JUNE 2018 # 43

the Pathologist™

Life or Death Research?

Human decomposition facilities give us insight into what happens after death

18 – 31

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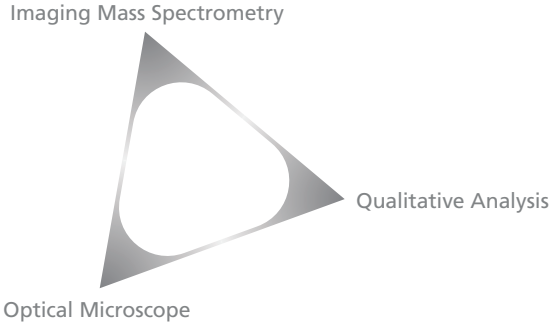

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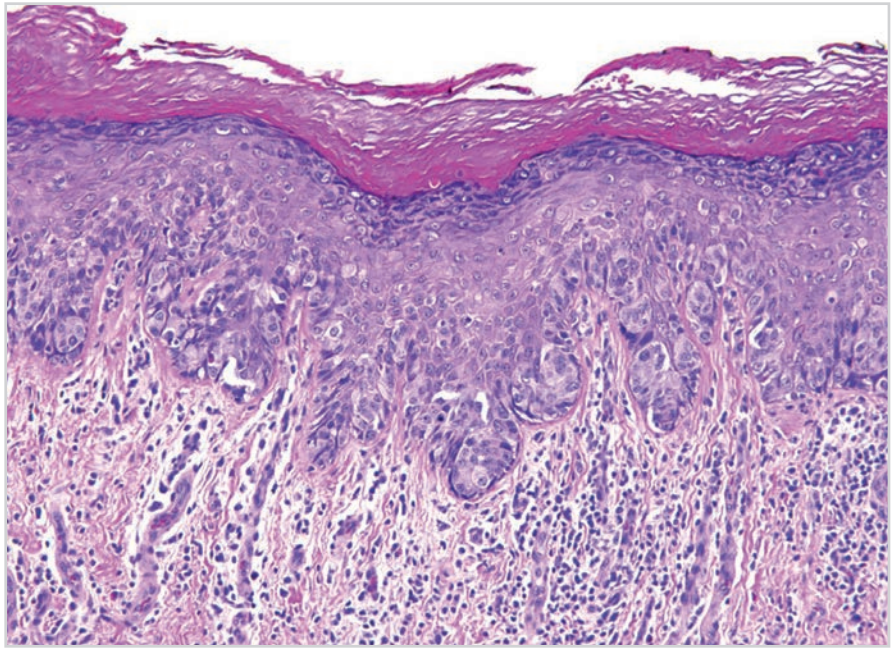
Case of the Month



A 55-year-old woman presented with a vulvar lesion that was biopsied. The malignant cells with clear cytoplasm were negative for melanoma markers, but reacted with an antibody to one of the cytokeratins. Which antibody most likely reacted with these tumor cells?.

Antibody to…

a Cytokeratin CK1

b Cytokeratin CK5/6

c Cytokeratin CK7

d Cytokeratin CK20

To register your guess for this month's case, please go to http://tp.txp.to/0618/case-of-the-month
We will reveal the answer in next month's issue!

May Case of the Month Answer

C. Medullary carcinoma

Renal medullary carcinoma is a rare tumor, predominantly found in young men and women of African origin who carry the sickle cell trait. In the microphotograph selected to illustrate the current case, two patterns can be seen: a reticular pattern resembling yolk sac tumors and a nondescript solid pattern. Several other patterns – such as papillary, tubular, or cribriform – may coexist in these tumors, which are known for their characteristic loss of nuclear SMARCB1 (INI-1) protein (1).

Reference

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On The Cover

A collage of photographs and images representing activities that take place at human decomposition facilities.

Upfront

In My View

the Pathologist

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Erratum

In our May article, "Stromal Secrets," Peter K. Gregersen was incorrectly listed as the author of the piece. In fact, the article was authored by William Aryitey, based on an interview with Peter K. Gregersen.

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From 1995 to Infinity – and Beyond!

Medicine and medical education are changing radically – so how can we make sure these changes are always for the better?

While browsing the "free books" table at my local grocery store, I came across a wonderful specimen called "Learning Medicine: 1995." A quick flip through revealed what I was already expecting: noticeably out-of-date suggestions interspersed with wise – but very general – advice (along the lines of: "Make sure you try a number of specialties before deciding on a career!"). Unsurprisingly, references to computer- and Internet-based learning were all but absent, and as for looking up diagnostic criteria on your tablet or reviewing slides on your laboratory's digital pathology system? Such things were the stuff of dreams (or movies) back in the mid-1990s…

It was startling to see just how much the world has changed over the last couple of decades. Articles are now online-first (or online-only). Patients can log into web-based portals to review their own medical records (and Google anything they don't understand, perhaps leading to even greater confusion). Pathologists can scan slides into their computer systems, annotate them digitally, give their software verbal commands, send images to experts on opposite sides of the world in mere seconds, review and sign out cases while relaxing on the beach… The list is endless.

With these positive changes come new challenges. From the earliest stages of their careers, pathologists must now be competent and confident with digital technologies. Bioinformatics, formerly only the domain of specialist scientists, is beginning to reach into every corner of the clinical laboratory. Workloads are increasing as the patient population grows and ages – especially when technological solutions are expected to replace workforce increases. And students who were once expected to grapple with advice like "talk to mentors in different specialties" are now tasked with Wiki creation, software programming, or even virtual reality medical training.

It's clear that medicine is advancing rapidly – and medical education is keeping pace. But are all of these changes making life better for doctors (and thus for their patients as well)? Are some presenting more obstacles than improvements? And, if so, how can we shift the balance so that we're using new technologies to our best advantage? If you have an opinion or an experience to share with your colleagues, let us know (edit@thepathologist.com); we'll be happy to disseminate it in both traditional and futuristic (if you're in 1995) ways!

Michael Schubert
Editor

Upfront

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

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

Email: edit@thepathologist.com

Study co-authors Nathan Skene and Julien Bryois. *Credit: Stephan Zimmerman.*

Searching for Schizophrenia

Researchers have identified the cell types most commonly associated with schizophrenia mutations

With symptoms that vary in degree or frequency and significantly overlap with other conditions, mental illness can be hard to identify – let alone definitively diagnose. But for at least one such disorder, scientists from Sweden's Karolinska Institutet are tackling the problem with a combinatorial approach.

The researchers blended their understanding of brain cellular taxonomy (the different cells of the brain and the genes used by each cell type) with the genomic loci implicated in schizophrenia in a successful attempt to identify which specific cell types might be associated with the condition (1). Their discovery? That the genes commonly altered in schizophrenia are consistently associated with pyramidal cells, medium spiny neurons (MSNs), and some types of interneurons. Furthermore, not all mutations are equal; the changes that affect MSNs are separate to those affecting pyramidal cells and interneurons, meaning that each cell type may play a different role in the disease process.

What does this mean for doctors and patients? In the future, it may be possible to diagnose schizophrenia or select specific treatments based on a patient's mutation profile and the cells most likely to be affected in each individual case. It's also possible that genomic information could lead to more accurate long-term prognoses and predictions of treatment side effects.

In short, although schizophrenia is currently diagnosed and treated based on clinical signs and symptoms, it may one day become the domain of laboratory professionals.

Reference

1. *NG Skene et al., "Genetic identification of brain cell types underlying schizophrenia", Nat Genet, [Epub ahead of print] (2018). PMID: 29785013.*

Primary Open-Angle Genetics

A landmark study, over 100 IOP-associated genetic variants, and the future of glaucoma care

Increased intraocular pressure (IOP) and primary open-angle glaucoma (POAG) go hand-in-hand; IOP is the most important risk factor for the disease. But why pressure increases has always been a mystery. Now, the largest genome-wide association study (GWAS) on IOP to date – a meta-analysis of 139,555 European participants – has provided over 100 potential clues (1).

In total, 112 genomic loci were identified to be associated with IOP and POAG, of which 68 were novel. Significantly associated genetic loci included *ANGPT1, ANGPT2, LRIG1* and *FER*, which are involved in angiopoietin-receptor tyrosine kinase signaling; *ME3, VPS13C, GCAT* and *PTCD2*, which are important for mitochondrial function; and *DGKG*, which is involved in lipid metabolism. The upshot? The findings open doors for potential screening of at-risk patients, personalized glaucoma care, and the discovery of new mechanisms of IOP regulation. Anthony Khawaja, lead author of the study, tells us more.

The inspiration

"Patients with POAG or ocular hypertension frequently ask why they have high IOP and, until now, we have not been able to answer them. Twin studies have suggested it was partly genetic, but analyzing all the globally available data on nearly 40,000 people only identified eight genetic loci associated with IOP. We were excited to use the huge UK Biobank cohort to discover new loci for IOP, as we can now tell our patients it is a combination of over 100 genetic variants. Each of these contributes a tiny amount to raising IOP but, collectively, they can have a big impact."

The impact

"A very striking finding of our study was that these genetic loci predicted a substantial proportion of POAG in two independent studies (area under ROC: 75 percent). This opens up possibilities for targeted screening of people with a high genetic risk, which could allow early diagnosis and the prevention of irreversible vision loss. Currently, general population screening for glaucoma is not recommended because false positive rates are too high. We also hypothesize that some genetic variants will predict response to different IOP-lowering modalities."

The challenges

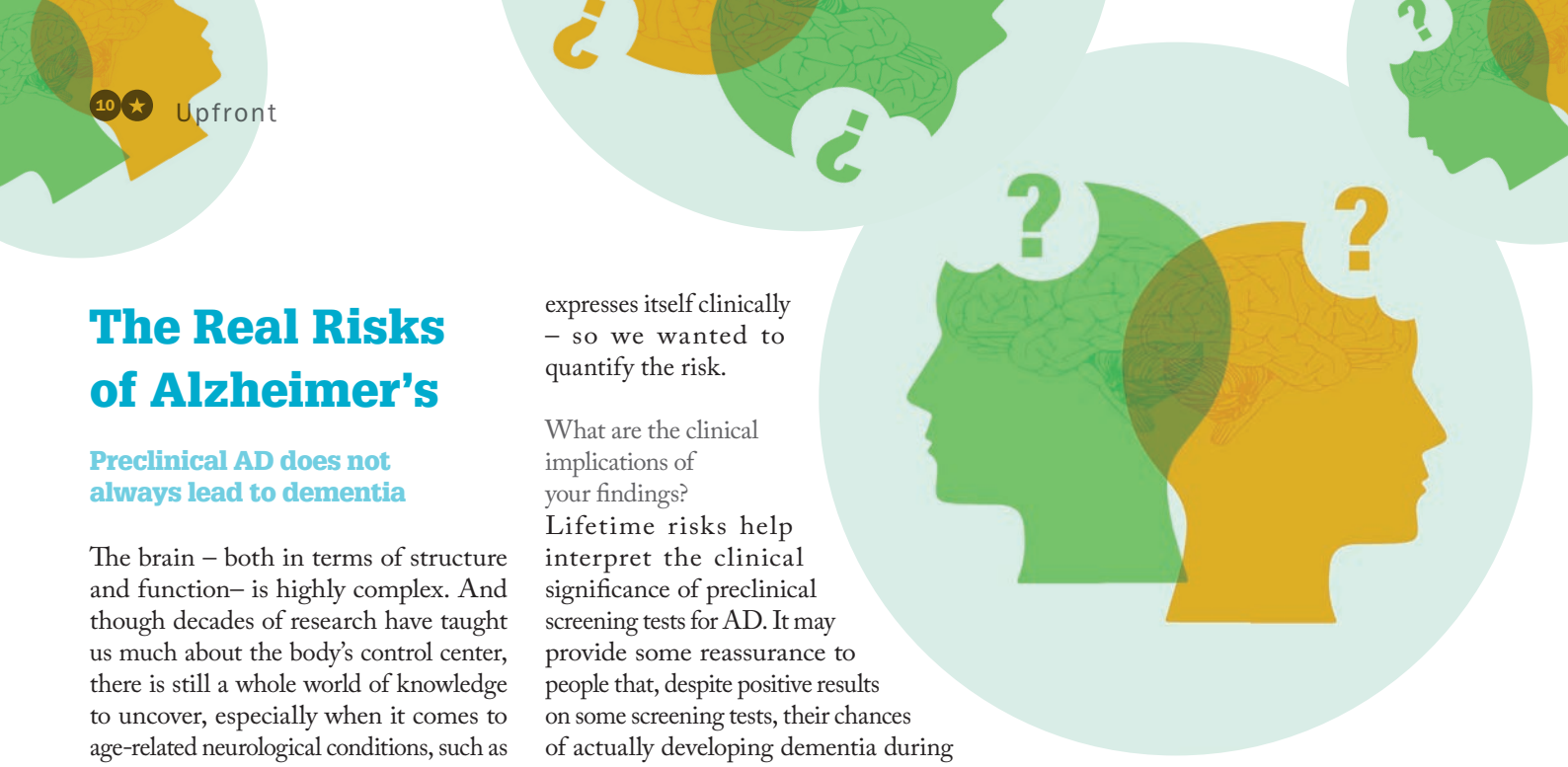
"Making sense of the 112 loci individually is a challenge. Using a pathway approach helps us identify genes with associated biological functions. Lymphangiogenic factors were identified as important, and this points to Schlemm's canal [a lymphatic-like vessel in the eye] as an important site of outflow resistance leading to variation in IOP. This finding challenges the previous dogma that the trabecular meshwork is the primary site of outflow obstruction in POAG."

The future

"We will be examining whether subsets of genetic variants predict response to [laser surgery] and prostaglandin therapy, which could potentially lead to precision glaucoma management. An effort will also determine whether these genetic variants can improve screening of glaucoma in a large population in the Netherlands."

Reference

1. *AP Khawaja et al., "Genome-wide analyses identify 68 new loci associated with intraocular pressure and improve risk prediction for primary open-angle glaucoma", Nat Genet, [Epub ahead of print], (2018). PMID: 29785010.*



The Real Risks of Alzheimer's

Preclinical AD does not always lead to dementia

The brain – both in terms of structure and function– is highly complex. And though decades of research have taught us much about the body's control center, there is still a whole world of knowledge to uncover, especially when it comes to age-related neurological conditions, such as dementia. Alzheimer's disease (AD) – the most common form of dementia – has become an increasingly significant issue as life expectancy in the developed world has risen. But the more we understand about the disease and its pathology, the closer we edge to a viable treatment.

A study by researchers at the University of California, Los Angeles (UCLA) has estimated the lifetime risk of AD for people with preclinical disease and found that they have a low likelihood of developing overt disease in their lifetime (1). To learn more about the findings and their clinical significance, we spoke with Ron Brookmeyer, first author of the study and Professor of Biostatistics at UCLA.

Why did you focus on preclinical risk?

We have been working on forecasting AD dementia globally for many years. With the development of new biomarker tests for preclinical disease, we started estimating the number of people with preclinical AD. In a companion paper we published several months ago, we determined that the number of people in the United States who have preclinical disease is about 46.7 million (2). We wondered how many of those would actually progress to AD dementia during their lifetimes. The preclinical period is long and variable, so in elderly populations, people may likely die of other causes before the disease expresses itself clinically – so we wanted to quantify the risk.

What are the clinical implications of your findings?

Lifetime risks help interpret the clinical significance of preclinical screening tests for AD. It may provide some reassurance to people that, despite positive results on some screening tests, their chances of actually developing dementia during their lifetime are low. For clinicians, our results emphasize a cautionary note that preclinical conditions may actually never become clinical. We find that age, gender, and preclinical disease state all affect the lifetime risk. For example, 90-year-olds with no preclinical symptoms (that is, without mild cognitive impairment) all have very low lifetime risk, regardless of their preclinical state. The low risk can be attributed to a short life expectancy. One message for the most elderly populations who do not have any other cognitive symptoms is: there may not be much to be gained from preclinical disease screening. On the other hand, if patients from the same population have mild cognitive impairment in the presence of amyloid and neurodegeneration, the risk becomes quite high.

How will your model develop over time?

We hope that it will be an evolving formula. Going forward, larger longitudinal cohorts will become available, which will help us refine the transition rates (from one disease state to the next) used in our model. Also, we expect to see the development of improved biomarkers with increased sensitivity and specificity. For example, the development of biomarkers for tau pathology is an area of active research. Lifetime risk is a very useful concept that can be applied to many disease and neurodegenerative processes. It helps answer a critical question asked by patients and clinicians: what is the probability that an individual with a preclinical condition will develop clinical disease during their lifetime?

What's next?

We want to further refine our model to incorporate other pathologies related to non-AD dementias. We need to better understand how multiple mixed pathologies interact with and affect the lifetime risks of developing dementia. We would like to incorporate other factors, such as the *APOE-4* gene, into the model to further refine our risk estimates. It will also be important to have studies in more ethnically diverse populations to refine the risk estimates for various populations throughout the world.

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PSA: A Shared Decision

Patients, partners, and providers should work together to optimize prostate cancer screening

"As a urologic oncologist and health services researcher, I am interested in the downstream effects of changes in health policy […] on population-level outcomes for men at risk for prostate cancer and other urologic cancers." Christopher Filson, Assistant Professor of Urology at Emory University School of Medicine, acknowledges the difficulty of selecting populations for prostate cancer screening using prostate-specific antigen (PSA), and of limiting screening to those who will reap the greatest benefit. The outcome? A reduction in overall testing – as observed in a recent study (1) – and, hopefully, more appropriate management for both those who are screened and those who are not.

But is a decrease in prostate cancer screening a bad thing? Filson doesn't think so. "The controversies surrounding prostate cancer screening with PSA testing stem from the inherent complexity of the subject matter, as well as strong vested interests and prior biases from people involved in the conversation," he says. It's hard to deny the strong association between a large population-level decrease in prostate cancer mortality in the United States after broad adoption of PSA screening – although, Filson adds, some do not admit to a causal linkage between the two. Continued efforts to identify those who would benefit most from PSA screening (such as those with strong family history) will reduce unnecessary testing and treatment in those with less to gain (such as men over 75 years of age).

Some, however, fear that screening fewer men may lead to underdiagnosis. Filson says, "There should be continued efforts into accurately figuring out how to assign risk of prostate cancer for men considering screening. This includes finding who may be at higher or much lower risk." He also highlights the importance of considering that some patients may have graver concerns – such as more severe medical conditions – that would increase the likelihood of their death within five years of prostate cancer diagnosis, making treatment unnecessary and sometimes ineffective.

To work properly, though, this common-sense approach needs buy-in from all parties. "The discussion around PSA screening should take place between patients, partners, and providers, keeping the risks and benefits of different approaches in mind. It should be a multidisciplinary effort between health services researchers, epidemiologists, urologists, radiation oncologists, primary care physicians, and others. Advisory bodies and professional groups should continue to craft guidelines related to PSA screening and emphasize the importance of shared decision-making."

Reference

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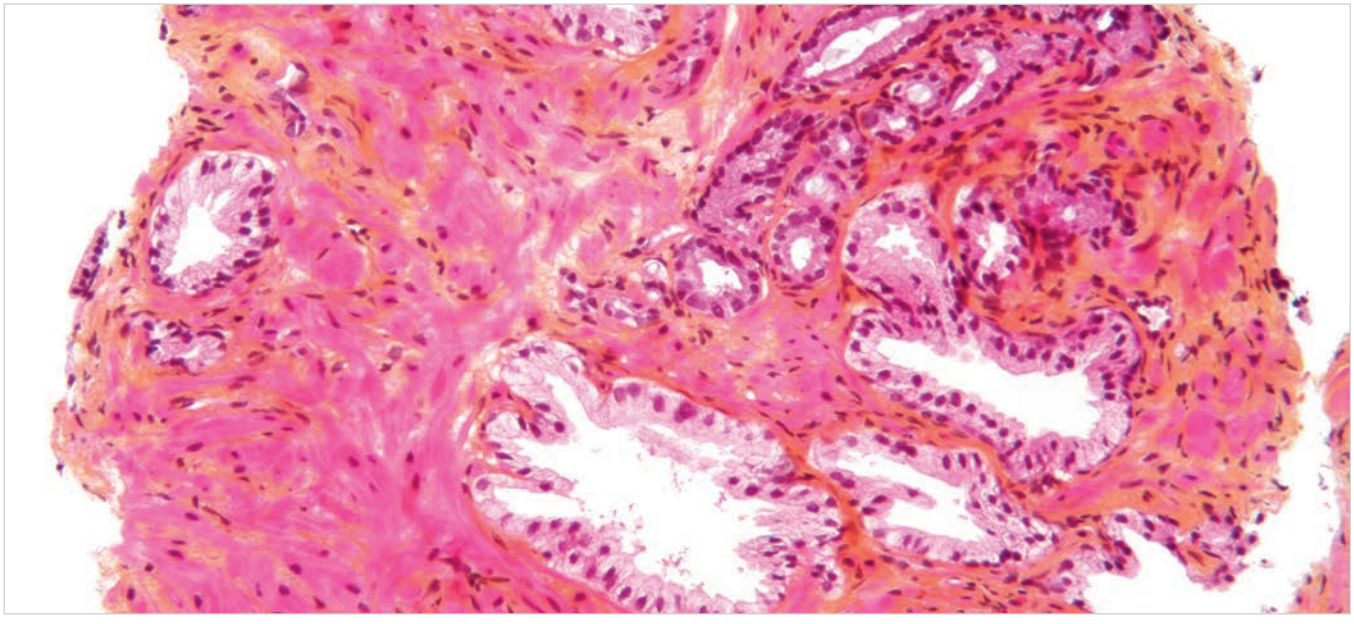

An Oncogenic Species

Are humans causing cancer in other animals?

Cancer is not only a devastating diagnosis for humans; it's also bad news for animals. But although we often hear of pets and domestic animals (common subjects of comparative pathology studies) encountering the disease, it rarely comes to our attention in more exotic species. Nevertheless, wild animals do get cancer – and it may, in fact, be the fault of humankind.

Researchers from the Arizona State University School of Life Sciences have pointed out in a recent paper (1) that humans as a species are changing the environment around them – by polluting, by dispersing chemicals, by releasing radiation, and even by changing the eating, sleeping and breeding habits of animals in the wild. "Human activities are known to strongly influence cancer rate in humans," said lead author Mathieu Girardeau (2). "So, this human impact on wild environments might strongly influence the prevalence of cancer in wild populations." In the paper, humans are defined as an "oncogenic species" – one that moderates its environment to cause cancer.

The scientists are now working to develop biomarkers they can use to measure cancer rates in wild animal populations. It's their hope that if humans are, in fact, increasing the incidence of the disease in other species, we can still change our habits and reverse the trend – for our benefit as well as theirs.

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1. *M Girardeau et al., "Human activities might influence oncogenic processes in wild animal populations", Nat Ecol Evol, [Epub ahead of print] (2018).*
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Looking Right Through Mosquitoes

Spectroscopic analysis can rapidly and cheaply detect the presence of Zika in insects

Near-infrared spectroscopy (NIRS) is nothing new in the world of noninvasive diagnosis, but a multi-institutional team spanning Australia, Brazil, and the USA have found a new avenue of detection for the technique. Study lead and research fellow in the Centre for Animal Science at The University of Queensland, Maggy Sikulu-Lord, says, "I started using NIRS in 2009 and I found it fascinating that I could shine a light on a mosquito and discover the insect's age. That was fun, so I decided to explore the technique more deeply." That exploration led to the development of a NIRS-based tool to identify Zika virus in mosquitoes, to help keep track of the endemic disease (1).

The procedure involves simply shining a light onto the head and thorax of an intact Aedes aegypti mosquito, yielding Zika detection with 94.2–99.3 percent accuracy. Not only that, but the technique is 18 times quicker and 110 times less expensive than RT-qPCR, the current standard. The investigators believe this boost over RT-qPCR could make their technique a viable option to help monitor the spread and growth of Zika across the world. Sikulu-Lord says, "We hope that public health officials will embrace this tool for surveillance of mosquito species and age. Our plan is to set up processing centers and provide surveillance services for a fee."

The range of the technique spans beyond Zika, with possible applications for diseases such as malaria, dengue, yellow fever, and chikungunya. Additionally, the researchers have successfully used NIRS on houseflies, beetles, and fruit flies in the past, so there's the potential for use in a larger range of diseases.

"We are currently conducting field trials to validate our laboratory results. We are also testing it on other mosquito-borne diseases and we hope to develop a miniaturized version for real-time surveillance," says Sikulu-Lord. "We welcome mosquito surveillance programs around the world to partner with us in the development of this technique for global surveillance of mosquito-borne diseases."

Reference

1. *JN Fernandes et al., "Rapid, noninvasive detection of Zika virus in Aedes aegypti mosquitoes by near-infrared spectroscopy", Sci Adv, 4, eaat0496 (2018). PMID: 29806030.*

The Pathologist's Power List Returns for 2018

Who are the 100 most influential people in pathology today?

For the third time, The Pathologist features its celebration of pathology and the people who lead the field: the Power List. Last edition, we asked you, our readers, to nominate the early-stage laboratory medicine professionals who are going to shape the future of pathology. From hundreds of nominations, our expert judging panel assembled the top rising stars, highlighting skill in lab work, research, clinical care, and even outreach and advocacy.

In 2018, we return to celebrating 100 of the most influential people in pathology. Clinical workers, basic and translational researchers, industry personalities, and leaders of the field are all eligible for nomination – no matter what their subspecialty or how long their career history. If they've made an impact on pathology, we want to hear about it.

Tell us who you want to see on the list – and why! – using the link below. Nominations are open until July 20, 2018.

Nominate here: tp.txp.to/powerlist2018

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

Putting Pathology Back into Schools

An honors program for medical students with an inclination toward pathology

By Bruce Fenderson and Emanuel Rubin, Professors of Pathology, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, and Ivan Damjanov, Professor of Pathology, The University of Kansas School of Medicine, Kansas City, USA

We enthusiastically agree with the authors of last month's feature article (1) regarding the importance of encouraging students to learn more about the practice of pathology. One approach that has been successful at Thomas Jefferson University's Sidney Kimmel Medical College is an honors program for second-year medical students who have displayed aptitude and interest in pathology. This program was introduced as voluntary enrichment to our regular second-year pathology course in 1992 (2). Today, over 25 years later, despite all the curricular reforms and the amalgamation of pathology with other basic science courses into a common preclinical curriculum, it is still going strong.

Every year, 15 to 25 students (from a class of 260) are admitted to the honors program. These students spend the year interacting with a mentor in the Department of Pathology. At the end of the year, each student gives a presentation – either a poster or a talk – on a topic of their choice at a Pathology Honors Student Research Symposium. In some years, the oral presentations were recorded and uploaded to the departmental website; more recently, students have submitted abstracts that are posted to the Jefferson Library Digital Commons for ongoing reference (3). The level of scholarship is generally very high – in fact, some projects have even led to publications.

Through their participation in this program, students acquire a deeper understanding of the mechanisms of disease and the practice of pathology. Our residency program director, Joanna Chan, notes, "Most of the medical students at Jefferson who go into pathology were involved in the second-year pathology honors program and the Pathology Interest Society." Approximately two new students per year from Jefferson choose to pursue pathology.

The pathology honors program at Jefferson is funded in part by the Intersociety Council for Pathology Information (ICPI). Students are inducted into a national Pathology Honor Society and provided with colorful certificates and lapel pins. The ICPI also funds 53 Margaret Grimes, MD, Medical Student Interest Groups at participating medical schools, including our own, to further enhance students' exposure to pathology (4). We are grateful to the organization for their financial support.

We strongly believe that departmental enrichment programs like these are valuable to medical students because they often have an otherwise limited view of pathology in an integrated curriculum. It is increasingly difficult to maintain a strong footprint for pathology in undergraduate medical education, but we have proven that it is certainly not impossible. Year after year, we have been encouraged by the interest of our students, who keep recommending this program to their incoming junior colleagues. Apparently, nothing works so well as a word-of-mouth recommendation – and we hope that this enthusiasm for pathology education will continue to be passed down from one generation of medical students to the next.

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One Giant Leap for Healthcare

Artificial intelligence in healthcare brings people and technology together

By Geoff Twist, Managing Director at Roche Diagnostics UK & Ireland, Burgess Hill, United Kingdom

If there is one certainty in healthcare, it's that the field is all about people – people who deliver care, people who receive care, and people who invest in care. But a new certainty is emerging – that people alone are no longer sufficient. Now, technology is required alongside them to ensure quality, patient access, and healthcare delivery that is sustainable. So how would a combination of world-class technology, people, knowledge, and data work together in a model system for healthcare in the UK?

In May, Prime Minister Theresa May addressed the nation on the government's Industrial Strategy, highlighting the ways in which artificial intelligence (AI) can help in the fight against cancer, heart disease, diabetes, and dementia. AI is all about bringing together the combined knowledge and expertise of our people with the potential of technology. With the wealth of expertise in our National Health Service (NHS) and our desire to adopt new technologies, the UK really is ahead of the game in this arena and is well-positioned to manage the needs of its patients.

It is estimated that one in every two people in the UK will develop cancer during their lifetime (1), which amounts to over 2.5 million people in the country currently receiving cancer care (2). People living with cancer deserve the best possible diagnostics and treatment, which are best delivered by a combination of the expertise of our healthcare professionals and technological advancements.

As the NHS celebrates its 70th anniversary this year, digital transformation is clearly one of the government's key focus areas in supporting care access and quality across the country. Spearheaded by the NHS, the UK has been pioneering healthcare innovations and technology for several decades, attracting research investments from organizations across the world.

When coupled with other innovative technologies, such as digital pathology, AI can significantly enhance the quality, accessibility, and timeliness of care. Imagine a world where clinical decisions can be made based on a database of millions of patients and how they have responded to a variety of treatments. It would enable us to tailor treatment to the individual by comparing their DNA with that of thousands of others from all over the world. If we want to increase our levels of certainty around disease diagnosis and treatment selection, the importance of establishing digital platforms to store and analyze big data seems clear – and it's encouraging that we have already embarked upon this journey in the UK.

At this moment in British history, we have an enormous opportunity to build a cradle of scientific achievement for a better future. It is particularly exciting that the government has committed to investing 2.4 percent of GDP (about £80 billion) into research and development by 2027 (3). As the Prime Minister mentioned in her address, big data will be the key to supporting this R&D-driven future, and to facilitating further innovations. But it will require a change in culture around the use of data in the NHS and an infrastructure of its own. Another imperative, according to the Prime Minister in her speech, is partnership between government, industry, and academic institutions. A point that addresses a need to build not just the systems and infrastructure for patient care, but also skill and expertise in the industry, so that we can ensure that we are all equipped to use solutions like AI.

I believe that, with the Prime Minister's address, the foundations have been laid for a technology-enabled healthcare system in the UK. The next step? Ensuring that these innovations have the mandates and funding they need for implementation and broad diffusion in the market. Only in that way can we guarantee equitable access for all patients in the UK.

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#Twitter Homework

A new pedagogical paradigm in pathology education

By Kamran Mirza, Assistant Professor of Pathology and Laboratory Medicine and SCOPE faculty liaison at Loyola University Chicago Stritch School of Medicine, Maywood, USA

"When I was younger, we used to index and find these articles by hand," she said with a hint of disdain, proceeding to explain the fantastical comparative world of PubMed and RefWorks, and the ease with which things are done today. I was sitting in my fortnightly Medical Education Research certificate class. We were all ears, listening to our librarian relay tips and tricks of the trade. The room was teeming with many budding (and some fully bloomed) medical education aficionados. Everyone chuckled.

I remembered my PhD mentor describing how he had done polymerase chain reactions (PCR) using five different water baths, all at varying temperatures, with a rack of tubes that he had to manually move from one bath to the next. His arms flailing, he would emphasize how easy we have it now that a modern thermocycler can easily configure a "simple" PCR and run it automatically. Like magic. There's no doubt that things are orders of magnitude easier than they once were, and information is much easier to garner.

My mind wandered to my pathology elective students. I felt instantly older thinking about how easy it is for them to learn – million-dollar mannequins, virtual reality simulations, hands-on training, wonderful visuals, the ability to "Google" every word I say, in real-time, as I say it (oh, dear)! Jokes aside, it is an amazing time to be any type of student, but especially a medical student. In my practice, I try my best to relay the tremendous benefit of social media in medical education (or #MedEd) to my students – every chance I get. My residents always hear me say things like "amazing case, definitely tweetable," and I hear them groan. I persistently pester all trainees not on Twitter about their absence. "When are you going to get a Twitter account? Wouldn't you like to tweet about this lecture? This case? This department-catered lunch?"

It should come as no surprise, then, that I am getting a reputation for being crazed – at least with regard to adapting social media for teaching. Specifically, the value of Twitter for pathology education. Over the past year or so, I have instituted "Twitter homework" for my pathology elective students. Unlike residents and fellows (over whom I have no actual control), I am the director of the pathology elective – and I delude myself into thinking my medical students listen to me, understanding the benefits I so fervently advertise.

At the beginning of the pathology elective rotation, I ask all of my students to create Twitter accounts, reactivate their old ones, or – in rare cases – continue using their existing active accounts. Students do not have to put their real names or pictures on these accounts if they don't want to, and they are free to delete the accounts after the rotation is over. Tweeting (so far) is not part of their grade. Their mission is to tweet at least one pathology-related pearl of wisdom every single day. All information, naturally, has to be HIPAA-compliant and appropriate disclaimers about not representing the views of the institution should be in place. Although it hasn't exactly gone viral, I am proud to say that this project has definitely taken hold – and my students, at least anecdotally, do notice the benefits of #TwitterHomework. It gives me great pride to say that other pathology departments are now starting to notice our hashtag (#PathElective), and some even use it themselves! Isn't that superb?!

"We can, and should, access information immediately – because it's right there at our fingertips, if only we look."

This new pedagogical paradigm is derived from a continuation of the idea that we can, and should, access information immediately – because it's right there at our fingertips, if only we look. The Twitter pathology community's hashtags index diseases, criteria, classifications, morphologic appearances, variants, and innovations in diagnostic technique better than any book chapters ever could – and they do it all in real time. Often (especially in the world of molecular pathology), material is outdated by the time it is printed in books. Not only does Twitter index updated information well, it presents it in a highly succinct form – neatly tucked into 280 (formerly 140) characters and enhanced by the ability to add photomicrographs. It is a visual diagnostician's dream, and it also sits well with our millennial learners, who are used

to whizzing from one social media app to another, picking up nuggets of information from many sources at high speed.

If the correct sources are followed, Twitter knowledge is easily accessible at the touch of a button. In many ways, the platform is even more powerful than Google – because, in the world of tweets, one can reach out to the President of a society, a residency or fellowship program director, the head of the Centers for Disease Control, the surgeon general, or even the Secretary of Health and Human Services for the entire United States!

My students are required to tweet one thing every day. It has to be indexed with the #PathElective hashtag, and they have to mention my Twitter handle, @kmirza. Nothing else is mandatory, but it helps if they also hashtag #TwitterHomework and mention our department, @loyolapathology. This can be overwhelming to students who have never tried their hand at Twitter (and don't have a lot of experience turning information into tiny sound bites). I get it; when I first began, it took me days to come up with something I felt was smart enough to tweet. Thus, students have the option of simply retweeting something pathology-related that they find interesting. However, they can also up the ante by composing an original tweet related to their day, documenting what they did, or sharing any tidbit of pathology-related information they learned. In a very short time, I have seen some amazing gems come from these students; some have written tweets that are retweeted several dozen times. Just last week, one of my spectacular #PathElective students, Olivia (an aspiring ENT clinician who tweets under the brilliant handle @otolaryngolivia) was re-tweeted by the President of the UK's Royal Society of Pathology! Isn't that wonderful? These fantastic medical students have tweeted microbiology identification algorithms, blood bank tests (on their own blood!), molecular algorithms in oncologic testing, the physics behind chemistry analyzers, the history of Auer rods, links to amazing literature from all walks of medicine, pictures of them grossing de-identified organs, and beautifully captured images of the histologic stains they are seeing under the microscope every day. Imagine the pleasure experienced pathologists gain from seeing the next generation begin to explore their world – and imagine the enthusiasm the general public sees radiating from the all-too-quiet discipline of pathology!

"You expand your knowledge base a millionfold, because you opened it up to the entire world."

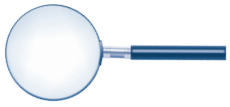
What I learned early on in my own Twitter experience is that distilling something down to the correct number of characters really makes you think about what you want to say. This cerebral act, I would argue, makes the pearl of information real and easily memorized. A factoid that not only goes out into the Twittersphere, but remains with my students for the long term. If a student goes into a lecture thinking, "Can I get a good tweet out of this?" then trust me when I tell you they will be paying attention to find that tweet.

Fringe benefits that I didn't even recognize when I started #PathElective include my ability to monitor what my students are learning on a day-to-day basis, even when they aren't rotating with me. This helps me individualize the program a bit more, so that I can make sure they are achieving both their goals and the objectives of our rotation at the same time.

The threads generated by these tweets can be fascinating. To make my point, while writing this narrative, I went to Twitter and looked up the #hemepath hashtag. The first tweet was a beautiful image of a common finding in the peripheral blood – although familiar, the images were superlative! The second tweet had images of an extremely tough case with a broad differential diagnosis. Possible answers were discussed in extensive threads that explored nuances to appeal to pathology learners at every level. The third was a tweet about the immunostaining pattern of an extremely rare tumor, and the fourth was a "zebra" diagnosis (something no one would have thought of) in a lymph node. It took me perhaps one full minute to skim through these tweets… and in that minute, I learned some amazing things. Better yet, because of Twitter's character limit, these educational points were all succinct, to-the-point, and well-articulated. The scenarios are never-ending: a student tweets, an attending replies and retweets, thousands of pathologists see the discussion (if the correct hashtags were used), and you expand your knowledge base a millionfold, because you opened it up to the entire world. True, the same could happen in any subject with engaged users – but it works exceptionally well in more visual careers like pathology and radiology.

The benefits of social media in education have been discussed and published at length. So have its benefits in publicizing pathology as a discipline; leveraging social media is now undoubtedly a key strategy in letting the world know who we are. But its innovation, up-to-date information, global education, critical evaluation, extensive outreach, and instant gratification all lend Twitter homework pedagogical benefits for zennials and millennials alike. It behooves pathology educators to fold some social media use into our teaching. Try it – I assure you that you won't regret it.

LIFE or DEATH RESEARCH?



WHAT HAPPENS AFTER DEATH

Human decomposition facilities offer insight into the post-mortem process that can help a wide variety of people – both the dead and the living

By Michael Schubert with Shari Forbes

Human decomposition facilities are popularly known as "body farms" – a nickname that often creates misunderstandings or minimizes the role these institutions play in looking after the living and providing assistance and justice to the families of the dead. In fact, these facilities provide a vital view of what happens to bodies after death in different environments and under different conditions. Such information is valuable not only for forensic investigations, but also following a natural or man-made catastrophe or for pure research purposes. The Australian Facility for Taphonomic Experimental Research (AFTER) is the only human decomposition center located outside the United States and, as such, it's an important resource for academics, law enforcement officials, and forensic pathologists working in the unique climate and geographical conditions of southeastern Australia and similar regions.

BEFORE AND AFTER

While living in Canada for seven years, I visited several taphonomic research centers in the USA and quickly saw the importance of having such a facility focused on Australia's unique environment. The way that soft tissue decomposes at US facilities is very different to what we experience in Sydney with climate, ecosystem and geology all playing a role. Thankfully, many of my collaborators in Australia also understood the need to have a facility to ensure that our research is reflective of our local climate, and that the information we give police and forensic services is as accurate as it can be. As soon as I returned to Australia in 2012, I started discussing the idea with my colleagues – only to discover that they had already been thinking about it for several years. From there, it was a natural progression.

Going from a proposal to a fully equipped facility was quite a lengthy procedure – three and a half years, to be exact. The first step was to determine whether or not our idea was legally viable. We contacted New South Wales (NSW) Health, who license anatomical teaching facilities in our state, and they were very helpful in explaining that there were no legal restrictions, so we could indeed conduct such research. We then contacted the local council where our site was to be based; they were very supportive of the idea and worked with us to ensure that we addressed all of the cultural and environmental requirements to approve the land for this type of research. Following that approval, we applied – once again successfully – to the Australian Research Council for funding. After its construction, the facility was licensed by NSW Health to have human cadavers and human remains on site. Once all of that was complete, in January of 2016, AFTER officially opened its doors.

I consider myself lucky to have ended up as Director at AFTER. I was selected in part because I had led the project from its beginnings, but my expertise in forensic taphonomy also helped; I was already conducting decomposition research using animal remains, so it was a natural transition to study human remains when the opportunity presented itself. Finally, the University of Technology Sydney (UTS),

my home institution, owned the land and had a body donation program, which made it the natural lead organization – so it was clear that the facility's director should be based there.

I am a graduate of the UTS forensic science program (from many years ago and before CSI came on the air!), so I have always had an interest in forensic research. My honors research focused on decomposition in buried environments (specifically cemeteries), as did my doctoral work, which had a focus on forensic burials. I originally chose forensic science because I loved science in general but also wanted to do something that had a clear impact on society; for me, forensic science seemed the obvious choice.

AFTER'S ADVANTAGE

The opportunity to study human remains has allowed us to have more confidence in our findings, and particularly in the information we give to the police. Indeed, the benefits of having a dedicated human taphonomic research facility were highlighted recently when we identified that pig remains – the closest proxy in decomposition studies – do not accurately mimic human decomposition in our local environment. That said, there are still many reasons to use pig remains; we continue to conduct animal decomposition studies, particularly to identify vertebrate scavengers – something we cannot do with human remains due to our licensing requirements. (As an anatomical teaching and research facility, all of our donors must be secure and accounted for at all times. If we allowed scavenging, there is a high risk that scavengers would remove bones from the site.)

Perhaps our greatest challenge is that we cannot replicate the data gathered during the decomposition of an individual cadaver, because no two bodies decompose in exactly the same way, even in the same environment. This reality is not unique to human decomposition; it's also true for animal remains, although some researchers argue that they may be more replicable. We find that, just as mammals are unique during life, they are equally unique after death – so we are only able to identify trends across our studies.

LOCATION, LOCATION, LOCATION

AFTER is based in a natural eucalyptus woodland that mimics the kind of remote forest on the outskirts of Sydney where police might search for the remains of victims. It is surrounded by a high-security fence with CCTV cameras and a small building at the entrance. The location belonged to UTS before AFTER's establishment and was provided to me to conduct animal decomposition studies when I returned to Australia in 2012. When we decided to set up a human decomposition facility, we quickly realized that it was an ideal location: remote, but still accessible for research, and with the type of terrain that was most likely to be helpful to police and search and rescue teams.

Our day-to-day routine is dependent on the kinds of projects that are being conducted and how frequently researchers need to collect data. For research on cadaver detection by dogs, we start our studies by collecting decomposition odors and identifying key chemical compounds as soon as a donor arrives. We then visit AFTER on a daily basis until the decomposition process slows and sampling can occur less frequently. We have 14 partner organizations and more than 80 researchers conducting their own projects, so it can get quite busy! We also run training days for our police partners and give tours to relevant visitors, such as visiting forensic pathologists or police from other states or countries. Training may simply involve giving a tour to a particular group (for instance, the Homicide Investigators Unit) to raise awareness about how we can assist them, or it may involve a physical activity (such as testing police Disaster Victim Recovery protocols in the case of a collapsed building, or training crime scene officers in victim recovery from clandestine graves). No two days at our facility are quite the same.

In terms of ethical guidelines, we are governed by NSW Health legislation, specifically under the Anatomy Act and the Human Tissues Act. The organization audits us regularly to ensure that we are following all processes correctly. All of our research projects must undergo an ethics review, but also require approval by UTS and the relevant partner organization(s). And, of course, all donors must consent to donation to AFTER.

We have received no negative feedback from the general public so far, which I consider very fortunate! We do spend a lot of time engaging with the public through media and presentations to raise awareness about our facility and the importance of the research and training we do, so that's obviously paying off. They also know whom to contact if they have any concerns or want further information. Typically, though, I am only contacted following a presentation or interview by potential donors who want information about signing up to AFTER. We find that people can relate to our research much better when we explain to them who our research is helping – for example, missing persons, victims of homicide, or victims of mass disaster.

A NEW ATTITUDE TOWARD DEATH

I do believe that people have a better acceptance of death once they have worked with human remains. They seem to find it easier to talk about death, particularly with family and friends. Certainly, I've found that to be the case with my own family. I am commonly told by partners and the police that their visits to AFTER were not as confronting as they had feared. Our location is actually a


"People can relate to our research much better when we explain to them who it is helping – for example, missing persons, victims of homicide, or victims of mass disaster."

very peaceful environment, which helps to reassure both those who work here and those considering a donation.

One of our main priorities at AFTER is to strive for the most valuable data from every donation, which means collaborating extensively across disciplines in forensic taphonomy. We have some difficulty getting funding for our research because granting agencies often think that the police should fund this type of research. Unfortunately, law enforcement agencies have very limited budgets for research, so we try to think outside the box in terms of where we apply for funding. Not everything we do is focused on crime and forensic science. Some of our researchers use AFTER to conduct archeological research, cemetery research, human rights investigations, and so on – and, as a result, we can creatively seek funding from other national and international sources.

AFTER is entirely supplied by body donors, who must give consent during life. There is one exception; a potential donor's senior next of kin can give consent at the time of death if they can demonstrate that the deceased did, in fact, want to donate their remains to science and specifically to AFTER. One such example would be someone who wrote their desire into their will, but did not complete a specific consent form. As a result, the majority of our donors are elderly and have died of natural causes, which skews our data to a degree, but does not make it any less valuable. We are starting to receive younger donors at AFTER as people become increasingly aware of our facility and the importance of our research to police and forensic services. I think the culture around death is starting to change, too, which may be why we are having younger donors consent during life.

COMMON MISCONCEPTIONS

The misunderstandings I hear most when I tell people what I do for a living are that we "farm" bodies at AFTER – or that we simply watch them decompose. There is a persistent belief among some people that our facilities must be threatening, graphic and grotesque, or that what we do is disrespectful to the remains. The prejudices sometimes extend to me – for instance, people may assume I should look like Abby from NCIS or Morticia from the Addams Family!

If I could tell pathologists one thing about human decomposition research, it's that we need more forensic pathologists conducting research in forensic taphonomy. Although our work can assist them, the few who currently work in the field are busy individuals with little time for research, so it is one of the disciplines we currently lack at AFTER. When I give tours to pathologists, they always share great ideas for research, particularly because they have their own experiences to draw on. I'd love to see more of that in the near future – for the benefit of the dead and the living.

Shari Forbes is Director of the Australian Facility for Taphonomic Experimental Research, Professor in the School of Mathematical and Physical Sciences, and a Core Member of the Center for Forensic Science at the University of Technology Sydney, Australia.

A FORCE FOR GOOD

The what, where, and why of human decomposition facilities

By Katie Zejdlik, Nicholas V. Passalacqua, and John A. Williams

In 1981, the proposal of a facility to study human decomposition was necessary – but, to many people, socially macabre and ideologically offensive. Over time, though, perspectives regarding this kind of scientific research have changed. Exposure to popular crime dramas, shock-value news reports, and general Internet content has affected how people view death and the dead. Additionally, social movements like those focusing on "green" burial practices are encouraging individuals to donate their bodies to human decomposition facilities, where they can both decompose naturally and contribute to forensic science.

The first human decomposition facility, colloquially known as a "body farm," was established by William Bass in 1981 at the University of Tennessee (UT), Knoxville, to scientifically address questions surrounding the rate and process of human decomposition. The second such facility did not arise until 2005, this time at Western Carolina University (WCU) in Cullowhee, North Carolina.Since then, six more human decomposition facilities have been built in the United States, as well as one in Australia (see Table 1). The term "body farm" comes from Patricia Cornwell's eponymous 1994 novel, which was inspired by the UT facility. Although the term "body farm" is widely used, "human decomposition facility" is the preferred way to reference this resource.

DELVING INTO DEATH PROCESSES

Taphonomic research facilities exist to study the process of human decomposition and the many factors associated with it: temperature, precipitation, soil chemistry, animal scavengers, insect activity, and more. Prior to the establishment of these facilities, animals such as pigs and rabbits were used as proxies for humans – but only recently, thanks to human decomposition facilities, have researchers demonstrated that non-human models like pigs do not follow the same decomposition patterns as humans (1). The primary activity that takes place at human decomposition facilities is the detailed analysis of decomposition under varying conditions, usually using some form of scoring system along with documentation by notes and photographs.

Name	Institutional affiliation	Location	Established
Forensic Anthropology Center (FAC)	University of Tennessee, Knoxville	Knoxville, TN, USA	1981
Forensic Osteology Research Station (FOREST)	Western Carolina University	Cullowhee, NC, USA	2005
Forensic Anthropology Research Facility (FARF)	Texas State University	San Marcos, TX, USA	2008
Applied Anatomical Research Center	Sam Houston University	Huntsville, TX, USA	2010
Complex for Forensic Anthropology Research (CFAR)	Southern Illinois University	Carbondale, IL, USA	2012
Forensic Investigation Research Station (FIRS; see page 25)	Colorado Mesa University	Grand Junction, CO, USA	2013
Australian Facility for Taphonomic Experimental Research (AFTER; see page 19)	University of Technology, Sydney	Yarramundi, New South Wales, Australia	2016
Florida Forensic Institute for Research, Security and Tactical Training (FIRST)	University of South Florida	Tampa, FL, USA	2017
ARISTA	Academic Medical Center	Amsterdam, the Netherlands	2018
Forensic Research Outdoor Station (FROST)	Northern Michigan University	Marquette, MI, USA	In progress

Table 1. All human decomposition facilities in the world with institutional affiliation, location, and year established.

Multiple facilities exist in different physiographic zones because each zone has specific temperature ranges, precipitation amounts, flora, and fauna that affect decomposition. For example, an individual placed outside during the summer months in Marquette, Michigan, will decompose at a different rate than one placed outside at the exact same time in San Marcos, Texas. The rural, mountainous surroundings of the facility in Cullowhee will encourage different modifiers to the semi-urban environment of the facility in Knoxville, despite being just over an hour's drive away. Smaller variables such as plants and animals compound these differences. For instance, vulture behavior in the wide open spaces of the Texas facilities is different to their activity in the wooded environment of the Appalachian Mountains. These details are necessary when trying to understand the post-depositional context of an individual found in the woods, a field, or a parking lot.

Formal research is conducted at these facilities with the aim of generating peer-reviewed literature that can strengthen the rigor of forensic reports and associated courtroom testimony. The ability to estimate the post-mortem interval or identify evidence of scavenger activity in a systematic, reliable way is important for assisting medico-legal professionals in resolving questioned deaths and identifying unknown individuals. Without the availability of scientific evidence to support professional opinions, subject matter experts can only debate post-mortem interval (time elapsed since death) estimates, leaving juries in an awkward position.

Researchers at these facilities also recreate cases encountered by law enforcement officials when necessary. For example, how does a body decompose when locked in a car trunk? When it has been burned using an accelerant? When it has been disarticulated? These unusual circumstances provide anomalous decomposition scenarios that can be difficult to interpret using traditional models. Human decomposition facilities can assist in understanding the post-deposition environment by recreating these events and studying how a body reacts in controlled environments.

TEACHING AND TRAINING

Human decomposition facilities provide opportunities for research, networking, and hands-on experience that not only help students determine what specific careers they may want

to pursue, but also provide knowledge beneficial to various professionals. Because multiple bodies can be observed in various states of decomposition, individuals can view several stages of decomposition at once and learn to recognize the difference between them, as well as methods for estimating the post-mortem interval. Students can also learn skills related to the identification of human versus non-human bone, scavenging behavior of animals, and best-practice search and recovery techniques to preserve the integrity of the scene. Throughout all of this research, these facilities also serve the medico-legal and law enforcement communities by providing continuing education and training to students and professionals in the search, recovery, collection and interpretation of human remains from various depositional contexts and stages of decomposition.

Research opportunities at these facilities are cross-disciplinary, collaborative, and constantly changing as new methods and technologies are developed. For example, active research at WCU's Forensic Osteology Research Station (FOREST) facility ranges from examining degradation rates of nuclear DNA in soft tissues and bone to estimating the post-mortem interval by examining the oral microbiome. Projects examining human decomposition fluid and soil chemistry, or the science of human remains detection dog scenting, bring together scientists from across the academic spectrum to understand not only the human decomposition process itself, but also its significant ecological effects.

Human decomposition facilities are valuable scientific resources. Despite this, seemingly few people know these facilities exist – and even those who do have misconceptions about what the facilities are used for and how they operate. One of the most common misconceptions is related to the origins of the bodies used in this type of research. Theories about "red market" acquisition of bodies, spaces for secret government disposal areas, and the collection of unknown and unclaimed individuals can be found scattered across the Internet. Of course, none of these are true. There are federal and state laws that dictate how and where human remains and tissue can be stored or deposited. Additionally, local institutional oversight and professional ethics influence the acceptance and study of human remains. In reality, these facilities operate similarly to any other scientific tissue donation

system. All human decomposition facilities have paperwork that identifies the transfer of remains from one next-of-kin or legal owner to another. Furthermore, all facilities have individuals who "pre-donate" their remains for study. Pre-donors are living individuals who decide that they want their body to be studied at one of these facilities and complete the appropriate paperwork to allow the facility to take possession of their remains after death.

FOR SCIENCE – AND SOCIETY

Finally, human decomposition facilities serve a social purpose as well – they act as a depositional alternative for individuals who cannot afford burial or cremation. Donation is free, and some facilities have funding to pick up donor's bodies within a specified driving radius. Another social impact is that this type of deposition is "green." Many people are interested having as minimal an environmental impact as possible after their deaths. They like the idea of giving back to nature – and, at least in the case of FOREST, resting peacefully in the sun-stippled landscape of the Blue Ridge Mountains.

Perspectives have changed a lot since 1981. The acceptance of human decomposition facilities and donation to them has had significant impacts on the medico-legal community and the development of the forensic sciences. They have helped bring closure to families and reliability to courtroom testimony. They are unique and valuable resources that will continue to contribute in multifaceted ways by providing a place for scientific endeavor while simultaneously addressing a variety of societal needs and interests.

Katie Zejdlik is Assistant Professor and Forensic Anthropology Collections and Director at the Forensic Osteology Research Station, Western Carolina University.
Nicholas V. Passalacqua is Assistant Professor and Forensic Anthropology Program Coordinator at Western Carolina University.
John A. Williams is Full Professor at Western Carolina University, Cullowhee, USA.

Reference

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FORENSIC SCIENCE AT FIRS

An introduction to the western United States' only taphonomic research facility

By Melissa Connor

As most scientists who study the process of death and decomposition know, research facilities are not one-size-fits-all solutions. Every region's climate, geography, and ecology are different, so what happens to one body in a particular location over time may be very different compared with another body at a second site. And that's why a single human decomposition facility for taphonomic research and forensic investigations is not enough; however, there are only eight such facilities in the world – six in the continental United States, one in southern Australia, and one in the Netherlands.

But even six facilities is perhaps insufficient in a country as geographically diverse as the United States. Of the six, only one – the Forensic Investigation Research Station (FIRS) at Colorado Mesa University – is situated in environmental conditions that represent most of the western half of the country (see Figure 1), making it a vital hub for research, teaching and services in the field of forensic taphonomy.

BIRTH VERSUS DEATH

In 2012, construction of the FIRS building began at Colorado Mesa University, inspired by a number of faculty members at the institution. When only the fences around the outdoor facility were up (nothing else had been built), I was hired for the job of Director through a competitive process – demand for the job was high. No wonder given that FIRS had an environment unlike any similar facility elsewhere in the country, making the prospect intriguing to those of us who work in forensic disciplines.

The first human donation to FIRS was received in 2013. By now, we have had over 70 donations, 20 of which reside in our skeleton collection. FIRS features a fenced outdoor facility of approximately two acres, as well as an indoor lab and classroom building of about 2,000 square feet. Its location was chosen specifically to provide balance – it's close to the main campus, but distant from any living areas.

Initially, some might have expected issues with public perception of the facility – especially considering some popular, yet not necessarily accurate, depictions of "body farms." Nevertheless, I really haven't experienced any such issues. Certainly, the research we conduct at FIRS (whether before or after death) is not for everyone, but most recognize the importance of the work. If anything, people can be too enthusiastic; I've had requests for elementary school and scout group tours! We don't offer any tours of the facility but, even if we did, I don't feel that viewing naked, decomposing human cadavers is appropriate at younger age levels. Generally, telling instructors that the remains are nude is a deal-breaker…

When law enforcement officers discover a human body, one of the first questions they ask is: when did the death occur? "We know a great deal about time of death determination," says Melissa Connor, forensic archeologist and director of the FIRS facility. "Often, on decomposed remains, that determination is made from mail not picked up, or from other ancillary evidence – but we are working on solid, quantitative physical methods."

The skeletal collections at FIRS and other taphonomic research facilities may, in Connor's opinion, be the best existing representatives of the skeletal anomalies and pathologies in modern populations – a handy resource for pathologists seeking to learn more about the diseases and disorders that might affect their patients.

KÖPPEN-GEIGER CLIMATE ZONES

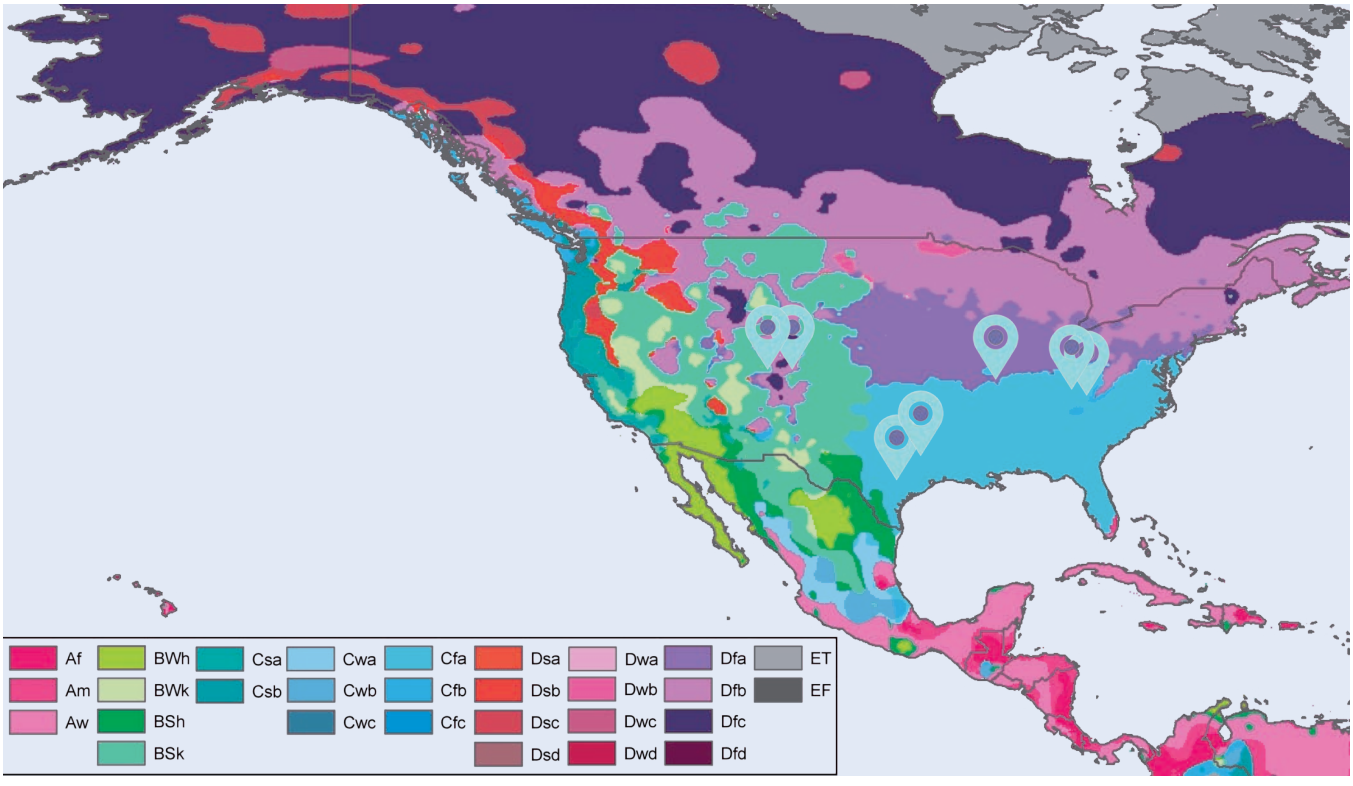


Figure 1. Human decomposition facilities in various climate zones of the United States in 2017. Adapted from a map by Tammy Parece, Colorado Mesa University, Grand Junction, USA.

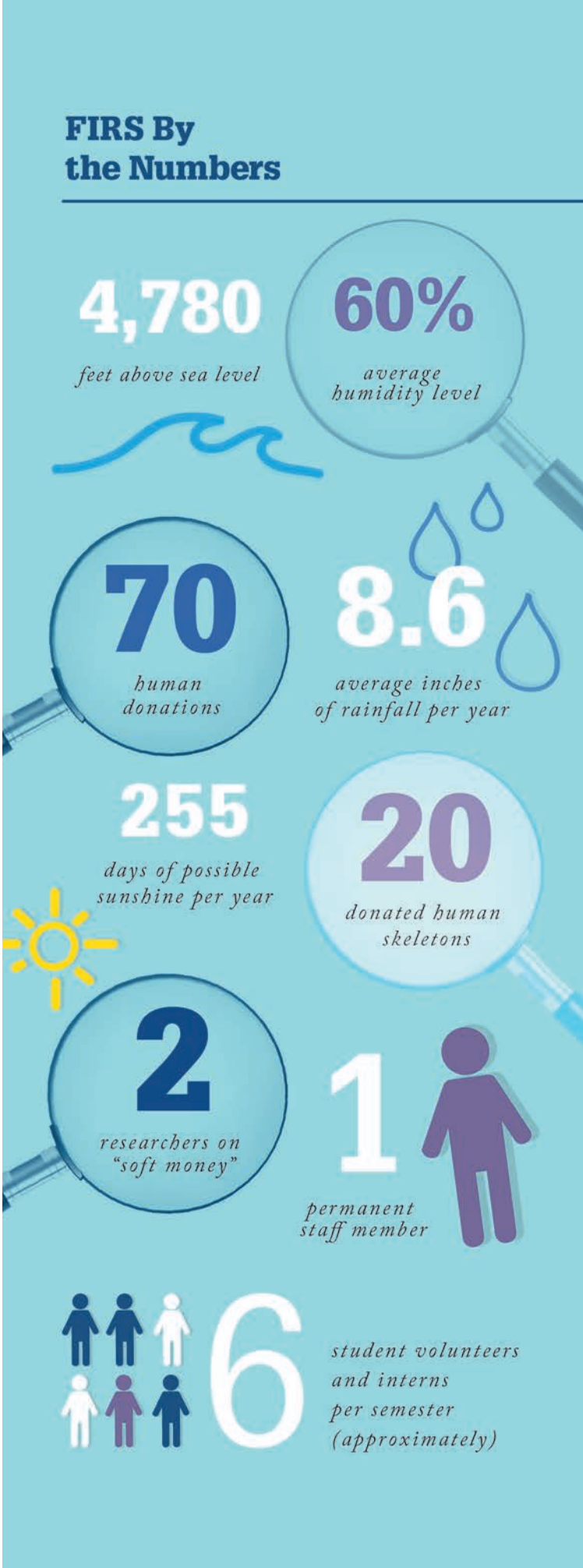
BEHIND THE CHAIN-LINK FENCE AT FIRS

Though tours may be inappropriate, we are very invested in the educational value of our facility. We run on a backbone of interns and student volunteers, who receive course credit in return for their assistance. Tasks that might be completed by our student workers in addition to their own research projects include maceration (the cleaning of a skeleton for placement in our collection), body placement, photography, labeling remains, data collection, or maintaining our databases. It's a great opportunity for hands-on learning and research experience, and it gives STEM subject students the chance to integrate and collaborate with social science students. In an increasingly interdisciplinary research world, I think that's invaluable.

Our daily routine begins with photographing the remains in the outdoor facility and documenting them on specific Likert scales like our Total Body Scale (TBS), which we use to measure decomposition. The system assigns a numerical value to a stage of decomposition for head and neck, trunk, and limbs. The individual scores are added together for the TBS, yielding a quantitative assessment of our qualitative observations. If there are insects on the remains, we may collect some for identification and for our records. There are always between four and eight research projects underway as well – and all data is eventually embedded into the FIRS collection.

Back inside, we upload the data into a series of spreadsheets and carry out quality assurance protocols. Meanwhile, we generally have a maceration ongoing; after a set of remains is brought in from the outside facility, we clean the bones for the skeletal collection. This involves an initial disarticulation in which we remove tissue that peels off or can be removed with EMT scissors. By then, we can usually place skeletal elements into containers to which we add dish detergent and hot water, which will soften the tissue and de-grease the bone. Tissue is removed as it softens, the water changed, and the round repeated as needed until the skeletal elements are clean. Then, they are dried and moved to the dry lab, where each bone is labeled with the donation number.We also have students working on the skeletal collection, both for research projects and for their own education. Finally, all of the day's work has to be documented and written up – and, speaking of writing, we usually have a couple of journal articles in different stages being batted around among authors. Everyday life at FIRS is quite productive!

Melissa Connor is Director of the Forensic Investigation Research Station and Professor of Forensic Anthropology at Colorado Mesa University, Grand Junction, USA.



MISSING: ONE HUMAN DECOMPOSITION FACILITY

The uniqueness of different regions means that each needs its own facility – so why doesn't the UK have one?

Michael Schubert interviews Anna Williams

The argument for human taphonomy research is a convincing one – a better understanding of the death and decomposition process, improved cadaver detection abilities, higher-quality forensic testimony in courts of law, and more. But despite the many points in its favor, there are still only a few facilities for the study of human decomposition worldwide. Notably, the United Kingdom lacks one – but that's a fact members of the Human Taphonomy Facility for UK Forensic Science (HTF4UK) project hope to change. We spoke to Anna Williams, who runs HTF4UK, to learn more.

WHY DO WE NEED HUMAN DECOMPOSITION FACILITIES?

Without these facilities, we can't do rigorous scientific experiments to determine the effects of certain human conditions on decomposition rates. Some experiments must be performed on humans; we can't use animal analogs to study the effects of smoking or drug use, or conditions like diabetes or cancer, or other lifestyle factors, such as diet. A vegetarian, for instance, is likely to decompose at a different rate to someone who eats meat because they will have different gut bacteria. But without human decomposition facilities, we can't do the research we need to help us understand these factors.

Research conducted at the existing facilities – particularly the one in Tennessee, because it has been around longer than any other – has shown us that decomposition is extremely dependent on local climate, environment, and conditions. Insects, scavengers, soil type, temperature, humidity, and rainfall all affect decomposition rate. And because the UK is so different to Tennessee or Australia, the data coming out of those facilities aren't terribly applicable to our forensic cases; I'd argue that it's essential for the UK to have its own human decomposition facility.

No two of the existing facilities are alike. Some, like the Freeman ranch in Texas and the AFTER facility in Australia, are very big; others, like the one at Western Carolina University or the one in the Netherlands, are very small. The Amsterdam facility, ARISTA – which currently houses only a single cadaver – is only 20 meters by 20 meters! Obviously, space isn't the only consideration; it's important to take into account location, security, and other factors – but it's too early to be thinking about such aspects for a UK facility at the moment.

What I would particularly like to see in a new facility is the opportunity to study water environments. None of the existing facilities is equipped for the study of water decomposition, which I think could make a human decomposition facility in a country with lots of rivers and lakes like the UK unique.

Human decomposition facilities are valuable in another way: they allow students to get hands-on experience with real human cadavers – invaluable if they intend to pursue a career in medicine or life science, especially subjects related to forensics. We don't want their first experience of a body to be their first day on the job; we want to expose them to the sights and the smells and everything that goes into researching with humans, so that they can make an informed decision as to whether or not it's the right career for them. I've always felt that it was incredibly important for my students to have exposure to the real thing – or as close to the real thing as possible.

I have people writing to me already, volunteering to help at a UK facility that doesn't exist yet! There's always a lot of interest from students, and the universities that house existing facilities have seen student numbers go up as a result. Whichever UK university takes on the task of establishing and running a human decomposition facility, I'm sure it will massively boost their recruitment; students will go out of their way to attend a university with such a unique opportunity for forensic and medical research and experience.

WHAT ARE THE OBSTACLES TO ESTABLISHING A NEW HUMAN DECOMPOSITION FACILITY?

One of the big challenges for us – and forensic science research in general – is funding. There's no government or research council funding for forensic science, so it's difficult to finance the establishment of a human decomposition facility. That said, I don't think it would be terribly expensive to set up such a facility. I think we'd need about £1 million to start with, which is relatively small fry compared with some large laboratories.

In addition, we would ideally like to see a minor change to the scheduled purposes of the Human Tissue Authority (HTA). Right now, institutions can apply to the HTA if they want to undertake activities using human tissues, but when they were coming up with those scheduled purposes, they didn't think about forensic taphonomy research, so that isn't included. And that technically means that this kind of work is outside the remit of the HTA and therefore doesn't require regulation.

However, those of us who want to start a human taphonomy

facility in the UK believe that it should be regulated by the HTA, so we are trying to request that they add forensic taphonomy research to their list of scheduled purposes. The work can go ahead without that addition to the scheduled purposes, but we'd prefer that it be regulated just as any other use of human tissue would be.

WHAT ARE THE MOST COMMON MISCONCEPTIONS ABOUT "BODY FARMS?"

I haven't encountered many misconceptions from the general public. Most people with whom I speak are very pro-human decomposition facility – although, of course, it's a self-selecting population of individuals who attend my talks or contact me via email, so they're always very supportive. I've also run an online survey – the largest ever conducted to date – to drill down into people's opinions on these facilities. How would they feel if there were one in the UK? How would they feel if there were one close to them? Would they be worried about house prices going down? Scavengers? The smell? But, perhaps surprisingly, the response has been overwhelmingly positive. As far as my own research and experience can tell me, people think a human decomposition facility is a good idea.

The only negative comments I've received have been from fellow academics. Some say that we wouldn't learn anything we don't already know – a very short-sighted argument in my opinion. We can't possibly know everything about how humans decompose in the UK, because nobody has ever researched it. There is so much to learn about how a body interacts with its environment in the UK – with our soils, insects, and scavengers – so, as one supporter put it, we don't know yet what we don't know. We need the opportunity to perform forensic taphonomy research so that we can find out what areas of knowledge we lack.

Another objection I've heard is that being able to donate to a facility might reduce the number of people who donate their bodies to medical schools for anatomy dissection. I find that contestable as well, because the medical schools with whom we have spoken have all said that they don't think that would be a problem. In fact, they would welcome an alternative option for body donation. Often, medical schools have to reject potential donors because they're unsuitable for anatomic dissection. Having a taphonomy facility to which they could donate would actually allow more people to donate to science.

Academics have also suggested that you can't obtain the large numbers of replicates that you need for statistically powerful experiments in human decomposition. First, I'm not sure that's the case; you might be able to get large enough numbers if you coordinated efforts between different body donation programs around the country or even abroad. You could place bodies from the necessary demographic groups into storage until you had enough to perform a large experiment. Second, such an effort might not even be necessary. I mentioned this concern to my colleagues at the Amsterdam facility, and they said that they didn't worry about statistical power in their experiments because they use their facility to do pilot tests. Over the years, they will gather a large amount of data – and, eventually, they'll be able to interrogate their database to separate out different demographic groups and look for patterns. But, at least to begin with, statistical power may not be a major concern.

WHAT WOULD YOU MOST LIKE PATHOLOGISTS TO KNOW ABOUT TAPHONOMY RESEARCH?

People – even other professionals – tend to think of forensic taphonomy research as disgusting, off-putting, or undignified. In my mind, it's no different to donating your body to medical science. If you were going for an operation and your surgeon told you that they had only operated on pigs before, you would probably be a little concerned. Similarly, we don't want our forensic scientists to stand up in court, where a person could go to prison or be set free as a result of their testimony, relying only on research that has been done on pigs. It's not good enough.

Forensic taphonomy helps us improve the accuracy of post-mortem interval estimation in people who have decomposed, especially those who aren't found immediately. But it's also incredibly important for finding missing bodies in the first place – something we currently find quite challenging. Human taphonomy facilities can help us improve the techniques we have for finding bodies (for instance, geophysics, aerial photography, or cadaver dogs). Cadaver dogs in the UK tend to be trained on animal remains, yet their job is to find human remains. A taphonomy facility would let us train them on human remains, which would not only allow us to do research into what they're finding and how well they're finding it, but also to do competency testing for the dogs, improving their accuracy and increasing the value of their evidence in court.

People don't consider forensic research valuable because it isn't directly saving lives like medicine, for example. However, for those who have been a victim of a crime or known someone who has died in a disaster, answers can help. People need to know what has happened to their loved ones, and a human taphonomy facility is one way to provide those answers about disaster victims, violent crime victims, or people who have gone missing and whose bodies have been found years later. This is the only way we can do the kind of rigorous research that we need to investigate those questions.

Anna Williams is Principal Enterprise Fellow in Forensic Science at the University of Huddersfield. She also runs the HTF4UK project (htf4uk.blogspot.com) and can be found on Twitter at @Bonegella and @HTF_4_UK.

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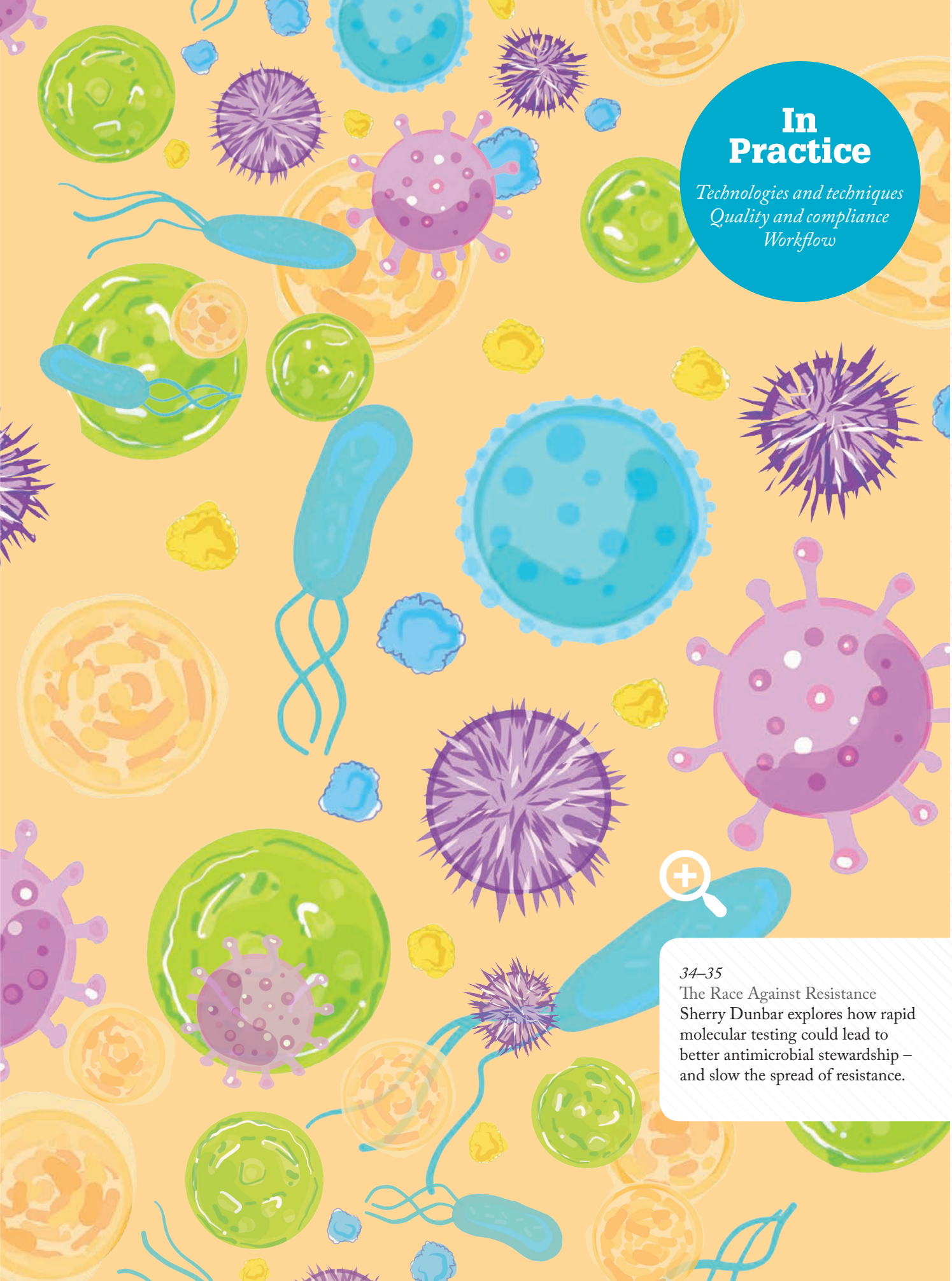

In Practice

Technologies and techniques
Quality and compliance
Workflow

The Race Against Resistance

Rapid testing could be the tool we need to successfully address antibiotic resistance

By Sherry Dunbar

For many medical situations, molecular testing has enabled previously unimaginable turnaround times to results, making it possible to get patients on the right treatment – or off the wrong one – very quickly. Nowhere is this more important than in the fight against antibiotic resistance. In patients with bacterial infections, rapid diagnostic results allow medical teams to select the targeted treatments most likely to be effective, avoiding prolonged use of the broad-spectrum antibiotics most likely to spur resistance.

Many hospitals have launched antimicrobial stewardship programs for the express purpose of reining in the spread of antibiotic resistance. These programs use every tool in the infection control toolbox – from basic education about handwashing to strict isolation protocols – to prevent both the transmission of resistant strains and the acquisition of new resistance mechanisms. Rapid molecular tests are a key element of these programs. Why? Because they help identify infected patients, detect antibiotic resistance profiles, and guide treatment selection. Some programs even go beyond the standard clinical guidelines, using diagnostic tools to screen all hospital admissions so that asymptomatic, colonized patients can be isolated to reduce the risk of resistant strain transmission.

At a Glance

- *Molecular testing provides rapid turnaround times and accurate results*
- *For bacterial infections, this can mean the difference between appropriate treatment and the risk of poor outcomes and increasing antimicrobial resistance*
- *To defeat resistance, labs must not only identify the causative pathogen, but also determine its most likely antibiotic susceptibilities*
- *Even in their early stages, rapid molecular diagnostics have yielded significant improvements in outcomes for patients with infectious diseases*

The rapid spread of resistance

It would be difficult to overstate the severity of the ongoing public health threat caused by antibiotic resistance. Infectious diseases long thought to be conquered have arisen again – and, in some cases, they are impossible to treat with current medications. Experts estimate the global death toll at 700,000 per year, and that number is expected to rise to 10 million by the year 2050 (1).

When the World Health Organization (WHO) released its first report on antimicrobial resistance in 2014, then-Assistant Director-General for Health Security Keiji Fukuda said in a statement, "Without urgent, coordinated action by many stakeholders, the world is headed for a post-antibiotic era. […] The implications will be devastating (2)." In the report, scientific experts detail findings such as the presence of carbapenem-resistant *Klebsiella pneumoniae* throughout the world (3). This bacterial strain, in some geographic regions, now makes up the majority of *K. pneumoniae* cases diagnosed – and it is resistant to even the last-resort treatment available.

Yet, believe it or not, this "unbeatable" bug is not even among the most urgent threats from drug-resistant bacteria. Globally, those threats include carbapenem-resistant Enterobacteriaceae, *Clostridium difficile, Neisseria gonorrhoeae,* methicillin-resistant *Staphylococcus aureus,* and tuberculosis (4–6).

"Getting results faster not only improves patient outcomes, but also helps check the spread of antibiotic resistance."

More and more, resistance is not limited to a single class of antibiotics. Pathogens are increasingly found to carry resistance markers for multiple treatments, making it difficult for treating physicians to get the upper hand. In a survey of infectious disease practitioners, the majority of respondents reported seeing at least one case in the prior year where the infection-causing bacterial strain was resistant to all available antibiotics (7).

Stewards of health

With the growing prevalence of antibiotic resistance, it is no longer sufficient for clinical laboratories to simply identify the pathogen responsible for a patient's infection; they must now also detect markers of antibiotic resistance to help physicians select the treatment most likely to be effective. Ideally, that treatment will be a targeted drug (to help prevent further acquisition of antibiotic resistance).

Rapid molecular diagnostics have revolutionized the way clinical labs meet these demands – and the speed with which they do it. Culture-based testing typically requires at least a day to identify the infectious organism, followed by two days or longer to reveal antibiotic resistance profiles. Molecular

testing, on the other hand, can deliver strain identification results in a couple of hours and report resistance markers in less than a day. Getting results faster not only improves patient outcomes, but also helps check the spread of antibiotic resistance.

Rapid diagnostics are also a powerful tool for antimicrobial stewardship programs, which typically aim to reduce the unnecessary use of antibiotics. Identifying bacterial strains early – or ruling out a bacterial source of infection altogether – makes it possible to get patients off the broad-spectrum antibiotics commonly used before diagnostic results are available.

In a recent presentation to the South Central Association for Clinical Microbiology, Ronald Reitenour, Area Coordinator for Microbiology, HAZMAT, and Disaster Preparedness at Riverview Health in Indiana, reported that, by adopting rapid microbial testing for its antimicrobial stewardship program, his hospital had reduced the average length of patient stays, improved outcomes, and lowered costs (8). Similar results have been seen at other institutions. In Florida, a study of more than 400 patients in several community hospitals found that the switch from traditional blood cultures to molecular testing decreased the average time to get patients on appropriate antibiotics by 30 percent – a time savings of 18 hours (9). The same study also showed that the molecular approach contributed to lower readmission rates. Finally, a third study showed that the move to molecular testing enabled doctors in the Orlando Health network to stop unnecessary antibiotic use 27 hours sooner than with traditional testing methods (10).

In some cases, medical teams have determined that it makes sense to expand the use of rapid molecular diagnostics to screen all patients admitted to hospitals, rather than just those with obvious infections. For example, many people are known to be colonized with *C. difficile*, even though they may be asymptomatic. Research has demonstrated that isolating these patients can reduce the rate of hospital-associated *C. difficile* infections – often a challenge in patients already suffering from other illnesses or injuries, and particularly so when the disease does not respond to antibiotic treatment. A study at an acute care facility in Canada found that, after the implementation of screening protocols for all patients, the incidence of *C. difficile* infections dropped substantially; in fact, the approach was estimated to have prevented 62 percent of expected infections and saved as much as CA$627,000 (11). In Denmark, a study in two university hospitals found that patients exposed to asymptomatic carriers of *C. difficile* were more likely to develop infections – 4.6 percent of those patients suffered *C. difficile* infections, compared to only 2.6 percent of patients who were not exposed to asymptomatic carriers (12).

Looking ahead

The epidemic of antibiotic resistance demands new solutions and creative approaches from all stakeholders, including clinical lab and hospital teams, diagnostic developers, and pharmaceutical and biotechnology companies. Rapid molecular diagnostics represent a relatively new weapon in the stewardship arsenal, helping to avoid two of the biggest contributors to the acquisition of drug resistance: unnecessary antibiotic use and prolonged exposure to broad-spectrum antibiotics. Increased adoption of these tests should significantly boost the effectiveness of antimicrobial stewardship programs and other infectious disease control measures, leading to a stronger defense against infection and better health for patients.

Sherry Dunbar serves as Senior Director of Global Scientific Affairs for Luminex, Austin, USA.

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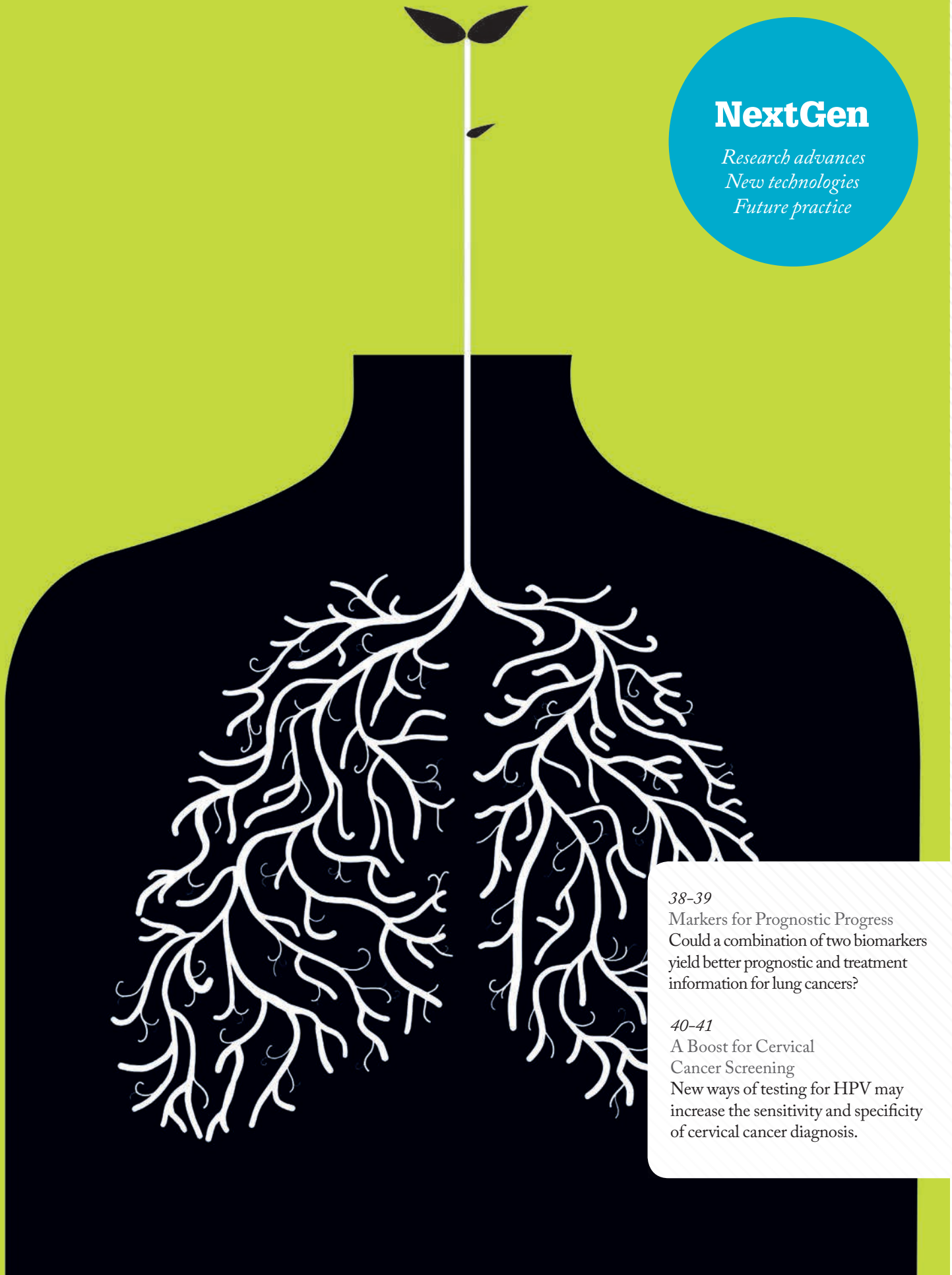

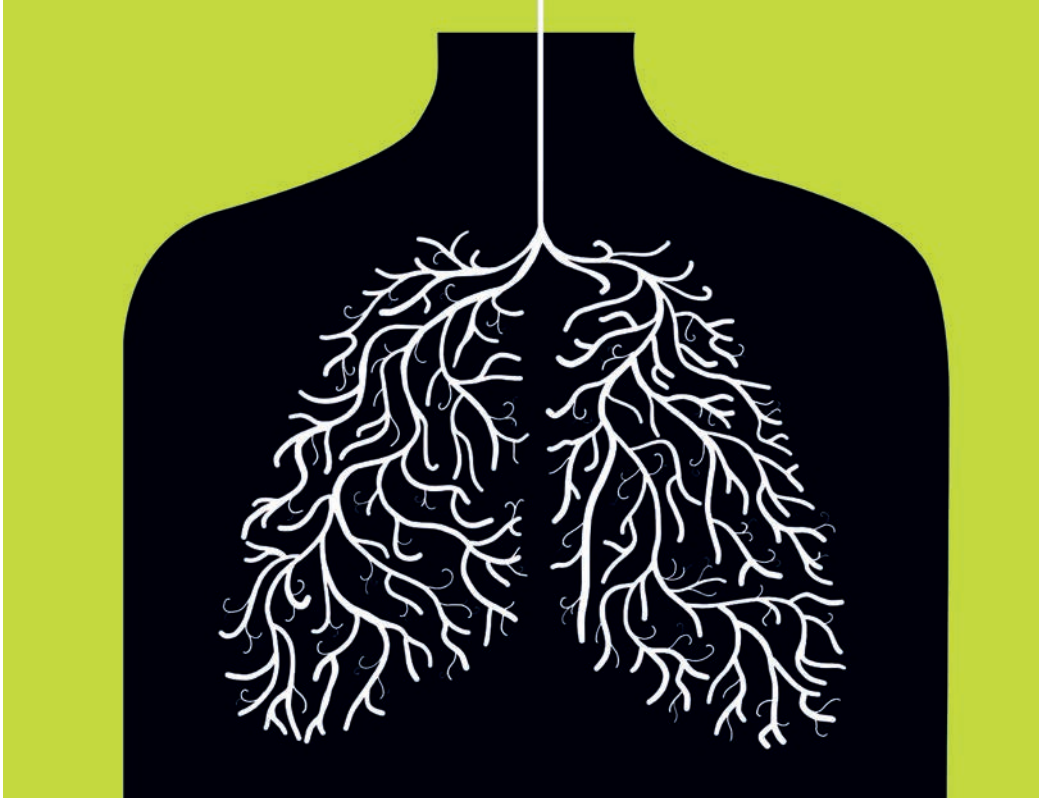

Markers for Prognostic Progress

A combination of new biomarkers could aid decision-making in the clinical management of early-stage lung cancers

By Michael Schubert with Ana Robles

Lung cancer remains the top killer worldwide among cancers, causing nearly one-fifth of all cancer deaths worldwide (1). But not every patient with lung cancer faces the same fate; those diagnosed early have a good prognosis, with one-year net survival rates for stage I cancers at 83 percent (compared with only 17 percent for those diagnosed at stage IV). It's clear that early diagnosis confers a strong survival benefit – and biomarker analyses that yield prognostic and treatment decision information only compounds this advantage.

At a Glance

- *Lung cancer is the most fatal cancer, causing nearly one-fifth of all cancer deaths worldwide*
- *To improve survival, it's vital to diagnose and treat lung cancer early, so we need better diagnostic and prognostic biomarkers*
- *A combination of markers, including HOXA9 promoter methylation and blood vessel invasion, may assist with prognosis of early-stage lung cancer*
- *Ideally, these two biomarkers could be used in combination with a range of others to yield the most detailed picture possible of an individual's disease*

Yet only about a quarter of lung cancer patients are diagnosed at an early stage, with approximately half diagnosed at stage IV. Every available piece of information counts when aiming for the best possible outcome – especially when the disease is spotted so late. The analysis and integration of different types of biomarkers is a core principle of precision oncology, as it allows us to track the potential course of a patient's disease, and to select and individualize treatment plans as quickly and efficiently as possible. To that end, Ana Robles and her colleagues (2) have identified a combination of an epigenetic and an immunohistochemical biomarker (*HOXA9* promoter methylation and blood vessel invasion, respectively) that may help inform the clinical management of patients with early-stage lung adenocarcinoma (see Figure 1).

Prognostic promoters

Tumor tissues commonly feature alterations in DNA methylation. Moreover, specific changes in methylation are consistent across tumors, meaning that their patterns can serve to discriminate tumor tissue from its normal adjacent tissues. Concurrent methylation in the promoter regions of developmental genes (collectively known as homeobox, or HOX, genes) is one such recognized feature of lung cancer. Among these genes, *HOXA9* has generally stood out for being the most differentially methylated between tumor and non-tumor tissues – and, therefore, the most potentially useful for lung cancer diagnosis and prognosis. Homeobox genes are epigenetically regulated in embryonic stem cells, which could mean that high *HOXA9* methylation identifies a less differentiated chromatin state, or even subpopulations of cancer stem cells that may be responsible for recurrence and resistance to therapy. Blood vessel invasion (BVI) is a recognized prognostic factor in many cancers and identifies neovascularization of the primary tumor, which is a critical step for tumor cell dissemination and metastasis. Why measure both together? The same biospecimen can be used for both, and each is an independent biomarker, so the combination is strongly predictive of poor outcome.

Many lung cancer prognostic biomarkers have been identified through the molecular analysis of fresh-frozen resected tissues – but this type of biospecimen is rarely available in routine clinical practice. To implement a new biomarker in the clinic, you need a robust and technically simple assay that can use materials generated

for routine pathology after surgical resection as an input – for example, formalin-fixed, paraffin-embedded (FFPE) blocks. FFPE tissues are generally available for the assessment of biomarkers after diagnosis and staging, and they are very useful in the discovery and clinical development of biomarkers; however, their value for molecular analysis can be limited because of low DNA quality. And so, evaluating an immunohistochemical biomarker such as BVI in parallel with an epigenetic biomarker is a valuable strategy for prognostic prediction.

Validating an assay in archival FFPE tissues facilitates its clinical translation. Droplet digital PCR (ddPCR) is especially suited to evaluate small biomarker panels because it's fast, simple, cost-effective, and ultra-sensitive. The technique speeds up the validation of new biomarkers to move them rapidly and efficiently along the pipeline to the clinic. The process of biomarker validation requires optimization of the ddPCR reaction for sensitivity and specificity. In the case of a methylated marker, this includes reaching an acceptable lower limit of detection of a control methylated DNA fragment on the background of unmethylated DNA, to mimic the conditions likely to be found in actual samples.

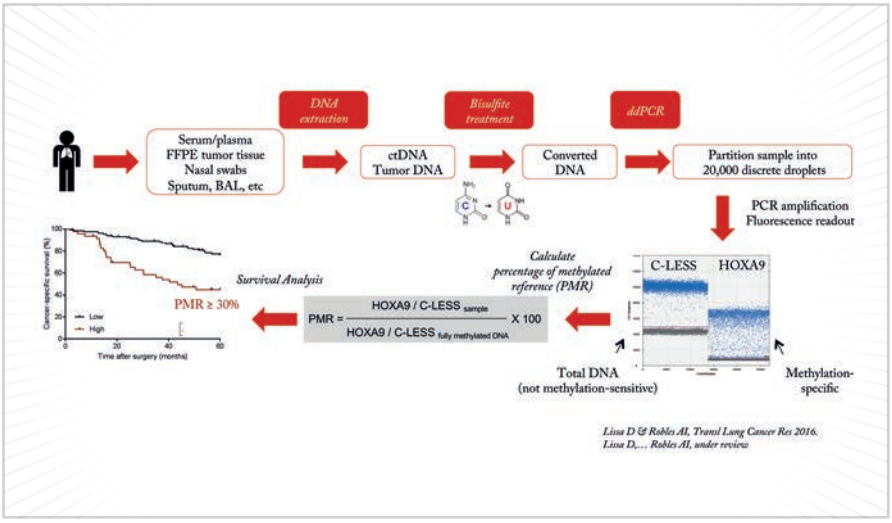

Figure 1. A schematic of the method developed by Robles and colleagues.

Beyond the lung

Neovascularization is a common theme in many cancers, so it seems clear that BVI has applications outside of lung cancer. *HOXA9* methylation has also been described in oral and esophageal cancers, so it's possible that this epigenetic biomarker could also have further applications, but it appears to have the highest prognostic value for lung cancer, where it has wide applicability. For instance, in the minority of Stage I lung cancer patients who receive adjuvant therapy, the *HOXA9* methylation assay is still prognostic. Additionally, the assay was able to provide prognostic information in lung cancer patients without a history of cigarette smoking.

At the moment, Robles is collaborating with a group interested in evaluating *HOXA9* methylation by ddPCR in their cohort of lung cancer patients. And there are plans to test the performance of the assay using FFPE tissues for the prognostic classification of individuals who developed lung cancer within the National Lung Screening Trial. In the context of this large screening trial, patients were diagnosed after a positive low-dose computed tomography (LDCT) scan. This type of screening is becoming widely implemented and is helping to diagnose lung cancer at an earlier stage. Up to 60 percent of lung cancers diagnosed after a positive LDCT scan are Stage I, which is the intended target of our prognostic assay. It's possible that, one day, the two tests could work together – LDCT scanning to detect the cancer in its earliest days, followed by methylation and BVI analysis for prognosis and to assist with treatment decisions.

Robles and her colleagues are also employing machine learning tools to integrate different omics data for individual patients with stage I lung cancer. The goal? A better understanding of the biology of the disease, so that we can identify the most informative biomarkers. In general, large prospective studies will be needed to validate the clinical utility of biomarkers. The hope is that, with novel technologies such as ddPCR and machine learning, they will be able to identify and validate biomarkers with ever-increasing speed and ease.

Ana Robles is an Associate Scientist at the National Cancer Institute, Bethesda, USA. Her research focuses on omics-based identification and functional characterization of clinically informative biomarkers of lung cancer.

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A Boost for Cervical Cancer Screening

Droplet digital PCR + HPV ccfDNA assay = diagnostic at low cost, with high specificity

By Liang Cao and Zhigang Kang

Despite a declining incidence rate in the US, cervical cancer remains the fourth most common cancer in women worldwide, causing 270,000 deaths in 2015, according to the World Health Organization. High-risk, persistent HPV infections are often a precursor to the disease, with about 0.8 percent of patients developing cancer over 10 to 30 years. The current HPV test with Pap samples, although very sensitive, can be relatively nonspecific and requires extensive follow-up testing for high-risk, HPV-positive patients. To tackle that problem, we and our colleagues at the National Cancer Institute (NCI) decided to create a more specific alternative by developing a blood-based HPV circulating cell-free DNA (ccfDNA) assay (1) – a test we believe would be a potentially valuable resource for the early detection of cervical cancer.

Our involvement in cervical cancers came about thanks to two main driving factors. First of all, there is a significant need for clinical biomarkers for the development of novel immunotherapies, including checkpoint antibody-based and T-cell based therapies (both investigational therapies originally invented at NCI). Specifically, there is an immediate need to select patients based on their HPV genotype for experimental T-cell therapies. Second, we recognized the real potential of using circulating cell-free HPV DNA for patient monitoring; the high copy numbers of virus genome per cancer cell and the lack thereof in normal cells led us to consider the use of such an assay for treatment assessment and recurrence evaluation.

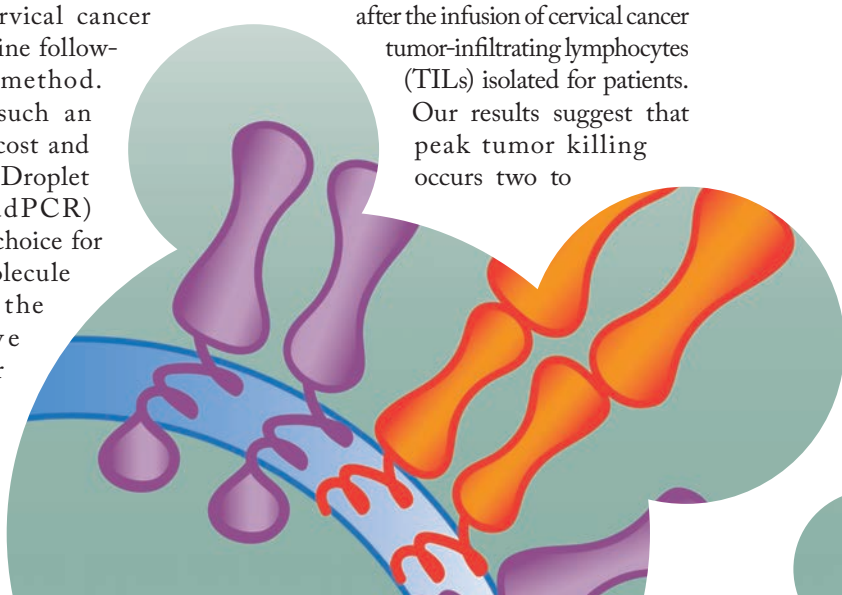
In our initial blinded tests in 2017, most patients had already undergone local surgical or radiation therapies, which meant that the tumor cells were no longer at the original site. We suggested that an HPV ccfDNA assay would complement CT scans in metastatic cervical cancer patients as a routine follow-up monitoring method. Why? Because such an approach is low-cost and non-radioactive. Droplet digital PCR (ddPCR) was the obvious choice for single DNA molecule counting – it's the most sensitive method for single molecule detection, and it provides accurate quantification without the need for test calibration. We observed the long-term clearance of HPV ccfDNA only in cervical cancer patients who had complete responses to an experimental T cell therapy.

"Many cancers in the near future will be treated based on molecular or mutational analysis, rather than histological classification."

Although our aim was to create a tumor marker, we were still surprised by the rapid induction of HPV ccfDNA immediately after the infusion of cervical cancer tumor-infiltrating lymphocytes (TILs) isolated for patients. Our results suggest that peak tumor killing occurs two to

At a Glance

- *Cervical cancer is the fourth most common cancer in women, causing 270,000 global deaths in 2015*
- *The existing test for human papillomavirus (HPV) – a key risk factor of cervical cancer – lacks specificity*
- *A combination of droplet digital PCR and a circulating cell-free HPV DNA assay offers higher specificity for the cancer*
- *Studies have shown a 100 percent success rate in identifying and genotyping HPV-positive with recurrent metastatic cervical cancer cases; the ddPCR method is undergoing clinical trials for patient selection for T-cell immunotherapies*

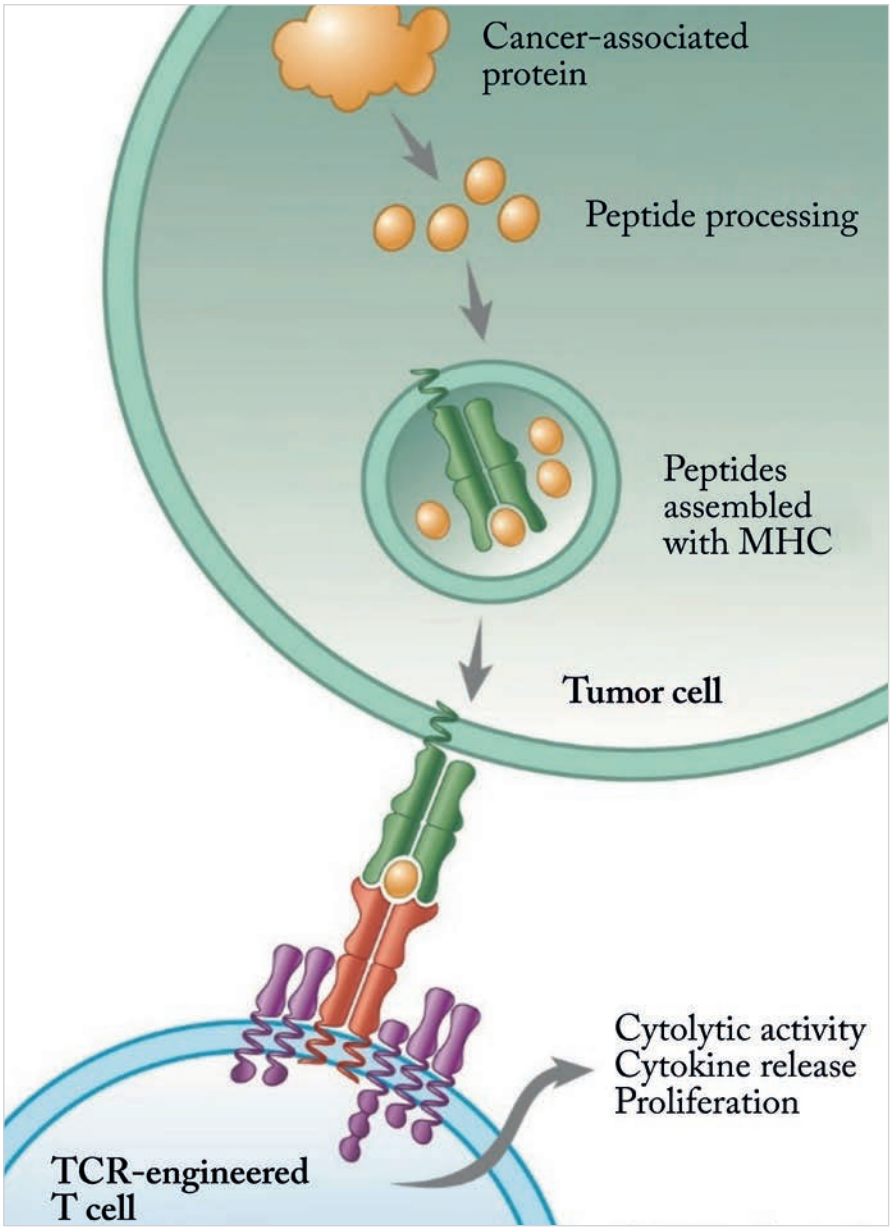


three days after TIL infusion, which means that ccfDNA analysis may provide useful proof-of-concept information for an early investigational therapy.

Our data further show that ddPCR-based HPV genotyping can also be very accurate in determining the viral genotype: we were able to correctly identify the HPV tumor genotypes in 87 out of 87 blood samples from HPV-positive cervical cancer patients. This would allow the selection of cervical cancer patients for HPV-targeted T-cell therapies. Quantitative PCR for ccfDNA has already been approved by the FDA for detecting *EGFR* mutations in lung cancer patients and is used for Epstein-Barr virus in nasopharyngeal carcinoma, so the precedent has already been set for its use in similar scenarios. Additionally, our ddPCR test is currently under clinical evaluation for patient selection in T-cell immunotherapies to replace the need for invasive biopsies. Over the next few years, the successes of these clinical trials will determine the test's potential as a companion diagnostic.

If our trials are successful, lab implementation should be relatively straightforward and could even translate to a number of applications beyond cancer diagnosis. For example, after liquid biopsy reveals genotyping, ccfDNA analysis can let you know how compatible the intended therapy is with the individual patient, thus bypassing an invasive tissue biopsy. Such an advance would mean that only patients with specific viral genotypes would be enrolled for the corresponding treatment. HPV ccfDNA could also be used to monitor a patient's response during therapy and provide information on the likelihood of disease recurrence. Our approach isn't intended as a replacement for CT scans, of course, but rather as a low-cost, non-radioactive alternative that could be used as a marker for routine cervical cancer testing.

Our assay is traveling beyond our own research. Colleagues within NCI are currently working on the commercialization of T-cell therapies by using the novel approach of T-cell receptor (TCR) transfer, using our assays to assist with their work.



Molecular diagnostics – either via tissue or liquid biopsy – is playing an increasingly significant role in determining cancer treatment, either with targeted or immunotherapies. Many cancers in the near future will be treated based on molecular or mutational analysis, rather than histological classification, so assays like ours are useful in facilitating that transition.

Liang Cao is head of the Molecular Targets Core Lab in the Genetics Branch of the National Cancer Institute.
Zhigang Kang is a staff member in the Molecular Targets Core Lab in the Genetics Branch of the National Cancer Institute, Washington, DC, USA.

Reference

1. *Z Kang et al., "Circulating cell-free DNA for metastatic cervical cancer detection, genotyping, and monitoring", Clin Cancer Res, 23, 6856–6862 (2017). PMID: 28899967.*

A New Look at Leukemia and Lymphoma

Flow cytometric immunophenotyping can assist with the diagnosis of a range of lymphoid and myeloid neoplasms

Flow cytometry is an example of a rapidly evolving IVD technology that is migrating from the highly specialized laboratory to routine clinical testing in the core lab. It has been widely adopted for the assessment of leukemias and lymphomas and is part of the trend toward early detection and monitoring, bringing diagnostics closer to patients. 2017 marked a milestone for the technology when the US Food and Drug Administration (FDA) granted de novo authorization for the in vitro diagnostic use of the first pre-formulated antibody cocktail for leukemia and lymphoma immunophenotyping.

Flow cytometric immunophenotyping evaluates the presence and absence of specific antigens for each individual cell in the specimen. Interpretation of aberrant immunophenotypes requires skill in recognizing the significance of different patterns. As part of the test manufacturer's available information, a unique case book has been created to aid in this complex pattern recognition. The following case is just one example.

Diagnosing B cell lymphoblastic leukemia/lymphoblastic lymphoma

A 33-year-old male presents with anemia, thrombocytopenia, and circulating atypical mononuclear cells. Using flow cytometric immunophenotyping, we are able to identify a phenotypically distinct population of cells with low light scatter properties that express CD10, CD19, CD34, and CD38. CD45 expression ranges from low density to very low density. Neither CD20 nor immunoglobulin light chain expression is noted.

Taken together, this is most consistent with a diagnosis of B lymphoblastic leukemia/lymphoma. Blast crisis in chronic myelogenous leukemia is also a diagnostic consideration. Correlation with clinical and laboratory data is recommended, and additional immunophenotyping may be warranted.

The dot plot in Figure 1 permits distinction of the usual populations including lymphocytes (Gate A, red), monocytes (Gate B, green), and granulocytes (Gate C, blue). Gate D (pink) is in the area typically occupied by myeloblasts, but may be used to highlight other populations. By applying different colors to the events captured by each gate, the various populations may be followed throughout the analysis (see Figure 2). Gates should be adjusted to conform to the naturally occurring separations among the populations but, where no separation is observed, users may make an estimate based on experience. The aberrant events in this sample fall largely within Gate D. Some of the events fall outside of Gate E, and Gates D and E may be adjusted.

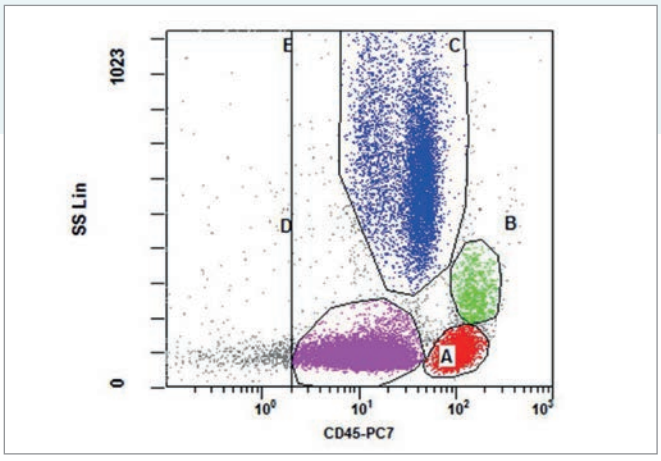


Figure 1. This CD45 vs. side scatter dot plot is ungated and shows all events collected. Gate E includes all CD45-positive events and may be used to set a stop count gate during acquisition to ensure that sufficient non-debris events are collected. Gate E may also be used to exclude CD45-negative debris from the analysis, but these events should not be ignored when analyzing a case, as some aberrant populations are CD45-negative.

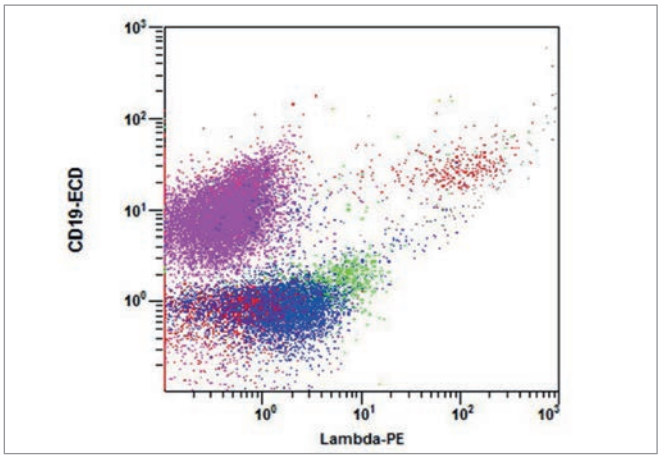


Figure 2. This lambda vs. CD19 dot plot is gated on E and shows all CD45-positive events. The CD19-positive events are split equally between lambda-positive and lambda-negative populations, consistent with polyclonal B lymphocytes. The aberrant population (pink) expresses CD19, but is negative for kappa immunoglobulin light chains.

The ClearLLab casebook includes 16 such illustrative clinical vignettes with characteristic findings typical of various lymphoid and myeloid neoplasms, as well as examples of patients with indications of an underlying neoplastic process, but in whom no immunophenotypic abnormality is identified. Users can also download the data to continue their diagnostic practice.

See http://info.beckmancoulter.com/casebook-usa for more information and to obtain a copy of the book and data.

The clinical flow team at Beckman Coulter Life Sciences are exhibiting at AACC 2018 at booth #3612. For more information on Beckman Coulter Life Sciences, see www.beckman.com/home

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The Lab of the Future – Now

A new flexible laboratory space allows for quick and easy adaptation to evolving medical needs

William Aryitey interviews Melissa Pessin

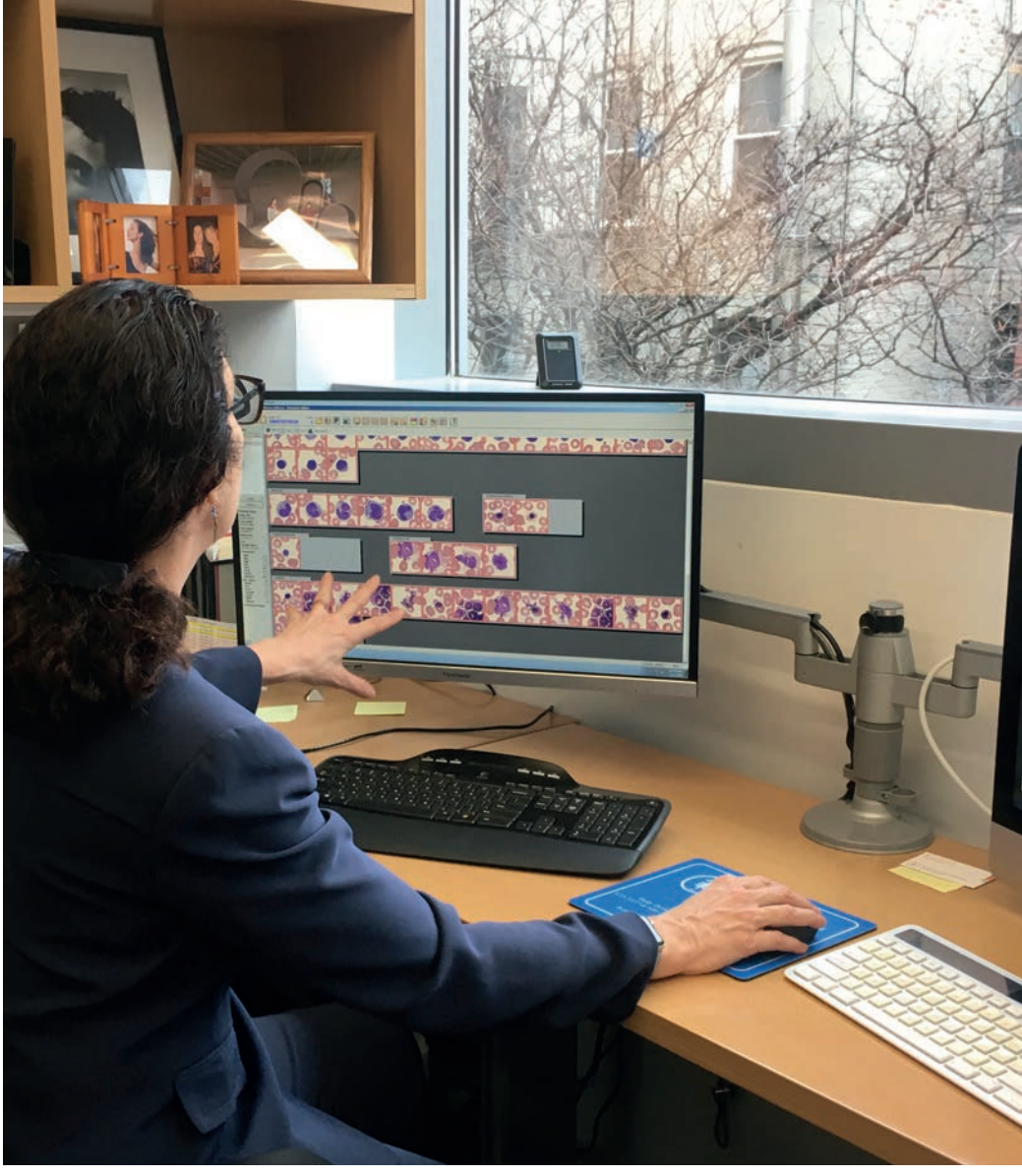
Growth and evolution are important aspects to embrace in science – and they're vitally important when it comes to the laboratories behind cancer testing. When Memorial Sloan Kettering Cancer Center (MSK) wanted to grow their laboratory to accommodate more staff and facilities, they saw an opportunity to review their approach to creating a lab and decided to build one from the ground up to make a space that could adapt to their needs as they grow and evolve.

Laying a foundation

The groundwork for the new building began nearly six years ago with supporting future growth at the top of MSK's priority list. The facility in use at the time was a challenge to remodel, so the decision to relocate led them to a spacious building – formerly an old garage. That construction posed quite a few challenges – digging into the ground uncovered an ancient creek bed – but as the rebuilding began, the team's ideas of what the lab could be grew more complex. MSK's Chair in Laboratory Medicine, Melissa Pessin, says, "We were starting almost from scratch, so why not push the possibilities as far as they could go?" The ambitious project came at the cost of time. The initial completion date was planned for 2015, but ended up being 2017. The results, however, seemed well worth the wait. "What we now have is a uniquely engineered building that is tailored not just for our current needs, but for what we anticipate needing in the future as well," says Pessin.

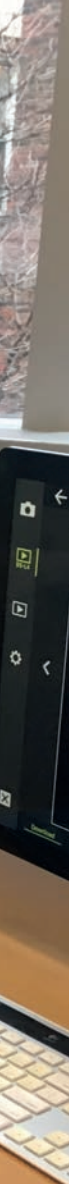
MSK's new lab is also the first in the United States to feature an automated line with a vertical transport module, which allows medical laboratory assistants (MLAs) to load specimens onto the system, transport them to another floor, and have the samples immediately transferred to an instrument, greatly reducing turnaround time. Pessin adds, "Here in crowded New York City, we're quite space-constrained, so the vertical transport module allows us to spread our workspaces across several floors without losing efficiency. It's a lot faster than having someone carry samples to another floor or using our ETV (elevating transfer vehicle) to send up batches. With the automated line, samples get to the floor they need to be in seconds."

The concept and execution of the building has been such a success that MSK's anatomic pathology colleagues are looking at the lab as a model for the planned expansion of their molecular facilities.



At a Glance

- *MSK has built a modern, forward-thinking clinical laboratory for its cancer center*
- *The open floor plan, mobile work surfaces, and uniquely designed vertical transport systems facilitate continuous workflow redesign and improvement*
- *Positioning the clinical leadership adjacent to one another fosters cross-specialty collaboration*
- *Focusing on the scientists' needs helps build a more efficient environment*



"With cancer care moving more and more toward the outpatient model, it's important for us to turn results around rapidly."

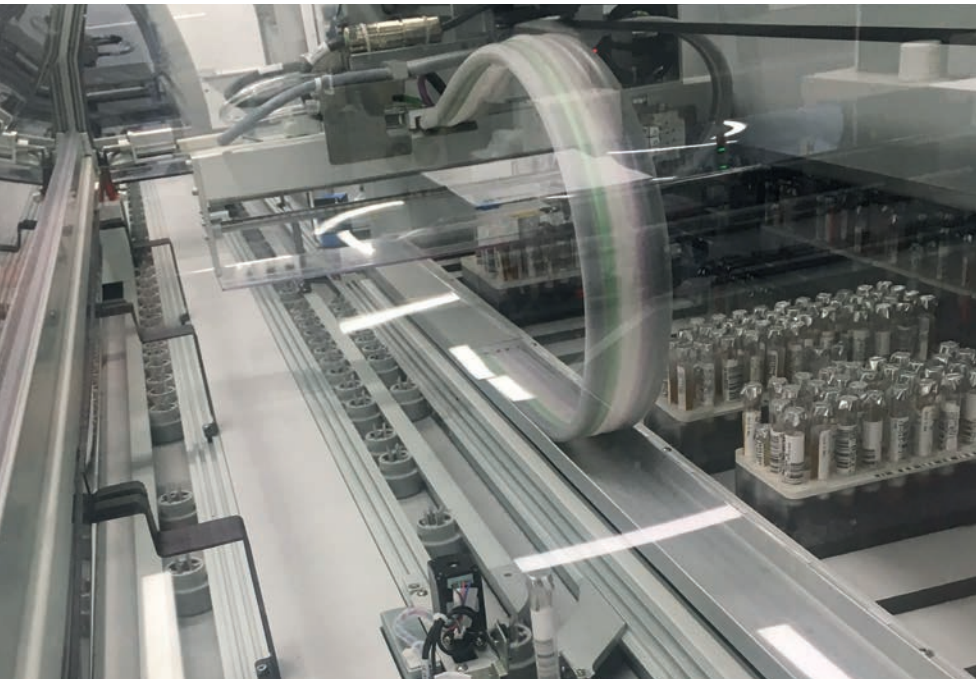
Design for collaboration

MSK has a number of locations in and around Manhattan, but also receives samples from Long Island, New Jersey, and Westchester. Those satellite locations conduct basic chemistry and hematology tests on site, but samples for other tests are sent to the new facility. "With cancer care moving more and more toward the outpatient model, it's important for us to turn results around rapidly and get them back to the requesting clinicians so that they can select and administer treatments quickly and efficiently," says Pessin.

The new building is currently up and running with services that include blood banking, clinical hematology, clinical chemistry, microbiology, cell immunology, flow cytometry, and a cell therapy laboratory (the first section to open in the building). And, alongside their plan for adaptation, the space has the capacity to expand into other areas. When designing the layout, the staff working in different labs were invited to provide input into their respective setups.

The microbiologists have lab automation equipment to speed up processes that have largely been manual – at least for bacteriology – and, in the future, MSK plans on adding a human leukocyte antigen laboratory to the facility.

"The new open plan structure has allowed more conversations across specialties, resulting in new ideas and great collaborations."



By focusing on flexibility and having the additional room to grow, CAR T therapy – which has become a prominent research topic since the early days of the building design – was easily accommodated. What happens now? When the cell therapy lab receives patient blood cells from the MSK donor room, the cell immunology laboratory characterizes those cells to ensure there are sufficient T cells prior to sending them on to various companies or an MSK lab for engineering. When the CAR T-cells are received, the lab makes sure that they are prepared for infusion before they are administered to patients. Another example of flexibility: the lights, power, water, and air are channeled through the ceiling, which means that certain lab areas can be shifted in size and position, depending on what tests

or services are needed at any time.

Pessin also notes that the work life of the pathologists has improved. There are no more cubicles (but to allow for the privacy required by HIPAA, there are real offices), and the new open plan structure has allowed more conversations across specialties, resulting in new ideas and great collaborations. Sometimes, when designing a lab, the comfort of the scientists working there takes a backseat to function – but that's a pitfall MSK made a strong effort to avoid when designing the building. "We provide terraces they can use when the weather permits, food areas if people don't want to eat off-site, showers in the basement, and – something I think the staff really appreciate – natural light. That can be a rarity for laboratory medicine professionals, because many places have labs in the basement. We wanted our staff to see the sun!"

Looking to the future

Currently, the teams are still working to further optimize their processes. Although the lab was designed with efficiency in mind, Pessin says, "It's difficult to plan the most optimal workflow in advance – especially in a space as unique as ours." Despite this challenge, they have already seen a great improvement in turnaround times, and, once microbiology automation is fully implemented, they expect to see tremendous further progress. With that system in place, they'll be able to obtain automatic, real-time readouts instead of manually checking on each bacterial culture every day – an upgrade that could save at least 12 hours. Among other improvements, they hope this will make a big difference to the length-of-stay for patients.

Pessin concludes, "We're all very excited to be in this building. And we are grateful to MSK for recognizing the value of its clinical laboratories and investing to help make things better for our patients. I hope that sharing our approach to workflow and lab design will help other hospitals and other laboratories optimize their own processes, so that we are all able to help our patients to the best of our abilities."

Melissa Pessin is Pathologist and Chair in the Department of Laboratory Medicine at Memorial Sloan Kettering Cancer Center, New York, USA.

Lessons Learned, with Pier Paolo Pandolfi

From philosophy to cancer research, Pandolfi has traveled a fascinating career path. Here, he shares his story – and the many tips and tricks he gathered along the way

Don't be afraid to make a U-turn toward your true calling

My first major was actually philosophy. In Europe, you have to choose either medicine or philosophy, so I chose the latter. My family were all in humanities. I really loved philosophy – and still do – but, during my studies, I realized the topics that stuck out to me were based in the core of scientific reasoning: epistemology, philosophy of science, logic, you name it. So, I asked myself: Do I just want to *discuss* science, or do I want to *become* a scientist?

Because of my late switch to medicine, I was quite old when I finally graduated. Luckily, the speed at which my early career was propelled made up for it. During my final year of study in medicine, we ended up cloning the translocation associated with acute promyelocytic leukemia (APL). That discovery was transformative for me, the research group, and patients – but it was just the first step; in the following years, we were able to model the disease in mice. It's because of this work that I was later recruited by Memorial Sloan Kettering Cancer Center in New York to run my own lab. While there, my colleagues and I completed the bench-to-bedside cycle by testing drug combinations that might cure APL. A derivative of vitamin A (ATRA) plus arsenic trioxide, or ATRA plus histone deacetylase inhibitors, proved effective and curative.

That early stretch of my career was during the Clinton era in the USA, when the National Institutes of Health (NIH) was extremely well-off, so it was a fantastic start for me. In subsequent decades, the economy has slowed down, but despite that and the restrictions and issues with this administration, I think the US remains a beautiful place for research (especially Boston!). It really is an exciting environment, full of brainpower, inspiration, and research.

The "eureka" moment can happen at any time – even after discovering limitations

The story of APL was a fantastic journey (1). Much more recently, we discovered that behind the metastatic process in prostate cancer is what we call a "lipogenic switch" – and we believe this could generalize to other forms of cancer

At a Glance

- *Career changes are possible at any stage – so it's important to follow your inclinations*
- *Don't be afraid to question the standard protocols or opinions in your field*
- *No one can excel at everything, but wise choices mean everyone can excel at something*
- *Rewards and honors are wonderful motivation – but don't forget that they belong to the team*

as well. In other words, we realized that cells prone to metastasis activate a lipid-building program, orchestrated via a SREBP transcription factor. This discovery was interesting in its own right because it was triggered by the loss of a gene called *PML*, which I had studied for a long time because it is involved in the pathogenesis of APL. We found that *PML* is also lost in 20 percent of metastatic prostate cancers.

This led to another "eureka" moment. We realized that the field might have made a fatal error in modeling metastasis in mice – simply by not taking into account an easily-missed consideration. The error was in their feed; the mice were fed the standard, relatively low-fat chow that had been the norm for mouse models for the past 20 years. When we switched the mice to a high-fat diet (combined with inhibitor drugs), lo and behold, we saw evolution into aggressive or metastatic cancers. The new model showed genetic, molecular, and environmental support for the notion that fat – either endogenous or exogenous – is a very important ingredient to fuel metastatic spread.

The first author of the study and I are discussing going deeper into our findings on all fronts, to better understand whether or not there may be a lipogenic signature in other diseases, such as prostate cancer. We're collaborating with a group that has collected prostate cancer samples from obese people in an effort to test which fats might provoke a negative effect. We're attempting clinical trials and discussing which of the SREBP inhibitory pathways are clinically viable. We have also talked about the idea of diet – can we do trials with diets? Can we put advanced prostate cancer patients on low-fat diets? But that's a conversation for another day.

To excel, you may need to make a tough call – there are only so many hours in a day…

In the early stages of my research, the idea that one would have genes that caused cancer was beginning to emerge, and that fascinated me. Since then, I've never doubted that I wanted to focus on oncology and molecular biology. As a student, the more lab work I did, the more excited I became by it, to the point where – relatively early on – I knew that I wouldn't be a practicing physician even though I am board-certified. Because of my APL work, I've been lucky enough to pursue my research aspirations and direct a scientific team since the beginning of my career.

> *"I may be the 'coach,' but in the end, it's the team that wins the game."*

Those who love lab work and want to see patients face a challenge; it's not easy to be cutting-edge on two fronts. Because each essentially requires 24/7 work, you'd have to clone yourself to excel in both! This is not to say that it's impossible, because I've known a number of people here at Harvard Medical School who have managed that difficult, but rewarding, path. My advice to those early in their career is to focus on either the research-based or the patient-facing aspect of medicine. However, as the field moves forward, especially in pathology, those two aspects are coming closer together – so maybe that decision won't need to be made in the future.

Enjoy rewards wherever you may find them – but remember that you rarely work alone

From my perspective, the many honors I've received have not been for me alone; they're always for my entire team, who all work tirelessly. I may be the "coach" but, in the end, it's the team that wins the game.

Work in this field is extremely demanding, so honors, in my mind, are a motivation to keep you going. I'm especially grateful to have been honored by my home country of Italy, where I received a knighthood in 2015. Even though I don't live there anymore, it's good to be recognized for my work, because people are sometimes rejected for leaving their home country to pursue work elsewhere. I've been fortunate to have tremendously positive relationships with my collaborators in Italy and often help with research there. I could have stayed in Italy, or even London, but opportunity called for me in the US, and I think any scientist should prioritize that over a sense of obligation to their home, especially early in their career.

There are very few things as rewarding as being recognized for something that not only does good for humankind, but also makes you proud and happy. Discovery, in its own right, is very rewarding – so the idea of understanding something better makes me extremely fulfilled, and the fact that it's a paid career is just a bonus!

The real lesson, and my eternal motivation, is to set the bar very high. We're in this game to cure cancer so we will have to fight hard with every bit of strength if we want to bring that goal to fruition. It's a tough battle, but one worth fighting.

Reference

1. *C Nardella et al., "The APL paradigm and the 'co-clinical trial' project", Cancer Discov, 1, 108–116 (2011). PMID: 22116793.*

The Astropathologist

Sitting Down With… Richard M. Linnehan,
Veterinarian/Astronaut, Houston, USA.

What initially prompted you to study veterinary pathology?

I was always interested in disease processes and epidemiology, but what sparked my interest in veterinary medicine was working for a local equine and large animal veterinarian in high school. I thought it was really cool that a human could actually help animals that big. I was interested in human medicine, too, but I was so intrigued by the veterinary side – especially exotic animals – that I decided to take that route.

I did my veterinary residency in comparative pathology and exotic animal medicine, and then did research and clinical work with zoo animals for several years. My main interest, even then, was in marine mammals and related ecosystems. I met the head of the US Navy's marine mammal program while in veterinary school, and I wanted to be the program's main veterinarian. Even though I had stayed in touch and geared my residency and extracurricular activities toward marine mammal work, I couldn't believe it when I got the job!

The program involved training teams of sea lions and dolphins to perform underwater searches – they were much better than human divers. The animals were never in danger, of course; we just relied on them to detect and report potential hazards. In fact, they were better taken care of medically and nutritionally than most people! We also did some pretty cool research – studies on reproduction, longevity, nutrition, and many other things.

How did that lead to a career as an astronaut?

Before I applied to veterinary school, the only other thing I had ever wanted to be was a fighter pilot. I was accepted into the Air Force and veterinary school at the same time, and my advisor convinced me to choose the latter. During my studies, I used to watch the shuttle launches and ask myself, "How can I still fly?" And I figured that, if the space program was sending up mission specialists, doctors, physicists, and geologists, they'd need a veterinarian as well.

I interviewed with them (for which I can thank my experience as a deploying military marine mammal veterinarian) and, in 1992, they called me to say, "Would you like to be an astronaut?" Well – of course I would!

When you look down at our planet from space, you realize that everything that seems so big and infinite… isn't. It made me realize just how important the concept of "One Health" is. For instance, I'm a veterinarian, so I do comparative pathology – avian, reptile, amphibian, mammalian, human, even invertebrate – but most healthcare professionals focus only on humans. "One Health" brings us back to the idea that it's all connected. Disease entities don't stick to a single organism or environment; they move between them. The planet is smaller than we think. It's a closed ecosystem, and everything that lives will eventually, in some way, affect everything else.

What was your role on your missions?

My first mission, STS-78, was a life and microgravity sciences mission in the Spacelab where we looked at how various biological processes work in space. We looked at the differences in how biological systems function in zero or microgravity versus normal gravity. Everything that has ever lived on Earth has evolved in a 1 G gravity field, so when you take that away, how do things respond?

The second flight – STS-90, or Neurolab – was much more involved. We were looking at nervous system disturbances brought on by spaceflight. We had a vast array of animals – crickets, rodents, even oyster toadfish. Fish are kind of wild because their neutral buoyancy means that they live in a pseudo-microgravity environment – but they rely on gravity to tell them up from down. So how do they maintain buoyancy and navigation in space?

We also liked to joke that we had four big primates on board on whom we performed most of our experiments – us. I was pleased to have the opportunity to use my veterinary degree and pathology training to help the future survival of humanity. If we can't figure out how to keep humans healthy and strong in space, then we're not going to go. We won't travel long distances to other planets, because by the time we get there, we're going to be so unhealthy and so discombobulated that we won't be able to function. I hope our operational studies will one day help humans take to the stars.

My final two missions were not life sciences-related, and allowed me to venture into the world of spacewalking. On STS-109, we rendezvoused with, repaired, and upgraded the Hubble Space Telescope. That was an awesome flight experience and a great mission. My last flight, STS-123, was to the International Space Station, where I and my spacewalk team helped build the space station. We installed the Japanese laboratory, called Kibo, and a giant robot called the Special Purpose Dexterous Manipulator that moves around the station and replaces worn-out parts.

What do you think is the most underrepresented aspect of pathology?

I think it's comparative pathology – the link between disease processes in humans, animals, and the environment. We haven't thought about it as much as we should because we're too focused on our own species, so we don't always consider that the same organisms and errors cause problems to other species as well, even though the presentations may be different to our own. We must remember that it's all interrelated.

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