. I think pathologists who specialize in a focused area naturally develop relationships with surgical and medical colleagues in the same area. An example is transplant medicine, in which the nephropathologist or hepatopathologist is integral to the team. Communication on such teams is often quite good, which is a real bonus for patient care. However, in general, pathology communication can be hit-or-miss. Often, the only direct communication between pathologist and surgeon is during a frozen section report. There is great opportunity to improve communication – from both sides.

*What is the necessary landscape for pathologist communication?*

Ideally, I think that pathologists and surgeons should have a very collaborative relationship that fosters clear, timely, and focused communication to guide patient care. Understanding the clinical picture is paramount. Quick communication of results (whether positive or negative) and asking clarifying questions about the clinical picture are always welcome. In the operative setting, understanding how the results of a frozen section may alter the course of an operation is important. Along those lines, it's similarly vital to tell the surgeon what is needed to make decisions – even though the pathologist can't make the "official" call themselves.

An example of this from my career was a late night/early morning operation in a patient with primary sclerosing cholangitis. There was little imaging evidence or gross evidence that the distal bile duct would be involved with tumor. However, my pathology colleague made sure he understood the clinical situation and the decision to be made based on the frozen. He clearly told me that he couldn't officially call it positive, but that he was very concerned, and that more tissue would likely not help him make a better call. Based on his concern, we extended our resection to include a pancreaticoduodenectomy (something we would not have done as a matter of course, because it increased the risk of postoperative complications). Ultimately, the margin in question was positive and the final margins were negative. This collaborative discussion in the middle of the night had a huge impact on the outcome of the patient, who is now eight years post-op.

Another important area in which surgeon-pathologist communication is important is the identification and marking of margins. Having my colleague come and ink a specimen in the operating room is a great pleasure. We both know that we are on the same page moving forward, and it humanizes our interactions, making further communication easier. Independent of how a particular specimen is marked, having the surgeon-pathologist team on the same page is important, and poor communication here can lead to inappropriate patient care decisions down the line.

*How can pathologists get from where they are now to where they need to be?*

I think specialty-focused teams can really facilitate this. Interactions in tumor boards, specialty multidisciplinary clinics, or other conferences help break down the physical and logistical divide that often exists between hospital operating suites and pathology labs. Phone calls or emails with questions about a case should be encouraged (in both directions). Finally, the pathologist-surgeon relationship is important and special. I encourage pathologists to come to my OR and talk, ink specimens, or just visit. Equally important, surgeons should be encouraged to visit the frozen area to review slides and discuss cases with pathologists. Too often nowadays, the locations of pathology departments and OR suites do not easily facilitate these activities, but that's an obstacle we need to overcome to establish and maintain collaborative relationships. It takes a team to achieve the best patient outcomes, and pathologists are important and integral members of that team.

## The radiologist

*Harpreet Talwar is Assistant Professor of Radiology and Chief of Breast Imaging at the University of Mississippi Medical Center.*

*What is the current state of pathologist communication?*

In my opinion, the current state of pathologist communication is, at best, decent. I have personally interacted with pathologists in both academic institutions and private practice. To me, it seems that pathologists in private practice seem to have a better grasp of the need (or perhaps a more deep-seated desire) to be more communicative with referring physicians for results and other critical findings. Are they keeping the referring physicians happy to retain their business, or do they have a greater sense of responsibility in patient care? I believe it may be a combination of the two. To maintain strong business with referring physicians, I believe private pathologists may want to keep them up to date with their patients' details – but I also believe that, in the process, they may achieve greater satisfaction in patient care. As far as academia goes, perhaps greater patient volume and/or the burden of other duties, such as teaching, may not give academic pathologists the luxury of time private practitioners enjoy. It is also possible that pre-established referral patterns instill a sense of security in the academic pathologist, making them think that a phone call (or lack thereof) will not necessarily have much effect. Unlike those in private practice, they have no additional incentive to keep their referring physicians "happy."

"PATHOLOGISTS HAVE TO GET OUT OF THEIR COMFORT ZONE AND BE RECOGNIZED AS ACTIVE PHYSICIANS IN PATIENT CARE."

*What is the necessary landscape for pathologist communication?*

Pathologists, as specialists, must be more communicative with referring physicians. In the age of personalized medicine and multi-specialty patient care, I believe it is judicious for each specialty to recognize the significance of their role in the care of each patient. We are encountering increasing numbers of medically complex patients (thanks to factors like longer lifespan and greater obesity), making it more important than ever that we take a unique approach to each patient's diagnosis and treatment. It behooves each specialty, including pathology, to participate as actively as possible by interacting with referring physicians. Rigorous communication between specialists also avoids unnecessary medico-legal pitfalls. Personally, I am a big fan of a quick phone call or email when I encounter a problem or an unexpected result in a breast biopsy. I try to include pertinent patient history and my own best guess (even if it's just "benign" or "malignant") in these brief points of contact, but in more complicated cases – for instance, amyloidosis of the breast – I prefer a discussion amongst all team members to select and implement the best treatment pathway. In multi-specialty tumor board meetings, I definitely rely very much on the pathologist's input to ensure concordance of results, markers, and margins so that we can optimize the patient's care.

*How can pathologists get from where they are now to where they need to be?*

Pathologists have to get out of their comfort zone and be recognized as active physicians in patient care. Multi-specialty tumor boards have defined the roles of each specialty and forced the traditionally "paraclinical" specialties, such as radiology and pathology, to be more involved in the decision-making process. Physicians have higher job satisfaction if they feel more involved in patient care – and the job description of a pathologist is moving toward ever more active participation.

I am not aware of any referring physician who would get annoyed at a pathologist who took the time to phone them about a patient. After all, who likes to log in to the EMR for test results when you can discuss them with the pathologist directly? I believe there are no situations where it's better to hedge and include a broad differential "just in case" than to have a conversation, however brief, about the patient's symptoms and the referring physician's thought processes.

*Join in the conversation or submit a question to Timothy Craig Allen by using #PathComm and tagging @pathologistmag on Twitter. Our author will be answering all questions on September 5th at 9:30am CT / 3:30pm GMT+1.*

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Empowering pathologists to build a better future for pathology

# Childhood Cancers Are Different

**The features that drive pediatric cancers are vastly different to those in adult disease – so how can we ensure that children are accurately diagnosed and treated?**

*An interview with Tim Triche, Co-Director of the Center for Personalized Medicine at Children's Hospital Los Angeles, USA*

How do childhood cancers differ from those in adults?

Adults acquire a mutational burden over the course of a lifetime; the longer you live, the more mutations you acquire and the greater the probability that you will develop cancer at some point. This growing load of mutations is why cancer in adults increases over time.

In contrast, infants and children have had no opportunity to accumulate mutations, so it's not possible that acquired mutational burden causes disease. Clearly, pediatric cancers arise from a different process. It comes as no surprise, then, that we find very few acquired mutations in childhood cancer; instead, we see a large number of patients with inherited gene defects and unusual features like copy number alterations, gene amplifications, or chromosomal breaks leading to gene fusions – alterations that are much less common in adult cancer. Adult cancers usually have mutational drivers, many of which are identifiable, so the pharmaceutical industry focuses on therapies that target those drivers – but because most childhood cancer is closely related to genomic alterations caused by development gone awry, the treatments that work for adult cancers are often not appropriate for pediatric disease.

How useful is genomic data in supporting advances in diagnosis, prognosis, and treatment selection?

Genomic data have changed everything. When we started doing genetic analysis of childhood cancer, we were assaying single alterations with tools like PCR and Sanger sequencing because we didn't have the knowledge or the technology to do anything more broadly. For example, when poor prognosis childhood neuroblastoma was linked to the amplification of a gene called *MYCN*, it quickly became obvious that we needed to develop an assay for that amplification. Test developers scrambled to create one (and succeeded) – but, of course, that was only one of multiple disease features we needed to examine. And so, for years, we kept developing one assay after another, each of which was critical to allocating patients to high- or low-risk treatment protocols, but none of which provided enough information in isolation. For example, patients with *MYCN* amplification may also have co-amplification of *ALK*, for which we have targeted inhibitors – but with a single-gene *MYCN* copy number assay, you wouldn't have that information.

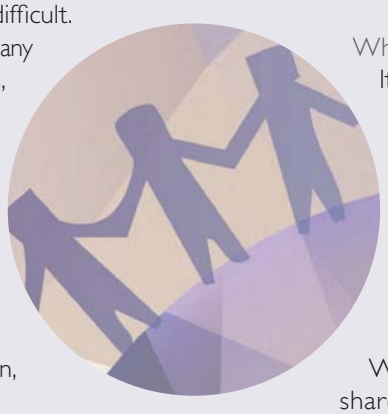
The solution? A platform for all of the necessary analysis – *MYCN* copy number, c-Myc expression, and all of the unique features we find in childhood cancer. As we've discussed previously, childhood cancer is fundamentally different to cancer in adults – and a major factor affecting its accurate diagnosis is that we see different drivers, like copy number variation and chromosomal breaks. Chromosomal breaks and gene fusions are not easily detected by DNA sequencing; they can be seen much more readily at the RNA level. Ideally, a pediatric cancer panel should look at both RNA and DNA to detect the entire spectrum of common abnormalities in children. At the RNA level, it should detect gene fusions and expressed gene abnormalities; at the DNA level, copy number alterations and sequence abnormalities, including insertions and deletions (InDels). Next generation sequencing (NGS) platforms can look at both to spot multiple abnormalities in one large, comprehensive panel, so they have been a huge boon to diagnostic accuracy and treatment selection.

What can we achieve in the future by using this technology more broadly?

Although pediatric oncologists and pathologists are a collaborative group, it can be very difficult to compare results when each physician performs different

assays in different institutions in different ways with different content. One of the most significant opportunities offered by a standardized panel that incorporates the important features seen in childhood cancer is that, for the first time, no matter where you run the assay, you'll get the same results – so, in theory, you can compare your data to that of someone at another institution or across the globe. This is essential for cancer in children, which is far less common than in adults. Learning what is and is not common – and, even more importantly, what is and is not clinically relevant – is correspondingly more difficult.

NGS methods generate many candidate abnormalities, or variants of unknown significance (VUS), but knowing which ones matter is an ongoing challenge that can be met only by increasing our knowledge about which ones relate to disease onset, progression, treatment, or outcome.



*"For the first time, no matter where you run the assay, you'll get the same results."*

Science and medicine are moving ever more toward collaborative approaches and shared data, and standardized results (or "common data elements") ensure that we're all sharing the same information. At our institution we have implemented an NGS panel that has been an extraordinary success. Over 60 percent of the patients we examined (more than 200 in the past six months) had at least one actionable mutation – something nobody expected. Now, in addition to our conventional tumor board, we have a bi-weekly molecular tumor board in which we discuss an average of six to 10 patients and make treatment decisions based on the childhood cancer panel test results.

### What is ICON?

It occurred to us early on that if researchers at multiple institutions are all running the same assay and accruing the same data, it provides a rich opportunity for collaboration. Why wouldn't we share that information so that everybody learned a little bit more? That idea was formalized in the creation of the International Childhood Oncology Network (ICON), which allows us all to share data, best practices, and potentially linkage to clinical treatment protocols matched to specific gene defects. This began with our own institutional database of Children's Hospital Los Angeles cases, but has now grown to include multiple databases of childhood cancer from published studies from around the world. Not only can oncologists and pathologists compare each new result they obtain to previous ones from around the world, but the new result also adds to the existing database, increasing its content and relevance. ICON is a mechanism to share that information – and it's our hope that it will foster more and better clinical research into childhood cancer than ever before.

### What distinguishes ICON from other such databases?

The biggest difference is that ICON is intended to be a clinically relevant, multiple-contributor, multiple-user, real-time database that contains both genomic and clinical data on the included patients. Many existing databases have very little clinical information linked to the genomic data, and each is typically focused on a specific type of tumor or tumors and a specific analysis platform. These can range from older microarrays to whole exome sequencing, commercial panels, custom panels, or advanced research methods like epigenetic analysis of methylation, histones, chromatin modifiers, and the like. Although each is useful in its own right, none necessarily leads to direct clinical utility; in contrast, a comprehensive, all-inclusive database can at least document incidence and linkage to specific tumor types. When combined with a core database of specific genetic defects linked to specific patients, incorporating common data elements representing the content of the panel, it becomes possible to decide – for instance – d whether or not a given VUS is likely clinically relevant. Alternative methods like statistical analysis of how often a given polymorphism occurs in a given population are useful guides, but fail to capture whether those variants are associated with disease. With larger numbers of cases, we acquire the power to decide based on statistical analysis linked to combined clinical and genomic data – a very powerful approach that is not possible without a database like ICON.

### How can others join ICON ?

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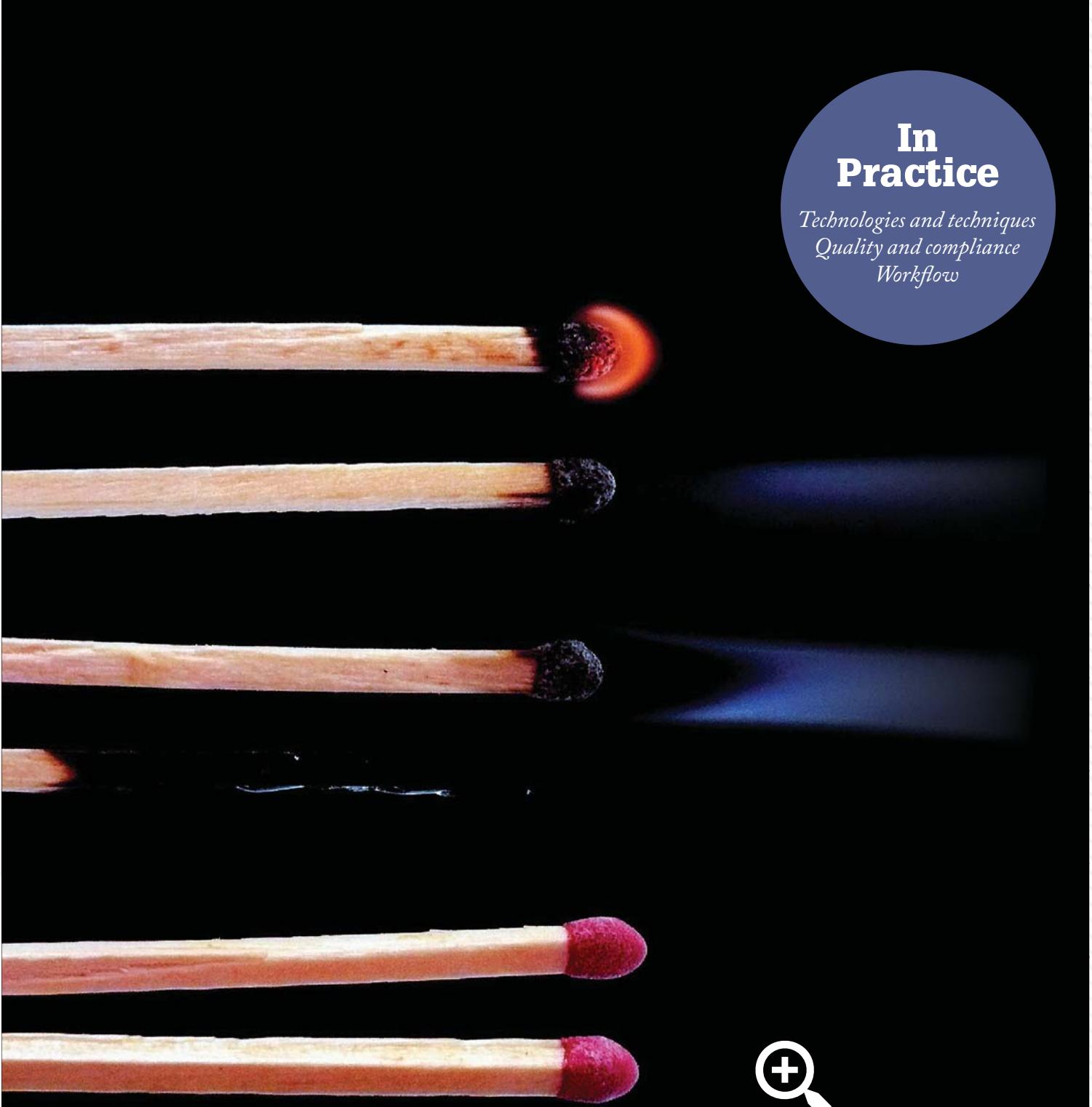


# In Practice

*Technologies and techniques*
*Quality and compliance*
*Workflow*

# Wellness: A New Kind of Best Practice

**To give patients the highest level of care, we must make sure that we ourselves are happy, healthy, and engaged**

*By Marisa Saint Martin*

As physicians, our practice goes beyond merely what we do at the microscope or in the clinical laboratory. It's well known that patient satisfaction is constructed on a foundation of healthcare provider wellness and satisfaction. When providers are engaged and happy, the result is safer and more efficient encounters with our patients. But is that how we always feel? And if not, what can we do to ensure that our patients (be they cells on a slide, blood in a test tube, or human beings in a hospital) are receiving our best care?

*At a Glance*

- *Pathologists, like all physicians, constantly face the challenge of burnout and other mental health issues*
- *To seek a resolution, we must approach the problem using a tri-dimensional strategy that considers three angles: institutional, group, and individual*
- *It's especially effective to target trainees – often at a high risk of burnout – who can then take what they have learned to their future workplaces*
- *Practical tips and tricks can help institutions implement resilience and wellness training*

## A dangerous situation

Data on physician burnout in the United States overwhelmingly points to a national crisis. Being a physician is, in fact, considered a risk factor for suicide – with an incidence rate previously reported as 1.8 times the national average (1,2). Pathology, unfortunately, is no exception to this rule; the burnout risk for pathologists is reported at about 42 percent (3). Not many departments of pathology and laboratory medicine address this issue, and even fewer pathology residency programs offer formal resilience training to help those at risk alleviate the strain. The burnout dilemma takes a multidimensional form: it involves the individual, the group, and the system. In the case of pathology, this means the individual pathologists, the laboratory or department, and the hospital or institution.

The burden extends to all colleagues in the laboratory and the healthcare arena; although the individual burnout statistics may be different for nurses, technologists, laboratory scientists, or clinicians, the fact remains that it is a systemic issue with no single easy solution.

There is hope, though. Wellness and resilience can be taught, and groups and institutions can put formal training into place to help those who work there to weather the storm. In our department at Loyola University Medical Center, we are approaching the issue with our residents using a comprehensive tri-dimensional strategy. Our goal? To provide them with tools to maintain the joy, humanity, and satisfaction of practicing pathology and laboratory medicine throughout their careers.

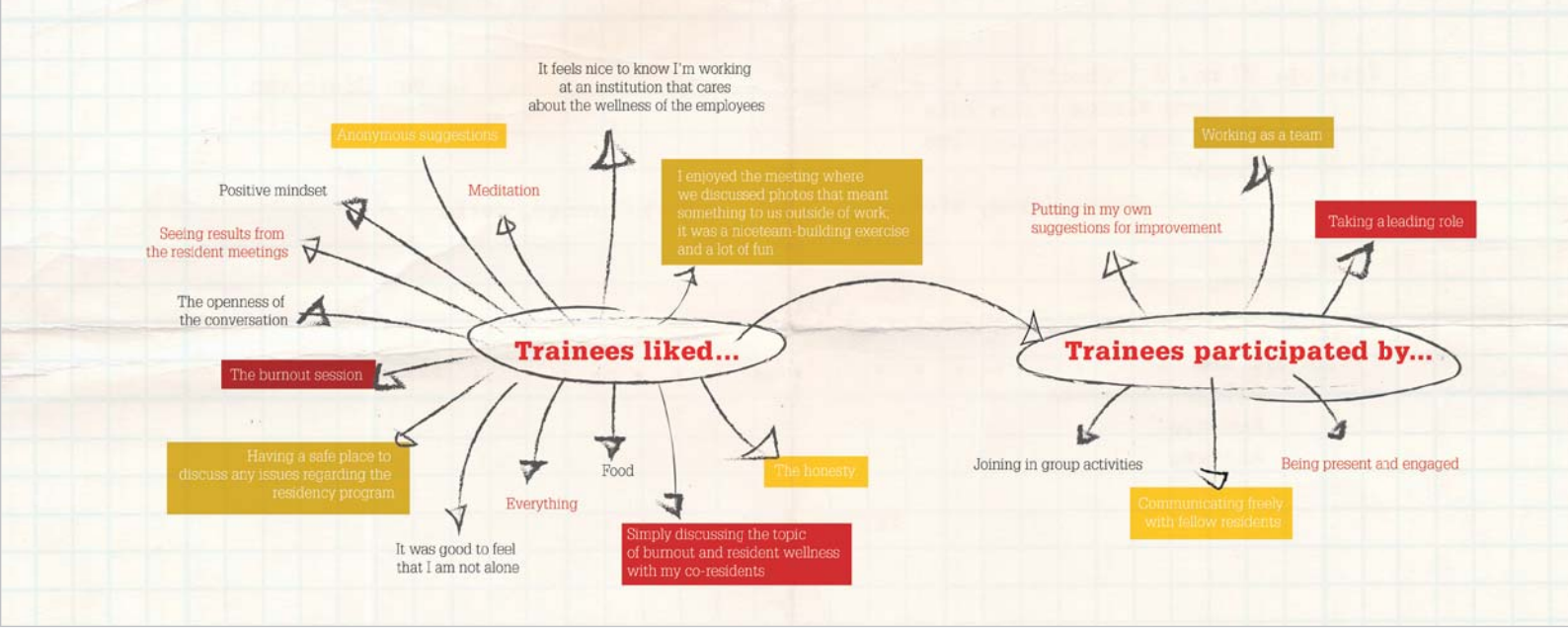
The tri-dimensional approach involves strategies for the institution, the group, and the individual. At the institutional level, we try to improve working conditions for all physicians. The administration at Loyola and at the Gottlieb Memorial Hospital plays a key role in this. In our case, the "group" refers to pathology department trainees (residents, fellows, rotating observers, and students). We spend time with them brainstorming ideas to better our department, and then – most importantly – we act on those suggestions. We already have requested several changes (such as new microscopes to make work easier and more comfortable), and we intend to continue developing and passing on new ideas. And, finally, we all have responsibility for our own individual wellbeing – so we've started a series of Wellness Talks to teach our trainees about different approaches to stress and burnout, including physical and mental health, mindfulness techniques, and more.

## Talking about wellness

Initially, we conducted a survey of our pathology residents that indicated an overall need for wellness and resiliency training. After some discussion as to the best approach, we settled on monthly talks (including a free lunch!), which we supplement with additional education.

I organize the talks myself, but the residents drive them. Each meeting starts with a moment to celebrate and be grateful for something, followed by a short talk on a specific subject, such as burnout symptom recognition, suicide prevention, physical health, the benefits of sleep, or the effects of gratitude on mental health. After the didactic portion of the meeting, we move into action items and brainstorm what we can do next to improve the department's wellbeing. We accomplish a lot with each session, but I think the biggest driver of attendance is that the attendees feel free to express their opinions in a non-judgmental environment. Because I want to respect the confidentiality of what is discussed at the meetings and give people a space to express themselves freely, only our trainees are invited to attend – and I make it clear to them that everything we discuss is private, except for action steps that they permit me to bring up with the people who can enact change.

Based on the success of these talks, we are now in the process of formalizing a wellness curriculum that will focus on stress prevention, management, treatment,




Anonymous responses to the six-month and one-year surveys on Loyola's wellness talks.

and professional and life purpose. Our ultimate goals are to increase wellness among our pathology residents to prepare them for a high-stress environment before entering the workforce, and to increase their ability to bring the tools they have learned to their new workplaces

## Tips and tricks

We have implemented a number of initiatives to assist our residents, many of which are applicable to all of our colleagues. What can other institutions take away from our approach?

- Ensure that your residents have access to sessions with trained resilience coaches. We provide this service in addition to standard psychological help, an Employee Assistance Program, a Care for the Care Giver Program, and chaplaincy services.
- Have a portal on your internal network that allows your staff members to access wellness and resilience resources, such as those named above. At Loyola, our residents and faculty can find these programs by tapping into our website's Resilience Page, so accessing them is quick and convenient.
- Foster a successful mentorship program within the department. This can focus on partnering new residents with those further along, or it can include all of your faculty members. Our institution pairs first-year residents with senior residents in first-time rotations, and each resident chooses a faculty mentor during their first year.
- Provide opportunities to learn mindfulness and meditation techniques. We discuss and practice those techniques during the wellness talks, so people receive regular refreshers and can ask for assistance if needed.
- If you are able to provide discounts to other resources, such as your institution's fitness center (or even a nearby gym or wellness facility), this can create opportunities for your colleagues to pursue wellness on their own time. For instance, pathology residents at Loyola receive discounted admission to the school's Fitness Center.
- Stay abreast of how well your initiatives are working and how your faculty and staff are feeling. We conducted a brief pulse survey to identify one positive, one frustration, and one thing that needs to be changed at the beginning of our study, then ran separate wellness surveys at the six-month point and after one year. Results showed a significant trend toward better individual stress control and a more positive overall environment.
- Consider working with other departments to develop an institutional resilience resource. This grants easy search access to volunteer activities and interdepartmental networking – activities that contribute to many people's overall wellness.

There is no one-size-fits-all solution. Each one of us may have a different way of achieving balance and managing the multitude of demands in our personal and professional lives. But remember: we don't have to travel this path alone. Together, we can create an environment where our personal goals and our love for medicine can coexist and thrive.

*Marisa Saint Martin is Assistant Professor of Pathology at Loyola University Medical School, Maywood, Associate Director of the Residency Program, and Laboratory Medical Director at Gottlieb Memorial Hospital, Melrose Park, USA.*

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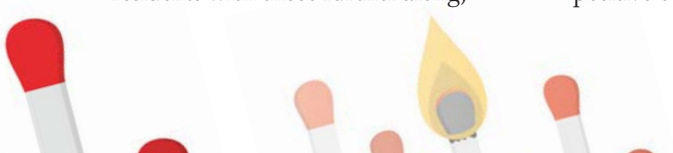

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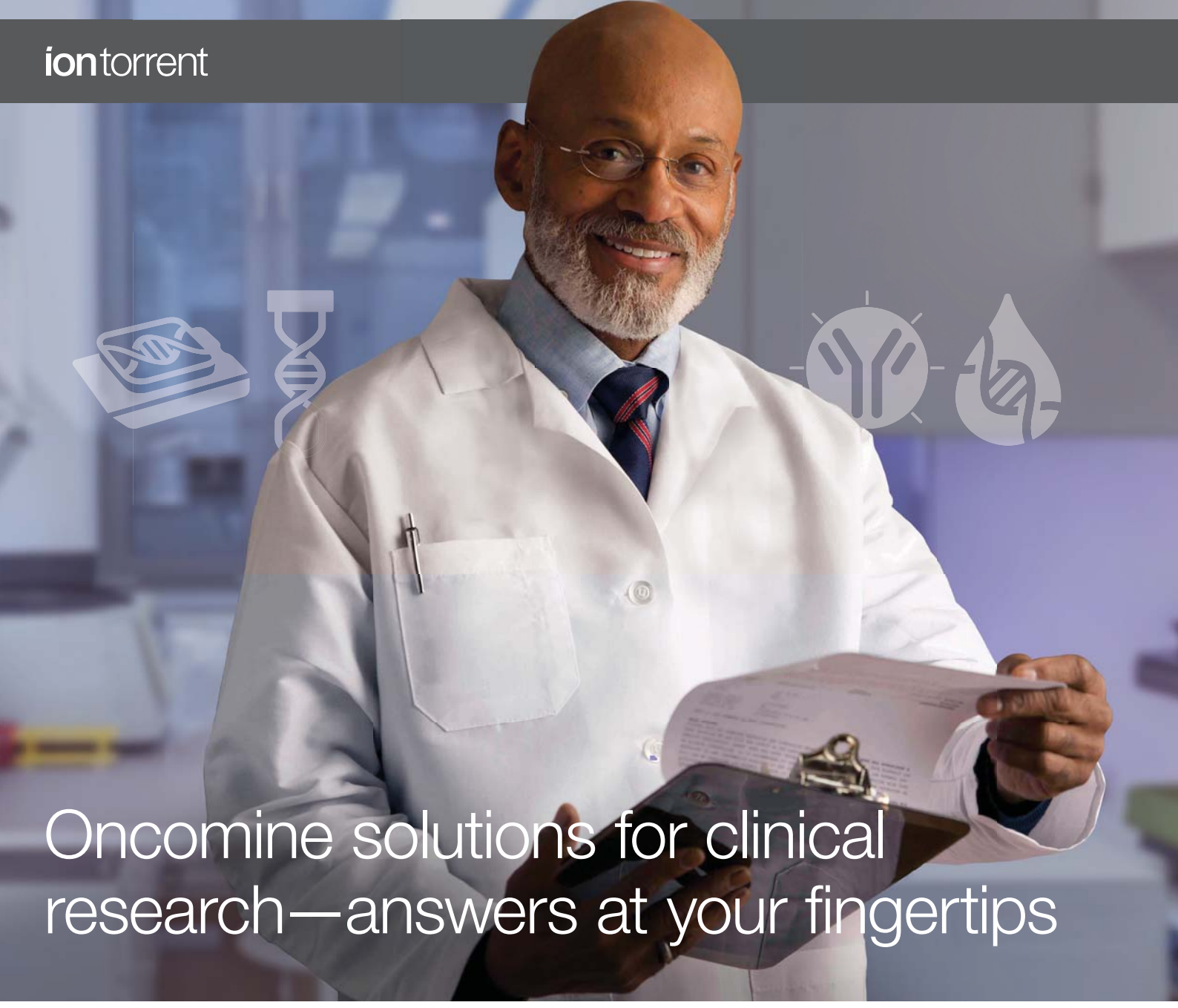

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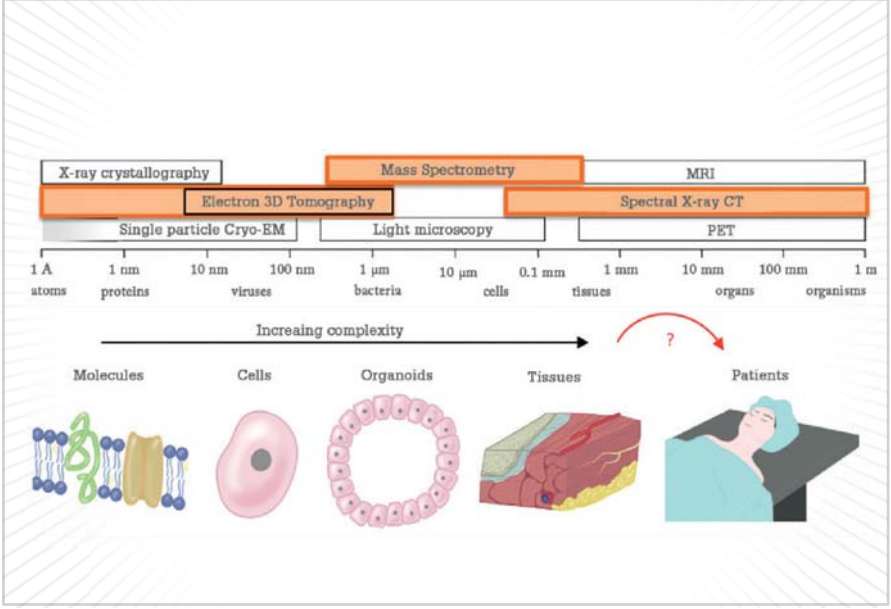
# The Inside Story

**The Maastricht MultiModal Molecular Imaging Institute (M4I) continues to break new ground in mass spectrometry imaging – providing pathologists with better diagnostic tools, and giving us a close-up view of the complex molecular machinery that underpins health and disease**

*By Ron Heeren*




Breaking boundaries is a key theme of my work, and pivotal to all fields of science. The motivating force of most scientists is to break through boundaries of knowledge – seeing something that no one has seen before is an awe-inspiring experience. Whether they are building better microscopes to visualize molecules in a cell, or better telescopes to detect far-away stars, scientists have the same drive – they want to see what they cannot yet see.

## *At a Glance*

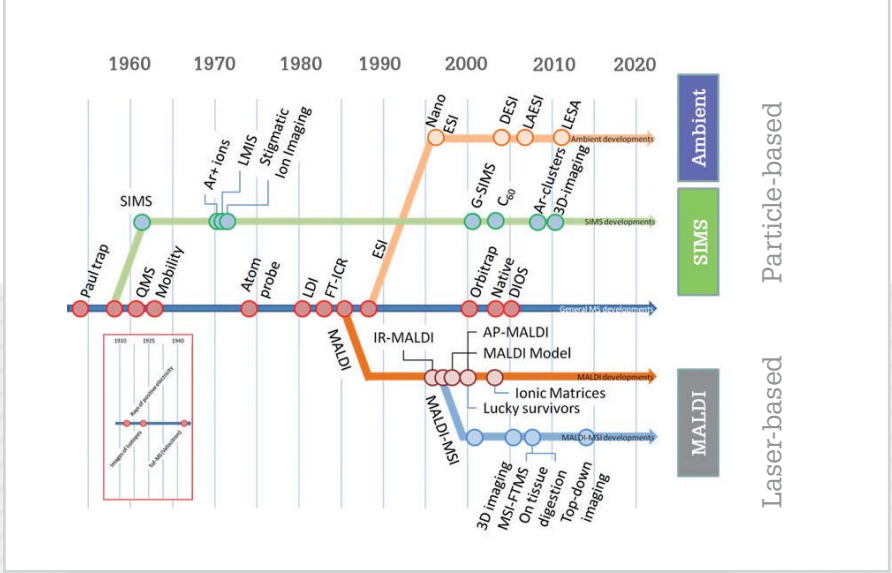
- *Cutting-edge research in mass spectrometry imaging (MSI) development, informed by detailed molecular data, can advance the field of precision medicine*
- *Researchers at the Maastricht Multimodal Molecular Imaging Institute are improving MSI to quickly differentiate between isomers and identify changes over time*
- *Integrated MSI tech in intelligent tools like the iKnife could become an invaluable tool to increase the accuracy of tumor resection and reduce the invasiveness of surgery*
- *Growing interest in MSI across multiple fields will hopefully lead to the creation of revolutionary targeted diagnostic aids*

On a more down-to-earth level, breaking boundaries between disciplines is a crucial facet of our work. We need to make sure that our knowledge crosses the boundaries of our own disciplines to answer the big questions society faces. Whether it is in life science, food, water or energy, input is needed across the boundary of mathematics, physics, chemistry, biology, and medicine.

I have always been driven by curiosity; I just love figuring out how the world around me works. If the switch on my bike light stops working it's not enough to simply replace it; I want to understand the problem and try to fix it. The same curiosity that sees me dismantling my bike light also motivates my work, albeit the questions I ask are much bigger! At the Maastricht MultiModal Molecular Imaging Institute (M4I), we seek to visualize fundamental molecular processes, and apply that knowledge to improve human health.

Clinicians often have very sparse information to work with – they are forced to make life-and-death decisions without all the pieces of the puzzle. It's clear to me that the future of medicine lies in clinicians' gaining much more detailed information about the patient to deliver more personalized treatment with a better outcome. This personalized medicine – or, as scientific visionary Leroy Hood terms it, personal, predictive, preventive and participatory (P4) medicine – is where I focus my work.

To make personalized medicine a reality, we must find a way to resolve the incredible complexity of the human body and apply it in clinical decision-making. And that involves gathering as much information as possible at the genome, proteome, and metabolome level and coupling it to disease manifestation, treatment choices and, ultimately, patient outcome. After we gather all of this data, we can start building complex clinical decision-making models. Developments in information technology, machine learning and artificial intelligence have already started to play an increasingly important role in this process, as the sheer volume of the available personal data becomes too daunting to interpret for an individual clinician (or researcher,




Reproduced from: RMA Heeren, "Getting the picture: The coming of age of imaging MS", Int J Mass Spectrom, 377, 672-680 (2015).

# History of Mass Spectrometry Imaging

**There are three main categories of mass spectrometry imaging (MSI): secondary ion MS, ambient MSI, and laser-based MSI**

In the 1960s, secondary ion mass spectrometry (SIMS) appeared as one of the first surface analysis technologies. Researchers employed energetic ion beams to generate secondary ions that would tell them something about the properties of a surface. At first, they focused on elementary surface composition, but they quickly realized that SIMS could be deployed to study surface chemistry, which piqued the interest of physical chemists. Modern SIMS instruments can study organic surfaces in unprecedented detail. Recent advances have included the implementation of gentle Ar-cluster beams that sputter surface without any organic subsurface damage, allowing us to build full three-dimensional molecular models of single cells. Equally revolutionary was the implementation of tandem mass spectrometry for structural identification, which moved the field from "pretty pictures" of individual m/z values to interpreted biological images. These technologies have found their way into application domains ranging from material sciences, catalysis, forensic sciences, semiconductor sciences, coating technology and, of course, biology and biomedicine.

Ambient MSI was developed when researchers realized that not all samples were suitable for the vacuum of a mass spectrometer. It took until early this century for a suitable ionization technology to be conceived – and desorption electrospray ionization (DESI) is still one of the main ambient imaging technologies for non-vacuum-compatible surfaces. It deploys a supersonic jet of charged droplets that impact the surface and pick up surface molecules. Like SIMS, it involves charged particles that impact a surface, but the desorption and ionization mechanisms are markedly different. The development of DESI resulted in a new field of imaging research and is used to directly study plant surfaces, hydrogels, water-containing polymers, drying paint and bacterial colonies on agar plates, to name just a few. It is also widely used in biomedical tissue imaging, as it requires little to no sample preparation.

Though SIMS and ambient techniques have been valuable, the laser-based technologies have arguably had the biggest impact on MSI. In particular, MALDI-MSI has revolutionized MS-based molecular pathology. The key advantage over the other two technologies is that MALDI-MSI can offer information on a much wider variety of compounds, including metabolites, lipids, peptides, proteins, and intact polymer molecules directly from complex surfaces. Even though every molecular class requires a different sample preparation protocol, the breadth of molecular coverage, even within a single class, is still unsurpassed. Spatial resolution has evolved over the years from hundreds of micrometers to just 1–5 micrometers, making the technology compatible with morphological features of interest to pathologists.

All three types of imaging, whether particle- or photon-based, have benefited from the technological advances in mainstream mass spectrometry. MSI can now be routinely performed on modern hybrid high-resolution instruments. In addition, developments in time-of-flight (ToF) mass spectrometry have provided new high-throughput approaches that allow us to screen a tissue section in 10–15 minutes, dependent on size and required spatial resolution. These two methods combined – high-throughput MS with high-resolution MS – are the cornerstones of MSI-based clinical diagnostics. At M4I, we routinely use them back to back – high-throughput MALDI-ToF-MSI to screen tissues from large patient cohorts, complemented with high-resolution FT-based MSI on selected samples to identify the molecular profiles found. New methods are surfacing fast; three years from now, the MSI field will undoubtedly look very different to today. As more and more disciplines adopt (and adapt) our technologies, I believe we will move from evolutions to revolutions in the years to come.

## Mass Spectrometry Imaging 101

*By Shane Ellis*

Mass spectrometry imaging is a molecular imaging technique that exploits a unique feature of every molecule – its weight. By measuring the weight (mass-to-charge ratio) of all the molecules from a small region of a sample, we can determine the spatial locations and concentrations of molecules present in the sample. By sampling many points on a sample, we can build detailed images (ion distribution maps) of hundreds of molecules simultaneously. This allows us to see how the presence of certain molecules alters others in the surrounding environment, and how localized chemical processes vary across a complex and heterogeneous sample. MSI involves a variety of techniques, such as pulsed-UV laser irradiation (MALDI), focused ion beam irradiation (SIMS), or charged solvent droplets (DESI). Each method has strengths and weaknesses, and here at M4I, we combine all three to help us find answers to complex biomolecular questions.

*Read more from Shane on page 40.*

for that matter). Data scientists will lead clinicians, and will in turn be led by clinicians, analytical scientists and epidemiologists. It's a nice example of knowledge crossing borders to improve healthcare on many levels.

How do we gather the data needed by modern medicine? For me, mass spectrometry and, more specifically, mass spectrometry imaging (MSI) is central to the endeavor. Mass spectrometry already provides insights into many of the molecular classes found in complex clinical samples, such as blood, urine, cerebrospinal fluid, and many more. Combined with modern chromatographic separation technologies (GC, CE, LC, LC×LC, and so on) mass spectrometry is capable of unraveling the molecular complexity that we need to form the input for our clinical decision-making models. MSI takes this detail to the next level, with analyses performed in the spatial context of cell and tissue.

At M4I, we have brought cutting-edge MS-based technologies together with high-end cryo-electron microscopy. In doing so, it becomes possible to image biological processes at multiple scales: a single molecule, the molecule in the context of a cell, the cells in context of diseased and healthy tissue, and that tissue in the context of the patient's biological system.

### Mass effort

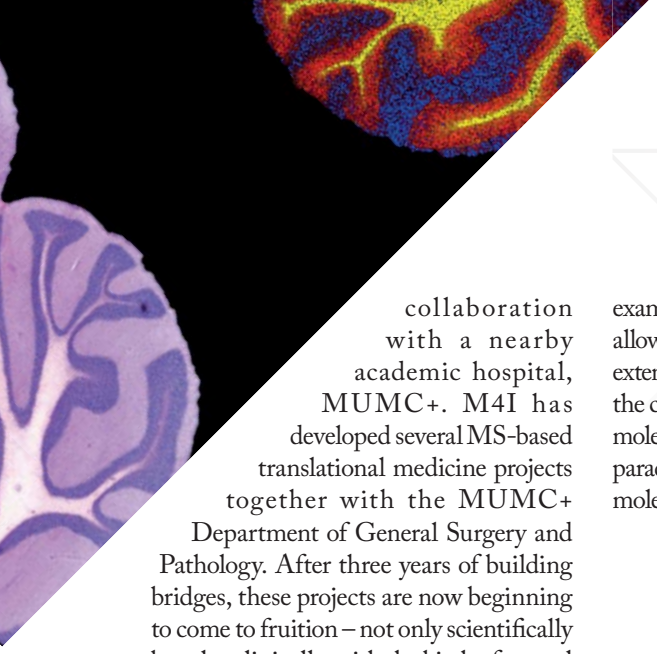
My group at M4I is pushing the boundaries of spatial resolution in MSI, including developing new tools to resolve molecular structures that have so far proved elusive. We are currently working on combining ion chemistry with MSI to apply imaging in a completely new way (see page 40) – if successful, this could result in a paradigm shift for the analytical application of mass spectrometry in structural biology.

Throughput is another key area for us. MSI provides orders of magnitude more detailed information for clinical diagnostics than conventional imaging techniques, but the information needs to be available to clinicians quickly. A diagnostic approach that takes hours to complete will not be adopted easily. We are working with the main MS vendors to deliver MSI-based tissue diagnoses to surgeons, pathologists and other healthcare professionals in a matter of minutes (see page 42), which will facilitate the translation of our work into personalized medicine, ultimately reducing diagnostic and treatment costs.

*"To make personalized medicine a reality, we must find a way to resolve the incredible complexity of the human body and apply it in clinical decision-making."*

Whether it's fundamental research, instrument development, or clinical translation, an important bottleneck is our ability to deal with the ongoing data tsunami. We need innovative data sciences and bioinformatics to digest the data as rapidly as we can now generate it (see page 43).

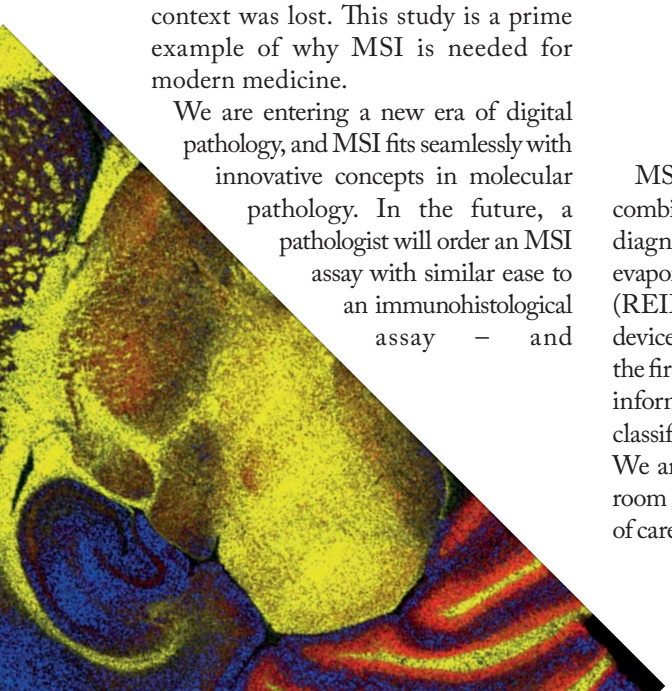
I believe that the team at M4I has the vision and drive to help move healthcare forward (read more about the work of some of our "rising stars" in the following sections). But to achieve our goals, it's crucial that our research is embedded in the clinic – for example, our



collaboration with a nearby academic hospital, MUMC+. M4I has developed several MS-based translational medicine projects together with the MUMC+ Department of General Surgery and Pathology. After three years of building bridges, these projects are now beginning to come to fruition – not only scientifically but also clinically, with the birth of several novel diagnostic assays that are now being validated for patient care. This type of interdisciplinary research is something I am passionate about – it is absolutely crucial to advancing MSI, and science as a whole.

A beautiful example is the recently published (1) result of a collaboration between M4I and Steven Olde-Damink's group at MUMC+ on non-alcoholic steatohepatitis (NASH). Using a mass spectrometry-based tissue imaging approach we established a novel classification model for NASH. Importantly, we found that this classification was only possible when the spatial context of the molecules was taken into account; we could not establish the classifier on a tissue homogenate in which the spatial context was lost. This study is a prime example of why MSI is needed for modern medicine.

We are entering a new era of digital pathology, and MSI fits seamlessly with innovative concepts in molecular pathology. In the future, a pathologist will order an MSI assay with similar ease to an immunohistological assay – and examine it on exactly the same platform – allowing diagnosis to be based on much more extensive molecular information. It also offers the combination of targeted and untargeted molecular diagnostics, which will be the true paradigm shift in personalized medicine and molecular pathology.



*"MSI can be employed to more precisely define a tumor margin on a tissue section, determine the degree of ischemic damage in an organ for transplantation, classify the severity of disease, and so much more."*

MSI-based molecular pathology can be combined with MS-based intraoperative diagnostics, as is being done with rapid evaporative ionization mass spectrometry (REIMS), with the "i-Knife" sampling device (see page 42). Our group has been the first to take all of our molecular imaging information and put it into models that classify tissue during a surgical procedure. We are building the molecular operating room of the future to improve the quality of care and treatment outcomes of patients.

## Scratching the surface

The potential impact of MSI is hard to overstate. Everything we experience, invent, touch, eat, and use involves some form of surface chemistry. MSI can help us to better understand all of these surfaces and their chemical interactions with their environment, provided we are careful to ask the right questions and design our experiments in the best way.

The most obvious impact will be in medicine. MSI can be employed to more precisely define a tumor margin on a tissue section, determine the degree of ischemic damage in an organ for transplantation, classify the severity of a disease, and so much more. The pharmaceutical sector will benefit from detailed information on local drug metabolism – researchers will be able to see if a drug reaches a target without the need for labels that could interfere with its mode of action. Better information on local drug metabolism and pharmacokinetics will be crucial to innovation in drug development.

The impact of MSI on science and society is already tremendous and can only grow. If the number of published papers is an indication of the impact of MSI, the best is yet to come! Read on to find out more about the young researchers breaking through scientific and technical barriers at M4I.

*Ron Heeren is Director of Maastricht MultiModal Molecular Imaging Institute (M4I), Distinguished Professor and Limburg Chair at Maastricht University, The Netherlands.*

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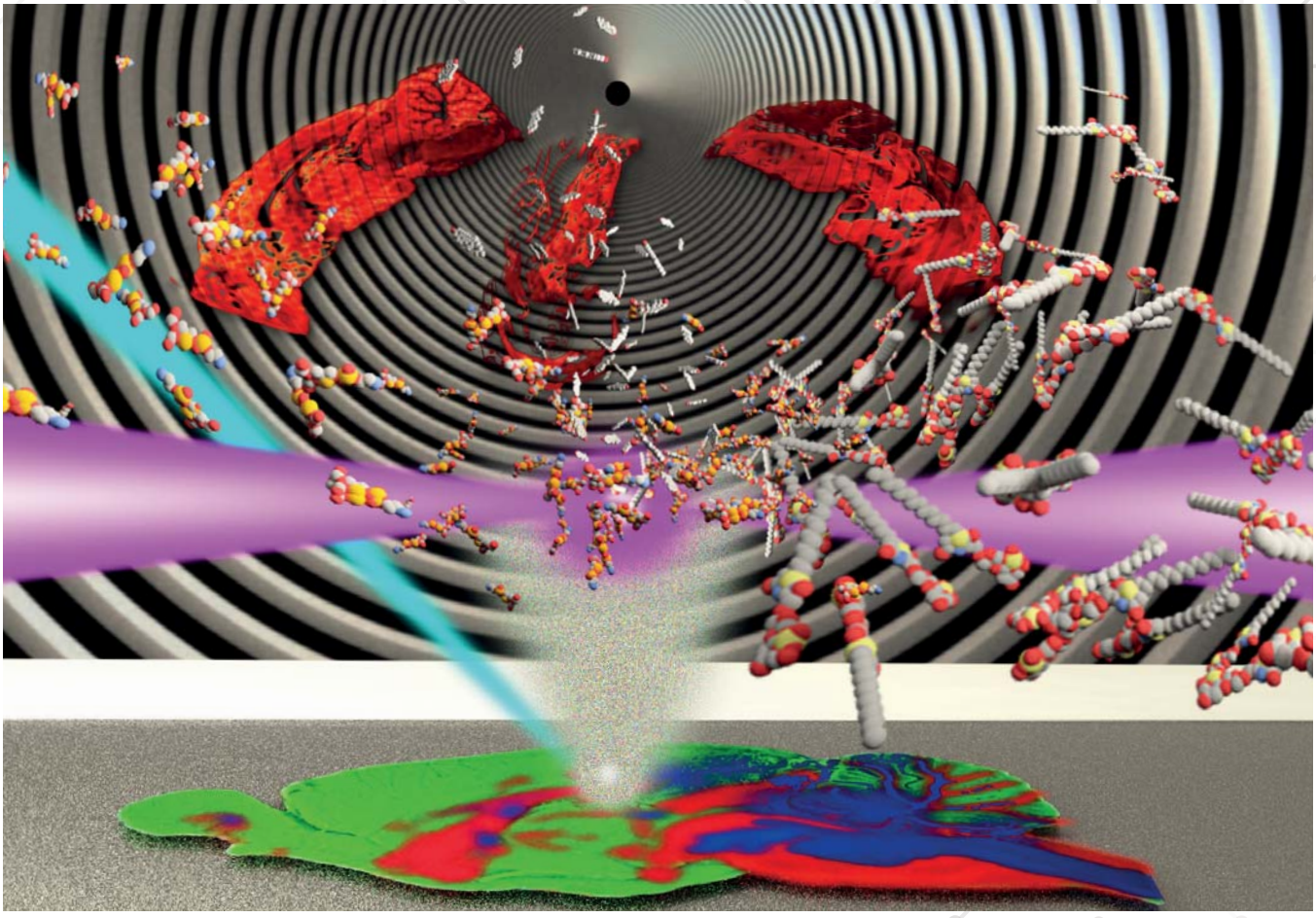

Artist's impression of MSI using laser-induced post-ionization (MALDI-2).

# The Imaging Innovator

**Shane Ellis is an assistant professor in imaging innovation and structural imaging. We caught up with him to find out how M4I is pushing imaging technology to its limits – and beyond**

What is the aim of your research?

My group develops new instrumental methods and applications to improve the chemical information we can extract from imaging data. I have a strong focus on lipids and find it fascinating that, in almost every tissue studied with MSI, a heterogeneous spatial distribution of lipids is seen, and yet the underlying reasons behind these distributions are not known. More generally, very little is known about the roles of individual lipids in cell metabolism and function – I want to add to our knowledge.

How are you improving MSI?

As a chemist, I want to know exactly what molecules we are seeing in MSI, but this goal is complicated by the presence of isomers. We are combining new MS/MS methods (such as selective gas phase ion/molecule reactions) with imaging to resolve structural isomers and discover exactly what molecules are contributing to a signal. By breaking down an image into the isomeric contributors, we can begin to understand the biochemical origin of MSI data. By combining this with the power of high-mass-resolving-power MSI using FT-based analyzers to reduce the search space for structural assignments, we would one day like to gain a cell-by-cell view of all active metabolic processes and how they are altered with disease.

We are also working on adding temporal data to MSI. With MSI, we acquire a static snapshot of a heterogeneous sample – but in reality, the molecules we detect are the result of a variety of dynamic processes. To capture this change over time, we are infusing isotope labels into animals so

*"In almost every tissue studied with MSI, a heterogeneous spatial distribution of lipids is seen, and yet the underlying reasons behind these distributions are not known."*

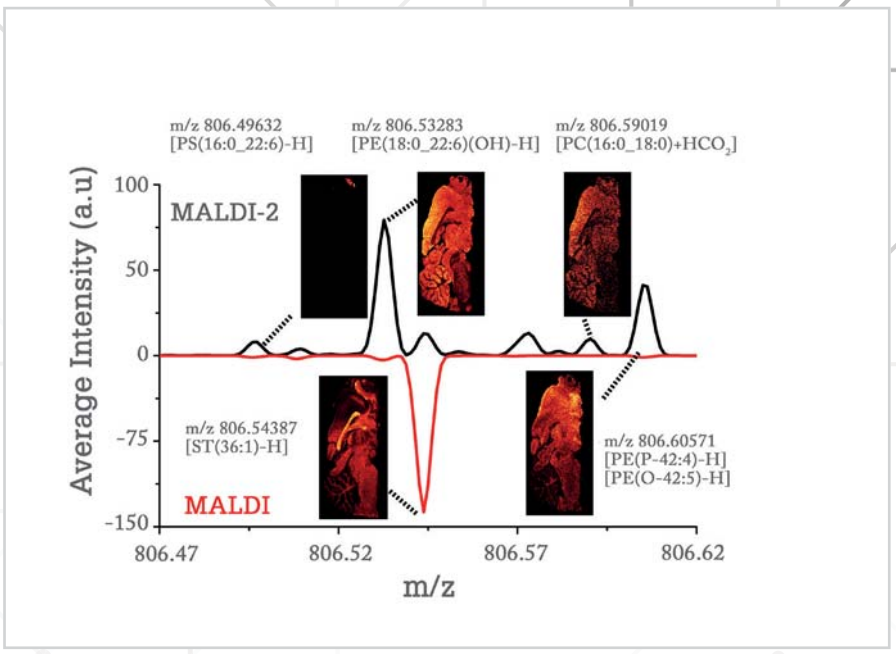


Figure 1. Comparison of MALDI coupled with laser post-ionization (MALDI-2, black trace) and conventional MALDI (red trace) for MSI of lipids from mouse brain tissue. MALDI-2 dramatically improves the ionization efficiency sensitivity for many lipid classes. All lipid assignments are performed with a mass error tolerance of 2 ppm, and in the majority of cases supported with on-tissue MS/MS. Reproduced from (5).

that we can monitor uptake of the isotope label into biochemical processes. This means we can directly view the turnover and synthesis of new molecules and differentiate new molecules (synthesized since label introduction) from old molecules (synthesized before label introduction). This provides a powerful and as yet largely untapped resource to image the kinetics of biochemical conversions within tissues.

Speed is also very important, especially for clinical applications of MSI. Modern ToF systems allow us to acquire data up to 20 times faster than a few years ago, but these methods are now at the physical limits of conventional ToF technology. M4I is heavily involved with the Medipix consortium at CERN, working on semi-conductor-based detectors for stigmatic imaging. With the Timepix detector and dedicated ion optics within stigmatic imaging mass spectrometers, we can acquire thousands of pixels in parallel (rather than one at a time). Instead of one detector, we have 262,144 detectors, each capable of recording both ToF and impact position (1–3).

## What's next?

The typically low ionization efficiencies of many molecules mean that we may only detect one in every 10,000–1,000,000 occurrences of a given molecule – this is the ultimate limitation in sensitivity. Work is ongoing at M4I and elsewhere to finally overcome this key challenge, either using targeted derivatization methods to convert certain molecules into more detectable forms (for example, by adding a fixed charge), or using the MALDI-2 method, where a second laser is fired into the MALDI plume. Pioneering work by wthe University of Muenster (4) and later by M4I (5) has shown that this method can enable up to two orders of magnitude greater sensitivity for certain molecules and significantly improves the depth of molecular coverage for an MSI experiment (see Figure 1).

I also think the use of MS/MS methods (both conventional and new variants) will continue to gain momentum, moving towards true molecular identification of signals observed in MSI. High mass resolution has been a huge advance, but ultimately this provides little structural information beyond elemental composition. For structure determination, MS/MS is needed. The challenge is that MS/MS is typically a targeted approach, and it's not yet clear how best to combine this with the untargeted nature of MSI.

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# The Clinical Collaborator

**Tiffany Porta, an assistant professor at M4I, tells us how the institute is translating MSI technology into the operating theater**

What is your goal?

My research group focuses on translational research and clinical imaging. My main interest is to provide new clinical diagnostic tools, with a focus on intraoperative diagnostics. Therefore, I am strongly connected with the hospital and working very closely with surgeons and pathologists. Our ultimate joint goal is to improve the clinical decision-making process (surgical and medical) that results in better patient outcome. This is what drives me and my research.

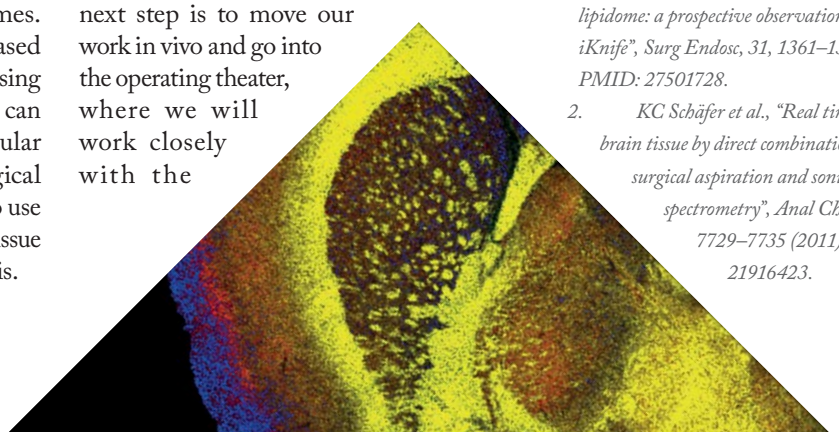
What problem do you hope to solve?

Surgery is the best hope of a cure in 80 percent of diagnosed cancer cases. Whether a cure can be achieved usually depends on the quality of the surgical resection of the tumor. At the moment, it is hard for surgeons to find the edges of the tumor and remove all the cancerous tissue. To find out if any cancer remains, pathologists evaluate frozen cut tissue sections; results are often not available for several days, and sometimes prove inconclusive. There is ample evidence that improving the accuracy of surgical resection would reduce the number of patients requiring further surgery and improve overall outcomes. This is where molecular profiling based on mass spectrometry comes in – by using a tissue (disease)-specific database we can provide real-time and specific molecular analysis of tissue and assist the surgical decision-making process. We can also use rapid molecular pathology of resected tissue to assist pathologists in their diagnosis.

Tell us about the iKnife…

The technology behind the "iKnife" or "intelligent scalpel" is rapid evaporative ionization mass spectrometry (REIMS) – developed by Zoltan Takats for the rapid classification of human tissue via MS analysis. It analyzes aerosols released during electrosurgical dissection using electric scalpel or forceps. The smoke generated during electrosurgery is very rich in molecular information, including tissue-specific profiles that discriminate between the tumor and surrounding tissue – data not available to the naked eye of the surgeon. The electrosurgical aerosol collected in real time is compared with a reference model to determine, within seconds, the type of tissue being cut (for example, tumor versus non-tumor). In a clinical setting, the data would be provided interactively to the surgeon as they cut the tissue. Through this rapid, on-line analysis, surgeons get immediate feedback to help them resect the tumor accurately, leaving no cancerous tissue behind. The beauty of this approach is that existing surgical devices need no modification to combine them with REIMS, the surgical procedure remains the same, and surgeons need no extra training. And for me, these are key points to accelerate the translation of the technique into clinical practice.

Currently, reference models are built ex vivo, which permits the creation of spectral databases for prospective use. In Maastricht, we are currently building databases on breast, colorectal liver metastasis, sarcomas, and head and neck tumors, which are validated histologically by expert pathologists. Our next step is to move our work in vivo and go into the operating theater, where we will work closely with the clinical staff and surgeons. The goal is to validate the databases that we are currently building ex vivo and work with clinicians towards integration of the iKnife in clinical routine.



What developments lie ahead?

Recent developments have concentrated on miniaturization of the system and making it minimally invasive. For example, integration of REIMS with an endoscopic polypectomy snare to allow in vivo analysis of the gastrointestinal tract is a promising methodology to explore internal structures in a minimally invasive way (1). High diagnostic accuracy for tumor type and known histological features of poor prognostic outcome in colorectal cancer was reported, based on a multivariable analysis of the mucosal lipidome. The potential of this approach for other minimally invasive procedures has also been demonstrated by combining real-time MS with surgical laser systems where aerosol is generated by thermal ablation. The molecular patterns generated are specific to the cellular phenotypes and can easily distinguish benign from malignant regions in patient biopsies, which opens the door for applications in a wide range of clinical areas. Additionally, the cavitron ultrasonic surgical aspirator, which is widely used for brain and liver surgery, can also be combined with the REIMS technology for intraoperative diagnostics (2).

*References*

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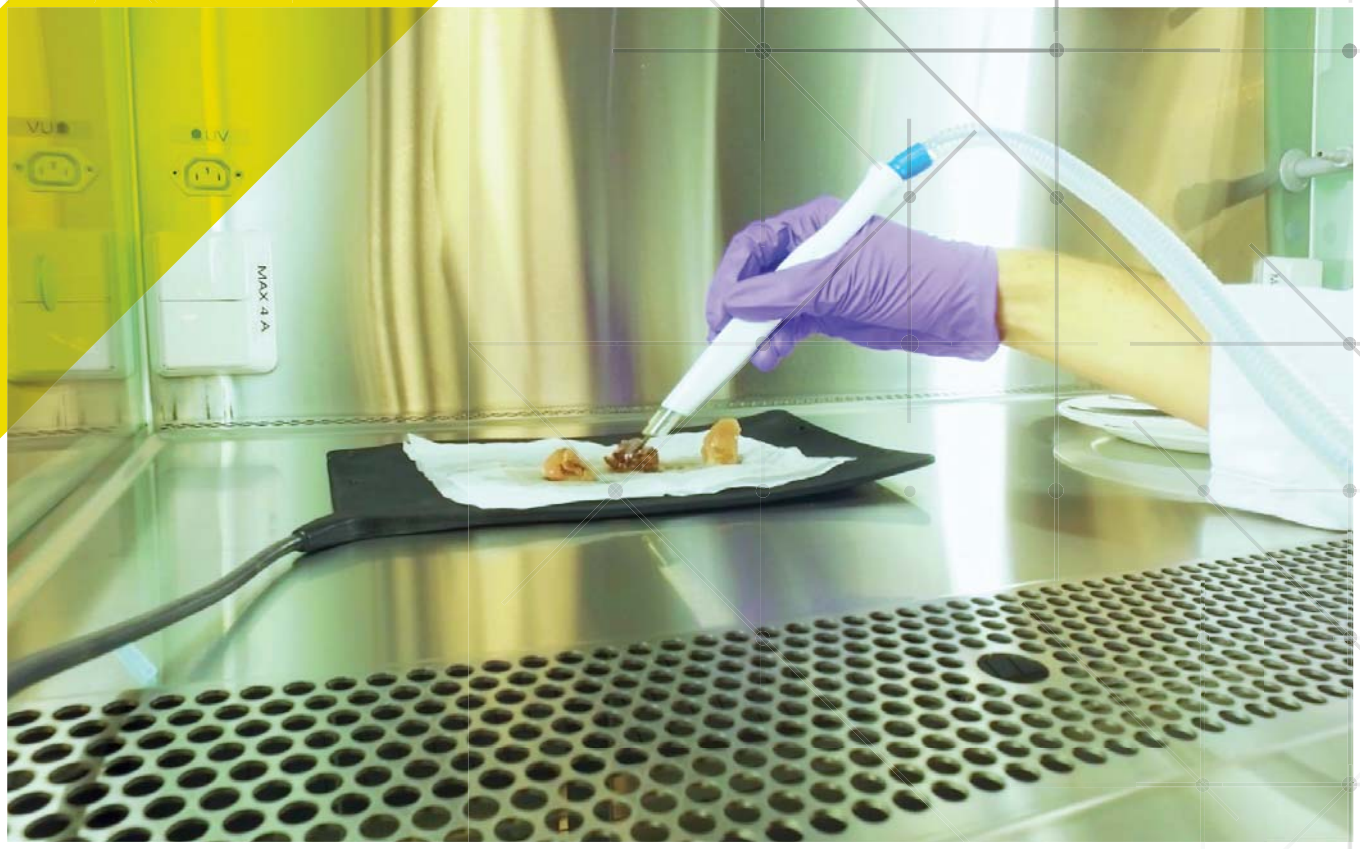


# The Big Data Explorer

**Assistant professor Benjamin Balluff develops innovative bioinformatics approaches that allow M4I researchers to master their data**

What is your goal?

I develop advanced data analysis methods for MSI of cancer tissues – revealing molecular heterogeneity within apparently homogeneous tumors. Intratumoral heterogeneity plays an important role in therapeutic failures and progression of the disease. I want to use MSI to pinpoint clinically detrimental tumor subpopulations for further in-depth investigation.

What are the challenges?

The analysis of MSI data is challenging in many ways – ranging from the optimal processing of gigabyte-sized data to selecting the correct statistical analysis. The rapid advance of instrument capabilities has increased demands on computational power and memory. What's more, this data delivers a degree of detail that the human brain is unable to process without the help of algorithms and clever data visualization tools. I develop new methods and algorithms that help to interpret the data and ultimately find answers to urgent biomedical questions. Integration of different (imaging) data modalities is a prerequisite for successful personalized medicine.

What new advances excite you?

With the rising popularity of MSI, more bioinformatics groups from outside of our field have become interested in this type of data, which in turn leads to an acceleration in the development of useful tools for the analysis of MSI data, including commercial solutions. I hope this widespread interest will help us, as a community, to achieve our aim of making MSI a robust diagnostic tool in a clinical setting.

Our focus is, of course, mainly on MSI, but there is a wider trend in life science to integrate data on the same subject from different modalities. We have to work together with different specialties and disciplines, and find a way to combine heterogeneous data (of different sizes and optical resolutions, at different scales, in different storage formats, and so on) using tailored software solutions.

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# Your Origin Stories – in Tweets

## What got you started on the path to pathology?

Earlier this year, we featured an editorial on the "magic of mystery" and how it could lead to an interest – and possible career – in science (1). We decided to follow up by asking what inspired you – our readers – to pursue pathology. And your responses came thick and fast! Here, with your permission, we've collected the stories you told on social media about your journey into pathology, and how you fell in love with the field.

*David Larson (@dmlarsonpath1):*
Last rotation of med school. Had wanted to do IM, but realized during acting internship that it wasn't for me. Friend suggested #pathology. Arranged for elective and loved it. Saw what #pathologists do day to day. Pathology class didn't do that. Have been loving it ever since.

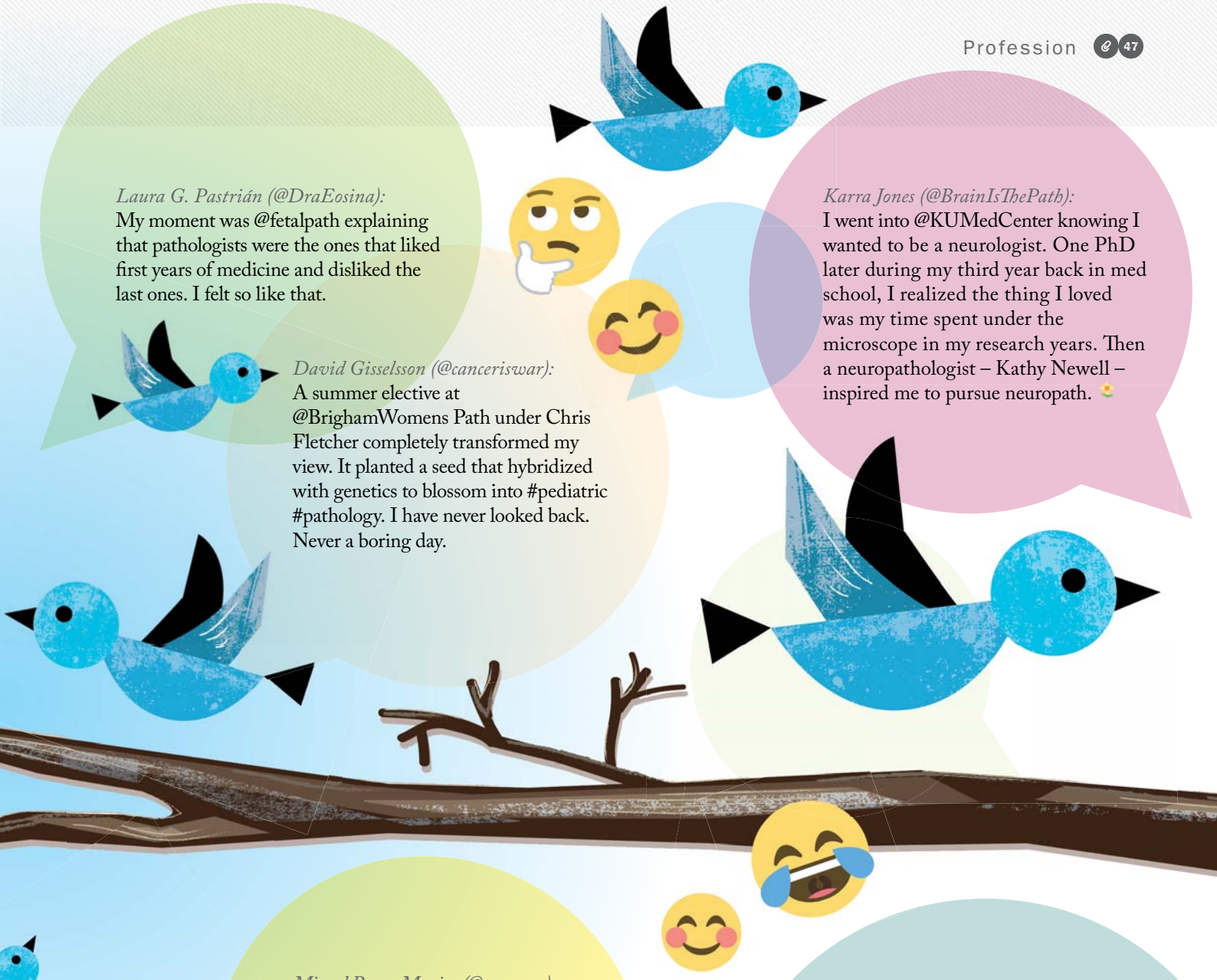
*Sara Jiang (@Sara_Jiang):*
I am that friend! And I think many of us on #pathologytwitter are – both virtually and IRL!

*Daniela Hermelin (@HermelinDaniela):*
My father was an ID doc with a mini-lab in his office, including a microscope, where I would be found perched. Inspired by his love for medicine and humanity. Fell in love, with pathology that is, in medical school: mechanism of disease, pictures, best teachers: received Path Award

My love solidified after my first general pathology elective, and second, and third and then fourth… Graduated medical school and then received a PhD in diapers, breast feeding and sleep deprivation. Began my pathology residency with five kids and pregnant (again).

Pathology residency about to be completed in four days and ecstatic to be starting transfusion medicine fellowship at #SLUPath #grateful

*Maria Martinez-Lage (@mlage):*
As a third year Neurology resident, I sought a #Neuropath rotation and was extremely lucky to spend two months @MGHPathology. I went back to Spain, decided to become a neuropathologist. 13 years later, the people who inspired me are my colleagues and I made great friends @PennPathLabMed



*Laura G. Pastrián (@DraEosina):*
My moment was @fetalpath explaining that pathologists were the ones that liked first years of medicine and disliked the last ones. I felt so like that.

*David Gisselsson (@cancerisWar):*
A summer elective at @BrighamWomens Path under Chris Fletcher completely transformed my view. It planted a seed that hybridized with genetics to blossom into #pediatric #pathology. I have never looked back. Never a boring day.

*Karra Jones (@BrainIsThePath):*
I went into @KUMedCenter knowing I wanted to be a neurologist. One PhD later during my third year back in med school, I realized the thing I loved was my time spent under the microscope in my research years. Then a neuropathologist – Kathy Newell – inspired me to pursue neuropath.

*Miguel Reyes-Mugica (@mreyesm):*
I wanted to become an internal medicine physician. I started as an instructor of #histology on my second year and then met my mentor #RuyPérezTamayo for my class of Pathology. Started doing research under him. That was enough. Experimental pathology and the beauty of histology!

*Jena Martin (@DrsDrMartin):*
During the second year of medical school when a retired pathologist explained Potters syndrome. Seemed so intensely interesting!

*Adriana Zucchiatti (@zucchiatti_):*
I always wanted to be a pediatrician, basically because I love kids. Then I worked one year in a peds little hospital and I figure out practicing peds wasn't the most exciting for me. I just started to read a lot about pathology and how it works and made the decision.

Now, I'm really, really happy with what I do, even in residency program.
The moral is that sometimes you have to take the chance and take risks, and it is possible everything turns out great. :)

*Irma Ramos (@iramos89):*
When attending a pathology practice on the third year of Medicine everyone commented how boring that seemed to them and I was like "Uoouu, have you seen that? *.*"

*Christine Salibay (@cjsalibay):*
Path profs suggested an elective. OB/family were always on my mind but by the end of third year, when I finished path elective, I was Path vs Peds – ultimately decided on a specialty that reminded me of how I like to think 🤔 and why I loved medicine in the first place –

– the basics: mechanism of disease and diagnosis. Plus, the lab people were amazing and reminded me of my awesome undergraduate research group :)

*Mary Kinloch (@saskmary):*
In despair on colorectal surgery rotation. Surgery seemed boring: you spend so much time to get it out & NOT GONNA LOOK INSIDE?! Then, walked into GI tumour boards where a well-dressed feller with a microscope was telling the surgeons what to do. I was like, I wanna be that guy.

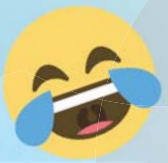
*Ashley Flaman (@ashleyflamanmd):*
First year med student at a lunch hour career presentation about pathology. Pathology resident presents a case – 50s M single lung nodule removed for suspected cancer. Resident puts up histo image & says, "it's not a tumor, it's a granuloma!" Me: I wanna be her. That resident: @saskmary

*Ashley Stueck (@LiverPath):*
I was seven when The X-Files premiered, and Scully was a forensic pathologist. The path was set! Of course, this was followed by learning more, shadowing, working in a path research lab, and electives. Forensics (still love!) changed to liver, but I always wanted to be a pathologist!

*Alicia Pomata (@AliPomata):*
First year med school, wanted to stay in the white, clean and cold lab forever looking to every single cell in the 🔬😂

*Mary Landau (@MPathyart):*
Standing in a gyn onc ward during my intern year in Ob/Gyn. I had just completed my gyn path rotation (and adored it), but even more pertinent, I had just completed 36 straight hours on call and only faced 12 hours off before my next 36-hour penance.

*Valerio Ortenzi (@ortens84):*
I guess when I was a little boy: my parents gave me toys to play, instead I used to disassemble them to understand what was going on inside… 😆😆😆



*Akinshipo Wariz (@AkinshipoWariz):*
I knew I would be an oral pathologist when the only textbook I bought in Dental school was Neville and Damm Oral and Maxillofacial Pathology.

*Lara Pijuan (@lara_pijuan):*
At second year of medical school when I had my first contact with #histology. I loved histological images and then at third year when I had my pathology classes I realized it was done for me… or I was done for Pathology 🤔😊I 💜 #Pathology 🔬

*MaríaElena PérezMartín (@ElenPath):*
At second year of MD School, I had my first contact with #histology and I ❤️ images (as Lara). And at third year, I had my path classes and I realized pathology was amazing. We dived deep into the real diagnostics of the disease. At fourth year, I met Dr. Burnier, Eye Path and I fell in 💜 with #Pathology 🔬

*Valerie Fitzhugh (DrFNA):*
I didn't match orthopaedics. Pathology was the only other specialty I rotated through in medical school that I could see myself doing for the rest of my life. 14 years later and I haven't looked back. #MyCalling #NoRegrets #Pathology #BSTPath #Cytopath

*Kalyani Bambal (@kriyer68):*
Loved histology in first year med school and then reinforced by pathology in second year. Was a foregone conclusion in itself. Went for MD Path in spite of offers for medicine and ped to the sheer consternation of my profs that time 🙀🙀

*Tweets have been edited for readability only.*

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# A Natural Gift for Pathology

**Sitting Down With… John Goldblum,** Chairman, Department of Pathology, Cleveland Clinic; Professor of Pathology, Cleveland Clinic Lerner College of Medicine, Cleveland, USA.

What inspired you to pursue pathology?

When I was a medical student, there was a second-year course in pathology. The teachers were the best I'd had, so they strongly influenced my choice. As part of the course, we each had a microscope and a pile of old, dingy slides on which we were supposed to identify disease entities. Somehow, I ended up as one of the students who went around explaining to everyone else what they were supposed to be seeing. Whatever wiring is required to look at a microscope slide and understand it, I seemed to have it – and liked doing it!

Within a week of starting my residency at the University of Michigan, I decided that the smartest people on the faculty were Henry Appelman, a world-famous gastrointestinal pathologist, and Sharon Weiss, a world-famous soft tissue pathologist. I said, "Whatever they do, that's what I'm going to do." I didn't know a thing about GI or soft tissue pathology, but I did know I wanted to learn from them.

How did you get so involved in pathology education?

When I first began to speak publicly, I was terrible at it. I was always nervous; I couldn't catch my breath; I think I might even have taken a beta blocker the first time I had to get up in front of an audience! Eventually, though, I learned to like it, and now I really enjoy it. I get a great deal of satisfaction from lecturing – even if the listeners only take away a small amount of useful information. I try not to include too much, and I don't expect people to remember all of it. When I'm sitting in the audience, I'm happy to take away one or two valuable points; that's what I would like others to be able to do when I teach.

With respect to textbooks, in 1997, Franz Enzinger decided he was not up to working on the fourth edition of the Enzinger and Weiss soft tissue pathology book. Sharon Weiss asked me, as one of her former fellows, if I would be willing to take his place. I didn't think I was in a position to do it, but she said, "You can do it. I trust you." And so I also wasn't in a position to say no! It was the first time I had ever written a textbook, so it took me about three years to finish. It was good practice, though, because my friend Rob Odze had the idea of working on a GI textbook with me. Eventually, the powers that be at Elsevier asked me to take over the 11th edition of the Rosai and Ackerman textbook on surgical pathology. You can imagine the scale of that task! I gathered three other world-class people to help me and it took us about five years, but we did it.

*"The most important thing to remember is to be a good colleague and team player."*

How do you maintain your work/life balance?

When I started at the Cleveland Clinic, it was extremely busy – but I was a young parent who didn't want to stay at work all day and night and never see my wife and children. My father was a hardworking dermatologist who rarely had time to spend at home, and although I admired his dedication, I didn't want to replicate it – so I tried to become exceedingly efficient at multitasking. When I'm at work, I run around like a maniac to get everything done. I keep breaks and socializing to a minimum so that I can accomplish what I need and then go home to my family.

I am hoping it's not going to be that long before I can sign out my cases from anywhere, which I expect will really help those who struggle with work/life balance. I already do a number of consults from China and other parts of the world digitally, and they're only a little more challenging than using the microscope, so I think we're inching closer. I hope that, in my lifetime, we get to that point – it's my goal to sign out cases from the beach!

What do you consider the high points of your career?

My biggest accomplishment is taking my department from 15 people and a limited reputation to a very large subspecialty department with an international reputation and about 70 pathologists. It's a job I only reluctantly accepted, but I ended up really liking it and building what I think is a tremendous department.

I'm also very engaged with organizational pathology. I got involved with USCAP early in my career and ended up running their education committee for six years and serving on the committee for 14 years. Eventually, I joined the board and became President of USCAP – and I'm still involved with them now. That's the other thing that makes me proud, because I believe that I not only derived tremendous personal and professional benefit from USCAP, but I feel I actually contributed to the organization's progress at a critical time.

What's your advice for young pathologists?

The most important thing is to remember is to be a good colleague and team player. That's how you're going to end up loving your job – by working with people whose company you enjoy. The people who are most successful in pathology are those who really like both the profession and the people they work with.

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