NOVEMBER 2017 # 36

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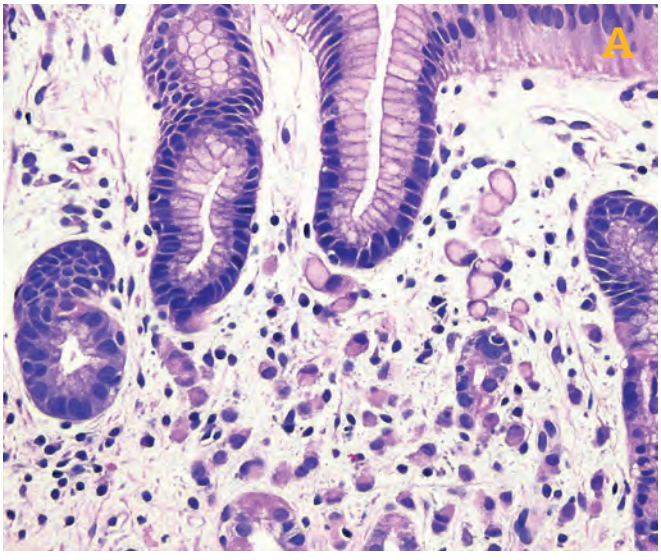
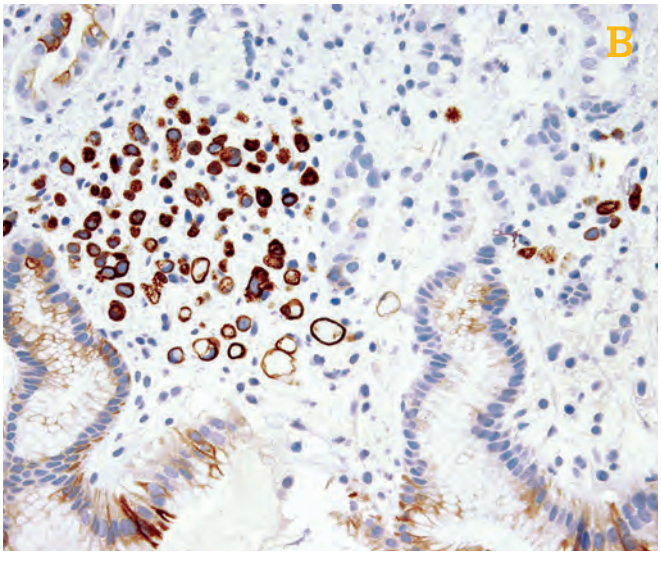
Case of the Month

This gastric biopsy was taken from an asymptomatic 30-year-old woman with a familial history of hereditary diffuse gastric carcinoma. Slide A was stained with hematoxylin and eosin, and slide B was stained immunohistochemically with the antibody to cytokeratin CK7.

Mutation of which gene most likely accounts for the pathologic changes seen in this biopsy?

- *A* CDH1
- *B* CTNNA1
- *C* STK11
- *D* RET
- *E* FOXL2





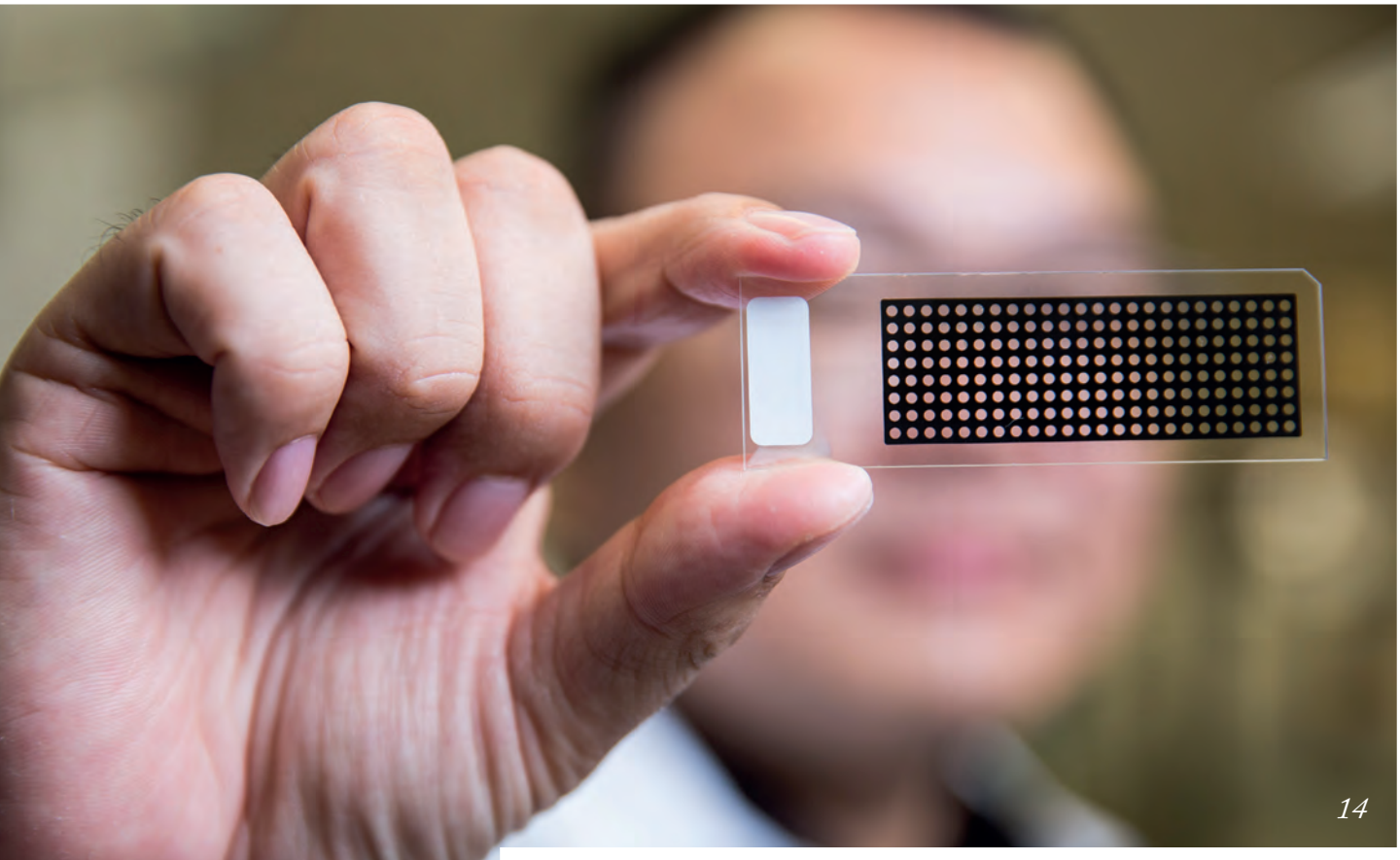
Answer to last issue's Case of the Month…

Histiocytic necrotizing lymphadenitis (of Kikuchi and Fujimoto) is a self-limiting, well-defined clinicopathologic disorder of unknown etiology. Microscopically, the lymph node architecture is partially effaced with dormant, non-hyperplastic follicles. Characteristic histologic findings include eosinophilic amorphous material, abundant karyorrhectic debris and viable cells. Absence of vasculitis is a clue to exclude a diagnosis of systemic lupus erythematosus. In cases such as this, clinical, serologic and pathologic correlation is crucial to arrive at a correct diagnosis.

Submitted by Seshadri Thirumala, Director of Surgical Pathology, Ameripath Lubbock, USA

To register your guess, please go to http://tp.txp.to/1117/case-of-the-month
We will reveal the answer in next month's issue!

Contents



On The Cover

A collage of images representing the richness and complexity of digital pathology.

Upfront

In My View

32

50

Feature

In Practice

Next Gen

Profession

Sitting Down With

the Pathologist

ISSUE 36 – NOVEMBER 2017

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Plugging Into Artificial Intelligence

There's no need to fear the digital revolution

"Have you heard the one about the pigeons?"
"The pigeons? Is this the start of a joke?"
"No. They did a study and found that pigeons were able to diagnose cancer as accurately as humans…"
"Oh, *that* study!"

Everyone is familiar with "the pigeon study" – a paper by Richard Levenson and colleagues that captured people's attention because of the absurdity of its subject (1). It seemed improbable that a creature often regarded as vermin could decipher breast tissue biopsies as well as a human – so no one seemed to mind when they did. People laughed and joked about it, but nobody objected. Nobody expressed fear that a pigeon might be about to take their job.

Swap the pigeon for a computer, though, and you might see a very different set of reactions. "Is it as accurate as a real pathologist?" "Can I trust it with my patients?" "Will it take away my job?" It's natural to fear the unknown – and to many pathologists, "artificial intelligence" seems closer to a science-fiction plot point than to a laboratory reality.

But artificial intelligence is already an integral part of many labs. Computer programs often support medical decision-making by providing algorithms for testing and treatment. Pathologists who use digital imaging can install software to help navigate, analyze and label images. There are tools for counting cells, identifying objects, and spotting anomalies in sequence data. There are even computer programs that convert pathologists' slide interpretations into final reports (2). Despite what Hollywood might like us to believe, AI is not the Terminator. It's not HAL 9000. It's simply a set of tools that can make pathologists' lives easier.

What might AI be able to do for pathologists now or in the near future? It may be able to spot tiny color variations, improving detection of abnormalities on stained slides. It may be able to quickly identify individual objects, speeding up cell counting. It may be able to "learn" what a malignant cell looks like and pick it out of surrounding healthy tissue faster or more easily than the human eye.

But does AI's continuing evolution mean that pathologists should fear for their careers? Most experts think not – and I agree. As a graduate student, I would have welcomed software that could count histones and detect the locations where they overlapped. It would have saved me hours of squinting at electron microscopy grids! No computer can replace the judgment of a skilled pathologist – but it can save time and resources that can then be devoted to the trickier diagnoses that only human intelligence can deliver.

Michael Schubert
Editor

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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?

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Database Discrimination?

Precision medicine often relies on population databases – but this may render it less effective for non-European patients

When is "precision medicine" not precision medicine? When it's used for patients of non-European descent, a new study from the University of Southern California reveals (1). Ideally, genetic mutations in cancer cells are highlighted in a comparison with normal tissue – but, in many cases, there's no normal tissue sample available. Genetic information from population databases can serve as a stand-in, but there's a catch: most of the genomes included in such databases come from individuals of European descent. What does that mean? Variants that are harmless in a given patient may stand out as potentially cancer-causing, simply because the population database lacks the information to identify them as benign.

"A physician could give a treatment that is toxic, ineffective or worse – unnecessarily," says David Craig, principal investigator and co-director of the Institute of Translational Genomics at USC's Keck School of Medicine. "This would be the case in the context of clinical decision-making based on tumor sequencing only." If reported mutations are interpreted as cancer-driving when they are, in fact, inherited and most likely benign, patients might undergo more intensive treatment than necessary, or might not receive the treatment best-suited to their particular disease profile.

"The amount of incorrect inherited information within a precision medicine cancer genomics report is very important, as that speaks towards the precision of the test," says Craig. "Precision is a part of precision medicine. In research studies attempting to discover new driver mutations and link them to therapy, imprecision lowers the overall chance that a study will yield meaningful new insights."

The study shows that precision is ancestry-dependent. In some populations, particularly those of European ancestry, the precision is good. In others, it drops precipitously. But the report doesn't stop there; it goes on to demonstrate analytical approaches to reducing imprecision. How? By deconvoluting normal and tumor tissues from the same sample, taking advantage of the fact that most specimens sent to pathology are not pure tumor to allow comparisons between the two.

So why don't hospitals routinely collect healthy tissue from cancer patients? Craig says there are many reasons. "Some that are really important, but not frequently discussed, are due to the regulatory uncertainty of explicitly collecting normal specimens, and how it impacts the ability of the physician to act quickly to identify the best therapy."

In the United States, for example, some state laws require additional genetic counseling prior to conducting tests involving inherited information (2). Regulation around germline testing could add uncertainty to the process and, according to Craig, many view this uncertainty as counterproductive. "Think of it from the perspective of an oncologist working with their patient. The ordering physician may be well aware of different cancer treatments, their effectiveness and how a patient may respond. However, there may be additional laws that require the patient to have genetic counseling before the test is ordered, as there may be incidental findings about family members. For many physicians, introducing regulatory uncertainty about what steps must come before even ordering the test is a major concern."

But understanding the nature of the problem also suggests a solution. "Our approach identifies ways to separate tumor and normal by recognizing most solid tumors are mixtures. We can use tools to computationally indicate which

mutations are from the tumor and which are inherited. We have made those tools available in an open framework (github.com/tgen/LumosVar) that allows the approaches and concepts to be adapted, integrated and validated within future clinical tests."

LumosVar is not currently a clinical test. It is a research tool and algorithm that its creators hope will lead others to test and validate approaches to deconvolute mixtures. "We hope it enables sequencing of archival samples from diverse populations when requiring a normal means losing diversity," says Craig. "In our studies, we have seen examples where access to archival tumor specimens is available for African and Asian populations, and we want to make sure that we can maximize the utility of these samples." It's vital that our understanding of genetics incorporate as many different populations as possible – because what begins as research on an underserved population may eventually lead to better care for those patients.

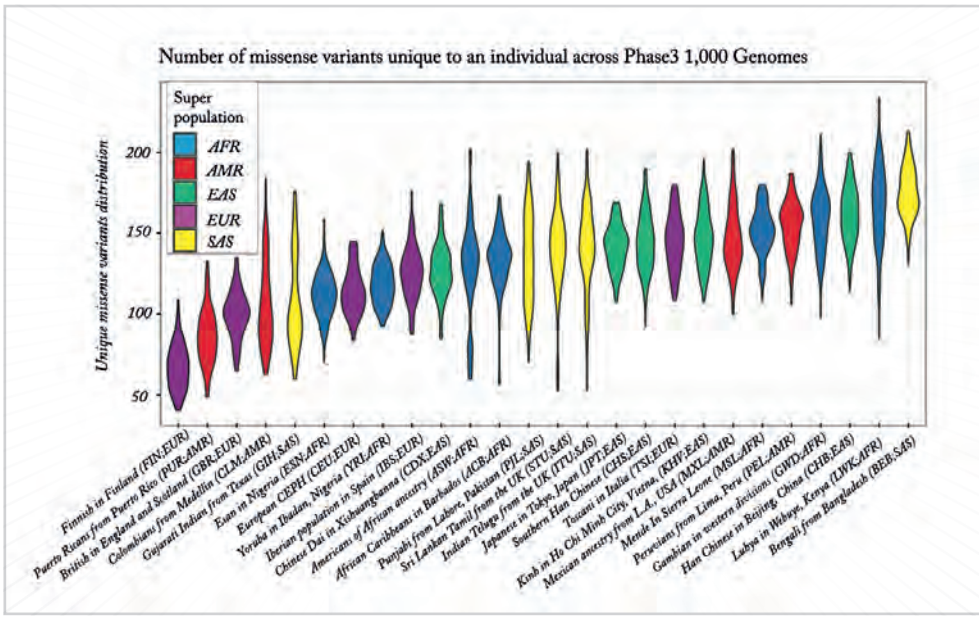

Figure 1. The number of unique missense variants in individual population subtypes. These variants are poorly represented in genomic databases and can lead to false positive results on genomic tests

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The Lady Doth Co-Test Too Much, Methinks

Current guidelines recommend the Pap smear and HPV testing for cervical cancer – but are both really necessary?

Adult women are very familiar with the Pap smear – an unpleasant necessity in the name of preventing cervical cancer. Once the sample is taken, cells are microscopically examined for morphological abnormalities that indicate a precancerous state. Ideally, any patient whose cells show such indications can then be treated for the condition before it progresses to cancer. But the Pap test is not infallible, and many factors can lead to a false negative result.

Current guidelines recommend co-testing using both the Pap smear and human papillomavirus (HPV) testing every five years – but given rising costs, co-testing may be an unsustainable approach. What if there were a more sensitive way to detect precancers than Pap testing alone? That's the question a research team at the National Institutes of Health's National Cancer Institute asked themselves, seeking a way to reduce the incidence of a cancer that affects over half a million people worldwide every year (1). To find out, they quantified the differences in cervical cancer detection rates between co-testing and HPV testing alone – and came up with a surprising result.

HPV testing demonstrated a clear superiority to cytology, identifying significantly more patients with either precancer or overt cancer. Did the Pap smear catch any cases missed by HPV testing? Very few, according to the study results – only 3.5 percent of precancers and 5.9 percent of cancers, translating to five cases per million screens in a year at most. The authors' conclusion? That co-testing isn't necessary; very few patients benefit from the addition of cytology. The most cost-effective option, the results suggest, is to forgo the Pap smear and focus solely on HPV testing for the future prevention and detection of cervical cancer.

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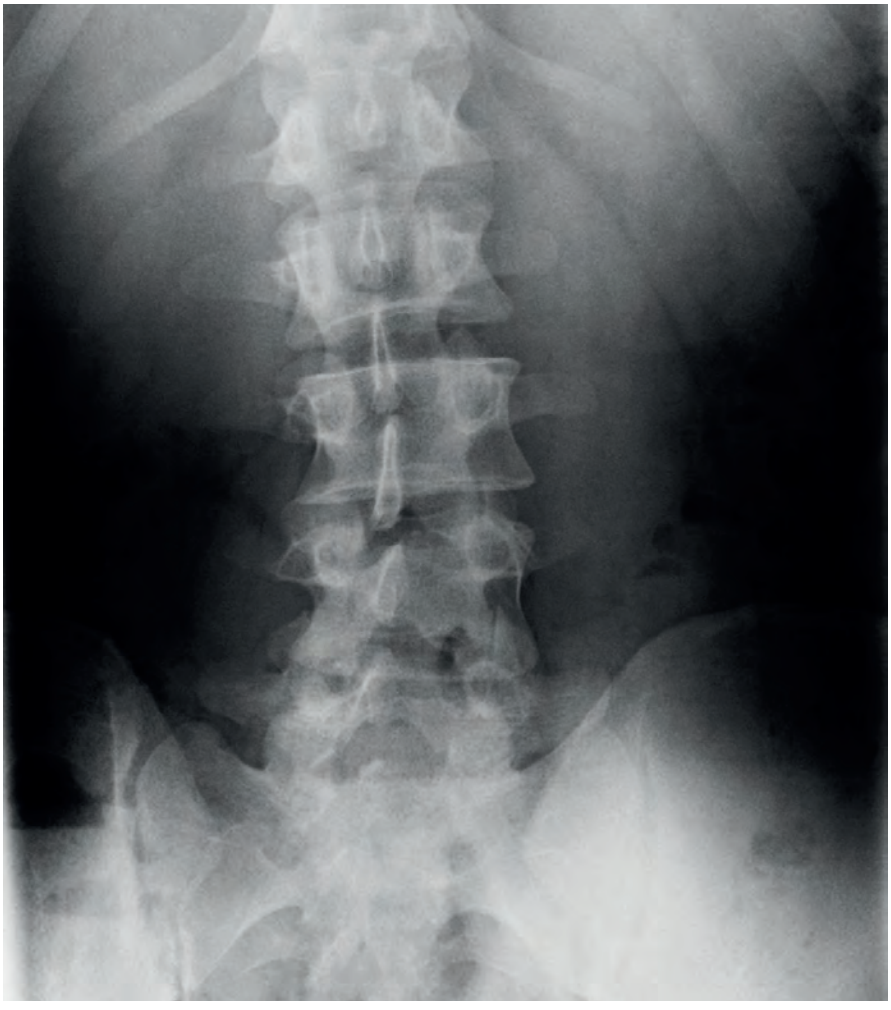
Spinal Tap

Metal speciation in cerebrospinal fluid may bring new understanding of neurodegenerative diseases



Debilitating and often incurable, neurodegenerative diseases could affect over 12 million Americans by 2030 (1). Finding treatments – or, even better, cures – for these conditions is a high priority. But first, we need to understand them.

High levels of metal ions in the cerebrospinal fluid (CSF) are currently thought to play a key role in protein misfolding – a hallmark of neurogenerative disorders, so a multinational team of researchers developed a method for simultaneous redox speciation of iron (II/III), manganese (II/III), and copper (I/II). Based on strong cation exchange chromatography and inductively coupled plasma sector field mass spectrometry (ICP-sf-MS), the new method was optimized and tested using real CSF samples taken from amyotrophic lateral sclerosis (ALS) patients and neurologically healthy controls (2).

"The underlying hypothesis of our studies is that, unlike cycling body fluids (for example, blood or serum) or excretory media, the CSF is in direct contact with the brain parenchyma and brain extracellular fluid," says Nikolay Solovyev from St. Petersburg State University, Russia. "So, slight changes of trace element speciation caused by exposure or redox dis-homeostasis related to neurological pathology would be more clearly reflected in the CSF than in other matrices." Less cerebrally put: higher levels of the primary species of interest detected in CSF could act as "red flags" for various neurodegenerative diseases (3).

Next, Solovyev and the team plan to complement their metallomics studies on ALS with non-specific metabolomics research to see how metal species interact with metabolites in the CSF with the ultimate aim of discovering candidate biomarkers.

Solovyev and the team want to apply analytical lessons learned in other disease areas, and will soon begin an investigation into copper speciation in Wilson's disease as part of a biomarker research project alongside new partners from Guildford, UK: "Here, we would like to improve the current approaches for ceruloplasmin determination using hyphenated techniques – and implement this into clinical chemistry. I would like to thank my colleagues from Germany, Italy and UK for our collaborations." *JC*

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Gut Feeling

Can the microbiome predict the likelihood of chemotherapy side effects?

Chemotherapy can come with a range of side effects, including severe diarrhea. Oral antibiotics can be used to reduce toxicity by protecting against infection and increasing the capacity to metabolize dietary substrates, but the indiscriminate depletion of gut microbes can directly impact the effectiveness of the chemotherapy. Libusha Kelly, Assistant Professor in the departments of Systems and Computational Biology and Microbiology and Immunology at the Albert Einstein College of Medicine in New York, has been studying how the microbiome can influence the likelihood of chemotherapy side effects.

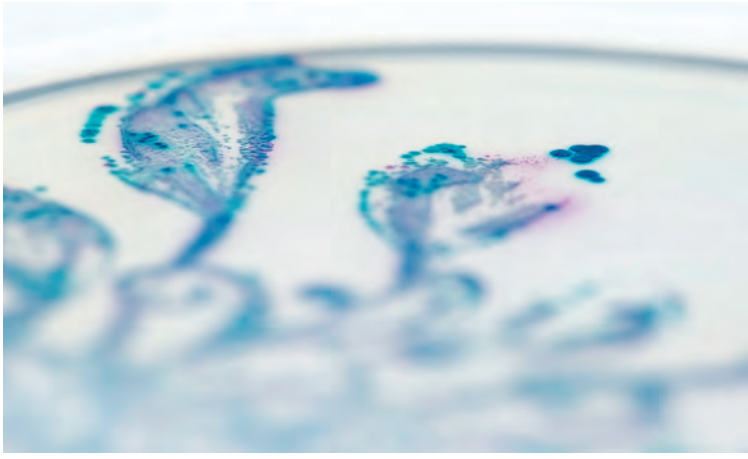
Kelly and coworkers focused on irinotecan (CPT-11), which, in combination with fluorouracil and leucovorin, is one of three first-line treatments for metastatic colorectal cancer. Severe diarrhea only seems to affect a subset of individuals taking the drugs – 30 to 40 percent when administered as a single agent, and 11 to 37 percent when used along with other therapeutics.

"In light of a study demonstrating that CPT-11's toxicity could be alleviated by inhibiting the *E. coli* version of a beta-glucuronidase (BG) enzyme in mice (1), we hypothesized that the gut microbiome metabolism would vary between people, and that it might be possible to identify who was likely to be a high versus low metabolizer of the drug based on the expression of certain genes – including BG genes – present in the gut microbiome," explains Kelly.

Using high-throughput genomics in combination with metabolomics, the researchers identified gut microbiome-derived metagenomic signatures linked to an individual's ability to convert the inactive form of CPT-11, SN-38G, to the active form, SN-38 (2).

According to Kelly, analyzing the composition of patients' microbiomes before giving CPT-11 might predict whether patients will suffer side effects from the drug. "High-throughput sequencing technologies have started to give us a glimpse into the incredible diversity of microbes that live in and on our bodies," says Kelly. "Our work with CPT-11 has implications for the many additional drugs that are glucuronidated via phase II drug metabolism and excreted to the gut. We anticipate that gut microbes may metabolize many additional glucuronidated drugs, with unknown consequences for patients."

The researchers are now collecting samples from colorectal cancer patients who are on treatment regimens that include CPT-11. "We will track these patients over time to find out whether we can predict, based on a fecal sample, which patients are likely to suffer an adverse response to CPT-11," says Kelly.



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Understanding Pancreatic Cancer Prognosis

Mutations in four main genes influence survival rates of pancreatic adenocarcinoma patients

Despite increased research efforts in recent years, survival rates for pancreatic cancer remain relatively low, with only 3.3 percent of adults surviving for five years with the disease (1), and researchers around the globe are working hard on new directions to aid in diagnosis, prognosis and treatment.

In a recent publication in JAMA Oncology, a group of US researchers studied 356 patients with resected pancreatic adenocarcinoma, and identified changes in four main driver genes that were associated with outcomes following surgery. Protein expression and DNA alterations for *KRAS*, *CDKN2A*, *SMAD4*, and *TP53* were analyzed using immunohistochemistry and next generation sequencing. The research team found that patients with *KRAS* mutant tumors had worse disease-free and overall survival than patients with *KRAS* wild-type tumors. In particular, patients with *KRAS* G12D mutations had poorer outcomes, with a median survival of 19.7 months (2).

The authors hope that a better understanding of the molecular changes affecting patient outcomes could improve treatment approaches, and two of the collaborators – David Linehan and Brian Wolpin – are partnering on a further project investigating new therapies and biomarkers for use in metastatic pancreatic cancer (3).

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More Precise Precision Medicine

Standard molecular analysis of breast cancer tumors isn't enough, say two researchers; only single-cell diagnostics can reveal the full picture

Precision medicine for cancer treatment sounds promising – sample the tumor, analyze the genome for cancer-related mutations, and then select treatment according to the genetic profile of the disease. And although the procedures involved may be complex, the concept itself is relatively simple – or is it?

In an opinion piece in Trends in Cancer, Syn Kok Yeo and Jun-Lin Guan argue that the current approach to breast cancer isn't good enough (1). Breast cancer tumors often exhibit a high degree of intratumoral heterogeneity – and so, they say, diagnostic professionals should be using single-cell technologies to truly personalize treatment.

"If you use a treatment that's targeting one subtype, which kills one type of breast cancer, often the other kind will actually expand," said Guan (2). "That defeats the purpose of treatment." Instead, he and Yeo suggest that single-cell analysis could reveal different cell types within individual tumors, including populations of cancer stem cells capable of differentiating into many different tumor types. These are especially concerning because they aren't genetically distinct, but can still give rise to tumor heterogeneity and thus to treatment resistance. The authors also highlight studies that suggest breast cancer cells may be able to interconvert between different subtypes, adding yet another layer of potential heterogeneity to a single tumor.

What can be done against this kind of dynamic heterogeneity? Fortunately, single-cell diagnostic technology is advancing rapidly. Yeo and Guan recommend adding such technologies to the laboratory's existing breast cancer diagnostic workflow, so that pathologists can use a more complete understanding of any given tumor to guide treatment decisions. Of course, that too is easier said than done; there are a number of questions yet to be answered before clinical approaches catch up to research methods. But with more attention on the potential for dynamic heterogeneity, Yeo and Guan believe we could not only better understand breast cancer, but provide more customized care to patients with challenging tumors.

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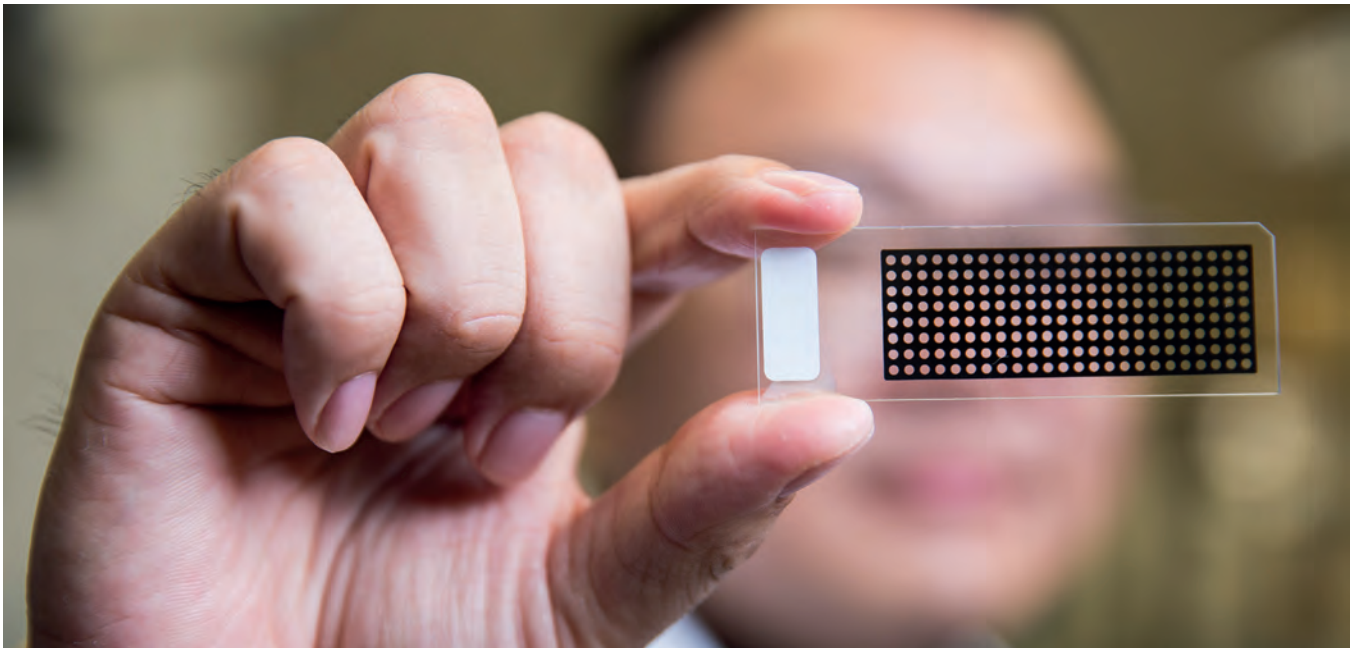

Dark Fields and Diagnostic Disks

New devices for detecting tuberculosis may speed up diagnosis and improve treatment

Tuberculosis (TB) is the eighth most common cause of death in low- and middle-income countries (1) and a challenging disease on many levels. To begin with, it's difficult to diagnose – symptoms like fever, weight loss and coughing apply to a wide range of illnesses, and many tests are inconclusive or subject to a high percentage of false positive and negative results, especially in patients with additional health problems. To reach a conclusion, doctors require a medical history, a physical examination, and a variety of tests, including skin tests, chest X-rays, sputum smears and microbiological cultures. Even after diagnosis, the battle isn't over; treatment is long, arduous, and side effects are common – and antibiotic resistance compounds these problems. But the longer patients go undiagnosed, the worse the odds of survival become – and it is more likely that they will spread the disease to others.

Tony Hu and his colleagues from the Arizona State University's Biodesign Institute decided to tackle the problem of diagnosis by developing a nanotechnology-based method of detecting and quantifying TB-specific proteins in circulation (2): an antibody-conjugated nanodisk that improves detection by high-throughput MALDI-TOF mass spectrometry. The disk first binds target peptides CFP-10 and ESAT-6, and then enhances the MALDI signal to allow quantification of the peptides at low concentrations. In the group's proof-of-concept study, the disks were highly sensitive and specific, successfully diagnosing culture-positive and extrapulmonary tuberculosis even in HIV-positive patients. The specificity was similarly high in healthy and high-risk patient groups. And during treatment, the nanodisks were able to quantify serum antigen concentrations to assess how well patients were responding.

It seems the new test has everything – speed, sensitivity, specificity, and the ability to offer conclusive results from a single, low-volume blood draw. But it's not the Hu group's only TB diagnostic; they've also developed another proof-of-concept device for use in resource-limited settings (3), which takes the form of a simple dark-field microscopy system with an LED light source, a dark-field condenser, a 20x objective lens, and the user's smartphone. It's small, light, and cheap at under US$2,000 – but the researchers aren't done yet, setting their sights on higher sensitivity, less weight, and a fraction of the cost.

The goal is to make high-quality TB care – and eventually, broad-range infectious disease diagnosis – available to every patient, regardless of location, health status, or resource availability.

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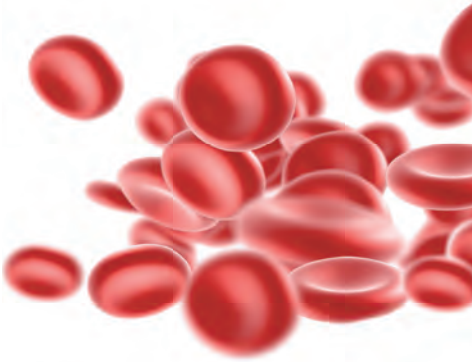

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In My View

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

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

Contact the editors at edit@thepathologist.com

Taking the "Bank" out of Biobank

Users agree that biobanks aren't delivering – but what's wrong, and how can it be fixed?

By Vanessa Tumilasci, Project Management and Communications, Trans-Hit Biomarkers Inc., Laval, Canada

Dominic Allen's article (1), "A Failed Model," highlights some of the reasons why biobanks are failing to provide the services for which they were designed. From the other side of the table – as users of biobanks, rather than administrators – we agree on many points.

One particular area of concern for us is the number of samples sitting unused in biobanks. Patients who donate tissues for research purposes expect their samples to benefit others in the future. They would likely be unhappy to learn that their samples had not been used – or, in some cases, are even under consideration for disposal! Too many biobanks are still proud to advertise the number of biospecimens they store – but this is an inappropriate measure of how good they really are. Donors provide their samples to biobanks to be used in research, not to be stored for an indeterminate amount of time. The saying "a good biobank is an empty biobank" refers to the continual distribution of collected samples for use in research to improve healthcare. Samples that just sit in a biobank and are not used do not fulfill their purpose. Hence, the efficiency should be evaluated by ratio: the number of stored specimens relative to the number of used and shared specimens. By that measure, a good biobank would be an empty biobank.

But even the phrase "biobank" itself has pitfalls. Referring to a biorepository of samples as a "bank" conjures up the wrong image. A bank protects your assets from being stolen by others, and eventually, may even help to increase those assets. But is this really what patients want for their samples? In our view, patients deliberately donate their tissues for "the greater good." They aren't seeking to help only themselves, or one or two others – they want to give all scientists, public and private, the resources needed to move medical research forward.

The other problem with the "bank" concept is that such repositories should not be intended for long-term storage – a specimen's intrinsic scientific value may decrease over time. All in all, the word "biobank" is a poor term; we recommend that those involved in biological specimen storage develop other terminology.

In his keynote address to attendees of the 2017 Global Biobank Week in Stockholm, Gregory Simon, Director of the Biden Cancer Initiative and himself a cancer survivor, suggested the term "trust." The "bio-trust" receives the samples from the donors in trust that they will be used for the purposes to which the donors have consented. It then distributes the samples to research groups in trust that the samples will be used for the betterment of healthcare and to benefit society as a whole.

Finally, we believe that biospecimens should be accessible to and shared by all scientists, whether public or private. The biotech and pharma industries are certainly among the biggest end-users of such specimens. However, as confirmed by two recent surveys (2,3), the respective requirements and expectations of biobanks and their industry clients are often not

aligned. For instance, 89 percent of companies consider existing collections in academic biobanks to be underutilized and the biobanks themselves unable to respond to their R&D needs.

To maintain the automotive analogy of "A Failed Model," the technology improvements applied to Formula One cars aren't reserved only for those specialist vehicles. They help all automobile manufacturers improve the safety of today's cars. In a similar vein, the benefits of industry biobanking aren't just for industry users themselves; in fact, we would say that they are crucial to the ultimate goal of putting the patient first!

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Digital Pathology Is Not Our Enemy...

It could actually be our strongest ally, but only if we get on board fast

By Dariusz Borys, Associate Professor of Pathology and Orthopedic Surgery, Chief of Orthopedic and Pediatric Pathology, and Director of the Digital Pathology Lab, Loyola University Chicago, Maywood, USA

Are we ready for digital pathology?

We've been asking ourselves this question for so long that it reminds me of my children riding in the backseat of the car on a long trip – "Are we there yet?"

I started my own long trip with digital pathology in 2003, as a junior resident presenting a poster at my first College of American Pathologists conference. I clearly remember thinking that it felt like every company in attendance was developing slide scanners. At the time, it took these devices 30 to 60 minutes to scan a single slide. Today, not only are they much faster – with scanning times as short as 30 seconds – but the images are also much better.

Since my first introduction, digital pathology has become a passion for me. At the University of California, Davis, I implemented digital pathology sarcoma tumor boards, which gave both me and my clinician colleagues a better understanding of our cases. We even correlated them with digital radiology to further expand our knowledge.

The turning point for me, though, came during my visiting professorship at the Rizzoli Orthopedic Institute in Bologna, Italy. During that month (July 2011), I was still consulting on all the bone and soft tissue cases at UC Davis. I had no problem diagnosing those cases even though I was on a different continent nine time zones away! The histological images had the same quality and accessibility as if I had been looking at them under my light microscope in my California office. That's when I lost all doubt that digital pathology would be the future of my specialty.

We pathologists have to understand that digital pathology is not our enemy. Instead, it can be our strongest ally. Digital pathology gives us the ability to access slides from anywhere, at any time. We can seek consults on difficult cases from experts anywhere in the world. We have the potential to get an answer in a very short time – much faster than waiting to send outside cases by parcel post.

"With digital pathology, we can review previous slides in the blink of an eye."

Every pathologist's nightmare is having a clinician call the next day for results on a patient with metastatic cancer to the lung and a previous history of cancer. To make that diagnosis, the first thing we would like to see is the previous biopsy, so that we can compare the tumor morphology. But the slides from that previous case, which may have been years earlier, are probably in storage – perhaps at a hospital several states away – and it would take far too long to receive them for review. With digital pathology, we can review previous slides in the blink of an eye and correlate them with our present findings.

These are only a few of the advantages of digital pathology and its application to daily clinical practice!

In April of 2017, digital pathology reached a major milestone – the FDA approval of the first digital pathology solution for primary diagnostic use in the United States. I – and many others – had been waiting anxiously for that day. We were sure that, when it happened, we pathologists would be ready to sign out cases digitally right away – and yet, it seems that most hospitals are still a long way away from embracing the change.

This summer, I was the keynote speaker at the 3rd Digital Pathology Congress in Chicago. I was surprised to find that most of the attendees were vendors; relatively few pathologists were there. Even the pathologists who attended the event did not really seem convinced when I told them that digital technology could replace light microscopes. It seemed to me that they preferred to stay in their small basement offices and sign out cases "the old way."

I must add, at this point, that I have nothing against the old way. I like to sit in my office and sign out cases while listening to classical music, too. However, we must remember that business is business – and health care is big business in America. Big laboratories are always looking for more revenue. They would be pleased to get more cases, and happy to have the ability to run their labs 24/7. If a representative from such a lab went to the CEO of a small hospital and proposed a faster turnaround time for surgical cases at a cheaper price, I feel sure that the CEO would be thrilled to sign up. He or she would certainly prefer to pay less – and perhaps even provide fewer benefits for those pathologists remaining in the basement.

If we do not wake up soon, we will become consultants without benefits. We will be paid less. We will work for big companies instead of hospitals. I think it's well past time for us to get out of the basement and start thinking more seriously about digital pathology opportunities.

Are we pathologists ready for digital pathology? We'd better be – because if we don't make the most of this opportunity, somebody else will.

The World (of IHC) Is Not Enough

As a qualitative assay, immunohistochemistry does the job. But when it comes to accurate quantitation, don't we need something more?

By Dean Troyer, Professor, Departments of Microbiology, Molecular Cell Biology and Pathology, Eastern Virginia Medical School, Norfolk, USA

Immunohistochemistry (IHC) detects PD-L1 as a companion diagnostic for pembrolizumab, a humanized monoclonal antibody used in cancer immunotherapy. The assay provides a semiquantitative score pathologists can use to determine the likelihood of treatment success using PD-1/PD-L1 inhibitors.

Recall that the original test for estrogen receptors in breast cancer was a quantitative radioimmunoassay (RIA). It required relatively large amounts of fresh or cryopreserved tissue. IHC replaced the RIA method largely because it fits into the existing histology workflow for formalin-fixed, paraffin-embedded tissue, making its convenience obvious. Histopathology became the go-to approach for personalizing breast cancer treatment, and soon, the HER2 assay also became part of the tissue pathology toolkit.

IHC offers a powerful way to determine whether a protein is present in cells or tissue – and where that protein of interest is located. But how much is present? We're able to say to some extent, but accurate quantitation remains challenging. Morphometric algorithms and technical automation don't overcome the intrinsic variables that affect IHC, such as fixation, tissue processing, antigen retrieval, antibody avidity, antibody titer, and chromagen development. So is it reasonable to assume that IHC can deliver everything we need?

Smaller molecules (<2000 kD), such as metabolites, are largely undetectable by IHC. Metabolites are part of the wider "omics" landscape, and metabolic changes have been associated with cancer since the initial description of the Warburg effect in 1956. Metabolomic studies have really evolved since those early days, and my colleagues and I have recently developed a way of incorporating metabolomics into the histopathology workflow by using alcohol as a primary tissue fixative, followed by secondary fixation in formalin and embedding in paraffin. The alcohol extracts metabolites and lipids, but preserves tissue architecture and allows proteins, RNA and DNA to remain in the tissue. Then, we use liquid chromatography-mass spectrometry (LC-MS) to determine the metabolites in the alcohol. Thus, we can perform repeated

microscopic analyses on the same tissue – just as we have always done.

Our new method, for which we have coined the term "histabolomics," overcomes several hurdles in the application of metabolomics to human tissues. One such hurdle is the small size of human tissue biopsies; an assay that competes for tissue will not be welcomed onto the playing field. Another is the need for normalization – the expression of the quantity of an analyte per unit of sample. In clinical chemistry, the analyte is expressed per volume of serum or plasma; tissue RNA is often expressed in relation to a housekeeping gene. But all of these approaches require extraction and disruption of the tissue. Normalization of metabolomics data is usually performed "post-acquisition," when the LC-MS data are analyzed, processed, and normalized in relation to total ion counts or similar values – or by tissue weight. Even if the tissue is weighed, the amounts of disease or tumor relative to non-diseased tissue and stroma remain variable. Histabolomics downscales the method to accommodate as little as 5 mg of tissue, the typical yield of an 18-gauge core needle biopsy. This bypasses the need for tissue cryopreservation, commonly used for metabolomics. When combined with a chemical labeling technique, the method is quantitative and normalized.

Histabolomics is complementary to existing methods of RNA and DNA analysis, and to in situ methods such as FISH or CISH. Both tissue metabolomics analysis and routine histopathology and IHC can be performed on exactly the same tissue. Although it's inconceivable to picture a future without IHC, it is entirely possible to imagine one where quantitative, normalized metabolomic data from human tissues is combined with histopathology, DNA sequencing, RNA expression and IHC to enhance clinical decision-making.

Such an approach is useful in distinguishing aggressive from indolent cancers, and my colleagues and I suggest that it could also be applied to other medical conditions where we operate with sparse or imperfect data – inflammatory bowel diseases, liver diseases, identification of drug targets, toxicology and more. In my opinion, pathologists should pursue diagnostic methods that yield as much information as possible, with as little impact as possible on the patient – and our histabolomics approach fits nicely into that picture.

Connecting Your Digital World

So you want to transition to digital pathology. Where will you store your images, and how will you share them with colleagues?

Practically perfect in every way

With almost infinite data storage and sharing possibilities available, how can pathologists match their infrastructure to their needs?

By Michael Schubert

It's clear that digital pathology is picking up speed. Recent FDA clearances (1) are removing the once-overwhelming regulatory obstacles, and the field is slowly expanding beyond its initial offerings. Previously synonymous with virtual imaging and long-distance consultations, the term "digital pathology" now stands for a range of new technologies, including artificial intelligence and algorithmic decision-making assistance – concepts that sound more like science fiction. Nowadays, these software-based tools are, in some cases, exhibiting precision and accuracy comparable to that of human pathologists. Have we truly reached a point where all of the roadblocks to full digital pathology adoption are removed? And, if so, will these computer-based tools support pathologists – or replace them?

The reality of a modern pathologist's day-to-day work is this: there are too few laboratory medicine professionals, and too many patients in need of their services. Anything that can lighten the load is welcome – provided, of course, that it is both a feasible and a functional option. Most pathologists already benefit from some form of digital work, be it teleconsultations, automated image analysis to verify a manual diagnosis, or even simply digitizing images for easier presentation or future referencing. But not every laboratory can implement even these basic improvements, let alone more complex ones. Many labs lack the necessary equipment (such as slide scanners, or the hardware and software required to process and analyze large image files), and a significant percentage of them lack the money (measured in hundreds of thousands, if not millions, of dollars) needed to switch to a fully digital workflow. And even in laboratories not limited by material considerations, the amount of time, effort, and staff buy-in required to make the transition from a well-established analog routine to a new, unfamiliar digital one can often prove insurmountable.

So with these obstacles still to be overcome, the question is not how much digital pathology is possible – but how much is truly practical? How is digital pathology practised in the labs that use it, and what tools and devices are indispensable?

Collaborating on collections

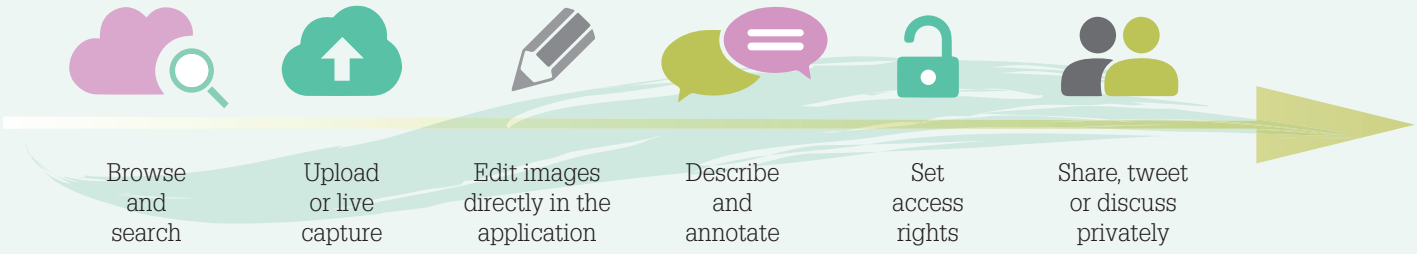
The first thing that leaps to mind when thinking of digital pathology is the ability to share findings – images, of course, but also the accompanying annotations, ideas and explanations. Digital images captured by whole-slide imaging (WSI) scanners, microscope cameras, and smartphones are used in many practices as quick references, for lectures and presentations, to consult with other medical professionals, or even for casual purposes like posting "pathology artwork" on social media.

In recent years, numerous platforms for the storage and sharing of digital pathology images have arisen, established by universities, non-academic organizations, and even individuals. Although useful educational and reference tools, these platforms nonetheless have downsides. For instance, they are usually limited to findings from specific sub-fields of pathology, or from specific diagnoses, or even specific regions. As such, they don't fully reflect the diversity of either the potential content, or of pathology itself. In many cases, they are often driven by a particular person or group within the organization – meaning that, if the budget (or the enthusiasm) for the project is not maintained, the database also won't be. Even commercially developed solutions, which sidestep these difficulties, have issues: they often require a fee for access, and usually focus heavily on WSI at the cost of other material. As a result, many pathologists and laboratories are either unable to access the content, or fail to find material that meets their needs.

Of course, no man is an island – and that is especially true of image database developers. No one pathologist can be expected to assemble a broadly useful collection of pathology images alone; he or she must involve colleagues, convincing them to undertake the same level of effort and dedication to providing images and growing the database. And if one pathologist wishes to use an image-sharing platform to upload a case and request assistance from colleagues, then those pathologists must also have access to the platform – which may require an investment of money, effort, or both. Collaboration should be as easy as possible; the more barriers stand in its way, the less likely it is to take place – and most pathologists would rather find a different platform than risk a valuable consultation with a colleague.

To social media... and beyond

Some solutions are easier than others – and social media has proven a good starting point. Pathologists have discovered that social media platforms, in particular Facebook and Twitter Twitter (see Figure 1), are effective places to exchange and discuss images among themselves. Some even take matters



A user's path through a well-designed image-sharing platform – from browsing to contributing.

Twitter in Numbers

15,785
pathology tweets in the past *30 days*

45
pathology hashtags used in the past *30 days*

Top 10 influencers (by tweets):

@kriyer68 = 124
@rdga_md = 112
@humanpathology = 84
@phhs_careers = 73
@nglmr1000 = 72
@smlungpathguy = 69
@elazzouzim = 68
@yasarkantar = 66
@jmgardnermd = 51
@draldehyde = 48

Top 10 influencers (by mentions):

@jmgardnermd = 738
@kriyer68 = 441
@vijaypatho = 425
@geronimojrlapac = 368
@draldehyde = 339
@binxu16 = 328
@smlungpathguy = 312
@slusagar = 233
@konzult_ = 166
@pembeoltulu = 149

Figure 1. Pathologists have embraced Twitter as a means of connecting and collaborating – including image sharing.

one step further, working with patient groups in ways that benefit both sides. Interestingly, such collaboration tends to take place outside working hours; social media's accessibility and ease-of-use make it a simple, low-cost tool that pathologists can use at any time – all that's needed is the smartphone every person already carries.

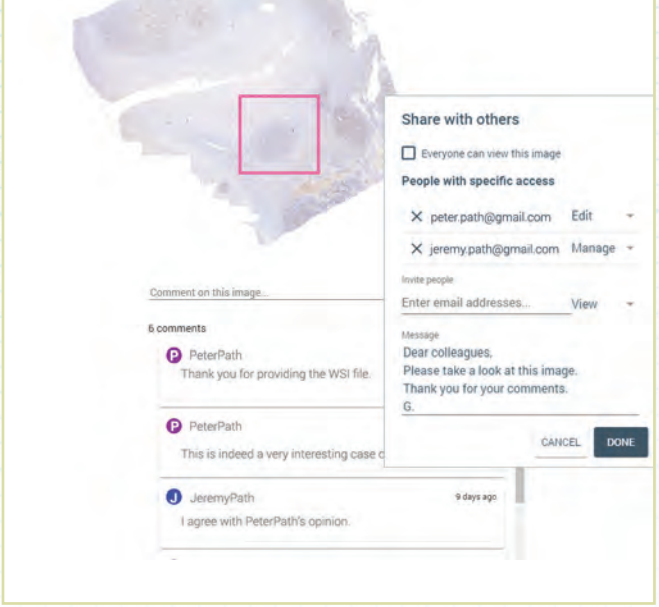
Social media makes an especially significant difference in regions of the world where pathologist expertise is wildly scattered and resources are limited. Laboratories without the money or equipment to safely transport patient samples can use digital images and their associated commentary to share the details of complex cases. Those that can't afford a dedicated specialist platform for image sharing can create a Facebook or Twitter account and gain access to thousands of experts with the ability to provide assistance. And those that can't afford expensive imaging equipment can post photographs taken with regular digital cameras, or even smartphones. Conversations can be as public or as private as desired, and hashtags and groups can help target questions to the patients and professionals most likely to be able to help.

But as convenient a solution as social media is, it still has limitations. When it comes to direct collaboration with colleagues, image sharing can still be complicated and cumbersome – because diagnostic second opinion consultations necessitate secure, private channels, and often require the sharing of whole-slide images (far too large and detailed for social media). To fulfill these professional needs, most pathologists use a suite of purpose-built software tools: scanning programs, image editors, annotation tools, cloud storage solutions and more. It stands to reason that they also need dedicated image-sharing platforms – services that can be used from any location or device and that combine affordability, security and easy collaboration. The wide range of laboratory setups available today should facilitate answers for patients – not present an obstacle to them.

Designing the ideal platform

What features does such an image-sharing platform need?

- *The ability to browse, search and share.* Pathologists should be able to look up images of particular conditions or features to use as educational references, or to compare with slides currently being used for diagnosis. They should also be able to upload their own images, whether as reference cases or to share with other professionals for informal assistance or a formal second opinion.
- *Ease of use.* All services should be accessible in one place, and from anywhere. For instance, a web portal that can be accessed via browser from a smartphone, tablet, laptop or desktop computer is ideal. Optional apps for smaller devices might enhance accessibility further. And as these types of tools are already familiar to most, the "intimidation factor" is significantly reduced, meaning staff are more confident and willing to engage with the technology.
- *Affordable and immediate.* Many labs cite startup costs as a major obstacle to digital pathology, whereas others have difficulty convincing IT and computing departments to assist with installation. A web portal that can be used without the need to install or integrate with existing technology removes those hurdles – and making it available low-cost or free of charge means there's no need to convince administrators or funders to provide a hefty budget.
- *The ability to serve as a hub.* All involved parties should be able to not only access the platform, but also participate in sharing, annotating, and discussing the images. Thoughtfully designing such a tool for group interaction means that it can be used effectively for education, expert exchange, research, and more.



So what can pathologists do to make the switch to digital images not only smooth, but useful? First, establish the parameters of your transition. What equipment do you have, or will you be acquiring? What hardware and software will you be using? What aspects of your workflow will become digitally based, and which – if any – will remain as they are? What resources are available to you?

No two laboratories have the same needs, so no two changeovers are the same – but regardless of how your own transition works, an image-sharing platform that is device-, location- and format-agnostic is a key part of making digital pathology a practical part of your daily work.

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A CASE STUDY IN DIGITAL NEPHROPATHOLOGY

By Helen Liapis

Nephropathologists are not new to the world of digital pathology. Digital electron microscopy images are used for routine primary diagnosis in many nephropathology laboratories around the world. Static ("store-and-forward") digital images are used in teaching and training, to share interesting cases over social media, and for numerous telepathology purposes, including quality assurance, conferencing, consultations and collaborative studies. Simultaneous remote access by multiple pathologists is currently the preferred method for collaboration in my specialty because of its ease, the speed of communication, and the complete absence of travel costs. Some hospitals with low case volumes have even implemented digital imaging for the interpretation of transplant renal biopsies, which means they no longer need to send out samples, or – even more costly – bring an expert in to examine the biopsies in person.

Whole-slide imaging (WSI), an extension of static images, allows for dynamic interpretation of the pathology on renal biopsies. One major benefit is that WSI is unbiased; whereas static images are subjective to the person taking the image, WSI allows for independent viewing and evaluation of all of the structures or findings on a given slide. Once scanned, whole-slide images can easily be stored, revisited or distributed – and, with the use of appropriate software, digitized images can even be used for morphometric analysis. WSI on scanned slides is increasingly used for clinical trials, allowing pathologists to review renal biopsies remotely. Even in-house biopsy review uses WSI; renal pathologists receive digital images from remote, affiliated hospitals to examine. User-friendly, web-based digital pathology consultation portals are excellent tools because of their ability to handle large image files, and because they bring together information from many different sources and present it in a user-friendly manner.

In short, innovations in digital pathology are transforming the pathology workplace from a strictly on-site, lab-based environment into one that can be accessed anytime, anywhere.

In the near future, I expect to see the digitization of renal biopsies in many more hospitals, universities and private laboratories. The advantages are many, and the cost relatively low in the long run. Of course, the necessary infrastructure is a significant expenditure – but the potential return on investment is great! Institutions can set up permanent libraries and databases for future use. Digital renal biopsy repositories will one day be used to standardize histopathological interpretations, scoring systems and protocols for material collection and data mining. Research will be performed from shared resources, yielding increased transparency, reproducibility and accuracy. Of course, there are still unanswered questions regarding the practical use of digital technologies in routine diagnosis – defining new standards, establishing reimbursement, licensing, credentialing, legal issues and more – but such questions are inevitable with any new way of working.

In nephropathology in particular, the use of diagnostic digital pathology is likely to increase. Why? Because of the complexity of renal biopsy interpretation, the acute shortage of expert renal pathologists worldwide, the high processing costs, and the demand for short turnaround times for final diagnoses. Nephropathology is a high-maintenance service that requires high volumes to be cost-effective. As technologies improve, scanning times decrease, and viewing becomes more efficient, digital nephropathology is likely to allow for lower operational costs and better use of expertise across countries and even continents. In my opinion, this is one of the biggest changes to occur in the practice of pathology in this century, and one that I expect to continue.

Helen Liapis earned her medical degree in Greece, was trained in pathology in the United States, and spent over 20 years as a faculty member at Washington University in Saint Louis, USA. The author of more than 140 peer reviewed scientific articles, books, and book chapters, she received the Renal Pathology Society's Jacob Churg Award in 2011 and Washington University's Distinguished Clinician Award in 2012. She was elected president of the Renal Pathology Society in 2014.

Digital Pathology: Behind the Scenes

You may well be familiar with the digital interfaces used in pathology, but how well do you know the supporting infrastructure?

By Mark Pastor

Digital pathology is a buzzword that conjures up high-end technology, striking computerized images, massive sequencing projects – the kinds of things one might see in a seemingly well-equipped laboratory in a TV show. But most viewers (and many pathologists) won't be thinking: where are all those detailed images being stored? How are those pathologists accessing all that sequencing data? In reality, every successful digital pathologist needs the support of an intelligent, high-performance infrastructure designed specifically for large, data-intensive workflows.

The search for storage

Sequencing is currently placing a particularly high demand on data storage; not only has the cost of sequencing dropped dramatically (especially for high-volume approaches), but it has also become faster than ever before, resulting in a huge increase

REMOTE RESOURCES

By Yasmine Lahoubi

Digital pathology has had a tremendous rise in the last few years, and has proven that it can be a viable alternative to working with conventional slides. Thus far, it has mostly been used in education, meetings and consultations – but now, with the first FDA-approved solution, we will see digital pathology's potential for primary diagnosis begin to unfold. Working digitally – sharing images and discussing them online – can be exceedingly helpful, especially in remote regions where young pathologists are often forced to work alone, with no experts in direct reach. It's a particularly significant issue in cytopathology, where pathologists frequently have access to limited tissue but must still conduct technically demanding examinations. Remote consultation allows young pathologists to discuss cases with experts, enabling them to confidently proceed with diagnosis, prognosis and treatment recommendations.

In many cases, though, smaller laboratories lack the sophisticated hardware (like virtual slide scanners) and software they need to truly take full advantage of telepathology. Pathologists working without those resources welcome any way of sharing and discussing images easily – especially if they can do so using just a standard web browser, or even via mobile phone (so that they can share snapshots taken directly with the phone's camera). For these pathologists – just as for those working with extensive resources – digital pathology is a huge advance that can only bring benefits.

Yasmine Lahoubi is a fourth-year pathology resident at Mustapha Bacha University Hospital, Algiers, Algeria, and a USCAP ambassador.

in sequencing operations and an ever-growing mountain of data.

The sequencing activities of the Swiss Institute of Bioinformatics (SIB) have massively increased over the last 20 years. Today, the organization handles about five separate projects each week, supporting approximately 300 active research teams across six different sequencing centers. With up to 43 terabytes of data generated each week, they have had to place storage at the heart of their infrastructure. With their current system, SIB researchers get high-speed access to sequencing and analysis data through multiple separate storage systems – nearly 1.5 PB of primary storage and 5 PB of economic tape archives, along with high-performance processing for genomics data. SIB's tiered approach keeps active data on primary storage for complex analysis and automatically moves it into the long-term archive as it ages. Over 600 users access the sequenced genomic data, either locally by tapping into the network in one of the SIB-affiliated data centers, or via a remote interface.

More recently, pathologists have begun seeking solutions to handle the data demands of high-resolution microscopy – a need that is likely to increase. For instance, earlier this year, researchers from the Massachusetts Institute of Technology developed technology to make extremely high-resolution images at a fraction of their former cost (1). As imaging technology becomes more capable and easier to use, pathologists will need higher storage capacity to handle their microscopy needs.

Things to think about

Instead of considering storage as individual silos, we need to take a broader view and accept it as a key part of the infrastructure that supports our operations. What is "infrastructure," from a data point of view? The term refers to a system that includes networking topology, computing resources, and storage. When we discuss storage, we have to consider attributes such as capacity, performance, cost, and connectivity, and the demands that any given laboratory places on those attributes. We must carefully think about current data needs, of course, but also future demand and how to manage data as simply and efficiently as possible.

One of the most common mistakes laboratories make when transitioning to a digital workflow is investing in a "closed" infrastructure that doesn't interface seamlessly with the lab's existing technologies (or those they may need to add in the future). To build storage infrastructure capable of handling a growing volume of scientific data, research institutions must find ways to blend different storage technologies: high-speed primary disks, object storage, tape archives, and the cloud. Many institutions begin by purchasing high-performance storage that meets the requirements of their initial, small-capacity environment, and are then forced to keep adding expensive storage as their needs increase. Eventually, those labs reach a point where costs are too high and backup isn't working well. And then what? Sometimes, their data is exposed because it lacks sufficient protection. Most of the time, they simply end up unable to expand their services because they can't afford the necessary storage space. The bottom line? Digital pathology is here to stay – and laboratory setups must be able to keep pace.

"To build storage infrastructure capable of handling a growing volume of scientific data, research institutions must find ways to blend different storage technologies."

Data storage is not the whole story. Once the initial storage space has been established, you still need to organize, manage and maintain your data. There are a number of tools available to help users manage files logically and efficiently – not according to assumptions made by non-medical professionals, but in ways that make sense for them and their workflows. Consider that – on average – 70 to 80 percent of stored data files are not in active use. Empowering users to decide which data can be archived to lower-cost media creates extra space on more expensive primary storage for information that pathologists need to keep at their fingertips. Such user-friendliness is key; instead of relying on the IT department to take actions like archiving, accessible software puts data organization and management into pathologists' own hands so that they can make decisions based on expert knowledge that they alone have.

To cloud or not to cloud?

Which is better – physical or virtual data storage? Ultimately, the answer comes down to the institution's overall storage strategy and the desired balance of capacity, performance, accessibility and cost. The elasticity and remote aspect of cloud storage are tremendous advantages for some applications, like short-term temporary workflows, but they aren't the best fit for every application. Cloud-based solutions are useful for "flexible demand," when storage needs increase suddenly or at an unpredictable rate; they're also good for situations where users need an off-site backup for their data to protect against potential disaster. The cloud also provides cost flexibility; most vendors offer a low price-per-gigabyte rate – but, typically, there are separate charges for activities such as data movement, file retrieval, deletion, and support, so contracts can be complicated, and costs can add up quickly. Cloud-based options can also create difficulties if you want to change vendors; data migration tools are usually provider-specific and can be tricky to use.

> "My best advice for laboratories considering a digital transition is to work out what resources they have available – and then carefully consider the needs of pathologists and laboratory professionals."

In comparison, on-site storage can grow with laboratories while keeping their data safe, secure and accessible. For ongoing, large-scale data storage, it's far more cost-effective than virtual storage, because there are no recurring fees – only a single, up-front investment. There's also the matter of moving your data; constantly porting it between your on-site system and the cloud can be time-consuming and carry with it high bandwidth and retrieval charges. But not all physical media are equal. Are you sure that flash drive is the best place to keep all of your most valuable images? Is that stack of 3.5" floppy disks in your desk drawer really what you want to use for your sequencing data? What exactly is object storage? With so many options, it can be difficult to choose the best – and most secure – storage solution for your needs.

My best advice for laboratories considering a digital transition is to work out what resources they have available – and then carefully consider the needs of the pathologists and laboratory professionals who will be using the system. They don't want to waste valuable time searching for data, or worry about whether or not they'll be able to store and protect the information they use. The key to successful digital pathology is to make data management as simple, secure and user-friendly as possible.

Mark Pastor is director of data intelligence solutions at Quantum. He is responsible for driving Quantum's data intelligence and storage solutions for high performance computing, AI, research and other large unstructured data environments, and also represents Quantum within the Active Archive Alliance and in the LTO Consortium.

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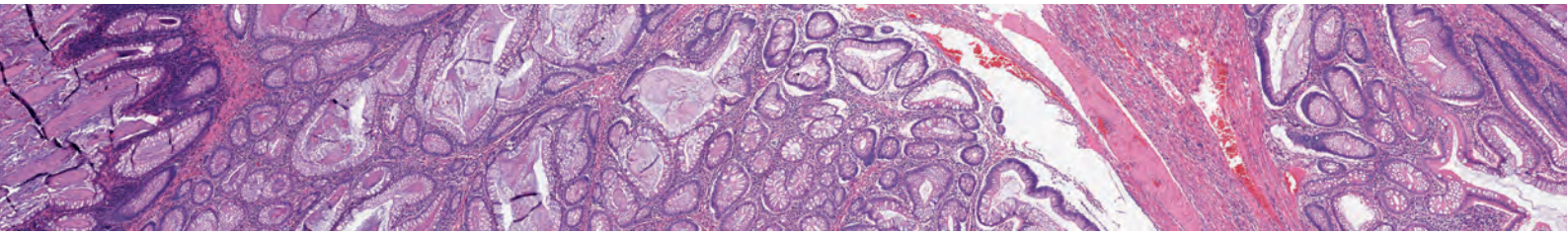
Global Engage

London, UK
30 November 2017
14:20 GMT

LIVE STREAM
THE BENEFITS OF COMPUTATIONAL PATHOLOGY



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Bad Grades for Gleason

A new grading system for prostate carcinoma – and how you can adopt it in your laboratory

By Jonathan Epstein

Prostate cancer is the fourth most common cancer in the world – and for men, the second most common cancer. And with incidence rates projected to rise significantly over the next decades, it's more important than ever to gain a full understanding of this highly variable disease. From vague symptoms to controversial tests (1), it can be difficult to conclusively evaluate a patient's risk even after diagnosis. Some forms of prostate cancer grow quickly, whereas others may remain indolent for years; some respond well to surgery alone, whereas others may need a range of additional therapies. So how can pathologists determine which prostate cancers present the highest risk – and which patients should be offered more aggressive treatment options? At the moment, the answer relies on classification tools like the Gleason score – but that system was first conceived over 50 years ago and is in desperate need of an update.

At a Glance

- *Prostate cancer is very common, but also highly variable*
- *Current grading systems are needlessly complex and can be difficult for patients to understand – leading to unwarranted anxiety*
- *A new grading system stratifies patients into five "Grade Groups" based on histological characteristics*
- *The new system has met with broad favor so far, including with the World Health Organization, and it can be used alongside existing Gleason scores*

A brief history of grading

Donald Gleason developed our current prostate cancer grading system between 1966 and 1974. Over the subsequent decades, the histological and clinical diagnosis of the disease – not to mention its treatment – has evolved. As a result, the first revisions of the original Gleason system were codified in 2005. But medical science moves quickly, and in November of 2014, 65 prostate cancer pathology experts and 17 clinicians (including urologists, radiation oncologists, and medical oncologists) from 19 different countries gathered in a consensus conference to further update the grading of prostate cancer.

Despite our attempts to keep pace with our growing understanding of the disease, both pathologists and clinicians agree that there are significant deficiencies with the Gleason scale. For instance, the grading system ranges from 2 to 10, yet 6 is the lowest score currently assigned. When patients are told that they have a Gleason score 6 out of 10, they hear that they have a more aggressive cancer and an intermediate prognosis – and, understandably, that frightens them. Every day, I talk to patients whose cases have been sent to me in consultation, and if they have a Gleason 6 cancer, I first say, "That's the best grade you can have," hoping to allay precisely that concern. Recently, I had a patient with newly diagnosed prostate cancer whose wife was battling a high-grade brain tumor. The husband was almost in tears because he had a Gleason 7 (3+4=7) cancer on biopsy, and he was convinced that meant he would not be around in the next few years to help take care of his wife. But despite a Gleason score of "7 out of 10" (which sounds advanced), Gleason score 3+4=7 cancers are relatively low-grade and virtually never result in death within even 10 years of diagnosis.

Also, both in the literature and for therapeutic purposes, various scores have been incorrectly grouped together with the assumption that they have a similar prognosis. For example, many classification systems consider Gleason 7 as a single score without distinguishing between 3+4 and 4+3, despite studies showing that the latter carries a significantly worse prognosis.

Grade Group	*Gleason Score*	*Definition*
1	3+3=6	Only individual, discrete, well-formed glands
2	3+4=7	Predominantly well-formed glands with lesser component of poorly- formed/fused/ cribriform glands
3	4+3=7	Predominantly poorly-formed/fused/ cribriform glands with lesser component of well-formed glands†
4	8	Only poorly formed/fused/cribriform glands, or Predominantly well-formed glands and lesser component lacking glands††, or Predominantly lacking glands and lesser component of well-formed glands††
5	9–10	Lack gland formation (or with necrosis), with or without poorly formed/fused/ cribriform glands†

† For cases with >95% poorly-formed/fused/cribriform glands or lack of glands on a core or at RP, the component of <5% well-formed glands is not factored into the grade.
†† Poorly-formed/fused/cribriform glands can be a more minor component.

Table 1: Histological definition of the new grading system for prostate cancer.

A simpler system

In 2013, my colleagues and I proposed the basis for a new grading system based on data from Johns Hopkins Hospital that suggested five prognostically distinct Grade Groups (2). The definition for the new grading system is based on the modified Gleason grading system and incorporates changes made in 2005 and 2014 (see Table 1). The new system was validated in a multi-institutional study of over 20,000 radical prostatectomy specimens, over 16,000 needle biopsy specimens, and over 5,000 biopsies followed by radiation therapy (3). The five-year biochemical recurrence-free progression probabilities for radical prostatectomy in Grade Groups 1 through 5 were 96, 88, 63, 48, and 26 percent, respectively. In the 2014 grading consensus meeting, there was broad (90 percent) agreement in favor of adopting this new system. Why? Four reasons:

1. The new classification provides more accurate stratification of tumors than the current system.
2. The classification simplifies the number of grading categories. Instead of Gleason scores 2 to 10, with even more permutations based on different pattern combinations, it proposes Grade Groups 1 to 5.
3. The lowest grade is 1 – not 6, as on the Gleason scale – with the potential to reduce overtreatment of indolent cancer.
4. The current modified Gleason grading, which forms the basis for the new grade groups, bears little resemblance to the original Gleason system.

The new grades would, for the foreseeable future, be used in conjunction with the Gleason system. Patients would receive both: "Gleason score 3+3=6 (Grade Group 1)." The new grading system and the terminology Grade Groups 1–5 have also been accepted by the World Health Organization for the 2016 edition of Pathology and Genetics: Tumours of the Urinary System and Male Genital Organs.

So what should pathologists and laboratory medicine professionals involved in prostate cancer diagnostics do? My recommendation is to familiarize yourselves with the new grading system and its histological definitions and – if possible – begin using it alongside your standard Gleason scoring. I hope to see widespread adoption of the new system in future, and I'm optimistic that it will assist with patient stratification, prevent over- and under-treatment, and, of course, improve outcomes for those diagnosed with the disease.

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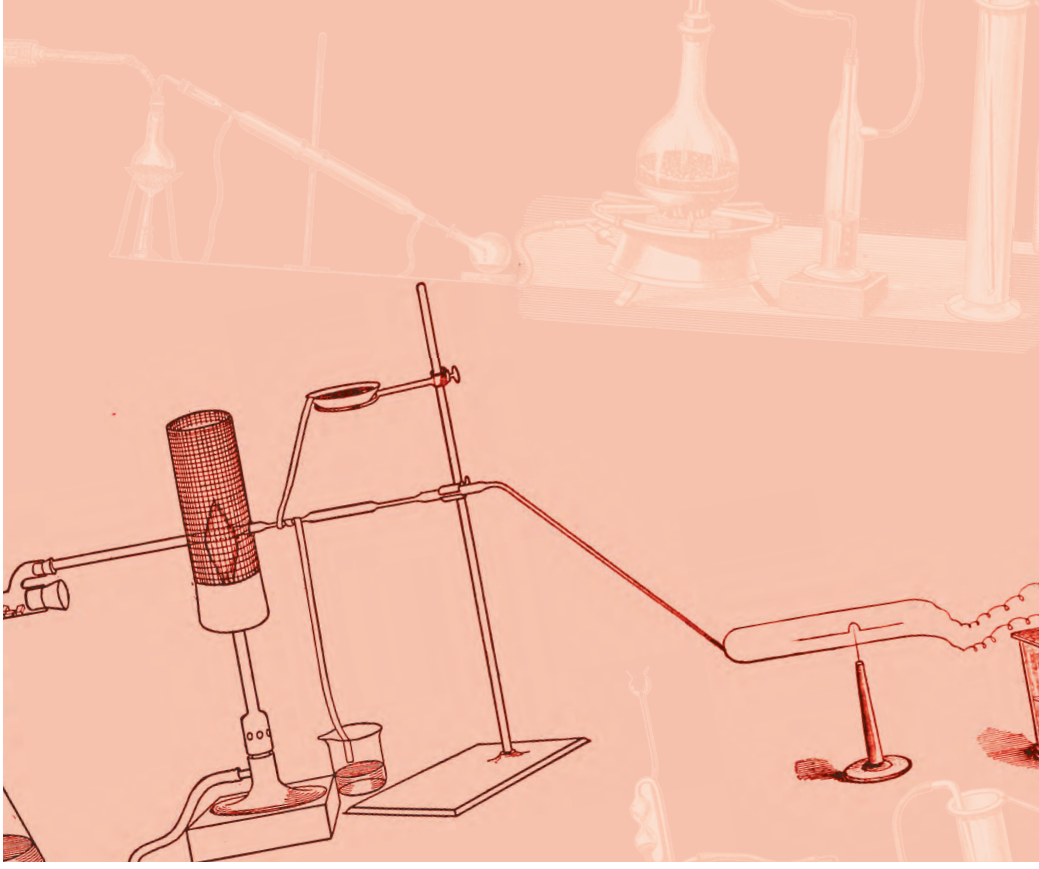


Testing, Testing Everywhere

The hazard of over-testing in hospitalized patients is very real – but how do we change ingrained habits?

Michael Schubert interviews Kevin Eaton

A patient lies in a hospital bed – pale, feverish, and obviously in pain. But with such nonspecific symptoms, how can the doctor possibly know what might be wrong? The answer, for many care providers, lies in laboratory tests – and the more, the better, in some cases. Who knows what might turn up in the patient's blood counts, metabolic panels, or renal function? Why risk not testing for something that might provide an answer, when it's so easy to tick every box on the requisition sheet?

Pathologists know that (at least when it comes to laboratory testing) more isn't always better. Unnecessary tests cost the laboratory time and resources. They cost the hospital money. And they carry a cost for the patient, too – anxiety, discomfort, and even more severe consequences, such as hospital-induced anemia arising from too many blood draws. Moreover, benefits are never guaranteed; increased testing may not actually reveal the issues affecting the patient, whereas it can result in unnecessary interventions or feed into a never-ending cycle of tests. So why do doctors continue to order tests their patients don't need?

We spoke to Kevin Eaton, lead author of a recent study (1) on over-utilization, to find out why recommendations against over-testing aren't working – and what interventions might result in greater success.

At a Glance

- *Lab test over-utilization is not only costly and confusing, it can also have a detrimental effect on patients*
- *Neither evidence-based recommendations nor educational intervention typically changes physicians' test-ordering patterns*
- *New guidelines suggest a combination of education, feedback and changes to clinical workflows and computer systems*
- *The combination approach has been shown to significantly reduce both the number of tests ordered and overall lab testing expenses*

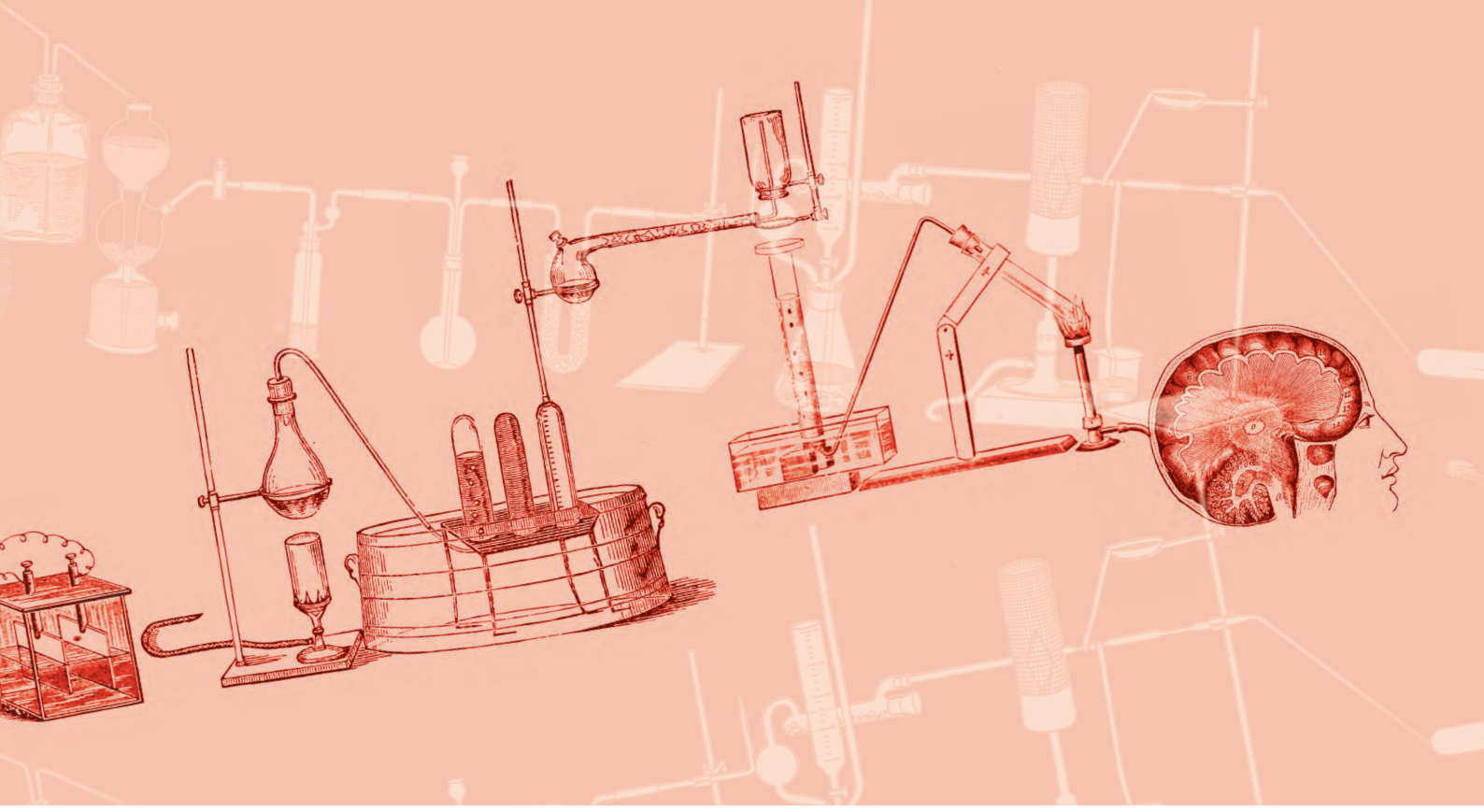
What are the dangers of excessive testing?

Several studies have shown that excessive lab testing can lead to hospital-acquired anemia (2–4), which in turn can lead to unnecessary blood transfusions and worse patient outcomes. Additionally, labs ordered without a high pre-test probability for a disease state are difficult to interpret and often lead to more unnecessary testing, which further contributes to rising costs and patient harm. It's a vicious cycle. And, of course, whether one test or a dozen too many, phlebotomy can be a painful experience for patients, so it can lead to patient dissatisfaction. In this era of patient-centered care, our first priority is the physical health of those entrusted to us – but we must also be aware of the psychological stressors of hospitalization, and that includes those that arise from medical testing.

Why do many care providers over-test despite recommendations to the contrary?

Many barriers to reducing excessive lab testing have been cited in the literature, including lack of knowledge of lab costs, provider inexperience, change in clinical status, fear of missing a diagnosis, or diagnostic uncertainty. Often, providers feel more comfortable with more information. In some cases, the practice is actually patient-driven; patients want to know if they have a particular problem, and they request or even pressure doctors to do the testing for them, even in situations where it may not be necessary.

Additionally, I think it is difficult for providers to acknowledge (or sometimes even care about) the downstream effects of excessive testing (such as more



"Ordering tests without a clinical reason makes the results difficult to interpret."

unnecessary tests, or hospital-acquired anemia). In daily practice, it's easy to lose track of the repeat CBC or whole blood hemoglobin ordered to follow up on a lab abnormality that turned out not to be a problem in the first place. More importantly, many providers – like me – can easily be influenced by anecdotal clinical encounters. It only takes one bad patient outcome, even one unrelated to a failure to test, to undo efforts to reduce repetitive lab orders. Also, providers may not even be aware of how many lab tests they are ordering in the first place. Busy clinical days leads to poor recall, and the sheer number of diagnostic lab tests ordered on different patients makes it difficult to have a "big picture" idea of one's ordering habits.

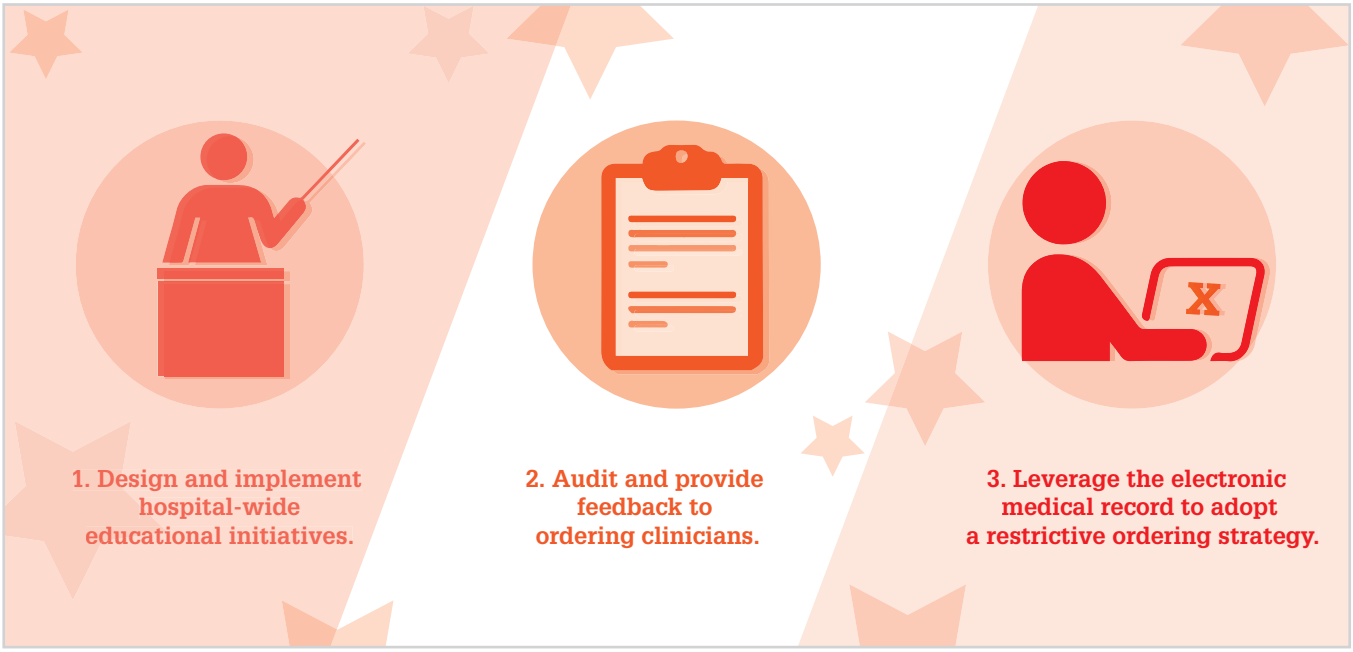
Because of these numerous barriers, many of which vary from provider to provider, strategies to reduce excessive testing can't rely solely on educational recommendations. As described in our implementation guide, there needs to be a multimodal strategy that includes educational initiatives, feedback for providers on their ordering patterns, and changes made to the electronic ordering systems that make it harder to order unnecessary tests.

What educational initiatives might encourage physicians to order fewer tests?

The key is to focus on educating providers about the appropriate indications for various laboratory tests. These recommendations can be decided by collaborating with various subspecialty experts to form a unified set of indications for various lab tests (perhaps starting with the most expensive and frequently misused). These, of course, vary between institutions but might include red blood cell folate testing, hepatitis C viral load and genotype, type and screens, or reflexive lupus antibody testing without a positive antinuclear antibody.

It's also important to educate providers on the downstream effects of unnecessary testing. Ordering lab tests without a clinical reason makes the results difficult to interpret. If there is an abnormal value, additional unnecessary testing is often ordered – only to find out, ultimately, that there wasn't even a problem in the first place. These "cascade" effects contribute to wasted value, patient dissatisfaction, and possibly unintended complications.

Finally, providers must be given personalized information on their own lab ordering practices. Many studies have shown that peer comparisons of lab orders helps to reduce excessive testing. Often, providers may not be aware of the extent of their ordering. Having the numbers in front of them can lead to an epiphany – and if that alone is not enough, comparing their ordering patterns with those of their more conservative peers could prompt them to reconsider their practices!



And how would you recommend reprogramming computer systems?

The approach to computer system adjustments needs to acknowledge that there are, in my opinion, two main categories of lab tests for hospitalized patients. The first are tests ordered to help make the diagnosis of a specific disease state (for instance, thyroid studies, antinuclear antibody, hepatitis antibodies, and more). The second category includes tests ordered to check and monitor a patient's health – such as blood cell counts, kidney function (basic metabolic panel), or liver function (hepatic panel).

To target the first category, electronic ordering systems can be programmed in a way that educates users on the appropriate indications for specific tests. These can be done in the form of non-intrusive computer alerts, which have been shown to have varying degrees of efficacy (5,6); it is true that some physicians may ignore them altogether, but others may take note of a pop-up that provides a list of recommended reasons for ordering a particular test. Potentially more impactful, though, would be to have testing algorithms that simplify decision-making by streamlining the appropriate indications for certain tests. For example, rather than having a provider order both a thyroid stimulating hormone (TSH) and a free T4 test, the provider can select a TSH algorithm reflex. The lab would then only reflexively send the free T4 order if the TSH result were abnormal.

To target the second type of labs (as discussed in our new guidelines), the electronic medical record-based strategies we've found most effective are those that simply don't allow providers to order repeating labs. A major contributing factor to over-testing is that labs like CBCs and BMPs are ordered to repeat daily on patients admitted to the hospital – but patients don't necessarily need these tests every single day of their hospitalization. Programming computer systems to eliminate the "repeating" lab option (or at least to limit the total number of repeats allowed to a maximum of *x* days) has been shown to reduce repetitive testing without preventing doctors ordering the tests that are truly needed.

How can pathologists tackle the main testing culprits?

The most common labs (CBC, BMP, CMP, and so on) are the ones often ordered as daily repeating labs for hospitalized patients – but they have the potential for significant downsides if the patient has been clinically stable. In the setting of clinical stability, abnormalities on these lab tests are difficult to interpret and often prompt additional testing, which can lead to excessive phlebotomy and hospital-acquired anemia. Anecdotally, I also feel as though rheumatologic tests (such as ANA, dsDNA, or anti-Smith antibody) are also frequently ordered inappropriately and can lead to further unjustified testing on patients. Both pathologists and primary care providers should pay attention to ordering patterns for these kinds of labs – and speak up when excessive testing carries the potential for harm. Be aware, though, that your mileage may vary. Over-utilized lab tests often differ between institutions depending on patient population and providers' preferences.

The "Choosing Wisely" campaign has made phenomenal progress in encouraging

the conversation about overutilization. These recommendations come from experts in different professional societies and lay the groundwork for institutions to advocate for improvement. Our implementation guidelines expand on the "Choosing Wisely" recommendations (7) to prevent lab test overutilization and help provide institutions with evidence-based strategies to implement initiatives for reducing repetitive laboratory testing in their own hospital systems.

What else can pathologists do? They can collaborate with other subspecialty experts to determine standard indications for different lab tests – perhaps starting by targeting the tests that are most expensive, or most often misused. They can educate providers on appropriate indications for different lab tests to help avoid unnecessary testing. They can even help develop safe testing algorithms – for instance, to build lab test orders that reflex to additional tests if (and only if) the first result is abnormal. These initiatives can potentially save a lot of tests from being ordered in the first place, improving the overall health and happiness of our hospitalized patients.

Kevin Eaton is a third-year internal medicine resident in Longcope Firm at Johns Hopkins Hospital, Baltimore, USA.

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A Renal Failure

Current acute kidney injury (AKI) tests are not sufficiently rapid and can even be misleading. Can two new biomarker assays offer a superior alternative?

By Marlies Ostermann

Acute kidney injury (AKI), formerly known as acute renal failure, is the term used to describe an acute deterioration of renal function that has been present for less than three months. It affects 10–15 percent of patients in hospital and up to 60 percent of patients in intensive care. Patients with pre-existing chronic kidney disease, heart failure and liver disease are particularly at risk. AKI has multiple etiologies but the most common causes are sepsis, hypovolemia and drug nephrotoxicity. The grades of severity range from early-stage AKI to complete loss of kidney function where renal replacement therapy is needed (see Figure 1). As a consultant in nephrology and critical care medicine, I take care of patients with AKI on a daily basis.

At a Glance

- *Acute kidney injury (AKI) affects over 10 percent of all patients in hospital, and more than half of the patient population in intensive care – but many cases are potentially preventable*
- *Current tests are limited in their ability to quickly and accurately diagnose AKI, which means that AKI can progress to more severe disease before it is recognized*
- *New biomarker assays, including cell cycle arrest markers, have potential to improve the diagnosis and management of AKI*
- *Earlier recognition of AKI could result in improved patient outcomes, reduced costs, and more personalized healthcare*

Adding injury to insult

AKI can be challenging to spot – patients may present with no obvious signs or symptoms – but given that many episodes of AKI are preventable, it's important to identify those people at risk and put measures in place to avoid drugs and procedures that harm kidney function.

In the UK, the National Institute for Health and Care Excellence (NICE) recommends assessing the risk of AKI in all patients before surgery or any other procedure that may cause AKI (for example, exposure to contrast agents). Following a potentially nephrotoxic insult, it is essential to check whether early AKI has occurred and to implement appropriate interventions to prevent further deterioration of renal function, if necessary.

Traditional tests to assess patients for risk of AKI include the measurement of serum creatinine and urine output. However, these tests are not kidney-specific and have serious shortcomings. The role of creatinine as a marker of renal function is limited by the fact that its half-life increases from four hours to 24–72 hours if glomerular filtration rate (GFR) decreases. As such, the serum concentration may take 24–36 hours to rise after a definite renal insult. Also, over 50 percent of renal function needs to be lost before serum creatinine levels rise.

Creatinine generation depends on liver and muscle function and, as a result, a true fall in GFR may not be adequately reflected by serum creatinine in patients with sepsis, liver disease or muscle wasting. Serum creatinine concentration is also affected by variations in volume status, which means that the diagnosis of AKI may be delayed or missed in patients with significant fluid overload. In addition, there is no standardized laboratory method for quantifying serum creatinine. Substances like bilirubin or drugs may interfere with certain analytical techniques, more commonly with Jaffe-based assays.

Finally, an important limitation of all creatinine-based definitions of AKI is that they require a reference value to describe "baseline" renal function. Ideally, this value should reflect the patient's steady-state kidney function before the episode of AKI. However, information on pre-hospital kidney function is not always available. Various surrogate estimates are frequently used, but there is no shared approach of determining baseline renal function.

Urine output is another important clinical marker but, like creatinine, it is not kidney-specific. In fact, urine output may persist until renal function almost ceases. Similarly, oliguria may be an appropriate physiological response of functioning kidneys during periods of prolonged fasting, hypovolemia or following stress or pain. These limitations and shortcomings can easily lead to both a delay in diagnosis of AKI, and also erroneous diagnosis of AKI, depending on the patient.

The need for a new approach

Patients with AKI have a high risk of short- and long-term complications, including mortality – especially in severe cases. The length of the stay in hospital is often prolonged, which contributes to a significant increase in healthcare costs. In 2014, the annual cost of AKI related to inpatient care alone in England was estimated at £1.02 billion, just over 1 percent of the National Health Service budget. The additional lifetime cost of post-discharge care for people who had AKI during hospital admission in 2010-11 was estimated at £179 million (1).

There is increasing recognition by patient groups, health care providers and administrators that AKI is also associated with long-term complications after discharge from hospital. Survivors have a

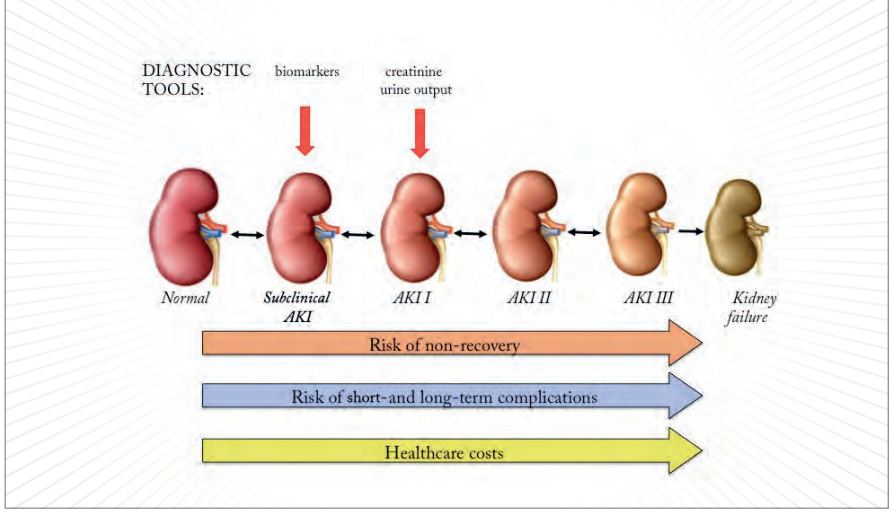

Figure 1. The role of biomarkers in AKI management.

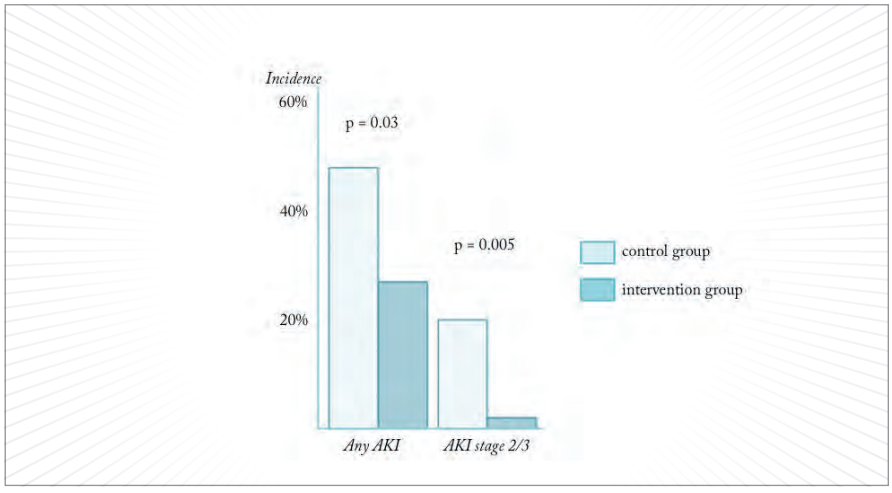

Figure 2. Biomarker-guided reduction of AKI after major surgery; adapted from (5).

higher risk of developing chronic kidney disease (including dialysis-dependent renal failure), cardiovascular morbidity (including myocardial infarctions and strokes), a higher risk of fractures, and are more susceptible to infections. They also often need prolonged and recurrent hospitalizations. The risk of developing both short- and long-term complications increases with AKI severity (see Figure 1).

An arresting discovery

In addition to my clinical role, I spend a lot of time teaching and training colleagues, including medical students, doctors and nursing staff. I lead an AKI improvement group that aims to improve the diagnosis and management of AKI across all specialties through the introduction of AKI champions and the implementation of AKI care bundles.

In the pursuit of new biomarkers for AKI, I was the principal investigator of the Sapphire study that validated the role of two cell cycle arrest markers in critically ill patients – urine insulin-like growth factor-binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases-2 (TIMP-2) (2). The study showed that urinary TIMP-2 and IGFBP7 predicted the development of stage 2–3 AKI within 12 hours and before a detectable rise in serum creatinine. In combination, the two markers performed much better than other biomarker tests. The availability of these new markers has allowed the identification of patients with evidence of kidney injury before a significant change in serum creatinine occurs – "subclinical AKI."

During critical illness in particular, patients are exposed to a large number of insults that are potentially harmful to renal function, often simultaneously or in succession. Recently, we showed that urinary cell cycle arrest markers exhibited a characteristic rise and fall in patients who were exposed to a potentially nephrotoxic drug and subsequently developed moderate to severe AKI (3). In patients who did not develop AKI, there was no significant biomarker rise. Importantly, during the early hours after an exposure to a renal insult, when urinary cell cycle arrest markers increased, serum creatinine levels did not change. These results are particularly relevant to clinicians and pharmacists who are often on the front lines when it comes to AKI and have the greatest need for information concerning the interpretation of these biomarkers.

Tests that allow earlier diagnosis of AKI provide an opportunity to intervene earlier and have great potential to improve the short and long-term prognosis (see Figure 1). Prevention of severe AKI is associated with a shorter stay in hospital, a reduced risk of needing renal replacement therapy or treatment in the intensive care unit, and a decreased risk of developing chronic kidney disease, including end-stage renal failure. Prevention of severe AKI also reduces the number of nephrology consults and avoids the need for investigations that are typically ordered for patients with AKI, including scans and renal biopsies.

Moreover, adequate identification of patients who are at risk of or have developed subclinical AKI presents an opportunity to prevent the injury and its sequelae by influencing decision-making and clinical management. For instance, we can avoid antibiotics and other potentially nephrotoxic exposures, including contrast administration, if we know that a patient has a particularly high risk of AKI. It may also determine where the patient will be managed in hospital; for instance, a high-dependency unit rather than a general ward.

Improving and preventing disease

Ivan Göcze and Alexander Zarbock have clearly demonstrated that biomarker-based identification of high-risk patients and early implementation of an AKI care

Defining Neonatal AKI

Diagnosing acute kidney injury (AKI) is often a challenge in adult patients – but what extra problems does it pose in premature and term newborns? Here, Patricio Ray, a nephrologist with the Children's National Health System and the George Washington University School of Medicine, USA, shares his efforts towards a more standardized approach to kidney injury in infants.

What's wrong with the current definition of neonatal AKI?

Current definitions are not sensitive enough to identify newborns undergoing the early stages of AKI during the first week of life. For example, different studies estimating the percentage of infants in neonatal intensive care units (NICU) with AKI range from 8 percent to 40 percent, depending on which definition is used.

Why is diagnosing AKI in infants such a challenge?

AKI is diagnosed based on the identification of an acute decline in the glomerular filtration rate (GFR), which is estimated indirectly in clinical practice by assessing changes in serum creatinine (SCr) levels. Creatinine is a protein that is produced by the muscle and is filtered by the kidney. Other methods to estimate the GFR of newborns are difficult to implement in clinical practice. Most neonatal AKI studies prior to 2005 used an arbitrary definition of AKI, including a SCr value ≥ 1.5 mg/dL. In 2012, a new definition of neonatal AKI was implemented based on the Kidney Disease Improving Global Outcomes (KDIGO) definition. These guidelines defined the early stages of AKI (stage 1) based on the rise in the SCr values (≥ 0.3 mg/dL within a 48 hour period), and a decreased urine output (< 0.5 mL/kg/hr for six to 12 hours). These definitions, however, fall short because the SCr levels during the first days of life reflect the maternal SCr values, and the urine output is less reliable in newborns. Therefore, these definitions are not sensitive enough to identify the early stages of AKI during the first week of life. In 2013, the National Institute of Diabetes and Digestive and Kidney Diseases, part of the National Institutes of Health, recognized the limitations of the standard AKI definitions and convened a meeting of neonatologists and nephrologists to discuss this issue.

Could you describe your new approach to diagnosing AKI in neonates?

Our research is focused on developing new biomarkers to identify the early stages of AKI in critically ill neonates during their first days of life. This is a critical period of life in which the kidney is maturing and all nephrotoxic stimuli should be minimized. Our new approach consists of following the rate of SCr decline, rather than waiting for the SCr levels to rise to > 0.3 mg/dL within 48 hours. Our approach is based on the following observations:

- The first-day SCr levels reflect the maternal SCr values and can't be used to estimate the GFR of newborns
- A newborn kidney that is functioning properly should "clear" the residual SCr levels transferred from the mother through the placenta in a timely manner
- By looking at how quickly neonates clear their first day SCr levels, we could predict how well their kidneys are working

A term newborn born with a first day SCr level ≥ 0.8 mg/dL who is at high risk of developing AKI or needs nephrotoxic antibiotics to treat or prevent an infection is an ideal candidate for our test. We are currently assessing the normal rate of SCr decline for preterm infants, in particular those under 34 weeks of gestational age. The SCr decline is not useful once the neonates reach their normal SCr levels during the first week of life, or in very low birth weight infants under 30 weeks of gestational age, in whom the SCr levels do not decline significantly during their first week of life.

What still needs to be done to fully validate this test and bring it into clinical use?

Laboratories should develop their own normal SCr decline curves, taking into consideration the methods used to measure the SCr, gestational age, and the standard error of these measurements. As well as AKI, the test is able to identify all neonates with impaired renal function, acute or chronic, during the first week of life. The test could potentially be used in all NICUs supported by laboratories that measure SCr levels in a reliable manner to identify and manage term and near-term infants with impaired renal function – and could potentially improve clinical outcomes.

bundle can prevent the development of AKI and reduce AKI severity in patients after surgery (4,5) (see Figure 2). Göcze also reported a reduced length of stay in hospital with associated cost savings (5). The results are impressive, and good news for patients and healthcare providers.

In short, delays in recognizing AKI are associated with increased risks for the patient, and increased costs for the healthcare provider. Amid the increasing need for personalized medicine in which care is directly influenced by the risk profile and phenotype of the individual patient, improved testing for AKI represents a real opportunity to better tailor treatment.

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An AKI Alert

Computerized clinical decision support steps in to help prevent AKI

By John Kellum

The problem

AKI is a serious and surprisingly common issue among hospitalized patients. The kidney filters toxins out of the blood, so infections, trauma, and major surgery – all of which release toxins into the bloodstream – run a high risk of damaging the kidneys. Not all potentially harmful toxins come from adverse events; the radiocontrast agents and drugs doctors use to help heal their patients also contribute to this injury. And, of course, age and chronic diseases (including kidney disease) are significant risk factors for acute kidney injury, and hospitalized patients are getting older and sicker.

Our solution

It was out of a desire to help those patients at risk of AKI that my colleagues and I developed a new decision support tool (1) – a relatively straightforward program that is built directly into the inpatient electronic medical record (eMR) system we use. The program finds all the previous serum creatinine values in a patient's record and analyzes them to establish a baseline. Then, it monitors subsequent creatinine results for any change and alerts clinicians to "possible AKI." It also offers additional support; if a physician clicks on the "possible AKI" alert, they receive information on the reference creatinine level, the stage of disease, and a prompt for further consultation (including the pager numbers of the relevant departments, such as renal medicine or intensive care).

We tested our new tool in over half a million patients – and those with AKI did very well. The mortality rate decreased significantly, from 10.2 to 9.4 percent, and the length of the average hospital stay went from 9.3 to 9.0 days (also a significant change). And despite an increase in diagnosed cases of both AKI and chronic kidney disease, dialysis rates for AKI decreased from 6.7 to 4.0 percent. We also observed less need for nephrology and critical care consults. Overall, not only were patients in better health, but they also required fewer hospital resources for successful recovery.

Could other hospitals do the same? Yes – and without difficulty. Once we had established the program, it was easy to implement across our system because we have a single eMR throughout. We are, of course, still constantly refining it, so I expect it will evolve over time. My colleagues and I see it as a platform to which we can always add extra features in line with new ideas and recommendations. It's not set in stone, and it's not exclusive to our hospital – like any change, it merely calls for the will and persistence of those involved in pursuing change.

John Kellum is Director of the Center for Critical Care Nephrology, CRISMA Center, and of the Center for Assistance in Research using eRecord, as well as Professor and Vice Chair for Research in the Department of Critical Care Medicine at the University of Pittsburgh, USA.

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HUMANITY IN SCIENCE AWARD

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Meet the Winner

Richard Jähnke

Richard Jähnke from the Global Pharma Health Fund (GPHF) has received the 2017 Humanity in Science Award for "development and continuous improvement of GPHF Minilab™ (www.gphf.org), which represents a breakthrough for the rapid and inexpensive identification of substandard and falsified medicines in low- and middle income countries in Africa, Asia and Latin America".

Richard received his award at a special jubilee reception in Berlin, Germany on October 2, 2017 hosted by KNAUER to celebrate the company's 55th birthday this year. Richard's work will feature in an upcoming issue of The Analytical Scientist.

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Tiny Patients, Huge Difference

Pediatric pathologists carry great responsibility – not only for their patients, but also for those surrounding them

By Marta Cohen

Pathology is in high demand. Many laboratory medicine specialists are heading for retirement and few new recruits are entering the field, so numbers are dropping. Not all subspecialties are equally troubled, but I know pediatric pathology is suffering from a dearth of new members each year, for which there are several possible reasons. Many pathologists don't realize it's a separate field at all, and those who do often don't see the appeal. Why choose a subspecialty where the patients are so different to the adults you trained upon, and where you must regularly face tough subjects, such as chronic disease and death investigations in children? But the reality is that pediatric pathology is a vital part of our work; nowhere in the Hippocratic Oath is it written that our healing art is for adults only. So what does the job of a pediatric pathologist really involve – and how can we draw others to the field?

At a Glance

- *Pediatric pathologists are overworked and in clear demand, but few new trainees choose to enter the field*
- *One vital aspect of our work is death investigation – we not only provide families with answers, but also provide key information in legal proceedings*
- *Unfortunately, clashes between the absolutes of the law and the uncertainties of science can make our jobs difficult*
- *To encourage more young pathologists to consider pediatrics, we need better pathology education, integration and networking*

Pediatrics in peril

My department at Sheffield Children's Hospital services 2.5 million people. There are fewer than 50 pediatric pathologists in the entire UK, and many of those work only part-time. When I joined the department in 2003, we only conducted 20 coroners' post-mortems a year. Now, because our team is so highly qualified and has so much experience, we have a much wider catchment area that yields about 90 post-mortem pediatric coronial examinations per year, covering East and West Yorkshire, Humberside, North Lincolnshire, Nottinghamshire and Derbyshire. In the last decade, we have done at least 950 pediatric coroners' post-mortems – in addition to all of our other post-mortem examinations. I have a very talented team, but even so, we can't keep increasing our workload indefinitely. We need more pediatric pathologists.

We must put pathology back into medical school – something I feel very strongly about, which is why a significant part of my professional life involves teaching and training. We need to promote pathology; we need to educate our colleagues; we need to network; but most of all, we need pathology to become a significant part of modern medical school curricula. Medical students are not exposed to enough pathology in general, meaning that pediatric pathology is hit especially hard. As in many areas of medicine, children are often treated as "small adults," with guidelines for their care being no different to those developed for adults – but this is absolutely wrong, and can even compound existing problems. Pediatric pathology is a niche discipline, and an expensive one, but it's clearly vital and deserves far more attention in medical education and specialty training.

> *"Nowhere in the Hippocratic Oath is it written that our healing art is for adults only."*

The European Society of Pathology (ESP) has a number of working groups, including several that deal with children's health issues. In a recent and very successful approach, the ESP has made a commitment to having its working groups organize meetings jointly. For example, we have recently addressed pediatric soft tissue tumors with the overall soft tissue working group, and focused on interstitial lung disease in children with the lung working group. Because of my interest in post-mortem microbiology, we recently signed an agreement between the ESP and the European Society of Clinical Microbiology and Infectious Diseases; going forward, we'll work together to tackle issues that affect both organizations.

Every aspect of pathology is reflected in pediatrics, so it's truly a "Renaissance subspecialty," and that puts us in a great position to share our expertise. By networking and interacting with special interest groups, we become more visible – and visibility, I hope, will make other medical professionals aware of what we do, and perhaps even attract new pathologists to work in pediatric care.

Sharing expertise

I specialize in pediatric death investigation, and whenever I'm asked to present on issues like bereavement or consent to post-mortem examination, I immediately agree. I help younger pathologists learn to conduct post-mortem investigations

in children, how to sensitively obtain consent from families, the vagaries of the Human Tissue Act, and so on. My colleagues and I also train police family liaison officers – the people assigned to work closely with families after sudden infant death. It's important for them to understand what we do – and vice versa, of course – so that we can work as a team to deliver better service. In addition, we offer general training for our users; for instance, we conduct a biennial study day to update obstetricians, pediatricians, nurses and midwives on our own services, paperwork, and general consent issues.

We are also very lucky to be able to offer a unique post-mortem MRI service at Sheffield Children's Hospital. We have two special researchers: Elspeth Whitby, who obtained her doctorate in fetal magnetic resonance imaging (MRI), and Amaka Offiah, who is a leading radiologist in skeletal dysplasia. In 2012, the three of us sat down and developed a business case for something completely innovative – the clinical provision of post-mortem MRI. We disseminated our clinical innovation project among obstetricians and started working with radiology to offer it as an option to parents who don't want a traditional post-mortem examination. Some aren't comfortable with the invasive nature of autopsy; some have cultural or religious reasons for declining it; some simply prefer the aesthetics of our procedure. It became a popular enough service that we later incorporated another keen pediatric radiologist, Ashok Raghavan. In 2015, we received the British Institute of Radiology/Bayer's Make it Better Award for "best improvement in an aspect of service delivery," and specifically for improving the patient experience – making the pathway less invasive, reducing delays, and improving the patient environment. Our method may not be the gold standard for pediatric post-mortem examination, but with our pathologic and radiologic findings combined, we can identify a relevant condition at death in at least 86 percent of cases. The traditional post-mortem has remained unchanged for a century, but pathology itself is changing – staff shortages, new technologies, cultural shifts – and our death investigations need to keep pace.

The perfect pediatric post-mortem

I have always had an interest in forensic pathology but, during my training, I learned that many countries have no regulations regarding the investigation of sudden infant death. I think it's important to look into the circumstances of unexplained deaths – after all, that's how we gain the understanding that

helps us to prevent future occurrences – so I began researching the topic. That's what I was doing in 2003 when I moved to Sheffield to fill a vacancy in pediatric pathology. It was a fateful move; within the next year, the Human Tissue Act was established, Baroness Heather Kennedy launched her report on the investigation of sudden unexpected death in infancy, and I was made head of my department. (The latter is significant because it meant that I was responsible for putting standard death investigation protocols into place – and then helping other hospitals do the same thing.)

Since those protocols were established, we've learned a great deal about sudden infant death. Two colleagues and I are currently presenting our findings on babies who have died of SIDS and demonstrate abnormal fatty oxidation in fibroblast culture. We believe this is due to as-yet unknown mitochondrial abnormalities on the respiratory chain; there are so many genes and enzymes in the mitochondria that we have barely scratched the surface. We are also identifying abnormalities in the hippocampus that have been linked to what we previously believed were harmless febrile convulsions – but we now know that babies with these convulsions have a higher risk of sudden death. That has led to much more thorough examination of the hippocampus during post-mortems. And we are collaborating with Daniel Rubens and Jan Marino Ramirez of the Brain Research Institute in Seattle to investigate the potential role of abnormalities of the inner ear and vestibular nuclei in cases of sudden infant death. There are so many things like this – brainstem abnormalities, unusual metabolic symptoms, subtle microbiological and toxicological findings – that have always been there, but we didn't know to look for them until recently. The 21st-century post-mortem will not necessarily have to include a full autopsy: blood and skin samples (for molecular genetics and metabolic investigations), a full-body MRI, and a thorough clinical history to identify risk factors for SIDS would help solve about two-thirds of the currently unexplained deaths in children.

"It's vital for us to step outside of our own area of expertise and explore the interface of different, but allied, disciplines."

What is the ideal post-mortem after an unexpected death in infancy? That remains to be determined. In the UK, at least, I expect that the Royal College of Pathologists will take a leading role in setting the standard. I'm currently involved with a team from NHS England focused on the commissioning of perinatal post-mortem services – although post-mortem MRI will not yet be included – but I think we need to learn what other departments

are doing and help disseminate that knowledge. After all, even the most brilliant innovation will have trouble gaining traction if only one group tries it!

It's also vital for us to step outside of our own area of expertise and explore the interface of different, but allied, disciplines, so that we can communicate with our colleagues in other departments. For instance, I work closely with the radiologists, metabolic team and geneticists at my hospital. We are part of the same diagnostic division, so we're able to have frequent meetings with them to figure out how to do the best possible job. What can we improve? How can we help them with their tasks? How can they help us with ours? They have the know-how and we have the cases, so we need to work together to define the perfect post-mortem.

The challenge of the courts

I first heard the term "shaken baby syndrome" in 2004. I didn't have a clue what it meant, because I had just moved to the UK from Argentina – and we don't have shaken babies in Argentina; it is very much a diagnosis driven, originally, by some forensic pathologists in North America and the UK who considered that the triad of subdural hemorrhage, retinal hemorrhages and encephalopathy – in the absence of fractures, bruises or any other evidence of trauma – is prima facie diagnostic of child abuse. This approach has not really taken off elsewhere. My new colleagues explained to me that the symptom triad was due to ruptured bridging veins in the brain, although others suggested that it could also be due to bleeding in the dura mater. As I had never seen it under the microscope, sampling of the dura mater became part of my post-mortem protocol, so that I could understand what they were describing. Eventually, I found a pattern of bleeding in younger babies who had been resuscitated and had experienced a period of hypoxia and raised intracranial pressure. I also found that some babies bled more than others, or seemed more vulnerable to that type of injury. We don't always know why, but that's part of the reason we conduct these investigations; the more we can learn about biological differences, the better we will be able to help others in the future.

"The more we can learn about biological differences, the better we will be able to help others in the future."

This concept of not being all-knowing is also important when, like me, your findings have to go beyond the walls of the hospital. As a pediatric pathologist heavily involved in death investigation, I am sometimes asked to go before family courts or the Crown Court in very challenging cases. Unfortunately, the nature of the courts is that everything has to be black and white; everything has to be true "beyond a reasonable doubt" or "on the balance of probability." But science consists of uncertainty! In this matter, at least, science and the law are on different tracks. And that's a problem – because when scientists don't feel comfortable interacting with the law, they decline to do so, which leads to a lack of experts in the complex medico-legal system. It's why I have withdrawn to some degree. The court system requires you to answer in absolutes – yes or no; black or white – and that, to me, is impossible in some cases.

Ten years ago, there was an investigation into pediatric forensic pathology in Ontario, Canada – the Goudge inquiry. To summarize, there was one pediatric pathologist, Charles Smith, who handled all of the forensic cases. Essentially, his word was law. But a problem arises when the courts are limited to just one or a few experts: if those few are wrong, innocent people can be imprisoned. In Smith's case, the issue is described in the report (1) as "a cautionary tale of the devastating impact that flawed forensic pathology and irresponsible expert testimony can have." After the review, innocent people who had been blamed for the deaths of children were released from prison – but, by then, the damage done to their lives and reputations was, in some cases, irreparable.

It goes without saying that no doctor or scientist should ever minimize the responsibility they are given when called before the court – but, at the same time, it is difficult to marry that responsibility with an uncertain diagnosis, or a symptom that has many possible causes. I know that I cannot change the system, so I choose to play my part through research instead of by being an expert witness. One day, I hope that my work will inform the law – and I will have helped without compromising my own ideals.

Whether your interest lies in the laboratory or the law, pediatric pathology is a varied discipline with a place for everyone. It's my hope that, with a more extensive introduction to pediatrics, more new recruits will choose this field – and that, eventually, we will be able to make both the healthcare and the legal systems a better place for children and their families.

Marta Cohen is a consultant pediatric histopathologist at Sheffield Children's Hospital, UK.

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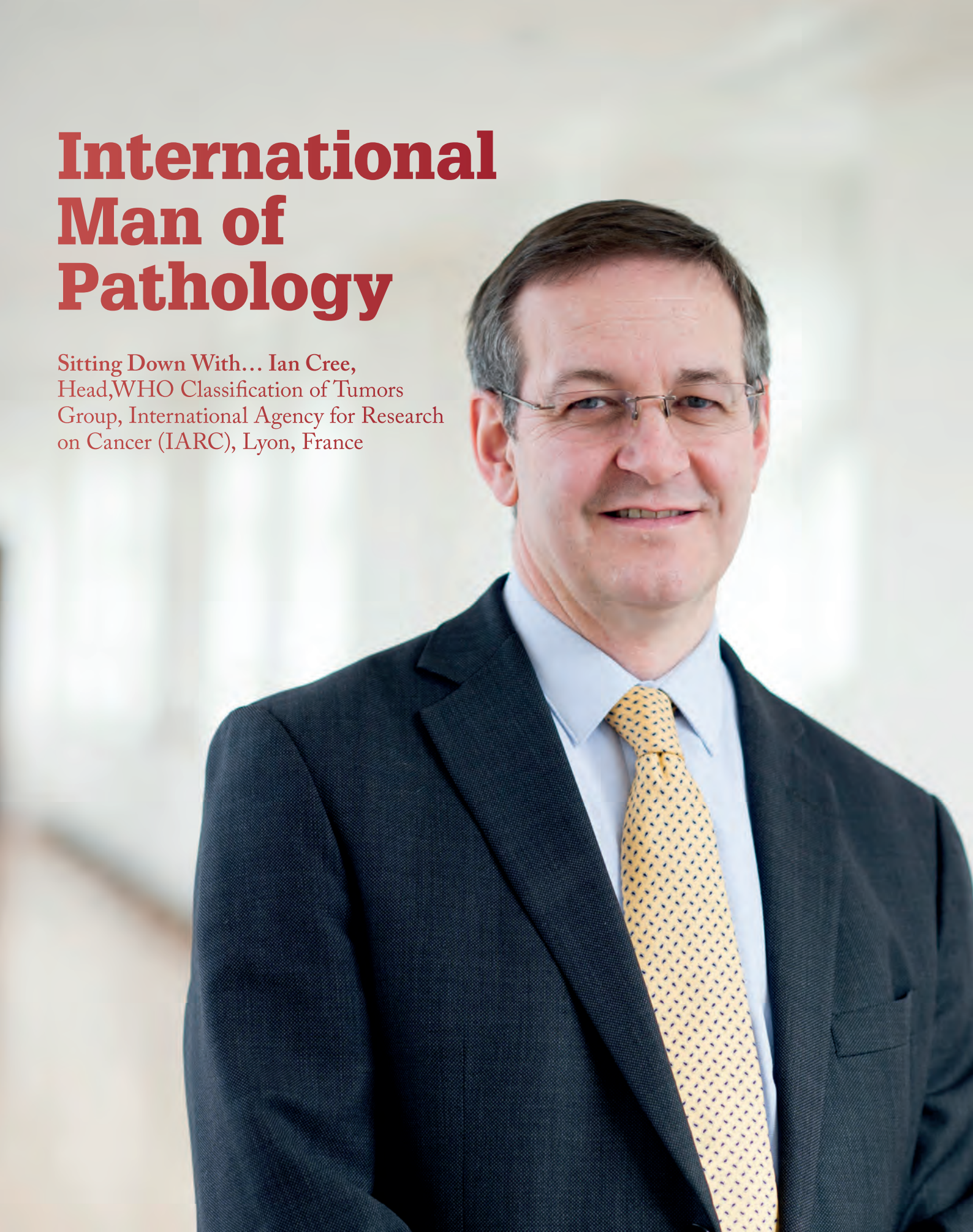
International Man of Pathology

Sitting Down With… Ian Cree,
Head,WHO Classification of Tumors Group, International Agency for Research on Cancer (IARC), Lyon, France



Tell us about your new role with the World Health Organization (WHO)…

IARC is an agency of the WHO, but based in Lyon, rather than Geneva. As head of the Classification of Tumors Group, I essentially hold the responsibility of publishing the WHO Blue Books. Part of my role is to think more deeply about cancer classification. At the moment, we classify by "sight" – by considering the organs in which the cancers occur. And we use the physiological appearance of the cancers, some genetic information, and so on. However, we are learning – from genetic information, in particular – that some cancers that look very different to us are actually similar. And others that look similar are actually very different. It seems very likely that there will be some reclassification of cancers in the future – so I will have my plate full.

How has your career prepared you for the new position? And how is the new role different?

I've had a pretty varied career. I started training as a histopathologist in Dundee, Scotland, but I did a PhD in immunology at the same time. Next, I moved down to Moorfields Eye Hospital and Institute of Ophthalmology, now part of University College London. I became a very specialized histopathologist, and at the same time continued to do research, mainly into cancer. I then headed down to the coast, and set up and ran a translational oncology research center in Portsmouth; I also took on roles with the UK National Institute for Health Research (NIHR) and the National Institute of Health and Care Excellence (NICE) on the Diagnostics Advisory Committee. Being a research-active pathologist with management experience certainly helps. Additionally, my work at NICE taught me a great deal about assessing evidence – something that's very important in my current role.

I'm now an international civil servant, which means I get a blue United Nations passport as well as my ordinary one – although it doesn't seem to help in airport queues! One of the best things about working at the WHO is being able to collaborate with people of many nationalities; gaining such an international perspective is perhaps more difficult when working with a national organization. I think this is very important for pathology, and for cancer.

"As pathologists, we sometimes undersell ourselves."

What advice do you have for others wanting to move up the ladder?

The most important thing is not to be frightened of the prospect. As a pathologist, you're taught to accept large amounts of information, synthesize it, and make decisions. I personally find it much easier to make decisions that could carry a financial risk than making decisions about whether someone has cancer or not. Pathologists make life-changing decisions like that every day, so it's a better fit than some might think. As pathologists, we sometimes undersell ourselves.

I'd also advise getting some experience and training, where possible. Most pathologists in the UK go through some form of training in administration as trainees, but I think very few of us actually get formal management training, and there's something to be said for learning the tricks of the trade. It's also helpful to join some committees and get involved, and look for role models and mentors to learn from. Finding mentors is never easy, but it's so helpful to see someone else succeed. You can get involved through the Royal College of Pathologists in the UK, and similar organizations around the world. You'll learn a great deal by doing so – I certainly did.

Whatever your career path, remember that the world is a relatively small place – get out and talk to pathologists in other countries, go to meetings, and get a wider perspective on your own practice.

What do you see in pathology's future?

It's an incredibly exciting time to be in pathology – and, in particular, cancer pathology. Things are changing more rapidly than I can remember at any other point in my career. We have an enormous amount of information coming from both within and outside of pathology, which needs to be incorporated into how we think about and diagnose disease, and how we collaborate with colleagues in research. Some great challenges lie ahead in that regard. At the same time, there are some real benefits to be gained from diagnoses that are not only correct, but also as full as they can be.

The molecular pathology revolution is already underway, and the computational pathology revolution is just starting – the areas of digital pathology and artificial intelligence (AI) are starting to provide real tools to help us in our work. I think some of the computational science may look a little scary at the moment, as it's pretty complicated. But the tools themselves don't need to be: it could be a case of the pathologist selecting an area on the image of their slide and pressing a button, and getting some information that could help them grade or stage a tumor.

Integrated pathology is something we need to embrace, especially integrated reports. We do have some problems, and there will be plenty of debate about what is important and what is not important for particular cancer types. But scientific debate is healthy – and I welcome it.

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