AUGUST 2019 # 57

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## The Case for a Universal Clerkship

Every doctor should be taught the basics of the laboratory



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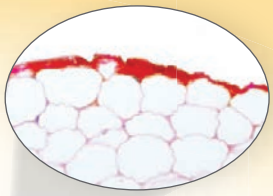


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CAP19 - College of American Pathologists Annual Meeting | Orlando, FL | Sept. 21-25
Musculoskeletal Tumor Society Annual Meeting | Portland, OR | Oct. 2-4
American College of Surgeons Clinical Congress | San Francisco, CA | Oct. 27-31

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# Case of the Month


A nine-year-old boy presented with anorexia and abdominal distension. He was febrile and pale, with generalized firm lymphadenopathy and hepatosplenomegaly.

Bone marrow evaluation aspirate and touch preps demonstrated 72 percent blasts. The biopsy demonstrated 100 percent cellularity with sheets of blasts and focally increased reticulin fibrosis. Peripheral blood demonstrated normocytic, normochromic anemia (Hb 8 g/dL), with an elevated white blood cell count of 239 x 10⁹/L and 25 percent blasts.

The blasts demonstrated a high N:C ratio; they were agranular, with no Auer rods seen, and stained negative for myeloperoxidase. Additional immunohistochemical stains demonstrated they were positive for CD34, CD19, CD79a, and CD10. They were negative for CD117 and CD3. Interphase FISH demonstrated *BCR-ABL1* fusion positivity in 98 percent of cells. Ultimately, the patient was diagnosed with pediatric chronic myeloid leukemia (CML) exhibiting a B cell lymphoid blast crisis.

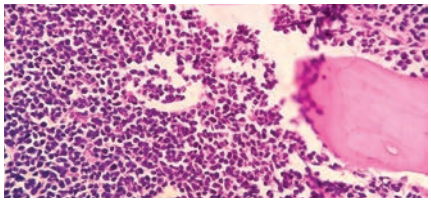
*Which of these features is true of adult CML patients when compared with pediatric CML patients?*

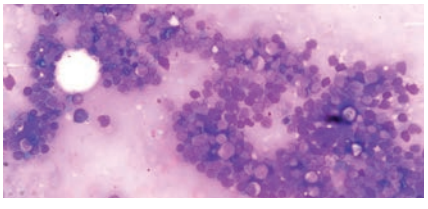
*a* Higher white blood cell count at initial presentation

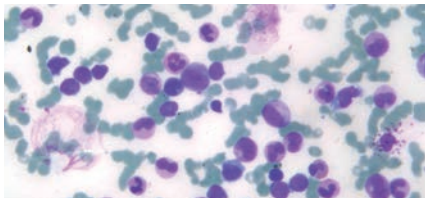
*b* More likely to obtain deep molecular response with imatinib therapy

*c* More likely to present in accelerated or blast phase

*d* More likely to have splenomegaly







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

*A. Wells' syndrome (also known as eosinophilic cellulitis)*

This rare inflammatory skin condition is thought to be a nonspecific hypersensitivity reaction (1). It typically appears as a sudden onset of large, well-circumscribed, edematous erythema that may have an annular configuration and are usually pruritic or painful. Over a period of days, edematous and erythematous lesions evolve into plaques with violaceous borders. Lesions resolve without scarring, but multiple recurrences are common (2). The histological pattern is characterized by dermal edema, diffuse dermal eosinophilic infiltrates, histiocytes, and flame figures (3). The flame figures are distinctive, but not specific for Wells' syndrome, so diagnosis should be based on the clinical presentation, course of the disease and recurrences, and histopathology.

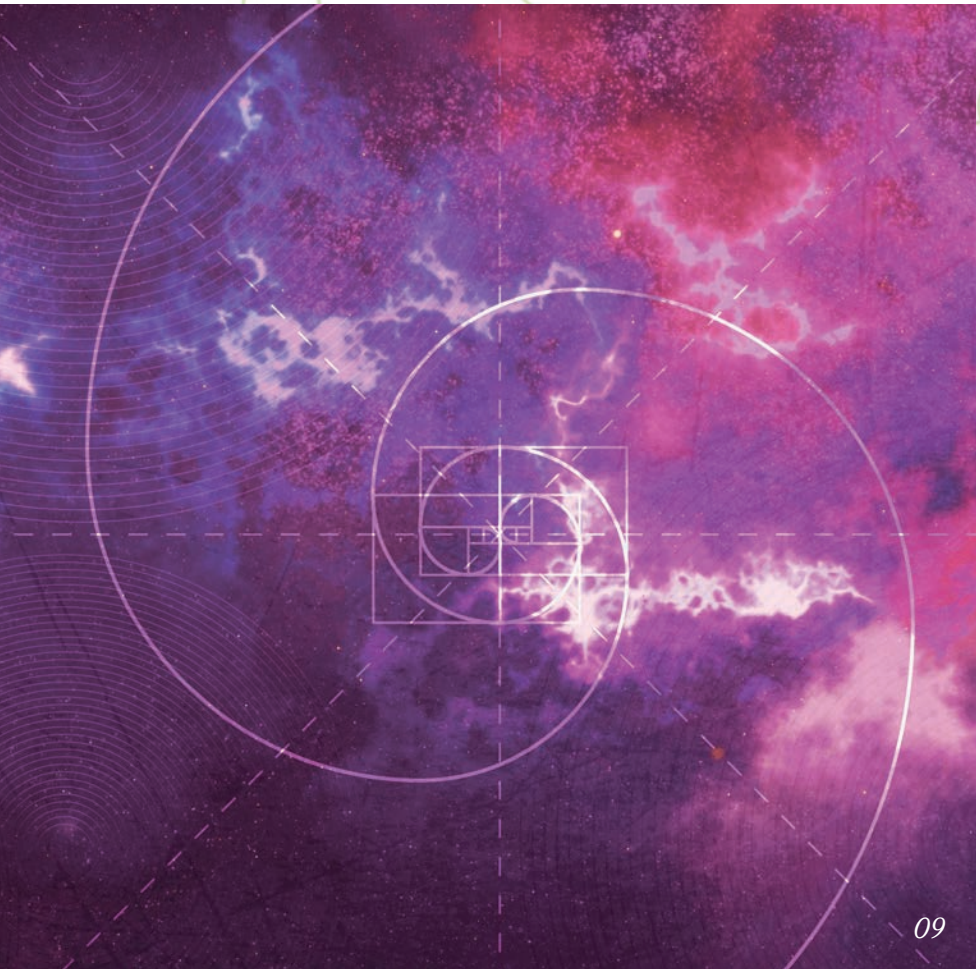
*Submitted by Muhammad Ahsan, Sahiwal Medical College, Sahiwal, Pakistan.*

*References:*

1. *AC Katoulis et al., Clin Exp Dermatol, 34, e375 (2009). PMID: 19489853.*
2. *LM Leiferman, MS Peters, Fitzpatrick's Dermatology in General Medicine, 8th edition. McGraw-Hill Education: 2012.*
3. *M Moossavi, DR Mehregan, Int J Dermatol, 42, 62 (2003). PMID: 12581147.*

**To register your guess, please go to http://tp.txp.to/0819/case-of-the-month**
**We will reveal the answer in next month's issue!**

# Contents







## On The Cover

*Pathologist Kamran Mirza and medical student Austin McHenry study the ins and outs of the lab together*



## Feature



## In Practice



## NextGen



## Profession



## Sitting Down With




the **Pathologist**

**ISSUE 57 – AUGUST 2019**





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# Keeping Up

*With so much information to digest, how do you balance continuing professional development with other tasks?*



Yesterday, curious about the latest news in the science of the small, I visited a microscopy and microscience conference. It's an event I have attended several times in the past but, each time I go, there's more to learn. Electron microscopy, atomic force microscopy, Raman spectroscopy, STORM, PALM, STIM, STED… Some terms I recognize from a graduate school career spent in chromatin biology and others from recent Nobel prize awardees but, increasingly, I'm encountering terms that are alien to me. DSTORM? MSPIM?

Diagnostic technology is exploding at an incredible rate. It's obvious in microscopy, where we have increasingly sensitive detection and visualization of increasingly tiny things, but it's no less true in other areas. Computational pathology springs immediately to mind; as the accuracy of AI-based approaches grows, diverse laboratories are opting to include such technology in routine workflows.

The challenge with such a rapidly expanding field is keeping up. Even recently trained professionals may find that their knowledge quickly becomes out of date, if not maintained – and there's so much to learn that hours spent exploring new developments can quickly outnumber those spent on other tasks. So how do you know when enough is enough? How much learning will keep you abreast of what you need to know without sacrificing the other aspects of being a good healthcare professional?

There's no one right answer to that question, of course; some disciplines see more rapid advancement than others, and some technologies require more training than others. And every learner is different – some might feel comfortable simply reading through an instruction manual, but others may want hands-on training or expert guidance. Regardless, it's hard to deny that pathologists and lab medicine professionals are being asked more and more – and there's less and less time to stay up to date on new developments.

What approach do you favor? What tips and tricks do you have for learning what you need without overlooking other work? Let us know how you do it (edit@thepathologist.com) and perhaps others can learn from your experience!

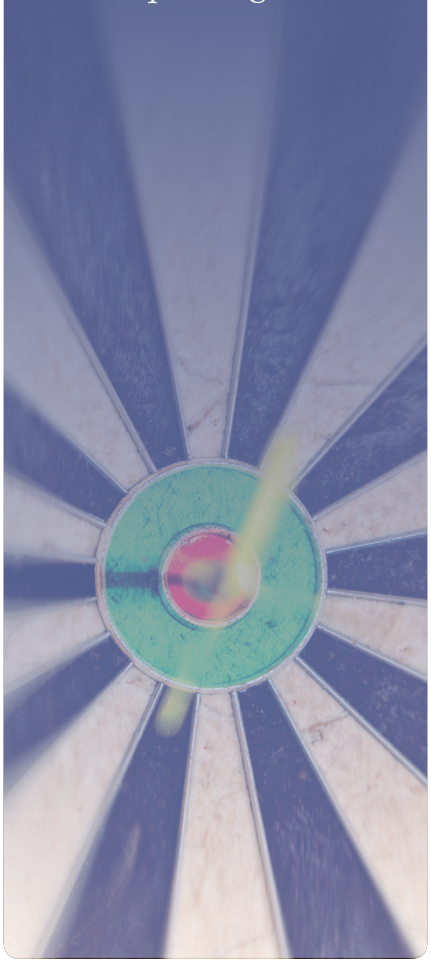
**Michael Schubert**
*Editor*

# Upfront

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

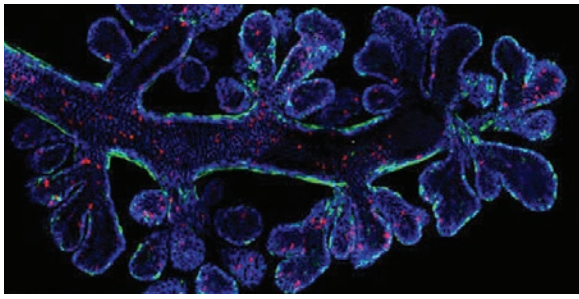
*Do you want to share some interesting research or an issue that will impact pathology?*

*Email: edit@thepathologist.com*



## Taking Aim at a Moving Target

### A new imaging technique allows us to see the evolution of cancerous cells



*Credit: Rios, Visvader et al., published in Cancer Cell*

How do cancerous tumors form? It's a question to which we don't yet have a detailed answer – but one that, if fully explored, could lead to better prevention, diagnosis, and treatment. Using a laboratory model of breast cancer, a team of researchers at the Walter and Eliza Hall Institute of Medical Research in Parkville, Australia, has developed a new imaging technique to observe individual cells within a tumor at high resolution and in three dimensions (1). The approach allows them to observe individual clones descended from a single precancerous cell to see how they change, which become cancerous, and which ones are most changeable or have potential growth or treatment resistance advantages. We spoke to study author Jane Visvader to learn more…

What enabled you to view breast cancer tumors in 3D at such a resolution?

The clearing agent was instrumental in enabling us to simultaneously perform immunolabeling and detect native fluorescence in large portions of tissue or tumors, and in allowing us to gain insight into tissue architecture at single cell resolution.

What is the most interesting discovery your new imaging technique made possible?

The pipeline involving 3D imaging at high resolution, together with the sorting and sequencing of individual clones, led to the unexpected finding that almost every clone had undergone an epithelial-to-mesenchymal transition (EMT). Although this process has been well-documented in cancers, it was presumed to occur in relatively rare cells, such as those along the leading edge of the tumor, before their extravasation into the bloodstream. In the p53/Pten deletion models we examined, the EMT was widespread and occurred at a clonal level. Of note, the molecular signature changed drastically from an epithelial to mesenchymal state, based not just on a small number of genes, but on hundreds to thousands.

These findings highlight the inherent plasticity of tumor cells and indicate that both epithelial and mesenchymal cells need to be targeted early in tumor progression. It is somewhat alarming that each clone had a propensity to shift towards a different (mesenchymal) state, indicating that cancer cells behave like moving targets.

What's next for this research?

Robust markers of the epithelial, mesenchymal, and hybrid cancerous states must be identified to allow more effective targeting – but this is a tough proposition and will require further research.

As it stands, our imaging protocol is simple to use, relies on a non-toxic clearing agent, and can be completed within three days. My colleagues and I hope that it will one day be adapted for use in pathology labs to diagnose and select treatment for specific diseases.

*Reference*

1. *AC Rios et al., "Intraclonal plasticity in mammary tumors revealed through large-scale single-cell resolution 3D imaging", Cancer Cell, 35, 953 (2019). PMID: 31185217.*

# IEM Identification

**Combining metabolomics and DNA sequencing could be the key to discovering new inborn errors of metabolism in children**

Although individually exceedingly rare, together inborn errors of metabolism (IEM) make up a sizeable portion of the broader spectrum of genetic disorders. Nevertheless, they remain underdiagnosed and undertreated (1). A multidisciplinary group based at the University of Texas Southwestern Medical Center in Dallas are working to improve our understanding of these diverse conditions. In a recent study, they combined genomic and metabolomic data to diagnose lipoyltransferase-1 deficiency (LIPT1D), an IEM characterized by abnormal brain development, seizures, and lactic acidosis (1). The team are optimistic that the new approach could provide the basis for more routine identification and treatment of IEMs.

"We've long known you can treat many IEMs if you pick up the underlying metabolic disturbance quickly," says Ralph DeBerardinis, Professor of Pediatric Genetics and Metabolism at UT Southwestern and a co-author of the paper. Phenylketonuria (PKU), a well-known IEM, is characterized by a failure to metabolize phenylalanine, resulting in the accumulation of phenylalanine and related metabolites in blood and urine – abnormalities easily detected by laboratory testing (3). But many other diseases remain poorly characterized and much more difficult to pinpoint – something that DeBerardinis hopes to address with advanced techniques. "It has become apparent that applying broad profiling technology will allow us to understand metabolic disturbances at a more granular level, helping us to uncover these conditions and ultimately to develop new therapies," he says (4).

Part of the problem is that current diagnostic approaches are narrow in scope. DeBerardinis certainly believes so; after all, even the most sophisticated clinical tests can only pick up a small fraction of potential markers. "You might be able to detect 50 biomarkers or so in a high-end laboratory," says DeBerardinis. "But there are potentially thousands of detectable metabolites in the blood – each of which could be associated with a novel IEM."

Could the combination of broad genomic and metabolomic profiling described by the group give a more holistic overview of a patient's potential disease profile, and even provide clues on how to tackle the deficiency? The early evidence is promising – the team identified a variant in *LIPT1*, a gene that codes for the lipotransferase required for 2-ketoacid dehydrogenase (2KDH) function. They were able to associate the variant with abnormal levels of various lipids, amino acids, and organic acids. The result has given DeBerardinis and his team confidence that their approach has merit. "This kind of information, this characterization of metabolic anomalies, can help us start to think about disease treatment," DeBerardinis says.

Of course, any abnormalities will have to be validated in patients – something DeBerardinis is quick to highlight: "We've already assessed the metabolic profile of around 500 patients suffering from an IEM," he says. "Those include about 100 with known IEMs and many others with diseases that we believe are novel." The results confirm something DeBerardinis has long suspected – that every person is metabolically unique, just as they are genetically unique.

"This approach allows us to identify new connections on the metabolic chart and hopefully develop ways to compensate for metabolic defects in IEMs."

There certainly seems to be plenty of reason for optimism, but DeBerardinis is keen to stress caution, at least for now. "We really need to know more about metabolic variability in the normal population first," he says. To get that data, the team are looking further afield. "We have established collaborations with medical geneticists in Pakistan, where the frequency of undiagnosed IEMs is high. Because that population has remained relatively understudied, there's opportunity for discoveries that will help us better understand and treat IEMs," says DeBerardinis. And although that project only began a few months ago, progress is already being made. "We have around 150 samples so far – we're very excited to see where the work takes us."

*References*

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3. *NA Hafid, J Christodoulou, "Phenylketonuria: a review of current and future treatments", Transl Pediatr, 4, 304–317 (2015). PMID: 26835392.*
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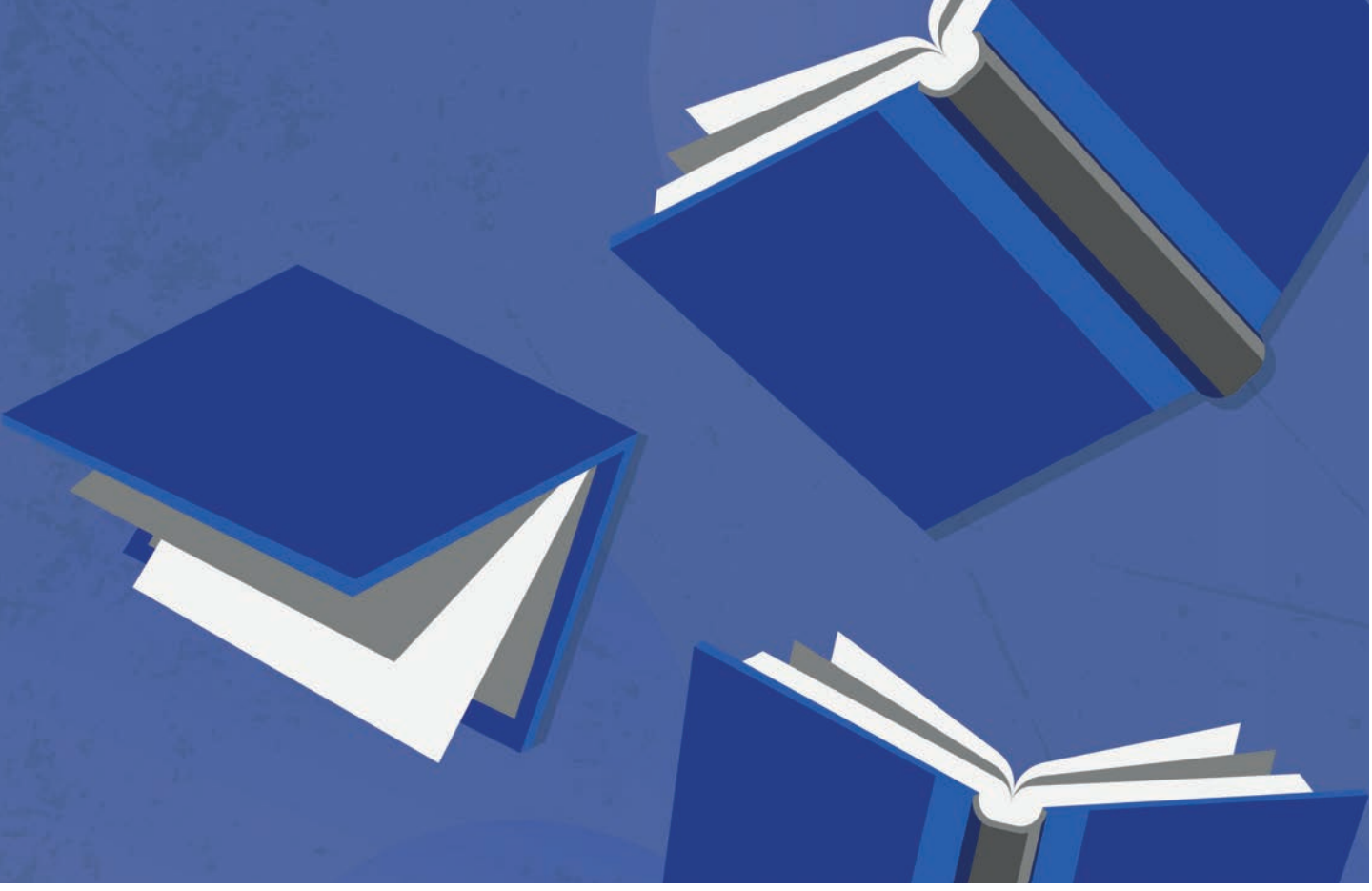

# The Blue Books are Back!

## The fifth edition of the WHO's Classification of Tumors series has arrived

When it comes to cancer, the classification of tumors is integral to accurate diagnosis. It also informs research into cancer causation, prevention, and treatment, making a consensus vital for pathologists around the world (1). That's what the World Health Organisation (WHO)'s Classification of Tumors series – colloquially known as the Blue Books – have been providing for over half a century. But in a rapidly evolving field that no longer relies solely on histopathological features, there is a need for more frequent updates on the way tumors are classified.

That's why, this year, a new and improved series of Blue Books will return for its fifth edition. Ian Cree, Head of the WHO Classification of Tumors Group, says that the redesigned books feature "a number of major improvements that will drastically improve readability, accessibility, and practicality." The revamped series will include a modernized layout with two columns of text instead of three (allowing for more and larger images), a multidimensional approach to classification, and tabs on the pages of different chapters to avoid confusion when moving between sections.

"We have done a lot of work on usability because these are essentially bench books, so pathologists need to be able to access them quickly and easily to aid diagnosis and classification," Cree explains. One worry is that people may use outdated versions of the book by mistake – so the new Blue Books will differ from their predecessors in simple yet effective ways: a distinctive lighter blue and a clear "5" on the spine.

Following extensive feedback, this will also be the first Blue Book series to appear in full online. "The dedicated website will be launched in September and will include up to nine books – two to three of the new fifth series and six of the latest books from the fourth series," explains Cree. The full classifications will be added to the website as they are developed, and the use of whole slide images promises an immersive digital experience.

The first book in the fifth series, expected in September, will describe digestive system tumors. Prepared by 168 authors and editors and contributed to by hundreds of pathologists across 22 different countries, the book has taken about 15 months to prepare. "The respondents that we surveyed wanted revisions roughly every four years; to deliver that, we've had to improve the process at every point," says Cree. "We now feel that the optimal time to develop each book is about a year." Along with the usual 12 books, the new series will also include collected works for pediatric tumors, hereditary tumors, and neuroendocrine tumors.

*Reference*

1. *I Cree, "Onward and Upward for the Blue Books", The Pathologist (2018). Available at: https://bit.ly/2SsXcwk.*

# A Golden Ratio for Gut Disorders

**Could the permeability ratio be used to diagnose and monitor gut disorders sooner and less invasively than traditional colonoscopy?**

Inflammatory bowel disease (IBD) is on the rise across the globe – especially in industrialized countries. By 2015, an estimated three million people in the US had received a diagnosis of either Crohn's disease or ulcerative colitis, the two conditions collectively known as IBD (1). Characterized by chronic inflammation of the gastrointestinal tract, symptoms of the disease include stomach pain and swelling, bloody diarrhea, and weight loss. Typically, IBD is diagnosed and monitored through colonoscopy, which assesses structural damage to the intestine's gut-blood barrier. But colonoscopy is invasive and requires anesthesia – and Marcin Ufnal of the Medical University of Warsaw might have found a better alternative.

Patients with IBD suffer from an impaired gut-blood barrier, which Ufnal and his team have harnessed to develop a novel test that compares the ratio of bacterial products in the patient's blood and stool. "We initially wanted to use the concentration of gut bacterial products in the blood, but this didn't work because there were significant inter-individual differences in bacterial composition, including geographic, dietary, and drug-related factors," says Ufnal.

In contrast, the blood-to-stool ratio of bacterial products isn't affected by differences in the composition and metabolic activity of bacteria. "The permeability ratio (Pr) assesses the extent to which bacterial products have passed through the gut-blood barrier," Ufnal explains. "A healthy individual will have a low Pr, whereas the ratio for an IBD patient will be higher." Specifically, the Pr analyzes short-chain fatty acids in just 1 mL of blood and stool, measuring their concentration via liquid chromatography coupled with triple-quadrupole mass spectrometry.

Ufnal believes that the technique could also be used to diagnose other disorders that affect the function of the intestinal wall, such as celiac disease. In addition, it offers promise for the detection of heart failure, high blood pressure, and liver ailments, because they may all result in a leaky gut that affects the concentration of bacterial products in the blood.

Future efforts will be directed toward assessing which bacterial metabolites are most useful in terms of calculating Pr. "We are doing a lot of basic research to look for bacterial products that aren't metabolized by the liver, because that can affect their concentration in systemic blood," says Ufnal. Given that gut disorders can develop before any structural changes can be seen with traditional colonoscopy, this method of diagnosing and monitoring IBD offers hope that symptoms can be controlled at the earliest stage.


*References*

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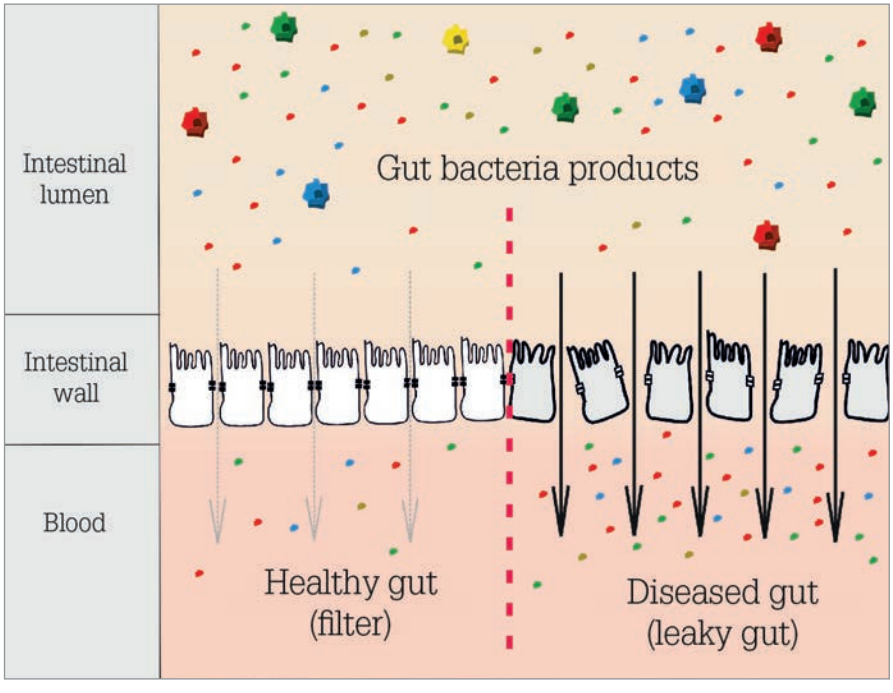
2. *K Jaworska et al., "Inflammatory bowel disease is associated with increased gut-to-blood penetration of short-chain fatty acids: A new, non-invasive marker of a functional intestinal lesion", Exp Physiol, [Epub ahead of print] (2019). PMID: 31243807.*

# 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*

## These Aren't the Findings You're Looking For

**When reporting unsolicited or incidental findings from research, include participants in the decision-making – and be less conservative**

*By Tieneke B. M. Schaaij-Visser and Gerhard A. Zielhuis, The Patient and Public Advisory Council for Biobank Research, the Netherlands*

Imagine you are enrolling participants for research on a hereditary disease. Part of the investigation involves extensive genome sequencing to identify novel causal genes. Then you "accidentally" stumble upon a gene mutation in one of the participants that has no relationship to the disease of interest, but does substantially increase the risk of a different serious disease…

In most European countries, the policy is only to report such unsolicited, or incidental, findings if they are clinically actionable. If, on the other hand, there are no treatment options for the condition, the study participant does not have to be informed. In fact, researchers are urged to be as conservative as possible and take all possible measures to avoid being confronted with such a finding – but, unfortunately, that is easier said than done.

To make life easier for those conducting such studies, ethics scientists in the Netherlands have developed guidance for the detection, management, and communication of incidental findings (1,2). This is a major step forward in making researchers aware of the possibility of incidental findings, and of how to handle them when they arise. That is why the Patient and Public Advisory Council for Biobank Research (3) enthusiastically encourages the use of the guide. We would also like to encourage researchers to ask, "Could we be less conservative?" For example, could you consider including participants in setting up policies and study designs?

Current times might ask for a pinch of liberalization for several reasons. First, large scale omics approaches, big data, and a learning healthcare system are all closing the gap between healthcare and research – and will increase chances of incidental findings. Second, patients and citizens are better informed, more involved, and better equipped than they were only a few short decades ago when it comes to their own health. Third, they are more assertive, and eager to collect all possible information to make their own health-related decisions. Fourth, the time, place, and clinicians involved in the diagnosis can also "make or break" the issue. And, finally, other factors – for example, family (planning), life(style) and career choices, and finances are becoming just as relevant to treatment decisions as the medical criteria for whether or not something is clinically actionable. And that's why it's relevant and valuable for individuals to have all the information related to their own health.

Notably, we do not deny that people have the right not to know. Nor do we envision that all individual data from research will be shared. We do stress, however, the importance of considering this issue before starting a study, and the helpfulness of using the guide to implement a tailored solution. It is particularly important to involve representatives of the envisioned healthy

and patient participant groups. Such partnerships will aid in ensuring that relevant and comprehensible information about unsolicited findings reaches the participants.

With these considerations, the current European default ("no reporting unless") may change into a strategy of reporting when informed representatives of the ultimate stakeholders consider the data relevant. Informed consent procedures may include a range of options for reporting research data (from "I don't want to know" to "only when actionable" to "as much as possible"). We're moving toward a possible new model – not the traditional study format in which results are returned to patients, but one with active participants who take it upon themselves to seek access to results. This will empower patients and citizens to better manage their own health data, and it will help researchers to fit procedures for informing participants to the needs and wishes of those participants.

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# Yes, You Can Be a Pathologist!

**For students to see pathology as a viable career choice, we must make the discipline visible in undergraduate medical education**

*By Rick Mitchell, Lawrence J. Henderson Professor of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, USA*

Throughout my career, I've been very involved in pathology education. Serendipity played a major role in that involvement. Throughout graduate school and in the first couple of years of medical school, I dabbled here and there – from teaching Mendelian genetics to fourth-graders in Manhattan to TAing microbiology for first-year med students. It was fun, but not something I saw as a major path forward. However, as I entered my pathology residency, my mentors, Ramzi Cotran and Fred Schoen, were ardent believers in the role of pathology (and pathologists) in medical education. Both were heavily involved in the writing and editing of the Pathologic Basis of Disease and Basic Pathology textbooks, and I was invited to contribute to a couple of chapters, eventually serving as editor on one edition of Basic Pathology and shepherding the Pocket Companion through several iterations. At that time, Fred Schoen was also directing the combined Harvard–MIT Health Sciences and Technology (HST) pathology course at Harvard Medical School. He encouraged me to run laboratory sessions, and then to give a couple of lectures – and I was hooked. Teaching at that level, to such outstanding students, was both exciting and terrifying, combining a sort of performance art with the satisfaction of providing the foundations for the next generation of physician-scientists.

When Fred stepped down, I took on the course and, through my connections to the HST program, became increasingly involved in overall curriculum design at Harvard Medical School. I have also been very active in the American Society for Investigative Pathology, chairing the education and programming committees for an international organization. Through all of this, I've been incredibly fortunate to have supportive chairs (Cotran, Michael Gimbrone, and Jeff Golden) who share the view that education is as important to the practice of pathology as the diagnostic and research components. I think I'd gladly give up a lot of things I juggle now (especially administrative responsibilities!), before I'd give up teaching; it's that satisfying.

Unfortunately, the current trend toward truncating preclinical basic science exposure means that students see

*"I'd gladly give up a lot of things I juggle now [...] before I'd give up teaching; it's that satisfying."*

pathology and pathophysiology mainly through the lens of a longitudinal and integrated curriculum where the word "pathology" might not even appear in a course description. In that environment, students do not get to clearly appreciate the role a pathologist can play in education and research. And, on the wards, most schools do not draw any attention to the function of the pathologist in diagnosis and driving patient care decisions; it is the exception, rather than the rule, for students to attend tumor boards and other conferences that highlight the critical responsibility of the pathologist. Most students have never seen an autopsy, a surgical pathology cutting room, the transfusion medicine suite, the frozen section room, or the clinical labs. As a result of this lack of exposure, the overwhelming majority of students never get a chance to understand that "pathology" is a career they can pursue. In the 2019 residency match for example, only about 200 US medical school graduates applied for over 600 pathology residency slots!

To stay visible and relevant, we need to push back on the preclinical education process; pathologists need to be represented on curriculum committees and be vocal about having a more obvious role. At a bare minimum, we should take five minutes out of our lectures and describe for the enthralled masses what a career in pathology can entail. We can also help the cause by encouraging greater foundational pathology content on the USMLE exams; there's no incentive for medical schools to teach pathobiology if their students are not going to be tested on it. In hospitals, pathologists should encourage their clinical associates to carve out time for "road trips" to the pathology labs, or even week-long experiences in pathology. For students on surgery rotations, this could take the form of following specimens to the frozen section room, to the cutting room (helping to find lymph nodes?), and to the final sign-out. For students on medicine rotations, this could involve going to tumor boards, working up patients for plasmapheresis, going to microbiology plate rounds, or learning some of the nuances of flow cytometry or molecular diagnostics. It's doubtful that pathology will ever become a mandatory rotation, but requiring it to be integrated into the experiences on other clerkships (beyond just another PowerPoint) will go a long way toward getting pathology on students' radars – and that's something we should prioritize at all costs.

# The Enemies of Pathology

## Why medical students and patients are unfamiliar with the laboratory

*By Andrei-Mihai Borcan, fourth-year medical student at "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

As I read the "Preaching Beyond the Choir" editorial in The Pathologist, it triggered my personal fears about choosing pathology as my future career. As a fourth-year medical student in Europe, I can feel the lack of appreciation from my peers as I express my desire to pursue pathology in the future. People still in training do not seem to perceive this extraordinary field to be as "noble" or "challenging" as the clinical or surgical specialities, and that puts a tremendous amount of pressure on people like me, who find pathology not only intellectually challenging, but probably the most diverse field of medicine as a whole.

And there, in our lecture halls and hospital wards, lies the greatest enemy of pathology – peer pressure. It's an inescapable fact that, even if great and successful pathologists (like my extraordinary pathology teacher, Gabriel Becheanu) teach us about their work and empower us to pursue this field, the ignorance of peers tramples the enthusiasm of many potential pathologists and diverts them from a future that might impact their – and their patients' – lives in a purely positive way.

With regards to patients and their understanding of pathology and laboratory medicine, leaflets and notes on pathology reports won't do much, in my humble student opinion. What I think we need to do is adapt. My suggestion? YouTube. Medical education channels run by pathologists that, through well-known topics (such as polyps, Barrett's esophagus, and common cancers) educate patients on diseases that are familiar to most, yet whose diagnosis unquestioningly relies on the input of the pathologist. Help people understand what you do by improving their overall understanding of medicine. Teach them about your field by explaining to them why you are so important in so many ways. Bring them closer to you by sharing information that for you is elementary, but for them is groundbreaking. Then they will see and respect you as you deserve.

Through initiatives like these, I hope that the future of your field (and hopefully mine as well in a couple of years!) is as extraordinary as the work you put into your diagnoses day in and day out.


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# Image Exchange – With Anyone

## How a digital image-sharing system can improve the speed and efficiency of patient care

*By Annie Pinfold, PACS Radiology Information Systems Senior Consultant at Oxford University Hospitals NHS Trust, Oxford, UK*

The most common way of sharing patient data between stakeholders – be they healthcare systems, insurance providers, or the patients themselves – has historically been via physical media: first written notes, then faxes, and ultimately CDs. But these are awful from a security, efficiency, and usability perspective. As a result, my colleagues and I are moving to a digital image exchange portal (IEP), which allows us to share images quickly and securely. All National Health Service (NHS) hospitals in the UK have a proven, trusted, and ubiquitous IEP network connecting them, so enabling secure digital exchange and access for all stakeholders over this platform was the logical choice. For instance, Oxford University Hospitals NHS Trust, where I work, shares the care of its patients with other hospitals, so enabling patients to quickly access their scans and X-rays using the IEP with Anyone extension will allow other clinicians to plan better care for them.

When a patient places a request for their imaging, we require either two email addresses or one email and a mobile phone number. The patient details are added to the IEP forms and the required images are chosen from a list. The transaction is then created and an email is sent to the patient, inviting them to download their images. The second email or phone number will receive an authorization code, which helps us keep the system secure. It works very well, but it's not entirely foolproof yet. We're currently looking into why certain studies fail to transfer, causing us to rely on CDs to get them to the clinical teams. Two-part authentication has caused us a few problems – but then, the previous password system did too, and we value the extra security. The vast majority of transactions go smoothly, though.

In addition, the transaction is usually done overnight. That offers patients quick access to their imaging, which they can then forward to clinicians of their choosing within IEP with Anyone. Many of our patients are overseas students or visitors; we need to ensure that they have quick access to their studies in their home country, so they can continue any necessary treatment with a full diagnostic imaging history. (You can also use the system to send the reports, but the Trust has chosen not to do this at the present time.) A couple of examples: I have provided images to armed forces personnel so that they can access them from wherever they might be stationed to ensure their treatment is continued. Studies have been provided to patients who have appointments at private clinics the day after their imaging has been conducted at our site. Patients searching for treatments and second opinions overseas can forward their studies in fewer than two days after they receive their IEP transacted images – something that could previously take two weeks by post.

There's a good argument for doing away with physical media and instead making patients' images accessible via secure web-based products. First, the vast majority of laptops and PCs no longer have CD drives. Second, the time needed to create CDs and print password letters, along with the cost of consumables used in their production, greatly outweighs the time and costs of IEP with Anyone transactions. Moreover, there are no lost or misdirected CDs or passwords – and, if we do have to issue a physical product, our software automatically creates CDs for Windows (although we still use a manual process for Mac CDs). We use physical media to transfer studies to hospitals that don't yet have IEP technology – some private clinics, Ministry of Defense medical sites, and remote hospitals in locations like the Falkland Islands.

*"Digital image access for both patients and healthcare providers is the way of the future."*

Because of occasional image transfer failures, it's vital to make sure you have a backup mechanism (such as a CD) to deliver the studies – but, as more IEP transfers are completed and the system is refined and improved, the need for that secondary delivery mechanism will reduce to almost zero. Regardless of whether patients access their imaging via IEP transfer or CD, though, you must provide clear and robust documentation in plain language to help patients download their images. Although accessing images is no more difficult than most online processes, it is still fairly new to people as a method of obtaining parts of their medical record, so user questions do arise.

In my view, digital image access for both patients and healthcare providers is the way of the future. It greatly reduces the costs and timeframes associated with sending studies back and forth, enhances the security of the process, and ensures that nothing can be lost or misdirected. I hope to see many more healthcare systems using this type of technology in the near future.

# Improvement Through Engagement

## It's our job to raise the profile of the laboratory among patients and the public

*By E. Blair Holladay, CEO of the American Society for Clinical Pathology, Chicago, USA*

ASCP's dedication to the well-being of patients is evident by their placement in our mission statement: "to provide excellence in education, certification, and advocacy on behalf of patients, pathologists, and laboratory professionals." Although all of our products and services affect patients tangentially – for instance, educating and certifying our community means that we deliver better patient care, whereas our global health efforts provide quality laboratory services for low-resource settings – we apportion significant resources to raising public awareness of the clinical laboratory. And that requires a multi-faceted approach, which includes strengthening relationships between the laboratory and the clinical care team, talking directly to patients about their diagnoses, and educating patients on the role of the laboratory so they can, in turn, be proactive with their healthcare.

In 2012, ASCP joined the American Board of Internal Medicine (ABIM) Foundation's Choosing Wisely campaign. The campaign's goal is to promote conversations between clinicians and patients to provide safe, evidence-based, and truly necessary health care. As experts in laboratory medicine, pathologists and laboratory professionals are uniquely qualified to help clinicians and patients choose the best testing for their needs. Over the past several years, ASCP has released over two dozen recommendations that decrease overused or outdated tests and provide guidance for appropriate test selection. These recommendations decrease the burden on healthcare systems by "following the data" to order the right test for the right patient at the right time.

Acting as consultants for the clinical care team, although essential, is not the only way pathologists and laboratory professionals can educate the public about laboratory medicine. We can also explore ways to discuss diagnoses with patients directly. ASCP Vice President Kimberly Sanford engages patients on a daily basis. Her practice is different than most pathologists'; her workplace has more in common with a clinical care setting than a laboratory. About 20 patients a day are seen on-site for blood banking and apheresis procedures, and Sanford takes the time to speak with them about their procedures and answer questions about their diagnoses. She also encourages her residents to do the same. Because of these conversations, patients come away with a deeper understanding of their condition and an appreciation for pathologists. Diseases and their treatments can be complex and, as experts in disease diagnosis, we are uniquely qualified to engage patients during their care.

Yet another way for pathologists to bring the laboratory to public awareness is through ASCP's Patient Champions. The program raises awareness of the medical laboratory's role in patient care through patient stories. Our hope is that, through awareness, patients will feel empowered to ask the right questions, understand their diagnoses, and share their own stories with others. The diagnoses our Champions have received run the gamut: cancers, anemias, and even congenital kidney conditions requiring transplants. These Champions highlight not only how important it is for patients to understand the lab's critical role in their care, but also the value of effective communications between them and the laboratory team.

As pathologists and laboratory professionals, we have an obligation to focus on the person behind the slide and the sample. We have the opportunity to improve patient care by sharing our knowledge through collaboration with our peers, by engaging patients directly – and by empowering patients to engage with us. Doing so not only benefits our patients, but it also enlightens and strengthens our profession.

# THE CASE FOR A UNIVERSAL CLERKSHIP

## REGARDLESS OF SPECIALTY, NO DOCTOR'S MEDICAL EDUCATION IS COMPLETE WITHOUT PATHOLOGY TRAINING

*By Kamran Mirza and Austin McHenry*

As a physician, do you routinely rely on a tissue diagnosis to guide treatment? Do you consistently contemplate whether a deeper level of testing – perhaps molecular, genetic, or cytogenetic – would be a good use of healthcare dollars? Do you know who can help you make this call?

Maybe your specific subspecialty doesn't always demand it. But let me pose a slightly different question: Does a typical physician, during the course of their career, need to order and interpret a laboratory test to guide therapy? Do they wonder about whether they need a complete blood count (CBC) with differential, the CBC alone, or just the hemoglobin and hematocrit (H&H)? Do they care about proper test utilization? Is this part of their job?

The answer, of course, is yes – this is a routine responsibility.

So then why, after the second year of a typical medical school education, is pathology training an elective experience?

A solid understanding of every aspect of anatomic and clinical pathology is directly relevant to over 90 percent of practicing physicians every single day. We often hear that 70 percent of all healthcare decisions are based on pathology and laboratory medicine – and we certainly know that most, if not all, medical providers in practice invariably work with pathologists via consultation at some point. Nevertheless, when physicians in training are given the option of elective clerkships to further their understanding of our vital specialty, most choose not to engage. It's clear that these electives aren't quite hitting the target – so what is the alternative?

### A UNIVERSAL PATHOLOGY CLERKSHIP

In a typical allopathic US medical school, third- and fourth-year students traditionally have several required rotations: internal medicine, family/outpatient medicine, surgery, psychiatry, obstetrics/gynecology, and pediatrics. Most graduating physicians will pursue one of these fields, so exploring all six makes sense. The clerkships serve a multitude of functions: exposure to the field (as a possible career choice); exposure to the discipline for knowledge; and, most importantly, exposure of students to other disciplines whom they, as future physicians, will consult.

The emergency medicine doctor consults a general surgeon when an abscess seems too complex to drain at the bedside. The internal medicine doctor consults a psychiatrist when a patient exhibits signs of suicidality or psychosis. These physicians rely on consultants not because they don't know how to tackle relevant problems on their own, but because they know that a dedicated specialist can do it better. Deferring to expert opinion when

necessary means that our patients have the best possible quality of care – and, as a result, the best possible outcomes.

These expert consultations typically work because the consulting doctor has had some experience, however brief, in the consultant's field. Each can speak the language of the other – a language most likely learned during their medical school clerkships. Conspicuous by its absence from this list of clerkships, though, is our own discipline. All of the aforementioned specialties interact with ours, whether they know it or not. They order laboratory investigations and send material to pathology. They request expensive tests, interpret complex reports, and navigate the world of molecular diagnostics. In spite of this, most don't speak the language of pathology. They don't even know its alphabet. They don't know who pathologists are or where to find them; often, they don't even know what pathologists do or how we can help their patients. Would a clerkship change this?

## WHAT IS PATHOLOGY?

When most physicians think about the field of pathology, they associate it with definitive tissue diagnosis, a discipline to which they were exposed during their preclinical years in medical school. This understanding is accurate, but it is not complete. Medical students are exposed to the basic histopathologic features of common malignancies and disorders – but they do not typically receive any exposure to the journey a fresh tissue sample takes from patient to final diagnosis. They do not know how many steps are involved in the processing of the tissue, nor do they understand why certain cases take longer to sign out than others. They don't understand the role of a large team of professionals involved in their patient's care – the medical laboratory scientist, the pathologists' assistant, and a dozen others. The only "interprofessional" education most people have seen is the interactions between doctors, nurses, and pharmacists.

Although it is not necessary to understand the granular details of all pathology-related processes, it is necessary to be able to understand how and why things can go wrong. It is necessary to understand why a frozen tissue sample may report a less specific diagnosis than a permanent; why cells cannot be fixed for flow cytometry or cytogenetics; why an H&H (rather than a CBC with differential) will suffice when wondering about a patient's hemoglobin; why some tests need to ordered when the patient is in an outpatient setting; and why molecular testing of a tumor may or may not be helpful for a particular patient. Are these not relevant questions for every physician? Imagine that you, as a patient, go to your doctor and ask one of these questions. Would you have confidence in your physician if you were met with a blank stare? Most doctors learn the importance of these things through trial and error on the job – not as a feature of didactic teaching during medical school. The number of times lab professionals and pathologists are met with long, awkward pauses on the phone (or, worse yet, belligerent arguments that have no scientific basis) seems too numerous to count.

And fewer still of our colleagues seem aware that "the lab" is more than just tissue diagnosis. Laboratory medicine covers a vast range of disciplines – and yet, not only do most medical students never set foot in a clinical laboratory during their entire four-year education, they also never interact with the individuals who are present to be consulted on these issues. When the result of a test does not correlate with the clinical picture, the clinician needs to know whom to contact and how to speak their language. In the same way, when a clinician relies on laboratory testing to find a solution to an uncommon problem, they may not know which tests to order – and, to find out, they need to know with whom they should consult. Most doctors have developed their own algorithms to decide whom they contact, when to do it, and how to go about it – but wouldn't it be beneficial to know how a poorly filled blood bottle can change microbiologic culture results? Or that high levels of biotin may mask rising troponins in the setting of an acute coronary syndrome?

## PUTTING THE "PERSON" IN PERSONALIZED MEDICINE

If my impassioned plea isn't enough to convince you, let's turn our attention to personalized medicine.

"THESE ARE COMPLICATED TESTS WITH COMPLEX BIOINFORMATICS IMPLICATIONS AND DATA THAT MAY HAVE LIFE-ALTERING RESULTS."

Companies are now offering all sorts of genetic tests directly to patients at home. These are complicated tests with complex bioinformatics implications and data that may have life-altering results. Are non-pathologist physicians comfortable with all the questions that may arise from such testing? Will they be in the future?

At present, in the laboratory, these techniques are mostly relegated to patients with cancer; they are used to determine specific mutations that may help predict prognosis or indicate the likely success of targeted therapies. However, they are quickly propagating beyond oncology into other fields. Examples include the sequencing of drug-metabolizing enzymes, transcriptomics (mRNA expression levels), proteomics (molecular biomarkers that can often predict toxicity), and metabolomics. These are tests that will affect every physician's patients.

Let me offer an example. A recent addition to our precision arsenal is vitamin K epoxide reductase complex (VKORC1) and cytochrome P450 2C9 (CYP2C9) function testing. VKORC1 is a protein that regulates vitamin K levels in the body; CYP2C9 is an enzyme that metabolizes the blood thinning drug warfarin. If a patient has a molecular test in their chart that shows poor VKORC1 function and homozygous *CYP2C9* alleles, it is the responsibility of any physician who prescribes warfarin to know that the patient is at high risk of bleeding if started on the drug at normal titrating doses. Alternatively, assume a pathologist conducts a genetic test on a solid tumor and discovers a germline mutation of significance. Presumably, every physician who comes into contact with this patient needs to know what to do with this information, because the patient's problem is not a single cancerous tumor; it is, presumably, a lifelong genetic condition.

## ADDING A NEW CHECKBOX

In our experience, the lack of a clerkship also underlies most misunderstandings that non-pathologists have about a career in our field. Most pathologists have heard the concerned cry of, "But you're such a people person!" from colleagues who are worried that their choice of specialty may not be well-suited to a happy, outgoing personality. Most of these comments come from doctors who rarely set foot in the lab – and a clerkship could change this negative perception of our discipline. Medical students mentally check the boxes of possible career options after their clerkships end. "Yes or no: do I want to stay in this field for the rest of my life?" They run through the options. "Psychiatry: no. Internal medicine: no. Surgery: yes." But there's one glaring omission; pathology isn't even on their list! There is no box to check, so they never even give themselves the option of saying yes. And when exclusion is the default option for a field as fundamental as ours, it has a detrimental effect on healthcare as a whole.

When medical students do not receive exposure to pathologists, laboratory professionals, and the processes and tests we use, we risk the prospect of training an entire generation of physicians who may not know how to interpret the testing for which they are ultimately responsible. In fact, this isn't even a risk; in many ways, it is already our reality.

## LOGISTICS

In a perfect world, medical students would receive exposure to every specialty in medicine. Although logistical reasons

obviously make that impossible, it should be noted that most medical students have abundant time for elective clerkships in their fourth year. We argue that a short time spent in a combined anatomic and clinical pathology elective would give medical students enough exposure to understand how the processes of tissue diagnosis and laboratory testing generally function. It would make students include the pathology checkbox on their mental list of options, even if they ultimately choose not to pursue it. A clerkship would allow each and every medical student to make an informed decision about pathology as a career.

But how would this be achieved? Hundreds of medical students rotating through the Department of Pathology each year? It would certainly be no walk in the park. The trick to proper implementation may be involving them in patient care just like residents. We envision streamlined and efficient orientations, active involvement in grossing, frozen, signing out, clinical pathology rounds, and quality assurance and improvement projects. However, despite best intentions, this would be difficult to implement as a "usual" medical school clerkship. Even if medical students were assigned non-urgent cases (for instance, no cancers), the sheer volume of medical students per pathology department would render the clerkship a revolving door of students coming in and out. I can already hear the groans of medical school administrators and pathology faculty alike. Without some "out of the box" thinking, a typical four-week, nine-to-five rotation may face logistical issues too great to allow success.

So how do we make this clerkship a reality? One possibility is the implementation of a longitudinal curriculum that runs alongside the third and fourth year of medical school education. If championed correctly, this could be comprised of a series of didactic lectures, microscopy, and laboratory sessions that deal with a set number of students at a time. Students could learn about grossing and histology by seeing the gross room and working with 3D-printed organs. Frozen sections of vegetable matter, cytopathology on animal livers or spleens, and similar hands-on workshops would let medical students expand their pathology horizons without negatively impacting patient care. They could try their hands at processing blood and urine samples, looking for and reporting crystals in body fluids, spiking samples with interfering substances, and more.

A longitudinal program would also introduce the possibility of working with additional members of the healthcare team. Medical laboratory scientists, histotechnologists and everyone else who works in AP and CP labs would offer the valuable interprofessional learning experiences we want for our medical students. Between the didactics and practical labs, the rotation could include social media activities (1) and informal learning to impart pearls of pathology algorithms and information. This way, everyone would see the details they need – and, for those intrigued by their first taste of our discipline, the customary pathology elective would let them delve deeper on a case-by-case basis.

As healthcare changes and we scrutinize our expenditures more and more, we suggest that we might find easier or better solutions to our healthcare problems by including pathologists in the discussion, and by giving non-pathologist physicians a better understanding of microscopic diagnostics. These aren't theoretical possibilities somewhere in the nebulous future of our healthcare system; these are real, current issues. How medical students view pathology as a career; the way our colleagues perceive pathologists; the degree to which everyone needs to understand the dollars and cents of diagnostics – a trio of reasons as to why medical educators must begin to have conversations about creating a universal, non-optional pathology educational experience. Such an experience could take a number of forms – standalone or longitudinal, third or fourth year – but the time for creating such a clerkship is long overdue.

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*Reference*

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# TAKING THE (PRE-RESIDENCY)PLUNGE

## AUSTIN MCHENRY SHARES HIS EXPERIENCES AS A MEDICAL STUDENT WITH AN INTEREST IN PATHOLOGY

### HAVE YOU COMPLETED A PATHOLOGY CLERKSHIP?

During my medical training, I completed three pathology clerkships – all optional.

In my third year, I did a four-week rotation: two weeks each of AP and CP. That first introduction allowed me to see and appreciate the daily work flow of anatomic pathologists in practice in an academic setting; observe autopsies to see the anatomic principles of disease; and explore the different problems encountered in each subspecialty anatomic service. Because I had the opportunity to observe the interactions between clinicians and pathologists, I felt I gained a better understanding of the various roles of laboratory personnel (from residents and fellows to lab managers) and of the clinical laboratories themselves (where they are, who works in them, and what they each process). I was also given the chance to explore clinical consultation questions, troubleshoot errors in analytical tests, and learn about quality assurance and improvement outcomes. By the end of my rotation, I felt I understood the perspective of the pathologist when specific consultation questions arise – something that would stand any physician from any specialty in good stead.

In my fourth year, I did two stints in pathology. The first was a four-week rotation in dermatopathology, which was amazing because it let me dive deep into a single subspecialty for a prolonged period of time. I saw as many specimens as a typical resident on the service and learned about the difference between diagnosis in dermatopathology versus other anatomic disciplines. I then did four weeks of anatomic pathology so that I could improve my skills with "bread and butter" surgical pathology cases, learn basic grossing techniques, attend daily lectures, and see as many interesting cases as possible.

### HOW WERE YOUR CLERKSHIPS STRUCTURED?

At eight o'clock every morning throughout the rotation, we attended the residents' lecture series. Each topic (in both AP and CP) averaged four to five lectures. After that, the rest of our day's schedule depended on whether we were currently experiencing AP or CP.

For the rest of the morning, my time in AP was spent previewing cases with a resident on the service. Often, the resident would give me a few of the cases they had already seen and ask me for a blind description of what I saw. It wasn't necessary to find a definitive diagnosis, but it was considered a good start if I could at least suggest benign versus malignant. The most important skill that this part of the experience taught me was the ability to accurately describe what I saw.

In the afternoon, I reviewed assigned unknown slides by myself, and then with the resident or attending. I participated in sign-out with everyone on the service and followed up on cases that could not be signed out. Unscheduled but frequent occurrences included autopsy observations (even when not on that service), clinician consultations, gross room frozen section calls, and the opportunity to observe grossing, if the resident training me was on a grossing service.

CP was structured slightly differently. The mornings were dedicated to laboratory director-initiated didactic sessions about what takes place in the lab. In the afternoons, I took part in laboratory tours with lab techs (which often meant observing each position for a while as I rotated through the lab); learned about QI/QA projects currently underway; and was assigned papers to read and discuss the next morning. The apheresis clinic, in particular, involved taking a history and physical examination of each patient so that I could learn the indications for various procedures.

Why are these experiences important for all doctors?

Every doctor needs to know where their laboratory tests go and what the limitations of those tests are. That way, they will know what pathologists and lab medicine professionals need from them – in terms of sample type, quality, background information, and more. Most of all, it's important for all doctors to know that there are professionals available 24 hours a day to consult when they have questions on laboratory testing. For surgeons in

particular, it's important to show what constitutes a useful specimen – pathologists can't make an adequate diagnosis on permanent tissues if the quality is lacking. It's also good for students anticipating a career in surgery to understand the purpose and limitations of the frozen section consultation.

I know that, over the course of my clerkships, I gained an understanding of why certain cases take longer to sign out than others. I can now appreciate which cases are simple and which are more complex and require further consultation – not to mention which clinical tests are possible and which are not. I know what molecular testing is, its pros, and its cons; I understand the benefits and the pitfalls of analyte testing for quality control. Such knowledge will ultimately make me, and other medical students who pursue it, a better doctor.

For me personally, it has also been valuable to get to know the kinds of people who go into pathology and to identify good (and not-so-good) role models. I've also become familiar with the workflows of various types of pathologists, which has helped me to decide which subspecialty I may want to pursue in the future. Fellowship applications must be sent at the end of the second year of residency, so I'm glad I have a head start on making my choice!

## DO YOU HAVE A FAVORITE ANECDOTE FROM YOUR PATHOLOGY CLERKSHIPS?

I have several, each of which taught me a different lesson.

One took place in a transplant setting. Our urgent question: was the donor kidney viable? To find out, I ran to the frozen section room with Dr. Picken. The frozen section, pathology resident, and renal transplant surgeon were waiting. Everyone positioned themselves around the multiheaded microscope. "Yes, yes. This patient definitely had some long-standing hypertension. Is it too much? Hmm. I'd say somewhere between 15 and 20 percent of the glomeruli are sclerosed. Yes, 15 to 20."

The transplant surgeon stated that he did not know what to do with that information; the cutoff for rejecting a donor kidney was usually 20 percent. Dr. Picken looked again. "It is definitely less than 20 percent. Yes. Definitely." The transplant surgeon did not seem reassured. Everyone stared blankly at Dr. Picken, who then loudly asserted, "I would put this kidney in my daughter!"

After further explaining her rationale and pointing out other aspects of the donor's clinical history and data that supported her conclusions, the transplant surgeon was assured. Why was this experience so meaningful to me? It demonstrated the very real consequences of the pathologist's diagnostic abilities. Although the donor kidney's sclerosis percentage was borderline, the pathologist had to use more than just guidelines and flowcharts to prove her point. She was confident and acted as a true consultant – a true "doctor's doctor."

Another incident took place in the gross room, where I observed an intraoperative frozen consultation for a patient who was undergoing a routine laparoscopic abdominal surgery. The surgical team noticed a suspicious-looking adnexal cystic mass, which they biopsied and sent for frozen section. On gross examination, the cyst was clearly mucinous. However, it was unclear to all of us whether it was a benign cystadenoma or a cystadenocarcinoma. It was a bulky tumor, but still seemed lined by a relatively smooth capsule. The assumption was that it was probably benign. Yet, on microscopic examination, there was clear stromal invasion, cytologic atypia, and complex architecture. This was a malignant process. We were all pretty surprised, but could nonetheless make a diagnosis on frozen section. This was a great experience for me, because it allowed me to witness a good indication for intraoperative frozen section consultation. I continue to believe that most surgical trainees don't understand this topic well and don't have adequate training for it at present.

When I had the opportunity to observe residents in the gross room and follow their cases, I became acutely aware of the kinds of mistakes that are inevitable in surgical pathology training. I witnessed a resident's inability to make a diagnosis on a dermatopathology case because it was sectioned incorrectly. I became aware of what autopsy material can be overlooked and what needs to be saved. I came to understand how ordering the wrong stains on a case with very little tissue could actually be detrimental to final diagnosis because the block was exhausted before the right tests could be performed.

I was even fortunate to have the opportunity

# A LOOK AT THE OTHER SIDE

## BRANDON TRAC DISCUSSES PATHOLOGY CLERKSHIPS FROM A NON-PATHOLOGIST'S PERSPECTIVE

Although I don't plan to pursue a career in pathology, I did complete a pathology clerkship as my elective course. I had some interest in the discipline from the brief exposure I had through SCOPE (Students Curious in Outrageous Pathology Experiences – our pathology interest group), and I enjoyed some of the pathology from my second-year courses. However, I realized that I still did not know much about the career and lifestyle of a pathologist, so I decided to take the course to learn a little more about the specialty and the role of the pathologist in patient care.

The clerkship took place near the end of my third year of training. I worked with residents, fellows, and attendings, and I was able to rotate through different parts of the department every few days. For the most part, I shadowed whoever I was assigned to that day. I had the opportunity to participate in resident lectures and, if time permitted, had some one-on-one education with residents. I was also able to work with staff in the apheresis center and blood bank and partake in a quality assurance meeting with the staff there.

I think the biggest benefit of the clerkship was that it allowed me to gain insight into the extremely important and diverse roles that pathologists play in the daily lives of our patients. As a future clinician, I believe it is important for me to understand the many influences pathology has on my medical career. The main reason I personally pursued a rotation in this specialty was to gain an understanding of the role of a pathologist. The elective afforded me the opportunity to see all aspects of pathology, whether clinical or anatomic, and gain insight into how I can enlist the help of pathologists in the future to provide the best and most efficient care to my patients.

The rotation had one unique feature: I was asked to maintain a Twitter account and post pathology-related tweets daily. Although it might not seem like much, I actually found it helpful for reinforcing the new concepts and ideas I encountered every day. Before posting, I would look up a topic that was relevant to my work that day, read around it, and try to condense it into a short message that I could tweet out. It was a fun, interactive experience that allowed me to communicate with pathology enthusiasts from around the world.

If I could speak to those in charge of medical education, I would encourage them to consider creating a short pathology rotation that would allow students to learn about the variety of roles pathologists play in the care of a patient. Although it is impossible to capture everything that goes on in the laboratory in just a short time, it is definitely worthwhile for future clinicians to better understand the world of clinical and anatomic pathology – a specialty that plays a key role in patient care.

*Brandon Trac is a medical student at Stritch School of Medicine, Loyola University Chicago, USA.*

to see firsthand the effects of intraobserver variation and quality assurance. When signing a case out involving acute cellular rejection surveillance after a lung transplant, I was able to see the same case with two pathologists – one a thoracic pathology expert, the other not. They came to two slightly different conclusions on grade of rejection. I thought this was particularly interesting because, although this sort of thing is not unheard of among pathologists, the other medical students on my clerkship truly appreciated its consequences when they saw it unfold before them. The outcome had a very real effect on the patient: one conclusion indicated treatment for rejection, whereas the other did not. The daily quality assurance conference, where the case was ultimately reviewed, showed me the beauty of collaborative diagnosis.

## DO YOU THINK PATHOLOGY TRAINING SHOULD BE MANDATORY?

Ensuring that all medical students have some pathology training could save costs down the road by preventing improper laboratory test utilization. It would also expose medical professionals to an aspect of the hospital most doctors don't often see, thereby strengthening the entire institution's collaborative mission of patient care. We hear about this with nurses, doctors, and pharmacists – but we never hear about the laboratory professionals!

Pathology education can improve patient care. Providers are often unfamiliar with how laboratory professionals record and input results into the electronic medical record; if they were to spend time with the individuals who process specimens (rather than just those who manage the labs), they might gain a greater appreciation for what their results mean in the context of specificity and sensitivity. Just because a test result is positive does not mean it is a true positive.

To the non-pathologist audience, I would like to stress that this isn't about trying to get more students to pursue pathology. Although that remains an important topic, the message at hand is that all medical students should witness pathology education in a setting that is relevant for healthcare.

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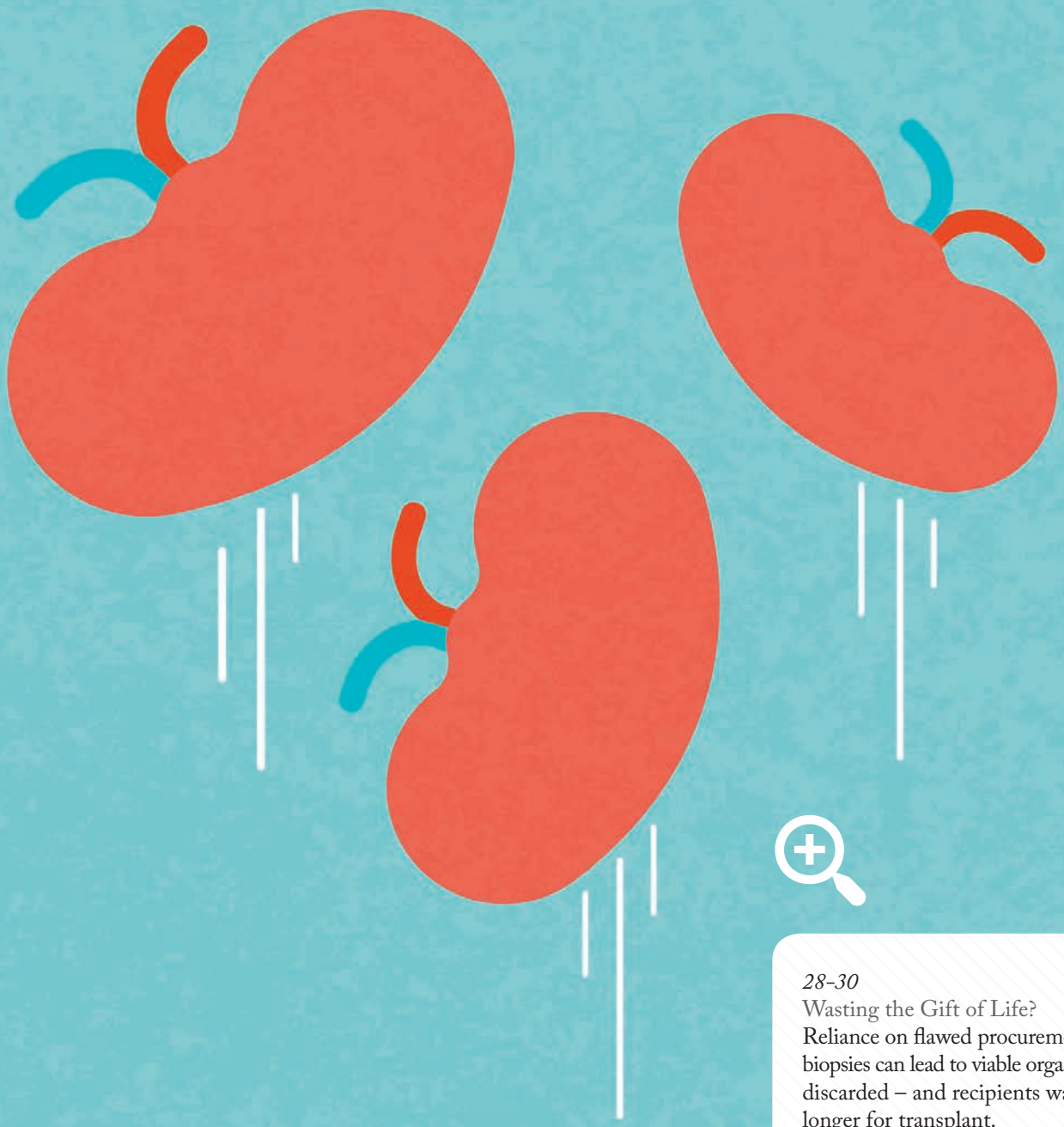


# Wasting the Gift of Life

**Our discard rates for donated kidneys are at their highest ever, thanks in part to unreliable and inconsistent procurement biopsies that need to be re-examined. How can we do better?**

*By Sumit Mohan*

Once a potential kidney donor has been identified, a simple but crucial question arises. Should the organ be accepted for transplant – or turned away? Factors such as donor and recipient characteristics, anatomic and immunologic information, and longevity matching considerations all influence this call and must be considered quickly. To help inform the decision, surgeons carry out procurement biopsies while the organ is being obtained; these occur in around half of all deceased-donor kidneys in the US (1). Deceased donor kidneys are a scarce and valuable resource – but, alarmingly, we find ourselves facing the highest kidney discard rate of all time, with one in five donated organs going to waste (2, 3). The findings of procurement biopsies play a telling role in these rates; they are listed as the main reason for discard in around 37 percent of kidneys that are procured but ultimately not used (4).

With the results of procurement biopsies contributing so heavily to the discard of potentially transplantable kidneys, it is vital to cast a critical eye over their efficacy at identifying organs that shouldn't be transplanted. A number of analyses have already raised questions about the reproducibility and predictive value of procurement biopsies, so we conducted our own study to assess their reliability (4). Across 116 kidneys that had undergone multiple procurement biopsies, we found only a 64 percent agreement rate between different biopsies, suggesting low reliability and consistency when it comes to the information that they present. A similar agreement was found between procurement biopsies and gold-standard reperfusion biopsies performed after kidney implantation.

## The problem with procurement

Why is there such poor agreement between procurement biopsies and reperfusion biopsies, as well as between sequential procurement biopsies? I think there are a number of factors that contribute to this inconsistency, starting with the environment in which they are conducted. There is great pressure to get these biopsies performed, processed, stained, and read in a relatively short space of time so that the surgeon can decide whether or not they want to keep the kidney. The biopsies tend to be frozen sections that are often read outside usual working hours (the "middle of the night phone call" is real!). Depending on who performs the biopsy and where it is completed, a hospital's facilities can also have an impact. For example, smaller hospitals might not have a kidney biopsy needle and will therefore have to perform a wedge biopsy, which results in more subcapsular tissue and overestimation of scarring.

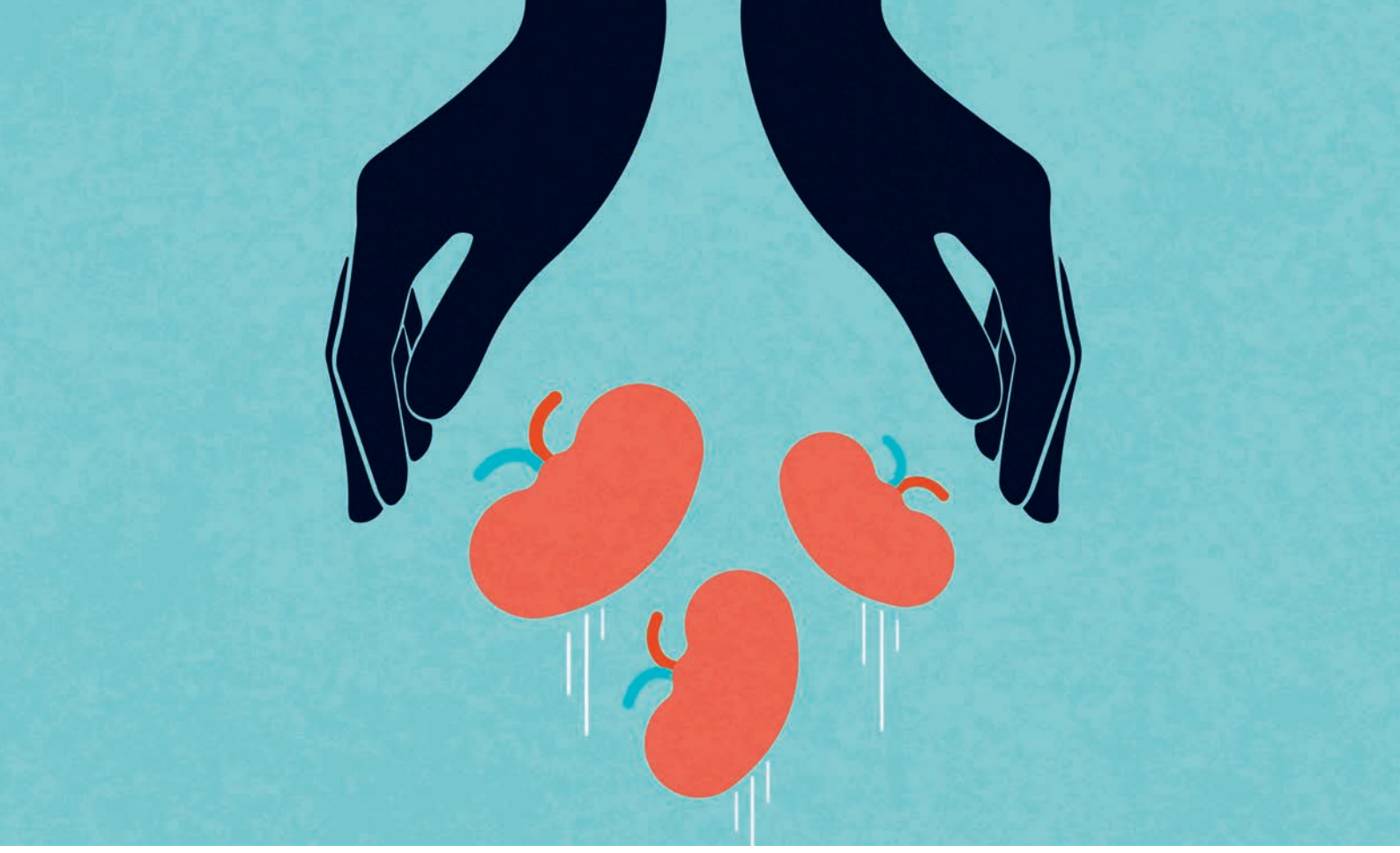
Other constraints with procurement biopsies arise because the frozen section procedure introduces a certain amount of artifact, making them difficult to interpret – an issue exacerbated by the fact that renal pathology is not a common skill. There are a relatively small number of renal pathologists available compared with, for example, surgical pathologists, so not everybody who reads the results of procurement biopsies has equal levels of experience. Additionally, given that they are often read in the middle of the night, it's not infrequent for trainees with much less experience to take on the task, which naturally introduces the potential for error, even with supervision.

Variability also occurs because there isn't enough standardization in the reporting of results amongst surgeons who carry out procurement biopsies. This is, in part, the result of a small procurement biopsy paper published around 25 years ago that investigated glomerulosclerosis. It showed that kidneys with glomerulosclerosis coverage over 20 percent were not suitable for transplant, whereas those with less than 20 percent glomerulosclerosis performed well (5). Although not true across the board, this threshold for kidney quality has taken hold and is used by many centers to decline an organ.

The issue is that there isn't a standardized protocol to enforce this measure, so everyone uses their own version. Reports frequently vary from "less than/more than 20 percent glomerulosclerosis" to "mild/moderate/severe glomerulosclerosis." It's also not uncommon to see reports that simply read "good kidney" without any numbers or further explanation. This kind of "information" effectively blinds the surgeons and forces them to apply their own interpretation of what constitutes mild, moderate, or severe disease. Surgeons carrying out the transplant often don't know the pathologist who completed the biopsy, where it was read, or whether it was

*At a Glance*

- *Many donor kidneys are discarded due to the findings of procurement biopsies*
- *These biopsies have issues with accuracy and consistency and are often read by pathologists with limited renal experience*
- *In our study, the findings of multiple procurement biopsies on the same kidney showed only a 64 percent agreement rate*
- *Standardization – and limiting our reliance on procurement biopsies – will lead to an increase in transplantation rates*



a wedge or a core biopsy. This last unknown can have important effects because they are so different – wedge biopsies are more superficial and can show a lot more scarring and glomerulosclerosis than you'd expect in the rest of the organ, requiring the surgeon to adjust their interpretation accordingly.

## Changing the rules

All of these issues contribute to the discard of a large number of kidneys that don't necessarily need to go to waste. Our belief is that it is rare to find anything on procurement biopsy that should preclude a kidney's use for transplantation. The primary concern for surgeons making the decision on whether to transplant or not is in deciding whether a deceased donor's kidney is diseased or injured. For example, if a patient has died with an isolated creatinine level of 3, it can be hard to discern whether that value is indicative of chronic kidney disease or acute kidney injury. In these sorts of situations, we can apply procurement biopsy results in the right way – that is, by using them to rule in the transplant of a kidney once the surgeon concludes that it's acutely injured, rather than chronically diseased. Unfortunately, in the US, many programs are using procurement biopsies the opposite way – applying the results to rule out the use of a kidney.

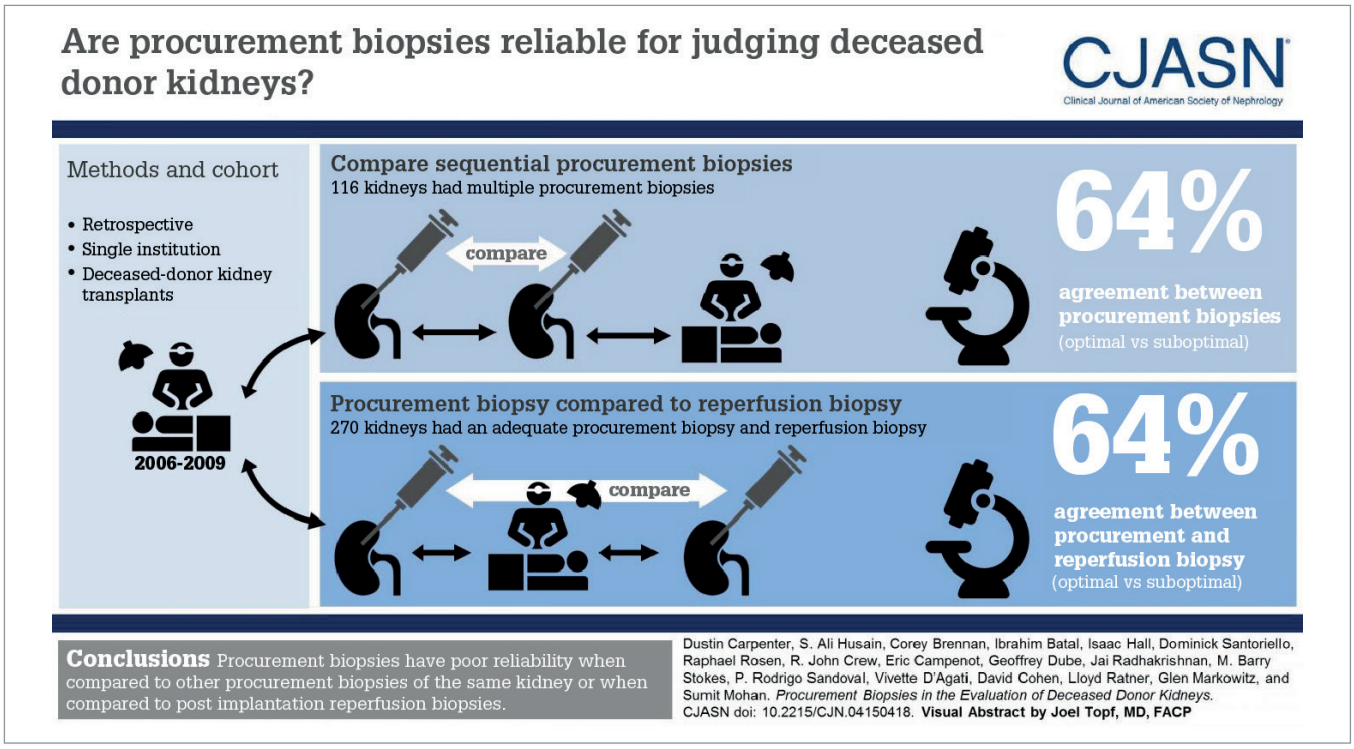
Part of the problem is that we have changed the way donors are described. Instead of paying close attention to the individual clinical characteristics of a patient, we place emphasis on a single score of clinical variables known as the kidney donor risk index (KDRI). The problem occurs when the kidneys of older donors are judged by their KDRI score and glomerulosclerosis percentage, which often leads to discard. In reality, 20 percent glomerulosclerosis in an older donor may be an age-appropriate amount of scarring, and the kidney would be fine for a recipient who is of a similar age. Essentially, this is double-counting the donor's age against them.

The gold standard of biopsies in this scenario is the reperfusion biopsy, which is performed after anastomosis to learn more about the success of the transplant. Performed in the absence of any time pressure, these core needle biopsies are consistently read by experienced pathologists using paraffin-embedded tissue and multiple stains. When comparing the findings of 270 reperfusion biopsies with those from procurement biopsies on the same kidneys, we found a 64 percent agreement rate between the two (4).

This low agreement between the two types of biopsy highlights the need to rethink our use of procurement biopsies. Reperfusion biopsies read by renal pathologists were consistently associated with post-transplant outcomes, whereas the procurement biopsies read by on-call pathologists were not.

## Operating change

We can – and must – do several things to rectify this growing issue. For one, I think we need to stop carrying out a biopsy when there isn't a prior indication that calls for one. This will be tough because everyone has become so accustomed to




having these results, but it would certainly bring down the high discard rates. Second, when we do carry out biopsies, they need to be standardized in terms of the process and the report. Pathologists can achieve this standardization by creating a set of criteria and developing a consistent approach to reporting results. I also think that pathologists should always have the clinical characteristics of the donor available to them. They should start by asking, "Is this an age-appropriate kidney?" and, "Is the amount of scarring we see on the biopsy consistent with the clinical history?" If so, then at least the surgeon can recognize that the findings are what healthcare professionals should expect and therefore not count it as a strike against the kidney.

We should also attach a degree of transparency to the person reading the procurement biopsy, perhaps by indicating their level of renal pathology expertise; although challenging to implement, I think it is a step in the right direction. Finally, when we perform a procurement biopsy, if we're going to use a scoring guide such as the KDRI, I think we need to incorporate the biopsy findings into that score so that there isn't an inadvertent double-counting of adverse factors.

From experience, my colleagues and I have found that kidneys are often turned away from other centers around the country due to the findings of a procurement biopsy. Some of those organs then get allocated to us in New York but, when we look at the biopsy, the quality is so poor that we can't understand it. Our region frequently completes a second biopsy – and it often disagrees with the first. It's possible that this is because of the haste with which the initial biopsy was completed. The median cold ischemia time in the US is currently around 16 to 17 hours, but is that truly the upper limit? Our center commonly transplants kidneys with over 30 hours of cold ischemia. Although fast action is key when it comes to kidney transplantation, this is still a reasonable amount of time and certainly enough to get things right. I urge pathologists conducting procurement biopsies to take time and care over the first one – better to spare a few additional moments than to risk discarding a perfectly acceptable kidney!

Limiting our reliance on procurement biopsy histology will result in greater organ utilization, which could drastically increase organ allocation efficiency and reduce the exceedingly high discard rates that we are currently facing. We all have the same goal: to ensure that every patient in need receives a healthy, usable kidney.

*Sumit Mohan is a nephrologist in the Department of Medicine at Columbia University, New York, USA.*

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# Fiber Fantastic

## Optic fibers could change the nature of disease diagnostics in the lung (and other organs)

*Jonathan James interviews Michael Tanner*

As fiber-optic technology develops at an ever-quickening pace, its applications continue to diversify (1). Now, a multidisciplinary team based in both Edinburgh and Bath, UK, present a new adaptation – a fiber-based screening device intended to aid clinicians treating severe lung conditions by providing in-depth biological information about distal regions of lung tissue (2). We spoke to Michael Tanner, one of the paper's authors, to find out more…

### What was the inspiration behind the project?

The work we published recently is one aspect of a larger project, Proteus, which aims to provide better diagnostic capabilities for people who arrive in intensive care with severe lung problems. There are two main aspects to our work. One is imaging in the lung using optical fibers to observe the presence of bacteria or other pathology-causing agents. In parallel, we are also attempting to better understand conditions in the distal lung because, as things like the acidity or oxygenation levels in these tissues change, they can tell us a lot about the tissue's health. In fact, our goal is to observe changes in response to treatment. That should help clinicians by producing a more immediate feedback loop.

### What are the problems with existing lung disease diagnostics?

Existing diagnostic technology often uses two approaches. The first – X-ray imaging – shows shadows on the lung, but these could be due to inflammation, infection, scarring, or many other causes. It is then possible to take a bronchial lavage (a liquid biopsy) during an endoscopic investigation. This involves delivering fluid into the lung and sucking it out so that it can be analyzed.

The approach is by no means perfect; lavage fluid can easily be contaminated by pathogens in the upper airways, leading to false positives. The technique can also be overly sensitive to pathogens that are not a problem. And the analysis can take time, delaying tailored treatment. In the interim, the clinician may choose to treat broadly, rather than take no action at all.

We have been developing optic fiber technologies to augment diagnosis with immediate feedback to the clinician on infection and tissue health. The technology we're discussing here is designed with the aim of enabling monitoring using oxygenation and acidity as indicators of disease. We hope to eventually combine this with other techniques to observe the presence of infection – technology toward which we've already made great progress (3).

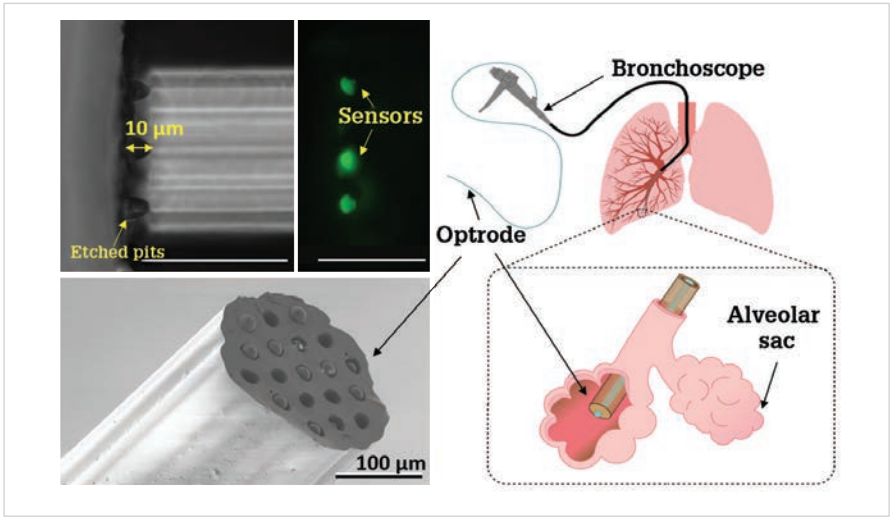
### How did you develop the technology?

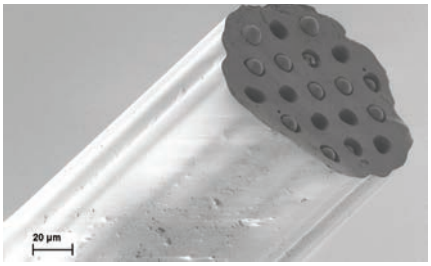
For us, the real challenge was ensuring that, when we miniaturized the optical fibers, we maintained a strong enough sensor at the end of the fiber. We also wanted to ensure that we could have multiple sensors arranged in a way that avoids overlap. You also need to avoid significant degradation of the sensors during use, and generally come up with an architecture that is small enough to reach a significant depth in the lung while still getting quite a complicated platform into the available space.

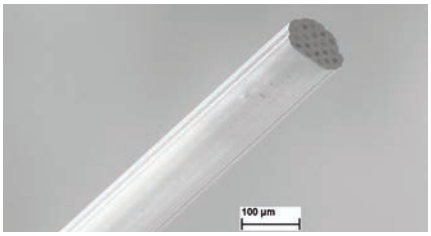
What we've managed to do here is establish a way that the chemical sensors can be produced separately from the final probe. They can be produced in a chemical lab – the sensor molecules themselves are fluorescent, and these chemical fluorophores can be attached to very small glass microspheres. On the optical fibers we set up multiple cores as independent, regimented channels. One of the sensors

### *At a Glance*

- *Diagnostic technology for lung disease is flawed – so there's a need for novel approaches*
- *A combination of chemical sensors and small, fiber-based probes offers a new way to examine the distal lung*
- *Fiber-optic technology can r each deep into the lung to provide diagnosticians with additional information*
- *New technologies must now be tested alongside current pathology approaches to demonstrate real-life benefits*




will be attached to each core because we have etched the channels into the end of the fiber.

### What have you found out so far about distal lung conditions?

What we've demonstrated at the moment is that we are able to take these measurements. We've been testing these sensors in various scenarios in ex vivo tissue, but we've yet to trial them in live patients. The bench model we've been using (whole excised lungs) has confirmed that we are able to see these small changes in the tissue environment – something that wasn't previously possible.

### How will this new technology change the work of those involved in lung diagnostics?

It provides additional information to augment lab-based pathology. Critically, these technologies need investigation alongside current pathology, so that we can tie changes in local oxygenation and acidity in with the progression of disease. For instance, these parameters may improve when a treatment is working, providing reassurance to continue. Miniaturized probes such as ours offer potential for continued monitoring. In the long term, it may be possible for optic fiber-based technologies to reduce the load on lab-based pathologists, or for integration of pathology into the ward via telemetric links to the monitoring instruments.

The key feature of the sensing probe we've developed is its small size. You could imagine putting it inside blood vessels, using it in keyhole surgery, or traversing blood vessels to reach organs other than the lungs. We hope that our approach can be applied to other organs – the liver in particular. For now, though, we have focused on the lung because lung diseases are a particularly large burden on health services and a difficult problem to tackle.

The next steps for us are manifold. We've not yet fully utilized our platform; although we've demonstrated a couple of chemical sensors in this architecture, we'd really like to expand further by measuring not only acidity and oxygen levels, but additional parameters at the same time. Following on from there, it comes back to what we've already discussed – demonstrating that monitoring these changes in the tissue can provide clinicians with useful feedback. We'll need to work in various models to study how different parameters change with tissue health.

### What drives you to translate this into the clinic?

It has always been our aim. A major influence on this project has been the pull toward clinical implementation and our desire not to remain stuck in the research lab. We don't want to be saying, "Oh wouldn't this be useful, wouldn't that be useful" forever; we want to actually apply these things.

Our project has taken a very different approach compared to a traditional university research project. As part of Proteus, funded by the Engineering and Physical Sciences Research Council, we're working across a number of universities and a number of disciplines. I am by education a physicist, but we also have chemists, biologists, and clinicians working on this. The key to ensuring that we are actually moving forward is the fact that a lot of the work is co-located on-site at the Royal Infirmary of Edinburgh. It allows us to keep focused on making real things happen.

The nice thing about this research work is how well it combines different disciplines. It's a nice example of the things we are doing to bring different subjects together and to work on something with real-life applications. That's certainly what's made us the happiest – getting our work out into the public domain.

*Michael Tanner is a Research Fellow in the School of Engineering and Physical Sciences at Heriot Watt University, Edinburgh, UK.*

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# Time, Money, and Tissue...

## Simultaneous multiplex IHC can save laboratories all three

*By Jason Ramos*

In the decades since Coons and colleagues published their revolutionary work on immunofluorescence detection of antigens in frozen tissue (1), immunohistochemistry (IHC) has become routine in the anatomic pathology laboratory. Each target antigen of interest has been individually identified within histological sections of formalin-fixed, paraffin-embedded (FFPE) tumors or other types of tissue (2). Single-marker IHC takes advantage of the labeling capabilities of horseradish peroxidase and alkaline phosphatase enzymes, in combination with their respective reactant chromogens, to produce a colorimetric stain for visualization under a light microscope (2,3). Alternatively, fluorescent reporters – fluorochromes – can visualize the antibody-antigen interaction, either by conjugation to the primary antibody (direct immunofluorescence) or via attachment to a secondary antibody that detects the species-specific primary (indirect immunofluorescence).

More recently, IHC users have shifted from the single-marker approach to multiplexed marker detection. Multiplex IHC methods can visualize multiple target antigens within a single tissue sample and can be further subcategorized as sequential or simultaneous (4). Generally, if the primary antibodies used are from the same host species, sequential multiplex IHC is required; otherwise, they can be cocktailed and incubated simultaneously.

But why use multiplex IHC at all? There are numerous advantages to visualizing multiple antigens simultaneously. Multiplex IHC maximizes the amount of data acquired from a single tissue sample – critical in conserving precious patient tissue. Unlike next-generation sequencing and mass spectrometry, in which the tissue sample is destroyed to test for individual target molecules, multiplex IHC also allows users to examine the spatial arrangements, interactions, and co-localizations of proteins of interest within the tissue architecture (5).

The complexity of the multiplex IHC protocol necessitates properly trained, highly skilled staff to achieve the most accurate and reproducible diagnoses. In clinical application, these technologically complex techniques require automation to achieve a simple, efficient, and easily understandable result for the clinical pathologist not well-versed in advanced multiplexing methods. Additionally, as the enhanced diagnostic utility of multiplex IHC is realized, the histology laboratory will experience increasing demand. Automation (and the associated standardization and reduction of variability) allows labs to achieve the quality, reproducibility, and speed necessary to meet this demand (6).

### *At a Glance*

- *Immunohistochemistry is a routine part of the anatomic pathology workflow*
- *By multiplexing targets, users can maximize their return from a single piece of tissue – often a precious resource*
- *Testing multiple targets in a single round also saves the laboratory time and money*
- *To fully benefit from the opportunities multiplex IHC offers, the next step is automation*

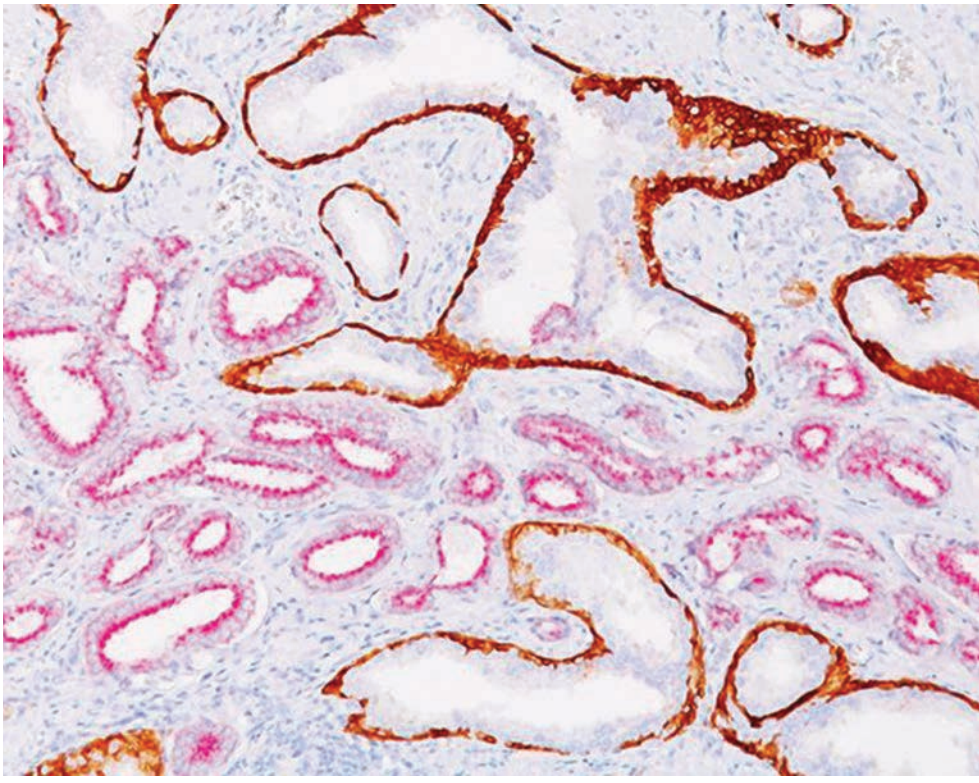

Figure 1: Prostate cancer stained with CK HMW + p63 + AMACR (RM). Multiplex IHC detection of CK HMW plus antibodies to p63 and AMACR in prostate adenocarcinoma biopsy. Strong AMACR (red) expression observed across the middle of the photomicrograph without corresponding basal cell layer (lack of CK HMW and p63 expression [DAB; brown]) indicates invasive PCa. Glands still containing basal cells (upper and lower portions of image) show signs of loss of a continuous basal cell layer surrounding the glands, indicative of prostatic intraepithelial neoplasia (PIN).

## Multiplex IHC for diagnostics

One driving factor in the early adoption of multiplex IHC for clinical diagnostics was urologists' collective move to use the smallest possible needle gauge to perform prostate biopsies. This caused pathologists great difficulty in reliably diagnosing (or ruling out) small foci of cancer; examining multiple minute tissue fragments was time-consuming and reproducibility of diagnosis was poor. The most glaring clinical need was the ability to differentiate between prostatic intraepithelial neoplasia (PIN) and carcinoma of the prostate. We also needed a way of clearly identifying, with high accuracy and specificity, any microinvasion or micrometastasis into adjacent prostate tissue. And, of course, this had to be done while conserving the limited amount of sample (prostate needle biopsies are thin filaments of tissue) and reducing the time to result.

With these constraints and needs in mind, a widely used antibody cocktail known as PIN-4 was developed (see Figure 1). It consists of one or two antibodies against high molecular weight cytokeratin (CK HMW), as well as antibodies to p63 and p504S (also known as AMACR enzyme). Studies have shown that combinations of CK HMW [34βE12], p63, and/or AMACR may be useful in differentiating normal prostate glands from PIN and prostatic adenocarcinoma (PCa) (7–9). In prostate tissue, CK HMW [34βE12] is a useful marker of basal cells of normal glands and PIN, a precursor lesion to prostatic adenocarcinoma; invasive prostatic adenocarcinoma, in contrast, typically lacks a basal cell layer (9–11). p63, a homolog of the tumor suppressor p53, has been detected in nuclei of the basal epithelium in normal prostate glands; however, it is not expressed in malignant tumors of the prostate (12). α-methylacyl coenzyme A racemase (AMACR), also known as P504S, has been shown to be a specific marker of prostatic adenocarcinoma (13–16). Additionally, prostate glands involved in PIN have been found to express AMACR, whereas the enzyme was nearly undetectable in benign glands (16,17).

Pathologists encountered great difficulty in colocalizing the three individual antibody signals (CK HMW + p63 + AMACR) on three separate

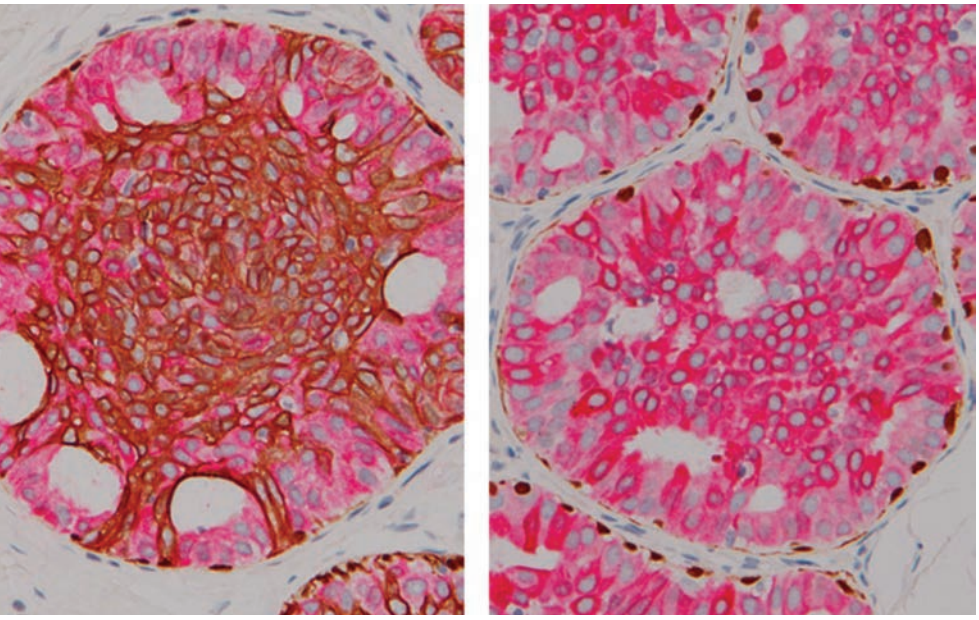

Figure 2: Breast lesions stained with CK5/14 + p63 + CK7/18. Multiplex IHC detection of cytokeratins (CK5, CK14, CK7, CK18) plus p63 in breast lesion biopsies. Breast basal cells express cytokeratins 5 and 14 (DAB; brown), myoepithelial cells express those same cytokeratins along with p63 (DAB; brown), and luminal cells express cytokeratins 7 and 18 (red). Left: In UDH, a polymorphic neoplastic proliferation results in myoepithelial/basal cells intermingled with luminal cells to reveal a heterogeneous, mosaic staining pattern. Right: ADH is a monomorphic neoplasia, typically derived from luminal cells, showing a homogeneous staining pattern across the affected ductal structure with little to no staining of myoepithelial/basal cells.

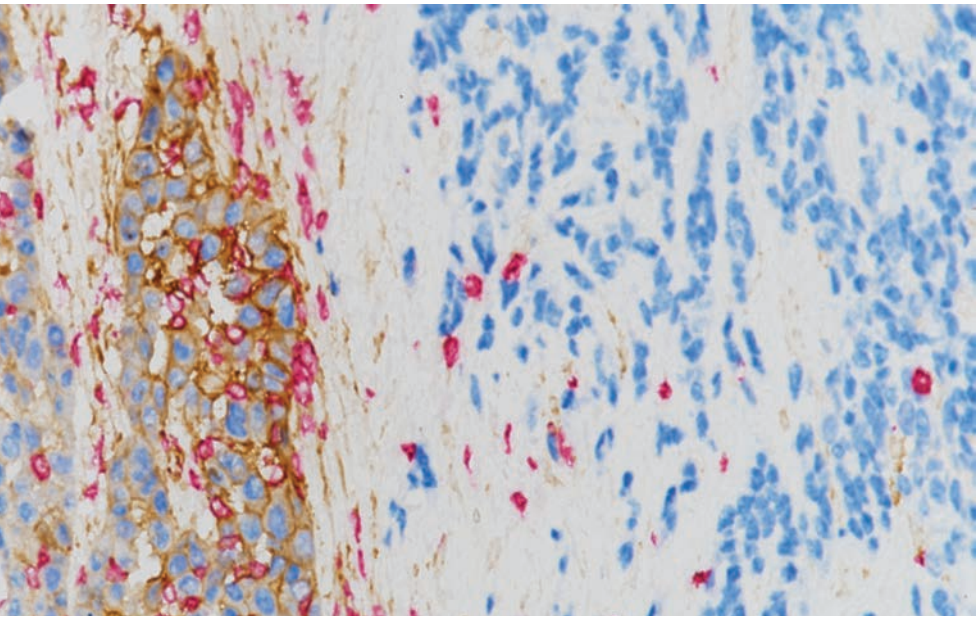

Figure 3: Melanoma stained with SOX10, PD-L1, and CD8. Multiplex IHC detection of SOX10, PD-L1, and CD8 helps define high proliferation zones in melanoma. SOX10 nuclear staining (blue) is observed in melanoma cells, with a subset of the melanoma (left) showing PD-L1(+) membranous co-expression (DAB; brown). High CD8 cytotoxic T cell staining (red) is associated with strong PD-L1 expression in the melanoma tumor cells. The SOX10/PD-L1/CD8 triple stain can help discriminate tumor cells from non-tumor cells and may facilitate quantifying or immunoscoring for accurate assessment.

slides. In many cases, it proved impossible because the biopsies themselves were small, with the suspected PIN or PCa areas smaller or even absent as the tissue block was cut deeper for serial sectioning. However, applying these antibodies to an individual tissue section in a multiplex IHC cocktail format allows for the simultaneous pathological evaluation of each of these critical markers in the same focus or foci of interest, drastically improving reproducibility. It also improves the diagnostic accuracy of invasive prostatic adenocarcinoma to near certainty (18) – which is why the PIN-4 cocktail has become the standard of care in testing prostate needle biopsies.

The clinical application of multiplex IHC has since been expanded to other tissues to give enhanced differential diagnostic information. In breast, the ADH-5 (CK5/14 + p63 + CK7/18) multiplex cocktail (see Figure 2) can aid in the differential diagnoses of usual ductal hyperplasia (UDH), atypical ductal hyperplasia (ADH), and ductal carcinoma in situ (DCIS) (19). UDH carries minimal or no increased risk of breast cancer, and these patients do not undergo any additional procedures; however, ADH and DCIS progress to invasive carcinoma in 4–5 percent and 8–10 percent of cases, respectively. ADH and DCIS patients are advised to undergo excision surgery, with radiation treatment added for DCIS patients (20). Histological differentiation between UDH, ADH, and DCIS has historically

been difficult, with poor concordance among pathologists giving rise to potential misdiagnosis and improper treatment. The addition of the ADH-5 multiplex cocktail to routine histopathology testing significantly reduced overdiagnosis of ADH lesions, reclassifying those lesions as UDH. Studies have demonstrated that up to 40 percent of lesions diagnosed as ADH on core biopsies ended up reclassified as benign upon re-examination after surgical excision (21,22) – meaning that all of those patients could have avoided unnecessary surgery upon initial testing using the ADH-5 multiplex cocktail.

## Multiplex IHC for therapeutic decisions

As the cancer treatment landscape has evolved, so have the diagnostic tools we use to make those critical therapeutic decisions. Now, immunotherapy is on the rise. A number of immune checkpoint inhibitors targeting either cytotoxic T lymphocyte antigen 4 (CTLA-4), programmed cell death protein 1 (PD-1), or its ligand (PD-L1), have recently received FDA approval for the treatment of multiple cancer types. However, up to 60 percent of patients treated with these inhibitors see little to no benefit (23). A critical aspect in proper application of these newly designed immunotherapeutics is to establish valid predictive biomarkers to enhance patient selection.

One proposed approach to determining patient response to immune checkpoint inhibitors is to analyze the tumor microenvironment. An immune-active tumor microenvironment is critical to patient response to immunotherapy (24). We must not only understand the dynamic nature of the tumor, but also determine its interactions with its microenvironment to define the algorithm of biomarkers that will predict response to checkpoint inhibitors. Multiplex IHC is well-suited to resolve and define these elements and interactions (25,26). Profiling the tumor microenvironment within tissues requires evaluating multiple markers, including inflammatory cell subpopulations, tumor-infiltrating lymphocytes, and immune checkpoints (see Figure 3).

## The next step forward

The automation of multiplex IHC is the next evolutionary step to maximizing its potential. The considerable throughput and performance demands placed on diagnostic laboratories for accurate, consistent, high-quality staining results will only increase as novel assays are developed. In turn, laboratories will demand more from their automated IHC staining platforms. New innovations that increase efficiency – such as simultaneous multiplex IHC technology capability, online deparaffinization, and energy-efficient, parallel-processing antigen retrieval – will allow laboratories to meet the throughput and performance demands and beyond, all while continuing to provide high-quality results. As we increasingly move toward multiplexing and automation in the anatomic pathology laboratory, we'll save time, money, and precious patient tissue.

*Disclosure: Jason Ramos is Vice President of Research and Development at Biocare Medical, Pacheco, USA.*

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# Career Connections

## At every stage of your career, mentorships are a valuable resource

*By Avrum Gotlieb*

No two laboratory medicine professionals share the same career path – and, similarly, no two have the same resources available to them to assist in their development. Some academic institutions may have career centers, formal programs (such as educational sessions or job shadowing), or reference materials. Others may provide little or no guidance. But one resource available at every institution is the experience of those who have gone before. That's why, regardless of where you are and what other options you have, mentorship will always be a vital part of career development.

### What is mentorship?

I define mentorship as a special bilateral relationship built on respect, integrity, and empathy. In such a relationship, the mentor and mentee enthusiastically interact to promote the mentee's career. The mentor is an advisor who acts to support the mentee in making work-life decisions by providing useful information and suggesting options. They want to see the mentee succeed and, in doing so, help build a strong academic community of confident and innovative scholars. Faculty are encouraged to have more than one mentor (but not too many), because each mentor will bring specific academic expertise and life experiences to issues related to gender, diversity, disability, economic perspectives, and much more.

Academic life can be complex. Understanding what lies ahead at each step of the way is invaluable when making decisions and plans for the future. Academic pathology is a long, tough road that requires hard work, motivation, and well-developed intellectual and applied skill sets. Individual pathologists must make difficult work-life choices and overcome numerous obstacles during training, job hunting, progression through the academic ranks, and beyond. One goal of the mentoring relationship is to promote resilience in the mentee and foster innovation in all aspects of academic work. Having an experienced colleague whose main motivation is to help you succeed will make the journey less onerous and difficult; in fact, in my opinion, it is absolutely essential.

This human relationship occurs in real time, so every piece of feedback helps mentees shape their thoughts and actions. Mentorship requires availability and attention from both sides. Mentees need to identify the areas where they need help, formulate appropriate questions, listen to their advisors, and, where appropriate, incorporate their input into solutions; mentors need to spot areas of difficulty for their mentees, listen to their problems and questions, and provide carefully considered assistance. When the relationship is working smoothly, mentors look out for their mentees, and mentees have a deep appreciation for the mentor's time and effort. It's a unique aspect of career development; you cannot get anything like it from a book, the Internet, a lecture on career development, or casual hallway consults. Whereas other resources are static, a mentor has not only been where the mentee is now; they are also aware of current events, the academic community in your region or specialty, and factors that may be unique to your situation. They can provide up-to-date, nuanced information and advice. If the relationship works, both participants build trust over time, leading to greater honesty, confidence in advice and conversations, and even comfort during stressful times. The mentor provides information, suggests options, and advises on how to achieve goals – but must not make decisions for the mentee.

### In my experience

I was very fortunate in having caring academic teachers and supervisors who helped me along the way. From them, I learned a lot about how to navigate the twists and turns of my own career. Some of these folks became mentors – and, when that happened, I always felt that they were on my side and would encourage me to follow the right path. Not everyone has the same career goals and priorities, and a

### *At a Glance*

- *Mentoring is a special relationship that provides long-lasting benefits to both participants*
- *Prospective mentees should seek out mentors whose careers, experience, and outside interests are compatible with their own*
- *Mentors must commit to advising mentees on how to navigate their careers by listening carefully, assisting informed choices, and helping identify and overcome barriers*
- *Although relationships within the mentee's discipline are highly informative, cross-disciplinary mentorships can offer surprising new insights*

true mentor will help you to achieve your own aspirations, rather than those that others may consider important. My own mentors provided me with opportunities to learn what it takes to achieve academic success, and to perform in a protected environment, allowing me to test myself and my skills.

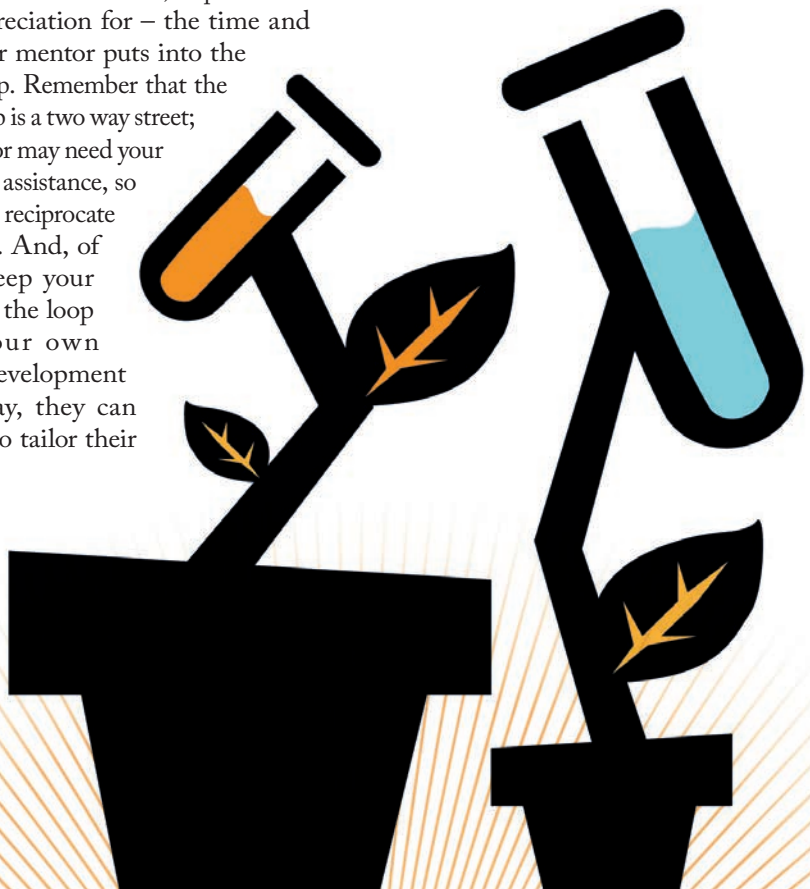
As a mentee, I was offered teaching and course development opportunities which, although they added a lot of work to my regular duties, were very valuable in my career development. Mentors were instrumental in providing me with research opportunities studying the pathogenesis of disease, and they encouraged and supported me to attend research meetings and clinical pathology meetings and courses. They made it very clear to me how one trains for an academic career in pathology and how to make the most of my residency, my fellowship, and then my junior faculty position.

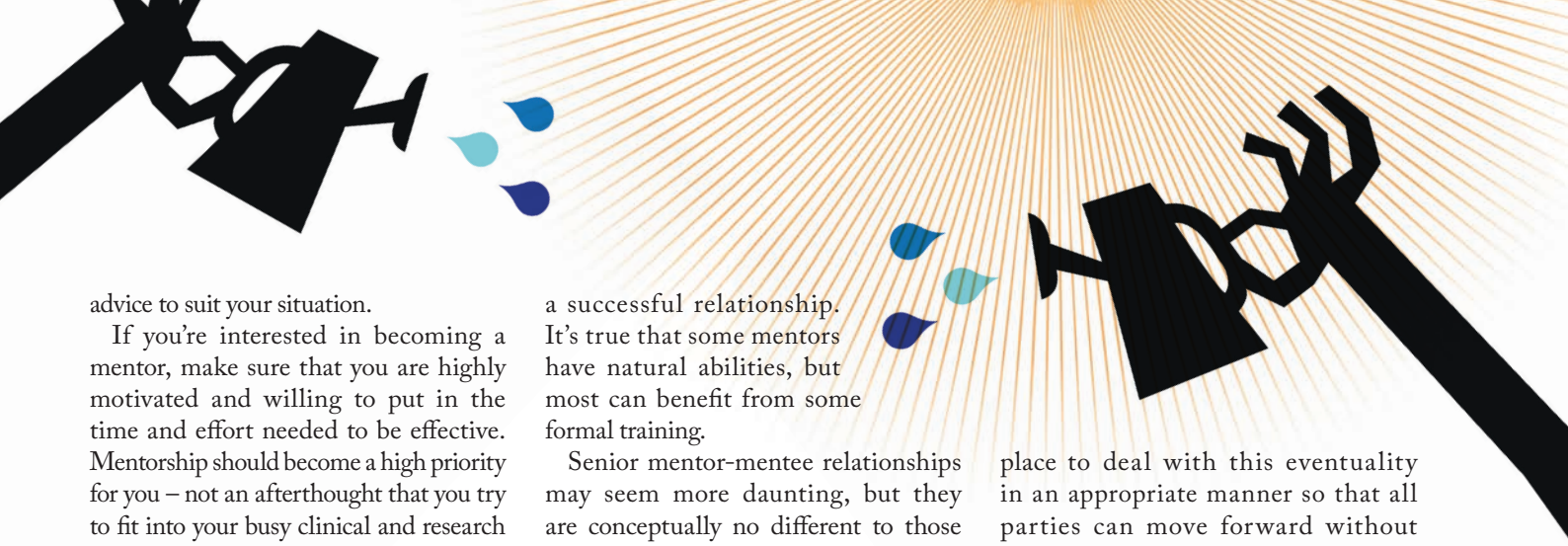
Over the course of my career, I have seen the nature of mentorship change; the approach isn't quite the same as it was when I was a young pathologist. Then, mentorship was a natural activity; many academics felt it was their duty to mentor the next generation. They valued the process and derived as much satisfaction from acting as advisors and role models as their protégés did from the informal education they received. Face-to-face interactions formed the backbone of the relationship and forged strong connections between mentors and mentees. As bureaucracy continues to creep into academic pathology, though, mentorship has become more formalized. This has both good and bad aspects. Mentors are trained, rules for mentorship are established, and outcomes are measured by both the mentor and the mentee. This ensures that both parties are safeguarded and can benefit from the relationship – but it also removes some of the spontaneity and can result in a "box-ticking" mentality. It's up to us as mentors and mentees to keep the spirit of mentorship alive forging relationships that are responsive and adaptable to the inevitable changes in our lives and our environments.

## Finding (and being) the right mentor

A good mentor fits well with your own work and lifestyle interests (and, for some, this may mean working with multiple mentors). One thing matters above all else: the mentor you choose needs to be truly interested in you as a person and as a professional. The relationship needs time to develop so that both participants are comfortable discussing intellectually or emotionally difficult issues in confidence. As a mentee, respect – and show appreciation for – the time and effort your mentor puts into the relationship. Remember that the relationship is a two way street; your mentor may need your advice and assistance, so be ready to reciprocate their help. And, of course, keep your mentor in the loop about your own career development – that way, they can continue to tailor their

*"Throughout my career, I've always had an instinct for finding really good teachers and collaborators, and I think that has been one of the most important advantages I've had."*





advice to suit your situation.

If you're interested in becoming a mentor, make sure that you are highly motivated and willing to put in the time and effort needed to be effective. Mentorship should become a high priority for you – not an afterthought that you try to fit into your busy clinical and research schedule. Select your mentees carefully and make sure that you are a good match; it's essential that you feel comfortable with your mentee and align your mentorship with their expectations. Many mentorships arise spontaneously from informal relationships or prior encounters, but some are initiated by matching. In fact, some departments require that all junior faculty have mentors, whether assigned or self-chosen. Although good mentorship cannot be forced, the importance these departments are placing on establishing those relationships is a clear indicator of the value they have to academic pathologists.

Mentorship should be a valued academic activity that departments and institutions recognize in performance evaluations, or even by offering mentorship awards. It is also an area of academic scholarship; some faculty may do research on mentorship and establish or direct formal mentoring infrastructures in their institutions. Pathology departments need to create opportunities for their faculty to mentor, whether formally or otherwise – and the most successful departments will set up mentorships for their non-pathologist staff members as well. For academic pathologists, some departments create an infrastructure that provides both a clinical mentor and a research/education mentor. Regardless of how many mentors you have and what resources each one offers, you – and they – can benefit from guidance aimed at establishing a successful relationship. It's true that some mentors have natural abilities, but most can benefit from some formal training.

Senior mentor-mentee relationships may seem more daunting, but they are conceptually no different to those involving junior faculty. The parameters, processes, and outcomes should be the same. At this level, though, it's important to take particular care that a hierarchical relationship does not develop and that academic supervisors and evaluations are not entangled with the mentoring relationship. Mid- to senior-level mentorships can be more challenging than mentoring early-career faculty because both parties are more entrenched in their thinking and must take more time to listen and identify one another's specific needs. Common topics discussed at this level include maintaining success, rebooting a career, or beginning to plan for a transition into retirement.

## Strengths and stumbling blocks

Mentorship promotes the creation of communities of pathologists and laboratory medicine professionals who care for one other and assist each other in a collegial way. By helping younger faculty move forward and do their very best, mentors enhance the brand of their department and institution, making them more attractive to faculty, staff, and students. A good reputation for – and attitude toward – mentoring can vastly improve recruitment and retention.

The only major downside is when the mentor-mentee relationship breaks down. Whether or not a department has a formal mentoring program, it must have processes in place to deal with this eventuality in an appropriate manner so that all parties can move forward without negative consequences.

Beyond the walls of your department, or even your field of study, mentorship is about forming a relationship to promote successful work-life balance. Many mentorship "rules" cross departmental and even discipline boundaries. And although professionals in your own field will be familiar with your discipline and how to effectively navigate it, non-pathologist mentors can promote innovation and paradigm shifts in your thinking. Don't limit your selection of mentors (or mentees) to faculty members in your field; consider other staff members who may have valuable insights about your department or laboratory medicine in general – or scholars in other disciplines who may bring new insights to your career.

For me, mentorship has been a very positive experience. As a mentee, I've benefited greatly in my career development; as a mentor, I've seen many students and colleagues successfully launch and grow their own careers. My mentorship interactions led me to put pen to paper to write two booklets on career development in pathology and, subsequently, a book for students, trainees, and junior faculty on career development (now in its second edition). I will continue to promote the benefits of mentorship and to guide as many prospective participants as I can to help my discipline – and its reputation – grow.

*Avrum Gotlieb is Professor of Laboratory Medicine and Pathobiology at the University of Toronto, Canada.*

# Standardize Lab Inspection Readiness Processes to Reduce Anxiety and Improve Efficiency

**Laboratories can nurture the ongoing process of quality assurance by streamlining, automating, and centralizing aspects of inspection preparation.**

*By Daniel Faasse, MHS, PA (ASCP)CM*

Laboratory inspections by COLA, CLIA, CAP, RCPath, and more are a source of anxiety and frantic activity for managers, pathologists, and other personnel. But these events don't have to be a cause for alarm; instead of a possibility for deficiencies, inspections should be greeted as an opportunity to affirm the lab is performing at its highest standards.

We recommend pathology labs take guidelines made available by accrediting agencies and incorporate them into a system to easily check compliance with quality standards. Automated systems that are kept current with latest requirements while encouraging ways to streamline processes can greatly assist. A centralized location for accessing and updating important documents; a system for tracking specimens or documenting non-conforming events; and a way to keep staff credentials up-to-date are all ways to ensure excellence in the lab.

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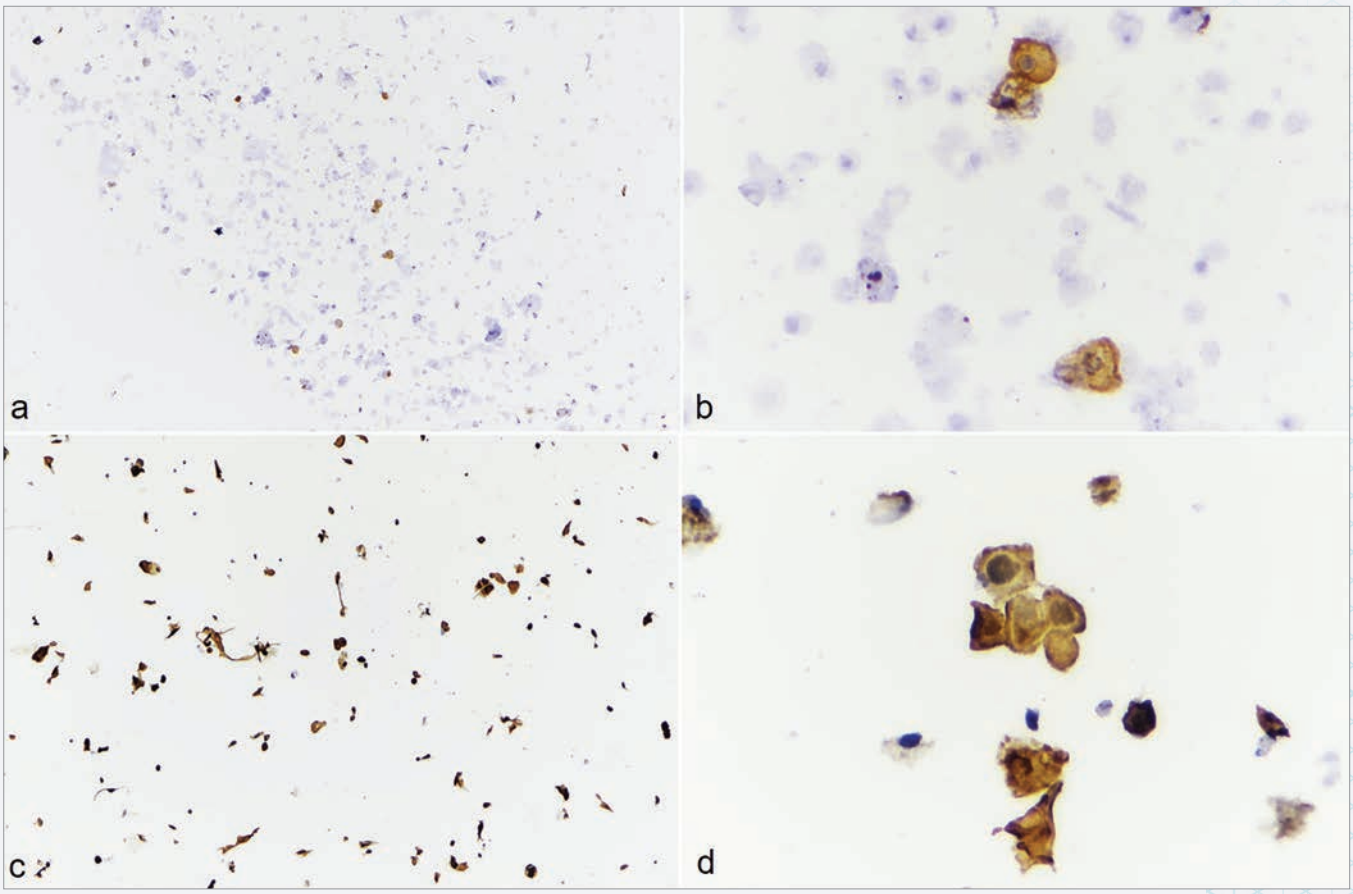

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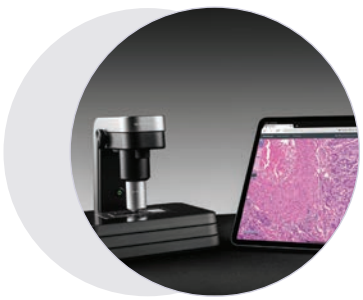

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# Working for the Global Good

**Sitting Down With… Ann Nelson,** Infectious Disease Pathology Consultant at the Joint Pathology Center and Visiting Professor of Pathology at Duke University, Durham, USA

What sparked your passion for global health?

I had always wanted to work overseas and make an international impact – I just didn't know how. Then, while working as a medical technician in a microbiology lab, the pathologist told me, "You need to go to medical school." As good as that sounded, this was in the 1970s, when getting into medical school – especially in California – was extremely competitive (about one in 30 applicants were successful). So I moved to Guadalajara, Mexico, to begin medical training; it was there that my interest in international health took off.

The university had a program called "Medicine in the Community," in which we'd go into rural communities for six weeks to complete vaccine campaigns and various public health activities. This kind of work combined all of my interests: travel, public health, and infectious disease. When I returned to the US for residency, I also took a keen interest in global health thanks to lectures from Daniel Connor, Head of Infectious Disease at the Armed Forces Institute of Pathology (AFIP). He'd spent a lot of time working with Denis Burkitt in Uganda throughout the 1960s, and that inspired me to work in global infectious disease pathology in Washington, DC.

Could you share your favorite project?

I was fortunate enough to move to Kinshasa in former Zaire to do the pathology for Project SIDA. Run jointly by the Centers for Disease Control and Prevention, the Tropical Medicine Institute of Antwerp, and the NIH, the program had a huge, cross-disciplinary impact and was the first international AIDS project in Africa. I worked there from 1986 to 1991 and was lucky enough to meet a local doctor who had just finished his Master's in Public Health. We got married a year later, and we've been together ever since! I think that experience and immersion in global health made me more of a hybrid than a laboratory pathologist. It was also fantastic to help found the organization now known as African Strategies for Advancing Pathology, which strives to improve and increase access to diagnostic pathology and laboratory medicine in sub-Saharan Africa.

I thoroughly enjoyed my work with the International Academy of Pathology (IAP) organizing international meetings and planning the development of educational systems in disadvantaged areas. At the 100th anniversary of the IAP in 2006, one of the Nigerian pathologists I worked with decided to label me "the mother of African pathologists." That's one of the most rewarding parts of my career, because I feel as though I have made a difference to people's lives. In fact, my old colleagues still write to me and say, "Mama, how are you doing?!"

*"Great leaders don't make themselves better; they make the people around them better."*

What do you find most challenging about your work?

One of the biggest challenges is motivating others to participate in global health, because it's often difficult to convince them that it's something we should be concerned about when we have our own problems. It's felt like talking to a wall at times, but I think the AIDS epidemic massively changed people's perspectives. A lack of resources is also frustrating, especially when a country can't afford to order the supplies needed to take care of its patients. That's not a problem that I can fix directly; it's a case of convincing people to fund what's important, not just what's high-profile.

What advice would you give to others who want to make an impact?

You have to climb the ladder. Don't think you're going to make an impact on day one; instead you have to build a network by having a skill set and being humble and willing to learn. It's also important to have confidence in yourself and to speak up, especially when you think everybody already knows what you're going to say. Sometimes they don't; sometimes, your ideas are novel and you engage with people who can offer new opportunities. As time goes on, you will start defining where you will make a difference – but be prepared for this to change over time.

What else would you still like to achieve?

I'm extremely proud of my career. I've lectured – mostly on HIV – in around 25 countries across every continent other than Antarctica; more recently, I have delivered talks on mentoring and pathology capacity work. Since retiring in 2015, I have placed a much heavier emphasis on mentoring. I currently work on the ASCP's education subcommittee for global pathology, helping people in Africa go to conferences, develop new projects, and with general practice.

I was awarded the IAP's gold medal in 2012 for lecturing around the world, and I tell people that I'm the first person who received it simply for being nice! I firmly believe that great leaders don't make themselves better; they make the people around them better by giving them the tools they need to make a difference. That's what I want to achieve now. I'm not going to be around to practice in 10 years and I need to know that there are enough global health workers for the future. My continued goal is to help pathology grow in Africa and to nurture a new cohort of young people in the US who are dedicated to this ambition. I will keep doing this as long as I'm healthy and needed!

**TAGRISSO® (osimertinib) tablets, for oral use**

Brief Summary of Prescribing Information.

For complete prescribing information consult official package insert.

## INDICATIONS AND USAGE

### First-line Treatment of EGFR Mutation-Positive Metastatic Non-Small Cell Lung Cancer (NSCLC)

TAGRISSO is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test *[see Dosage and Administration (2.1) in the full Prescribing Information]*.

## DOSAGE AND ADMINISTRATION

### Patient Selection

Select patients for the first-line treatment of metastatic EGFR-positive NSCLC with TAGRISSO based on the presence of EGFR exon 19 deletions or exon 21 L858R mutations in tumor or plasma specimens *[see Clinical Studies (14) in the full Prescribing Information]*. If these mutations are not detected in a plasma specimen, test tumor tissue if feasible.

Information on FDA-approved tests for the detection of EGFR mutations is available at http://www.fda.gov/companiondiagnostics.

### Recommended Dosage Regimen

The recommended dosage of TAGRISSO is 80 mg tablet once a day until disease progression or unacceptable toxicity. TAGRISSO can be taken with or without food.

If a dose of TAGRISSO is missed, do not make up the missed dose and take the next dose as scheduled.

### Administration to Patients Who Have Difficulty Swallowing Solids

Disperse tablet in 60 mL (2 ounces) of non-carbonated water only. Stir until tablet is dispersed into small pieces (the tablet will not completely dissolve) and swallow immediately. Do not crush, heat, or ultrasonicate during preparation. Rinse the container with 120 mL to 240 mL (4 to 8 ounces) of water and immediately drink.

If administration via nasogastric tube is required, disperse the tablet as above in 15 mL of non-carbonated water, and then use an additional 15 mL of water to transfer any residues to the syringe. The resulting 30 mL liquid should be administered as per the nasogastric tube instructions with appropriate water flushes (approximately 30 mL).

### Dosage Modifications

Adverse Reactions

**Table 1. Recommended Dosage Modifications for TAGRISSO**

| Target Organ | Adverse Reaction[a] | Dosage Modification |
|---|---|---|
| *Pulmonary* | Interstitial lung disease (ILD)/Pneumonitis | Permanently discontinue TAGRISSO. |
| *Cardiac* | QTc[†] interval greater than 500 msec on at least 2 separate ECGs[b] | Withhold TAGRISSO until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec, then resume at 40 mg dose. |
| | QTc interval prolongation with signs/ symptoms of life-threatening arrhythmia | Permanently discontinue TAGRISSO. |
| | Symptomatic congestive heart failure | Permanently discontinue TAGRISSO. |
| *Other* | Adverse reaction of Grade 3 or greater severity | Withhold TAGRISSO for up to 3 weeks. |
| | If improvement to Grade 0-2 within 3 weeks | Resume at 80 mg or 40 mg daily. |
| | If no improvement within 3 weeks | Permanently discontinue TAGRISSO. |

[a] Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4.0).
[b] ECGs = Electrocardiograms
[†] QTc = QT interval corrected for heart rate

Drug Interactions

*Strong CYP3A4 Inducers*

If concurrent use is unavoidable, increase TAGRISSO dosage to 160 mg daily when co-administering with a strong CYP3A inducer. Resume TAGRISSO at 80 mg 3 weeks after discontinuation of the strong CYP3A4 inducer *[see Drug Interactions (7) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

## CONTRAINDICATIONS

None.

## WARNINGS AND PRECAUTIONS

### Interstitial Lung Disease/Pneumonitis

Interstitial lung disease (ILD)/pneumonitis occurred in 3.9% of the 1142 TAGRISSO-treated patients; 0.4% of cases were fatal.

Withhold TAGRISSO and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed *[see Dosage and Administration (2.4) and Adverse Reactions (6) in the full Prescribing Information]*.

### QTc Interval Prolongation

Heart rate-corrected QT (QTc) interval prolongation occurs in patients treated with TAGRISSO. Of the 1142 patients treated with TAGRISSO in clinical trials, 0.9% were found to have a QTc > 500 msec, and 3.6% of patients had an increase from baseline QTc > 60 msec *[see Clinical Pharmacology (12.2) in the full Prescribing Information]*. No QTc-related arrhythmias were reported.

Clinical trials of TAGRISSO did not enroll patients with baseline QTc of > 470 msec. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia *[see Dosage and Administration (2.4) in the full Prescribing Information]*.

### Cardiomyopathy

Across clinical trials, cardiomyopathy (defined as cardiac failure, chronic cardiac failure, congestive heart failure, pulmonary edema or decreased ejection fraction) occurred in 2.6% of the 1142 TAGRISSO-treated patients; 0.1% of cardiomyopathy cases were fatal.

A decline in left ventricular ejection fraction (LVEF) ≥ 10% from baseline and to less than 50% LVEF occurred in 3.9% of 908 patients who had baseline and at least one follow-up LVEF assessment.

Conduct cardiac monitoring, including assessment of LVEF at baseline and during treatment, in patients with cardiac risk factors. Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment. For symptomatic congestive heart failure, permanently discontinue TAGRISSO *[see Dosage and Administration (2.4) in the full Prescribing Information]*.

### Keratitis

Keratitis was reported in 0.7% of 1142 patients treated with TAGRISSO in clinical trials. Promptly refer patients with signs and symptoms suggestive of keratitis (such as eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye) to an ophthalmologist.

### Embryo-Fetal Toxicity

Based on data from animal studies and its mechanism of action, TAGRISSO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, osimertinib caused post-implantation fetal loss when administered during early development at a dose exposure 1.5 times the exposure at the recommended clinical dose. When males were treated prior to mating with untreated females, there was an increase in preimplantation embryonic loss at plasma exposures of approximately 0.5 times those observed at the recommended dose of 80 mg once daily. Verify pregnancy status of females of reproductive potential prior to initiating TAGRISSO. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose *[see Use in Specific Populations (8.1, 8.3) in the full Prescribing Information]*.

## ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

Interstitial Lung Disease/Pneumonitis *[see Warnings and Precautions (5.1) in the full Prescribing Information]*

QTc Interval Prolongation *[see Warnings and Precautions (5.2) in the full Prescribing Information]*

Cardiomyopathy *[see Warnings and Precautions (5.3) in the full Prescribing Information]*

Keratitis *[see Warnings and Precautions (5.4) in the full Prescribing Information]*

### Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in the Warnings and Precautions section reflect exposure to TAGRISSO in 1142 patients with EGFR mutation-positive NSCLC who received TAGRISSO at the recommended dose of 80 mg once daily in two randomized, active-controlled trials [FLAURA (n=279) and AURA3 (n=279)], two single arm trials [AURA Extension (n=201) and AURA2 (n=210)], and one dose-finding study, AURA1 (n=173) *[see Warnings and Precautions (5) in the full Prescribing Information]*.

The data described below reflect exposure to TAGRISSO (80 mg daily) in 558 patients with EGFR mutation-positive, metastatic NSCLC in two randomized, active-controlled trials [FLAURA (n=279) and AURA3 (n=279)]. Patients with a history of interstitial lung disease, drug induced interstitial disease or radiation pneumonitis that required steroid treatment, serious arrhythmia or baseline QTc interval greater than 470 msec on electrocardiogram were excluded from enrollment in these studies.

Previously Untreated EGFR Mutation-Positive Metastatic Non-Small Cell Lung Cancer

The safety of TAGRISSO was evaluated in FLAURA, a multicenter international double-blind randomized (1:1) active controlled trial conducted in 556 patients with EGFR exon 19 deletion or exon 21 L858R mutation-positive, unresectable or metastatic NSCLC who had not received previous systemic treatment for advanced disease. The median duration of exposure to TAGRISSO was 16.2 months.

The most common adverse reactions (≥20%) in patients treated with TAGRISSO were diarrhea (58%), rash (58%), dry skin (36%), nail toxicity (35%), stomatitis (29%), and decreased appetite (20%). Serious adverse reactions were reported in 4% of patients treated with TAGRISSO; the most common serious adverse reactions (≥1%) were pneumonia (2.9%), ILD/pneumonitis (2.1%), and pulmonary embolism (1.8%). Dose reductions occurred in 2.9% of patients treated with TAGRISSO. The most frequent adverse reactions leading to dose reductions or interruptions were prolongation of the QT interval as assessed by ECG (4.3%), diarrhea (2.5%), and lymphopenia (1.1%). Adverse reactions leading to permanent discontinuation occurred in 13% of patients treated with TAGRISSO. The most frequent adverse reaction leading to discontinuation of TAGRISSO was ILD/pneumonitis (3.9%).

Tables 2 and 3 summarize common adverse reactions and laboratory abnormalities which occurred in FLAURA. FLAURA was not designed to demonstrate a statistically significant reduction in adverse reaction rates for TAGRISSO, or for the control arm, for any adverse reaction listed in Tables 2 and 3.

**Table 2. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in FLAURA***

| Adverse Reaction | TAGRISSO (N=279) | | EGFR TKI comparator (gefitinib or erlotinib) (N=277) | |
|---|---|---|---|---|
| | Any Grade (%) | Grade 3 or higher (%) | Any Grade (%) | Grade 3 or higher (%) |
| **Gastrointestinal Disorders** | | | | |
| Diarrhea[a] | 58 | 2.2 | 57 | 2.5 |
| Stomatitis | 29 | 0.7 | 20 | 0.4 |
| Nausea | 14 | 0 | 19 | 0 |
| Constipation | 15 | 0 | 13 | 0 |
| Vomiting | 11 | 0 | 11 | 1.4 |

**Table 2. Adverse Reactions Occurring in ≥10% of Patients Receiving TAGRISSO in FLAURA* (cont'd)**

| Adverse Reaction | TAGRISSO (N=279) | | EGFR TKI comparator (gefitinib or erlotinib) (N=277) | |
|---|---|---|---|---|
| | Any Grade (%) | Grade 3 or higher (%) | Any Grade (%) | Grade 3 or higher (%) |
| **Skin Disorders** | | | | |
| Rash[b] | 58 | 1.1 | 78 | 6.9 |
| Dry skin[c] | 36 | 0.4 | 36 | 1.1 |
| Nail toxicity[d] | 35 | 0.4 | 33 | 0.7 |
| Pruritus[e] | 17 | 0.4 | 17 | 0 |
| **Metabolism and Nutrition Disorders** | | | | |
| Decreased appetite | 20 | 2.5 | 19 | 1.8 |
| **Respiratory, Thoracic and Mediastinal Disorders** | | | | |
| Cough | 17 | 0 | 15 | 0.4 |
| Dyspnea | 13 | 0.4 | 7 | 1.4 |
| **Neurologic Disorders** | | | | |
| Headache | 12 | 0.4 | 7 | 0 |
| **Cardiac Disorders** | | | | |
| Prolonged QT Interval[f] | 10 | 2.2 | 4 | 0.7 |
| **General Disorders and Administration Site Conditions** | | | | |
| Fatigue[g] | 21 | 1.4 | 15 | 1.4 |
| Pyrexia | 10 | 0 | 4 | 0.4 |
| **Infection and Infestation Disorders** | | | | |
| Upper Respiratory Tract Infection | 10 | 0 | 7 | 0 |

* NCI CTCAE v4.0

[a] One grade 5 (fatal) event was reported (diarrhea) for EGFR TKI comparator

[b] Includes rash, rash generalized, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pustular, rash pruritic, rash vesicular, rash follicular, erythema, folliculitis, acne, dermatitis, dermatitis acneiform, drug eruption, skin erosion.

[c] Includes dry skin, skin fissures, xerosis, eczema, xeroderma.

[d] Includes nail bed disorder, nail bed inflammation, nail bed infection, nail discoloration, nail pigmentation, nail disorder, nail toxicity, nail dystrophy, nail infection, nail ridging, onychoclasis, onycholysis, onychomadesis, onychomalacia, paronychia.

[e] Includes pruritus, pruritus generalized, eyelid pruritus.

[f] The frequency of "Prolonged QT Interval" represents reported adverse events in the FLAURA study. Frequencies of QTc intervals of >500 ms or >60 ms are presented in Section 5.2.

[g] Includes fatigue, asthenia.

**Table 3. Laboratory Abnormalities Worsening from Baseline in ≥ 20% of Patients in FLAURA**

| Laboratory Abnormality[a,b] | TAGRISSO (N=279) | | EGFR TKI comparator (gefitinib or erlotinib) (N=277) | |
|---|---|---|---|---|
| | Change from Baseline All Grades (%) | Change from Baseline to Grade 3 or Grade 4 (%) | Change from Baseline All Grades (%) | Change from Baseline to Grade 3 or Grade 4 (%) |
| **Hematology** | | | | |
| Lymphopenia | 63 | 5.6 | 36 | 4.2 |
| Anemia | 59 | 0.7 | 47 | 0.4 |
| Thrombocytopenia | 51 | 0.7 | 12 | 0.4 |
| Neutropenia | 41 | 3.0 | 10 | 0 |
| **Chemistry** | | | | |
| Hyperglycemia[c] | 37 | 0 | 31 | 0.5 |
| Hypermagnesemia | 30 | 0.7 | 11 | 0.4 |
| Hyponatremia | 26 | 1.1 | 27 | 1.5 |
| Increased AST | 22 | 1.1 | 43 | 4.1 |
| Increased ALT | 21 | 0.7 | 52 | 8 |
| Hypokalemia | 16 | 0.4 | 22 | 1.1 |
| Hyperbilirubinemia | 14 | 0 | 29 | 1.1 |

[a] NCI CTCAE v4.0

[b] Each test incidence, except for hyperglycemia, is based on the number of patients who had both baseline and at least one on-study laboratory measurement available (TAGRISSO range: 267 - 273 and EGFR TKI comparator range: 256 - 268)

[c] Hyperglycemia is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: TAGRISSO (179) and EGFR comparator (191)

## DRUG INTERACTIONS

### Effect of Other Drugs on Osimertinib

Strong CYP3A Inducers

Co-administering TAGRISSO with a strong CYP3A4 inducer decreased the exposure of osimertinib compared to administering TAGRISSO alone *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. Decreased osimertinib exposure may lead to reduced efficacy.

Avoid co-administering TAGRISSO with strong CYP3A inducers. Increase the TAGRISSO dosage when co-administering with a strong CYP3A4 inducer if concurrent use is unavoidable *[see Dosage and Administration (2.4) in the full Prescribing Information]*. No dose adjustments are required when TAGRISSO is used with moderate and/or weak CYP3A inducers.

### Effect of Osimertinib on Other Drugs

Co-administering TAGRISSO with a breast cancer resistant protein (BCRP) or P-glycoprotein (P-gp) substrate increased the exposure of the substrate compared to administering it alone *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. Increased BCRP or P-gp substrate exposure may increase the risk of exposure-related toxicity. Monitor for adverse reactions of the BCRP or P-gp substrate, unless otherwise instructed in its approved labeling, when co-administered with TAGRISSO.

### Drugs That Prolong the QTc Interval

The effect of co-administering medicinal products known to prolong the QTc interval with TAGRISSO is unknown. When feasible, avoid concomitant administration of drugs known to prolong the QTc interval with known risk of Torsades de pointes. If not feasible to avoid concomitant administration of such drugs, conduct periodic ECG monitoring *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

## USE IN SPECIFIC POPULATIONS

### Pregnancy

*Risk Summary*

Based on data from animal studies and its mechanism of action *[see Clinical Pharmacology (12.1) in the full Prescribing Information]*, TAGRISSO can cause fetal harm when administered to a pregnant woman. There are no available data on TAGRISSO use in pregnant women. Administration of osimertinib to pregnant rats was associated with embryolethality and reduced fetal growth at plasma exposures 1.5 times the exposure at the recommended clinical dose *(see Data)*. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically-recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

*Data*

Animal Data

When administered to pregnant rats prior to embryonic implantation through the end of organogenesis (gestation days 2-20) at a dose of 20 mg/kg/day, which produced plasma exposures of approximately 1.5 times the clinical exposure, osimertinib caused post-implantation loss and early embryonic death. When administered to pregnant rats from implantation through the closure of the hard palate (gestation days 6 to 16) at doses of 1 mg/kg/day and above (0.1 times the AUC observed at the recommended clinical dose of 80 mg once daily), an equivocal increase in the rate of fetal malformations and variations was observed in treated litters relative to those of concurrent controls. When administered to pregnant dams at doses of 30 mg/kg/day during organogenesis through lactation Day 6, osimertinib caused an increase in total litter loss and postnatal death. At a dose of 20 mg/kg/day, osimertinib administration during the same period resulted in increased postnatal death as well as a slight reduction in mean pup weight at birth that increased in magnitude between lactation days 4 and 6.

### Lactation

Risk Summary

There are no data on the presence of osimertinib or its active metabolites in human milk, the effects of osimertinib on the breastfed infant or on milk production. Administration to rats during gestation and early lactation was associated with adverse effects, including reduced growth rates and neonatal death *[see Use in Specific Populations (8.1) in the full Prescribing Information]*. Because of the potential for serious adverse reactions in breastfed infants from osimertinib, advise women not to breastfeed during treatment with TAGRISSO and for 2 weeks after the final dose.

### Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating TAGRISSO.

Contraception

TAGRISSO can cause fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1) in the full Prescribing Information]*.

*Females*

Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose *[see Use in Specific Populations (8.1) in the full Prescribing Information]*.

*Males*

Advise male patients with female partners of reproductive potential to use effective contraception during and for 4 months following the final dose of TAGRISSO *[see Nonclinical Toxicology (13.1) in the full Prescribing Information]*.

Infertility

Based on animal studies, TAGRISSO may impair fertility in females and males of reproductive potential. The effects on female fertility showed a trend toward reversibility. It is not known whether the effects on male fertility are reversible *[see Nonclinical Toxicology (13.1) in the full Prescribing Information]*.

### Pediatric Use

The safety and effectiveness of TAGRISSO in pediatric patients have not been established.

### Geriatric Use

Forty-three percent (43%) of the 1142 patients in FLAURA (n=279), AURA3 (n=279), AURA Extension (n=201), AURA2 (n=210), and AURA1, (n=173) were 65 years of age and older. No overall differences in effectiveness were observed based on age. Exploratory analysis suggests a higher incidence of Grade 3 and 4 adverse reactions (13.4% versus 9.3%) and more frequent dose modifications for adverse reactions (13.4% versus 7.6%) in patients 65 years or older as compared to those younger than 65 years.

### Renal Impairment

No dose adjustment is recommended in patients with creatinine clearance (CLcr) 15 - 89 mL/min, as estimated by Cockcroft-Gault. There is no recommended dose of TAGRISSO for patients with end-stage renal disease (CLcr < 15 mL/min) *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

### Hepatic Impairment

No dose adjustment is recommended in patients with mild to moderate hepatic impairment (Child-Pugh A and B or total bilirubin ≤ ULN and AST > ULN or total bilirubin 1 to 3 times ULN and any AST). There is no recommended dose for TAGRISSO for patients with severe hepatic impairment (total bilirubin between 3 to 10 times ULN and any AST) *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

Distributed by: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850



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TAGRISSO is approved as a first-line treatment for patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R mutations, as detected by an FDA-approved test[1]

## First-line TAGRISSO® (osimertinib): **Now** With **2 FDA-Approved** Companion Diagnostics[2]

**cobas® EGFR Mutation Test v2**[2,3]

- PCR-based assay
- Used with either tissue or plasma samples

**NEW APPROVAL!**

**FoundationOne®CDx**[2,4]

- NGS-based assay
- Used with tissue samples

**NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend osimertinib (TAGRISSO®) as a preferred first-line treatment option for patients with sensitizing EGFR mutations and metastatic NSCLC.**[5] According to the NCCN Guidelines®, biomarker testing is recommended for all appropriate patients with mNSCLC, including testing for sensitizing EGFR mutations, before selecting first-line therapy if clinically feasible.[5,*]

*The NCCN Guidelines for NSCLC provide recommendations for individual biomarkers that should be tested and recommend testing techniques but do not endorse any specific commercially available biomarker assays.

## Learn more about treatment with TAGRISSO at **TAGRISSOhcp.com**

### IMPORTANT SAFETY INFORMATION

- There are no contraindications for TAGRISSO
- Interstitial lung disease (ILD)/pneumonitis occurred in 3.9% of the 1142 TAGRISSO-treated patients; 0.4% of cases were fatal. Withhold TAGRISSO and promptly investigate for ILD in patients who present with worsening of respiratory symptoms which may be indicative of ILD (eg, dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed
- Heart rate-corrected QT (QTc) interval prolongation occurred in TAGRISSO-treated patients. Of the 1142 TAGRISSO-treated patients in clinical trials, 0.9% were found to have a QTc > 500 msec, and 3.6% of patients had an increase from baseline QTc > 60 msec. No QTc-related arrhythmias were reported. Conduct periodic monitoring with ECGs and electrolytes in patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Permanently discontinue TAGRISSO in patients who develop QTc interval prolongation with signs/symptoms of life-threatening arrhythmia
- Cardiomyopathy occurred in 2.6% of the 1142 TAGRISSO-treated patients; 0.1% of cardiomyopathy cases were fatal. A decline in left ventricular ejection fraction (LVEF) ≥10% from baseline and to <50% LVEF occurred in 3.9% of 908 patients who had baseline and at least one follow-up LVEF assessment. Conduct cardiac monitoring, including assessment of LVEF at baseline and during treatment, in patients with cardiac risk factors. Assess LVEF in patients who develop relevant cardiac signs or symptoms during treatment. For symptomatic congestive heart failure, permanently discontinue TAGRISSO
- Keratitis was reported in 0.7% of 1142 patients treated with TAGRISSO in clinical trials. Promptly refer patients with signs and symptoms suggestive of keratitis (such as eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye) to an ophthalmologist
- Verify pregnancy status of females of reproductive potential prior to initiating TAGRISSO. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose. Advise males with female partners of reproductive potential to use effective contraception for 4 months after the final dose
- Most common adverse reactions (≥20%) were diarrhea, rash, dry skin, nail toxicity, stomatitis, fatigue and decreased appetite

**Please see Brief Summary of Prescribing Information on adjacent pages.**

EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; mNSCLC, metastatic non–small cell lung cancer; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; PCR, polymerase chain reaction; TKI, tyrosine kinase inhibitor.

**References: 1.** TAGRISSO® (osimertinib) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2018. **2.** US Food and Drug Administration. List of cleared or approved companion diagnostic devices (in vitro and imaging tools). https://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/ucm301431.htm. Updated October 24, 2018. Accessed November 30, 2018. **3.** cobas® EGFR Mutation Test v2 [package insert]. Branchburg, NJ: Roche Molecular Systems, Inc.; 2018. **4.** FoundationOne®CDx [technical specifications]. Cambridge, MA: Foundation Medicine, Inc.; 2019. **5.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Non-Small Cell Lung Cancer V5.2019. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed June 7, 2019. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. To view the most recent and complete version of the guideline, go online to NCCN.org.

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TAGRISSO® osimertinib