SEPTEMBER 2018 # 46

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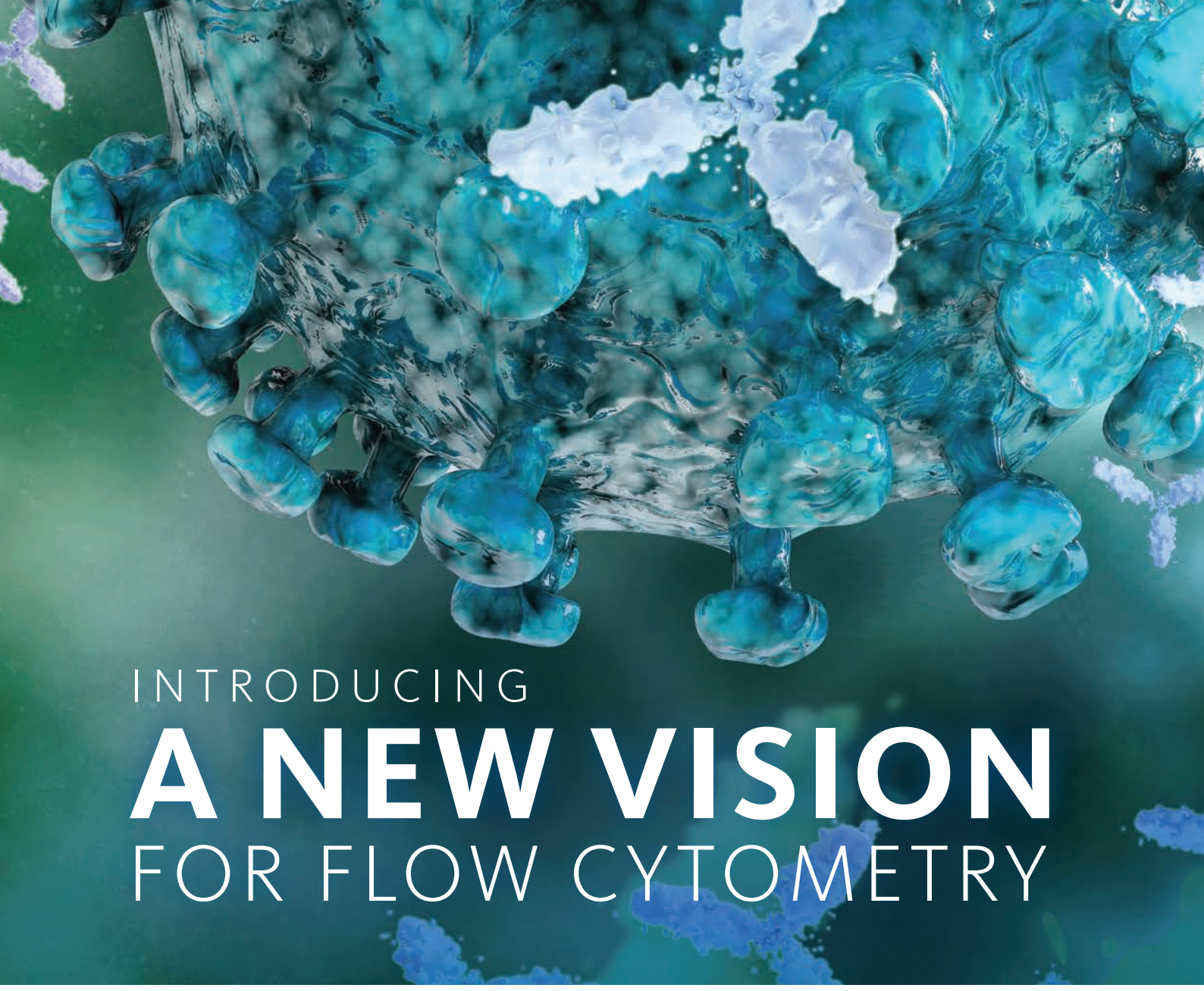

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Case of the Month

A 32-year-old man presented with painless right ear swelling for the past eight months. There is no ear discharge or fever. PAS staining shows no fungal hyphae.

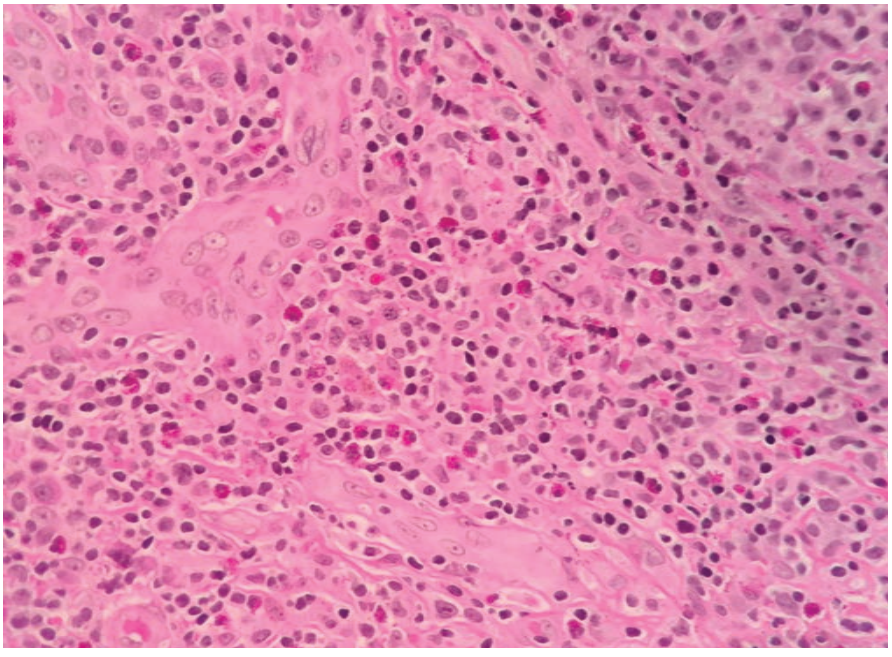
What is your diagnosis?

a *Hodgkin lymphoma*

b *Angiolymphoid hyperplasia with eosinophilia*

c *Parasitic infestation*

d *T-cell lymphoma*



Answer to last issue's Case of the Month…

B. Choroid plexus papilloma

This tumor was diagnosed as a choroid plexus papilloma, WHO Grade I, with extensive calcifications and metaplastic bone formation. Choroid plexus papillomas are rare, slow-growing, benign neoplasms that arise from choroid plexus epithelium and represent 0.3–0.8 percent of all central nervous system neoplasms. The hallmark of these tumors is a papillary architecture. Papillae are composed of cuboidal/columnar cells with basally placed nuclei recapitulating normal choroid plexus architecture (1). The presence of calcifications and ossification is an uncommon phenomenon, particularly to the extent seen in this case.

Reference

1. *DN Louis et al., World Health Organization Histological Classification of Tumours of the Central Nervous System. International Agency for Research on Cancer: 2016.*

Submitted by Ada Baisre, Associate Professor of Pathology and Laboratory Medicine, Rutgers-New Jersey Medical School, Newark, USA.

To register your guess, please go to http://tp.txp.to/0918/case-of-the-month
We will reveal the answer in next month's issue!

Contents

On The Cover

To celebrate the 2018 Power List, this cover features a selection of our finalists.

From the ASCP

Feature

NextGen

Sitting Down With

the Pathologist

ISSUE 46 – SEPTEMBER 2018

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A Powerful Tool

The Pathologist's Power List is not the final word – rather, it's the opener to a conversation

Welcome to the 2018 revival of The Pathologist's Power List! Here, we celebrate the field of pathology and laboratory medicine in a unique way: by asking those in the field to highlight the colleagues and mentors they feel have made – or are continuing to make – a difference to the discipline today.

The Power List is understandably a polarizing topic. It has the potential to spark (hopefully friendly!) competition between those on it – or to raise questions about those who are not. Some race each other to the top. Some energize others to nominate deserving candidates. Some take the list as an opportunity to return the skill and kindness shown by a favorite teacher, highlight the achievements of a peer, or identify a former student who has done much for pathology in only a short career. But the one thing the Power List is guaranteed to do is start conversations.

Whether or not you agree with the list of finalists; whether or not you nominated any candidates; whether or not you yourself are on the list; it's certain that, around the world, professionals in our discipline (and possibly outside of it) will be looking eagerly through the pages, trying to spot friends, colleagues, or even themselves. Some readers will show it to colleagues who were unaware of its existence. Others may even identify a potential future mentor or collaborator by scrutinizing the finalists' biographies. And someone will ask: what makes a great pathologist? (Or, what can I do to be on the next Power List?!)

And as long as it inspires conversations, challenges us to improve, and encourages us to talk with passion about our discipline and those who shine a spotlight upon it, The Pathologist's Power List is doing its job. Thanks to everyone who nominated candidates, and sincere congratulations to everyone who made the final list!

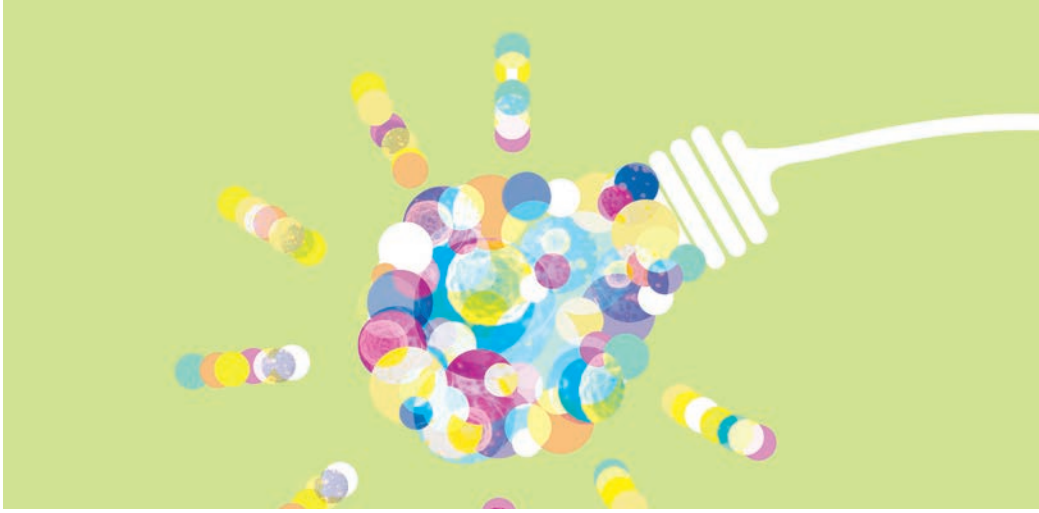
Michael Schubert
Editor

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



Express Insight into Bladder Cancer

Can miRNA expression levels improve subtyping and treatment of bladder cancer?

Bladder cancer: the ninth most common cancer worldwide, with nearly half a million new cases diagnosed each year. Unfortunately, less than three-quarters of those receiving a diagnosis will survive five years, and only about half can expect a decade. Why have those survival rates not significantly improved over time? The disease's heterogeneity may be at least partly to blame, which is why Jun Zhu, Professor of Genetics and Genomic Sciences at the Icahn School of Medicine, opted to investigate a particular subtype of bladder cancer known as p53-like bladder cancer.

"p53-like muscle-invasive bladder cancers are generally resistant to cisplatin-based chemotherapy, but exhibit heterogeneous clinical outcomes with a prognosis intermediate to that of the luminal and basal subtypes," explains Zhu, who is also Head of Data Science at patient-centered predictive health company Sema4. "There are recommended approaches for the treatment of luminal and basal bladder cancer subtypes. However, the optimal approach to p53-like bladder tumors remains poorly defined, so we urgently need novel therapeutic targets and better means to risk-stratify such tumors."

MicroRNAs, or miRNAs, post-transcriptionally regulate gene expression by binding to mRNAs. In humans, base-pairing of a miRNA and its target mRNA is not perfect; rather, it is initiated by six to eight matched nucleotides, meaning that a single miRNA can target many genes and impact multiple biological pathways. The flip side? Such promiscuous binding means that the level of miRNA available for its target genes may be reduced. "Many studies show that miRNA expression levels don't reflect miRNA functional activity well," says Zhu. "Thus, we developed a computational approach – ActMiR – to infer miRNA activity based on expression levels of miRNAs and their predicted target genes."

The procedure requires three pieces of information: (i) miRNA expression levels of each sample; (ii) mRNA expression levels of each sample; and (iii) the predicted target genes of each miRNA. The ActMiR method consists of three steps. First, the researchers estimated the average "baseline" expression of each target gene (while the miRNA was not impacting expression). Next, they defined the "degradation" levels as the difference between the observed expression levels of targeted genes for each sample that were affected by the miRNA and the baseline expression level. Finally, they used a linear model to represent the relationship between degradation levels and baseline expression of target genes for each sample; the coefficient represents the activity of miRNA.

When searching for miRNA biomarkers, says Zhu, most studies associate miRNA expression and clinical phenotypes. "Our approach is unique in multiple ways. First, our computational

approach leverages miRNA activity instead of miRNA expression level to associate with clinical phenotypes. Second, we know that miRNA activities depend on genomic background, so we subtype bladder cancers and then quantify miRNA activity in each subtype." The outcome? Two new prognostic miRNAs identified in p53-like bladder cancer.

"We examined the direct functional target genes of these two prognostic miRNAs and identified biological pathways significantly enriched for functional target gene set of each miRNA," Zhu explains. "The functional target genes of miR-106b-5p were enriched in the bone morphogenetic protein (BMP) pathways, which are associated with bladder cancer invasiveness and tumor recurrence." In in vitro experiments, the researchers showed that knocking down miR-106b-5p expression increased bladder cancer cells' invasiveness, whereas overexpression of miR-106b-5p expression decreased invasiveness.

Bladder cancers are not routinely subject to molecular subtyping due to the heterogeneity within subtypes. "Our results suggest that miR-106b-5p activity can further categorize p53-like bladder tumors into more and less favorable prognostic groups, which provides critical information for personalizing treatment option for p53-like bladder cancers," says Zhu. "We predicted potential therapeutic candidates that might specifically benefit miR-106b-5p underactive p53-like bladder cancers." He and his colleagues are now refining their computational method by taking into account the combinatorial targeting of multiple miRNAs; they are also applying it to additional cancer types. For the p53-like bladder cancer project, Zhu is working with collaborators to test miRNAs and miRNA-drug combinations as therapeutics within in vitro and in vivo models.

"We showed in our analysis that the percentage of p53-like bladder cancer patients responding to PD-L1 blockade immunotherapies is around 20 percent," Zhu adds. "Even though tremendous progress has been made in immunotherapy development, personalized treatments for the p53-like bladder cancers are still urgently needed. We need to accelerate our in vitro and in vivo validation experiments to demonstrate the value of personalized treatments based on molecular subtypes of bladder cancer."

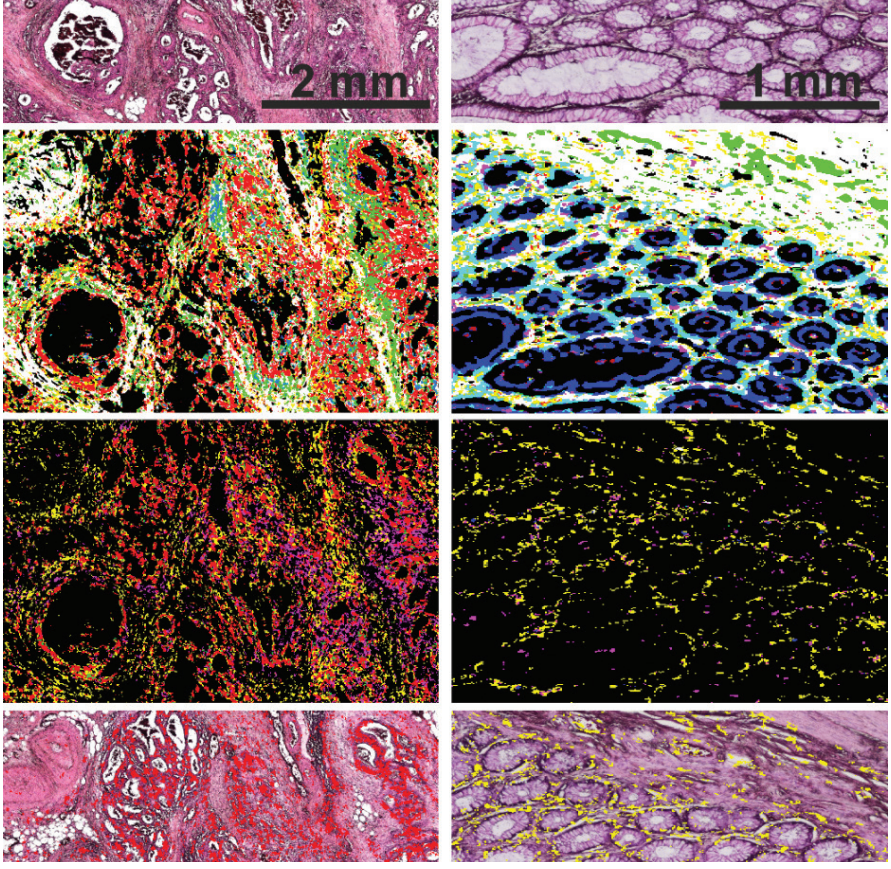
Reference

1. *E Lee et al., "Identification of microR-106b as a prognostic biomarker of p53-like bladder cancers by ActMiR", Oncogene, [Epub ahead of print] (2018). PMID: 29970902.*

No Label? No Problem!

Frederik Großerüschkamp and Klaus Gerwert

describe label-free digital pathology for diagnosis and biomarker research



Credit: Frederik Großerüschkamp and Klaus Gerwert

Today, the gold standard for clinical cancer diagnosis is the visual inspection of H&E-labeled tissue thin sections by a pathologist. Coming in at a close second is the immunohistochemical stain. But proper evaluation of these labeled samples depends on the pathologist's expertise and the reliability and reproducibility of the staining – aspects that may vary from one situation to the next.

To overcome that obstacle, we established a technique for classification of tissue thin sections that is both label-free and inter-/intra-observer-independent. Our infrared (IR) imaging uses spatially resolved infrared spectra as fingerprints for biochemical disease status. The spectra are automatically classified through bioinformatics, eliminating the variability introduced by a subjective observer.

In this new approach, we image the unstained tissue with an infrared microscope; the image is then classified bioinformatically. The resulting index color images represent the tissue classification – including cancer type, subtype, tissue type, inflammation status, and even tumor grading. As an example, we established a label-free classification of thoracic tumors and their subtypes with a sensitivity of 91 percent and a specificity of 97 percent compared with histological annotation (1). We even achieved an accuracy of 96 percent in the differential diagnosis of the subtypes of lung adenocarcinoma.

The main hindrance for clinical use has been the slow data acquisition speed of older IR imaging systems. In a pioneering study, we showed for the first time that a new laser-based wide-field IR imaging microscope could be used to accurately classify colorectal cancer tissue 180 times faster than previous IR technologies (2) – speed that makes it suitable for clinical use. Colorectal cancer is one of the most common tumor diseases and has high survival rates if caught at an early stage. We studied 100 samples of stage II and III colorectal cancer tissue and 20 tumor-free tissue samples and developed a workflow that enabled us to classify tissue for diagnosis in about 30 minutes (for large thin sections; smaller regions of interest take only a few minutes). Better yet, our new method carried a sensitivity of 96 percent and a specificity of 100 percent. What does this mean? In a very short time, we can gain an understanding of the tumor and its microenvironment without the risk of operator or equipment bias.

The spectral data obtained from the microscope can easily be combined with omics techniques to provide both spatial and molecular resolution. We recently demonstrated this approach for diffuse malignant pleural mesothelioma, a type of cancer mainly caused by asbestos exposure (3) to identify proteins expressed differently in two different tumor subtypes. The next step is detailed bioinformatic analysis to select biomarker candidates from the proteins identified. In our demonstration, all of the clinical immunohistochemistry biomarkers used today for mesothelioma could be identified on a small number of test samples.

Such automated image analysis will one day support pathologists in their daily routines and provide a second opinion in challenging diagnostic situations. It's our hope that it will pave the way for precise diagnostics and more specific biomarkers in precision medicine.

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2. *C Kuepper et al., "Label-free classification of colon cancer grading using infrared spectral histopathology", Faraday Discuss, 187, 105–118 (2016). PMID: 27064063.*
3. *F Großerueschkamp et al., "Spatial and molecular resolution of diffuse malignant mesothelioma heterogeneity by integrating label-free FTIR imaging, laser capture microdissection and proteomics", Sci Rep, 7, 44829 (2017). PMID: 28358042.*

Decoding Autism on Chromosome 16

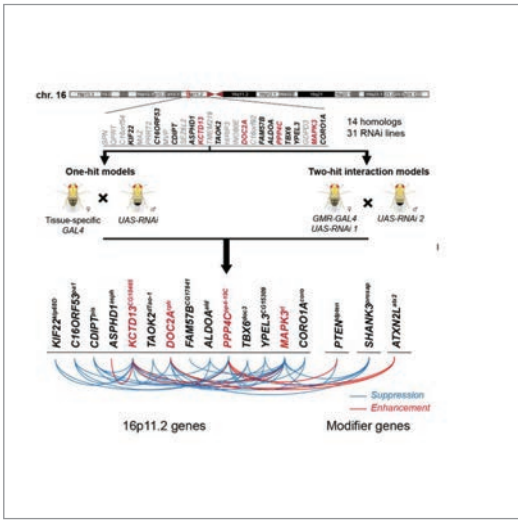
Santhosh Girirajan and colleagues map the hidden complexity of a common autism-linked deletion

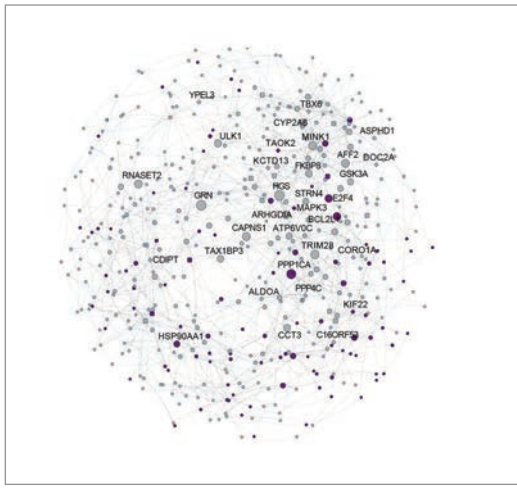
Why do individuals carrying the same genetic variant manifest such variable clinical outcomes – especially in the realm of neurodevelopmental disorders, such as autism? More than two dozen regions in the genome have been identified that, when deleted or duplicated, lead to neurodevelopmental disorders. The chromosome 16 deletion is one of the most frequent causes of autism, accounting for about 1 percent of all affected individuals. It has also been strongly linked with other phenotypes including obesity, epilepsy, and intellectual disability. The 16p11.2 deletion encompasses about 25 genes, of which several have important roles in nervous system development. Although single causative genes have been identified for classical deletion syndromes, such as Smith-Magenis syndrome, in the context of the 16p11.2 deletion, we were convinced that there could not be a single gene causing all of the above phenotypes; there had to be multiple genes with common functionality. So we began testing the effect of reducing the expression of individual genes – and pairwise combinations of genes – on neurodevelopmental phenotypes in flies (1).

So far, we have only mapped a general landscape of what could be going on within 16p11.2 and other copy number variants (CNVs) with variable phenotypic expression. The next step is to dissect each of these interactions in more sophisticated systems and map them back to specific sets of symptoms. In general, mapping specific genes for structural defects within CNVs has not been overly difficult because of the straightforward nature of identifying these phenotypes. For example, the *TBX6* gene accounts for the scoliosis phenotype observed a small subset of individuals with the 16p11.2 deletion. In contrast, identifying specific gene combinations with neuropsychiatric effects and correlating them with severity will be challenging because it will involve mapping genes and their interactions in combination with everything else in the genomes of individuals with the deletion. In the end, it all comes down to pathways and how genes "talk" to one another within networks.

We now plan to map gene interactions within CNVs and identify common pathways and their cellular mechanisms. Identifying the functional correlates might provide us some clues as to which genes, clusters, or specific pathways to target. Although we may develop some treatments for specific symptoms by repurposing drugs used to target similar cellular pathways, for others we might have to take what we find in flies to more sophisticated systems representative of human biology (such as mouse models, induced pluripotent stem cells, and organoids). Within the next five to 10 years, I would like to see deeper, quantitative phenotyping of clinical features in thousands of affected individuals with disease-associated CNVs, and more clarity of the molecular mechanisms underlying the patient phenotypes. I also hope that significant progress is made on identifying successful treatment strategies.

To get our discoveries into the clinic, we need to have constant interactions between clinicians, scientists, and affected families. While we map specific genes, interactions, and molecular pathways to specific clinical features, clinicians can use this information to identify individuals with subtypes of these disorders, which could inform prognosis. And with more detailed phenotypic and molecular profiles, it could help with customized treatment and management strategies.





Credit: Girirajan laboratory, Penn State

Reference

1. *J Iyer et al., "Pervasive genetic interactions modulate neurodevelopmental defects of the autism-associated 16p11.2 deletion in Drosophila melanogaster", Nat Commun, 9, 2548 (2018). PMID: 29959322.*

In My View

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

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

Contact the editor at edit@thepathologist.com

See Me, Hear Me!

We pathologists must make ourselves more visible and better known to healthcare professionals and our patients

By Nadeem Zafar, Chief of Pathology at VA Puget Sound, Seattle, USA

Pathology's visibility both within and outside the healthcare sphere is becoming a subject of increasing attention – at least among pathologists! Whether or not our quest for a voice has penetrated the outside world is another question, and one I am not sure can be answered in the affirmative. Despite our critical input into various aspects of healthcare, we are considered a "small fish" and often ignored or underappreciated at the enterprise level.

The issue is fundamental: do we as pathologists have the skill set to sell ourselves in a world of bigger, more aggressive, and – most importantly – more visible medical professions: medicine and surgery? Not only in undergraduate, but even in graduate medical education, we are essentially governed by rules that are more suited to these larger fields. We typically never ride the leadership wave without support from members of these fields. Of course, none of these "more visible and acknowledged fields" can function without pathology (and radiology – the two diagnostic disciplines), but we do not get anywhere near the recognition we deserve from our colleagues in those fields. It's not just a matter of wanting to be seen, either; the lack of visibility costs our field – and it costs our patients. Only 36.6 percent of US medical graduates opted for pathology as their future medical career in 2018, one of the lowest numbers ever (1). It is time for pathology professional organizations to work effectively with each other; otherwise, we will continue to watch the recruitment pipeline shrink, reimbursements for biopsies and other testing modules be cut, and our financial interests erode right in front of our eyes.

"Do we as pathologists have the skill set to sell ourselves in a world of bigger, more aggressive, and – most importantly – more visible medical professions: medicine and surgery?"

The author of a recent article on pathology's invisibility in the UK newspaper The Guardian (2) claims that she is not dejected – but the killer sentence in her piece is: "I know this cannot be changed." How did she come to that conclusion if she is, in fact, still bright and optimistic? Until now, I thought artificial intelligence (AI) was going to be the big, looming threat to pathology – but I was wrong. The big, looming threat is our inability to see the gathering storms, such as AI,

and ferocious planning for cost-cutting in medicine (and we would be among the first on the chopping block, potentially seeing some of our jobs outsourced once digital pathology is firmly established – much like in diagnostic radiology).

Embedded in the subconscious of our leaders in medicine is the thought that whatever happens will not hurt them so long as they can push the can far enough. I believe we should not be worried about these clouds; we should not even be worried about some of us being able to predict the coming storms – but we should be worried about our denial and our inability or unwillingness to deal with these looming critical threats. These changes may not impact senior pathologists within their professional working lives, but I see the practice of pathology changing over the next decades, and the pipeline is not oiled enough for new pathologists to be ready to face such challenges. I ask our leaders, who are willing to go above and beyond, to bring pathology to the forefront of medicine – and we need to realize that we are, or should be, those leaders.

References

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Making the Leap

Finding that all-important postdoc position can be a grueling process. How do you weather the storm – and hang on to your sanity?

By Anthony Stender, Assistant Professor of Forensic Analytical Chemistry at Ohio University, Athens, Ohio, USA

Have you ever gone to a party and felt like you were invisible to everyone there? Or worse, waited in vain for an invitation to a party you were longing to attend? Life as a job-seeking grad student can leave you facing the same sinking feeling.

There's a cynical STEM joke out there that has an air of truth: "Undergraduates who can't find a job go to graduate school. Graduate students who can't find a job get a postdoc, and then another postdoc, and then another..."

The problem that many graduate students face upon finishing school is actually getting that first job or postdoc position. In my case, I was seven months out of graduate school before a postdoc offer came, and I was definitely feeling like I would never get an invitation to the party. It was fortunate the call came when it did because, an hour later, I received another phone call – an offer to work at a home improvement store...

Finding a permanent job after graduate school is not an easy process these days, at least for the majority of students. Gone are the days when you could apply for 20 jobs, get 10 requests for interviews, and entertain at least three offers. (If you are currently a grad student or postdoc and you have employers fighting over you, there's no need to read any further!)

In the past five years, I have attended several career advice seminars and job fairs, in the hopes of gaining insight on how to stand out and get interviews. Unfortunately, these events seem to be exclusively targeted at undergraduates. Instead of finding valuable advice, I was nauseated by speakers pontificating about their surefire method of online networking and how to use bullet points properly on a resume. Another annoying practice of job seminars is to share optimistic statistics that suggest there are many jobs available and that unemployment rates are low in STEM. However, these statistics often describe scientists who answered a survey – not people like me – unemployed and therefore not part of the professional society that ran the survey.

When I was in full job-search mode, I figured out how to write my CV and a LinkedIn profile by looking at what other people were doing, but it was not a straightforward process. There is a perception that people with a graduate degree can learn to do anything, and require no help. In fact, many of us would benefit hugely from mentors who could offer practical advice on how to make a smooth transition from graduate school to the real-world workforce.

In looking back on my own journey from grad school to faculty position, my impression is that there isn't a "one-size-fits-all" approach. In theory, it should be easy (hasn't every scientist heard that one before?). Careers fairs sell the idea of a template solution, and many graduates enter their job search with unrealistic expectations. In reality, early-career job seekers need to work hard, be persistent, and keep an open mind when searching for a position.

Translational Proteomics: Solving the Reproducibility Riddle

Data analysis in proteomics is not fit for purpose – here's how we can get on track

By David Chiang, Chairman, Sage-N Research, Inc., Milpitas, USA

Proteomics, with its unlimited potential for biomedicine, has so far fallen short. I believe the reason is simple: sophisticated big data is being processed by simplistic bioinformatics with underpowered computers. Novices are dazzled by thousands of proteins characterized at the push of a button. But experts find that it is mostly common proteins that are correctly identified, much of the quantitation is suspect, and – critically – it is hard to tell whether an identification is correct. How can we improve the utility of proteomics for identifying important low-abundance proteins? The trick is to borrow data analysis from numerical data mining in physics, not abstract statistics.

Let's say we run a pneumonia sample to identify pathogens from proteins with a mass spectrometer. We process a gigabyte file with 50K raw spectra with a fast PC program that identifies and quantifies peptides and proteins from 20 percent of the spectra at 1 percent error. When analysis is so easy, who needs hypotheses or data understanding? We just need "better" software – defined as faster and cheaper and reporting more proteins. Of course, this assumes 1 percent error is enough, a self-estimated error is always robust, and quantity means quality – all of which are obviously incorrect.

As an analogy, imagine a novel space telescope with revolutionary accuracy, which eases data analysis; no cosmologist would acquire ad hoc imaging data and then shop for prototype software that identifies the most stars for publication, sight unseen. This unscientific approach would find thousands of bright stars but give irreproducible discoveries of faint ones. Content-rich physical data are heterogeneous, with varying signal-to-noise. Deep data require exponentially more computing to mathematically scrub.

Experts can best interpret tricky data. But it's impossible to uncover one-in-a-million breakthrough data points from particle colliders, telescopes, and now mass spectrometers without computers. Such data require semi-interactive divide-and-conquer – using servers to run overnight "what if" scripts to isolate interesting data pockets for interactive analysis.

For clinical research, 1 percent error is hopelessly imprecise. In infection research, where 99 percent of detected proteins are human, 1 percent false discovery rate (FDR) could mean no pathogen information. For every 10K peptides identified, 100 are incorrectly assigned to corrupt quantitation of 100 proteins.

Clinical research requires 100 percent accuracy for a few low-abundance proteins, not 99 percent including thousands of irrelevant abundant ones. It requires a precision paradigm centered on raw data, not probability models.

In conventional proteomics, data interpretation is outsourced to calculations few understand. Researchers choose a subjective search engine, rely on subjective probabilities to judge peptide IDs, depend on Bayesian inference to aggregate peptide IDs to identify a protein, and evaluate results quality with a single error estimate.

A precise and rigorous abstraction requires three changes. First, simplify protein inference by representing each protein with its longest identified peptide (ideally long enough to be protein-unique). Second, peptide ID filtering should use only physical mass data, not model-based parameters, such as search scores. Finally, the search engine must be demoted from a central role to merely an "educated guesser" of peptide ID hypotheses to be mass-filtered.

For example, in infection research, we develop a hypothesis, acquire data, and then interpret data. The experimental goal is to identify and characterize at least one critical peptide from its noisy spectrum. Importantly, this analysis can be manually validated by an expert.

We may hypothesize a certain pathogen, design a data-independent acquisition (DIA) experiment to maximize the odds of finding certain protein-identifying peptides, then do perhaps a dozen runs to try to capture literally one-in-a-million spectra relevant to our hypothesis. Deep research is inherently a numbers game; new technologies just help increase the odds.

In my view, the narrative that omics means hypothesis-free science is fundamentally flawed. The role of computers and artificial intelligence is to assist – not to replace – scientists who formulate hypotheses and interpret data.

Benchmarking: How Sure Are You?

And, more importantly, how can you use it to learn and improve?

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

Sometimes working with data can feel a little daunting. However, those of us who work in pathology and laboratory medicine work with data sets – whether they're patient results or weekly test throughputs – on a daily basis. We can't afford to be daunted by the staggering amount of data a laboratory produces each year. We also don't have the luxury of saying, "I'm not sure; this is why I'm not sure; and this is roughly how not sure I am." We have to be as close to perfect as we possibly can 24 hours a day, seven days a week, 365 days a year. How can we make immense amounts of information useful to us? How can we use this data to improve our laboratories? And how can we be sure that we're measuring up to our peers? In a word: benchmarking.

"Benchmarking is an opportunity to shine an objective light on our processes and find ways to make them better."

"Benchmarking" is a term is used to describe a variety of scenarios: comparing test volumes across departments, capturing the time from specimen receipt to reported results, comparing your gross revenue with other laboratories in the area, or determining if Lean manufacturing principles can be translated to a histology department. It boils down to accurately recording what you're doing, comparing those measurements with something similar, and using the results to find ways to improve.

Or not. Maybe we're all perfect and we don't ever have to change or do anything different.

You should be scoffing at that previous sentence, because benchmarking is an opportunity to shine an objective light on our processes and find ways to make them better. Let's use STAT turnaround times as an example. If you've set a goal to have all specimens marked STAT completed within an hour of receipt, but you run the numbers for the past year and discover you're hitting that goal for only 75 percent of specimens, it's not the time to despair. It's certainly not the time to berate your staff or shift the blame to other departments or hospital processes. Try and look at that number for what it is: an opportunity to study the entire process, see where the lag times are, and create solutions. Once you have a deeper understanding of the problem, you're better equipped to fix it.

Another aspect of this process is making sure we're meeting the same industry standards as our peers. For instance, knowing the reporting guidelines for colorectal cancer resections is the first step to meeting that standard. In other industries, this sort of comparison can be seen as a competition. Laboratory medicine and pathology are unique in that, although we might be business competitors with another laboratory, our collective objective is excellent patient care. Peer analysis is less a function of "can we beat them" but "how can all involved parties be sure we're providing the very best care for patients in our community?" So-called competitive benchmarking, in this instance, could be called community benchmarking, and it's just one more opportunity to improve.

Benchmarking can be an overwhelming task from start to finish, but keep in mind the reason you're doing it: to improve your laboratory so that it can provide excellent care to patients every single hour of every day of every year.

Welcome to

100 THE POWER LIST 2018

the **Pathologist**

Celebrating 100 inspirational and influential professionals in laboratory medicine

1 // Fátima Carneiro

Described as "an excellent and dedicated scientist," Fátima has contributed to multiple discoveries in the field of gastric cancer. She is currently Professor of Anatomic Pathology at the Medical Faculty of Porto, head of the Department of Anatomic Pathology at Hospital Sao João, and senior investigator at the Institute of Molecular Pathology and Immunology at the University of Porto. Nominators called her "a great pathologist and an excellent professor."

Fátima's research interests include the etiology and pathogenesis of gastric cancer, including the role played by Helicobacter pylori, its virulence factors, and the host's genetic susceptibility, and the molecular basis of disease. She also has an interest in the molecular basis of stomach cancers, in particular in cases of familial gastric carcinoma and hereditary diffuse gastric cancer. Fátima has written about 250 peer-reviewed publications, contributed chapters to well-regarded textbooks, and has served as editor, or on the editorial board, of numerous pathology journals.

A leader not only in her own field, but in pathology in general, Fátima has held many prestigious leadership appointments. Formerly President of the European Society of Pathology, she was also Portugal's delegate to the committee for the European Commission's Seventh Framework "Cooperation" health program. She has also been Coordinator of the Portuguese Network of Tumor Banks, Vice-President of the Portuguese Academy of Medicine, and a participant in multiple scientific committees, working groups, and organizations. She remains a member of the European Society of Pathology's Working Group on Digestive Diseases and of the European Association of Pathology Chairs and Program Directors, and she is organizer and coordinator of the University of Porto's doctoral program in basic and applied biology.

After all, who better to set such a leadership example than the winner of our 2018 Power List and "One of the best and most dedicated professors in the Faculty of Medicine?"

We asked Fátima what her most treasured accomplishments are so far, and she says, "Besides my major involvement in the pre- and post-graduate teaching and in diagnostic activity in histopathology and molecular pathology, I would like to highlight my two proudest achievements: Reaching seniority in the field of my main interest, gastric cancer; and international l networking through professional teaching and research initiatives, leading to collaborations across four continents."

2 // Elizabeth Montgomery

"One's legacy lies in the quality of what follows; seeing former trainees further advance the field of diagnostic pathology is a source of continuous gratification," says Elizabeth. Board certified in anatomic pathology, clinical pathology, and cytopathology, Elizabeth has followed her love of pathology from her first medical school experience with the field – despite her initial instincts toward becoming an actress instead! She is now Professor of Pathology, Oncology, and Orthopedic Surgery at the Johns Hopkins School of Medicine. Although initially trained in soft tissue pathology, Elizabeth taught herself gastrointestinal pathology, which led her to her current position and allowed her to share her experience through the authorship of 15 textbooks, including the "tumor fascicles" series and another series on biopsy interpretations.

Elizabeth's current research interests include Barrett's esophagus and the behavior of telomeres in translocation-associated and chromosome-unstable types. In addition to that work, she most enjoys traveling to give invited seminars and meet international colleagues; in fact, Elizabeth is currently working on her Spanish skills so that she can lecture in that language as well! She also enjoys examining cases with her fellows and is proud of the role she has played in the development of former fellows, many of whom have gone on to great successes.

3 // Jo Martin

Jo is currently President of the Royal College of Pathologists, Professor of Pathology at Queen Mary University of London, and Director of Academic Health Sciences and an honorary consultant at Barts Health NHS Trust. She is a histopathologist who specializes in neuromuscular disease of the gut and in renal pathology – and, in addition to her scientific and medical qualifications, she also holds a Master's degree in leadership. She has had a bright and varied pathology career so far: despite a PhD in neuropathology, she qualified as a generalist, headed a clinical support division, and worked as a clinical advisor to Ian Barnes during the Barnes review.

Now, Jo acts as a strong advocate for pathology and pathologists, encouraging improvements to pathology services across the country and working with the Royal College on public engagement projects to make pathology a better-known discipline. An eager proponent of new technologies, Jo actively works to promote digital pathology, scanning mass spectrometry, –omics, and more. But above all else, she believes that it is the people involved in pathology that make it a great discipline, and she believes strongly in pathologists' ability to change the field – and to change the face of medicine as a whole. When asked about the future of the field, Jo says, "We are on a rapid trajectory as the high tech, big brain, go-to experts for the whole of medicine and veterinary practice."

Adam Booth

Currently Chief Resident in Anatomic and Clinical Pathology at the University of Texas Medical Branch, Adam was named the College of American Pathologists' 2018 Resident of the Year.

He is also well-known on social media; one nominator says, "He pioneered the social media platform for Pathology for his institution and for the Texas Society of Pathologists," and another adds, "He is everywhere on social media, promoting pathology, patient advocacy, and education."

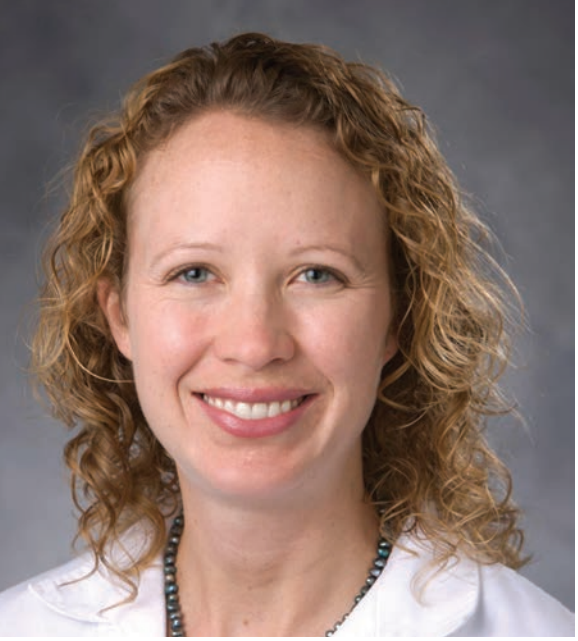
Adrian Newland

Adrian not only has a considerable track record within his field of hematology, he is currently the Clinical Advisor in the reconfiguration of England's Pathology Services, where nominators praise him for his constant work to improve the quality and efficiency of those services. "Adrian has been involved at a national level for a number of years providing leadership and challenge to the sector," says one nominator.

Alice Wort

Alice is a Microbiology Registrar in Newcastle upon Tyne (UK) and Chair of the Academy Trainee Doctor Group (ATDG), responsible for ensuring that ATDG is recognized as the voice of doctors-in-training.

"I love every day in microbiology. It is intriguing, stimulating, fascinating and caring. I love that we are responsible for the oldest and youngest patient in the hospital. We have to know everything from bacterial conjugation to how the hospital plumbing works. Never a dull day!" says Alice.



Allison Hall

Head of Breast Pathology at Duke Health, Allison works with a multidisciplinary team to deliver cutting-edge care to cancer patients.

She has built expertise in global health, recognizing the need for more data on cancers that arise in low- and middle-income countries. This work has grown out of longstanding collaborations between Duke and hospitals in Tanzania with the goal of generating data to better guide screening and treatment in Tanzanian women.

Allen Gown

A promoter of immunohistochemistry techniques, Allen generated many important antibodies used in diagnosis today. He is considered a pioneer of IHC in formalin-fixed, paraffin-embedded tissue. "He is an incredible teacher who has had a huge impact on pathology and on how we approach diagnosis," commented one nominator. "He is a great role model for how we can integrate new technology into diagnosis and treatment."

Andrew Hattersley

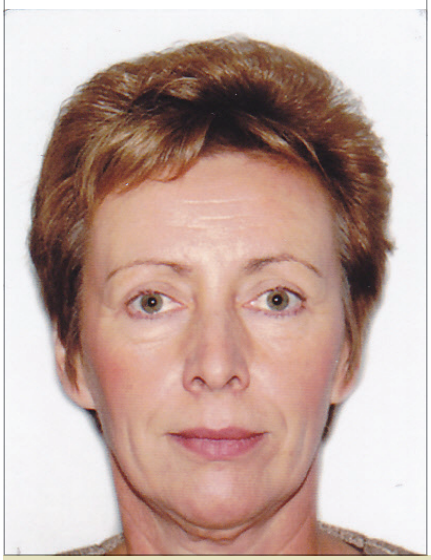
Andrew is Gillings Chair of Precision Medicine, Professor of Molecular Medicine, and Consultant Physician at the University of Exeter Medical School.

He is known for his work on the genetics of diabetes and currently heads an international research team studying monogenic diabetes, combining molecular pathology with other investigations to better understand the disease and make advances that can move quickly from bench to bedside.

Andrea Rita Horvath

Rita has been Clinical Director of the Department of Clinical Chemistry and Endocrinology of New South Wales Health Pathology since 2009, and is conjoint Professor of the University of New South Wales. Her nomination stems from her work in evidence-based lab medicine and leading efforts in international pathology

If she were to give advice to her younger self, Rita would say, "Challenges and mistakes are opportunities to grow – don't be afraid of them. Work hard and play harder!"



Anil Parwani

Anil is a Professor of Pathology and Biomedical Informatics at The Ohio State University.

His proudest achievements across his career so far are working with the Digital Pathology Association and College of American Pathologists to facilitate the approval of Digital Pathology Systems for Clinical Diagnosis in the USA, and working with CAP Digital Pathology Committee to publish guidelines for validation of whole slide imaging systems for clinical use.

Bin Xu

Currently Assistant Professor of Laboratory Medicine and Pathology at the University of Toronto and Staff Pathologist at Toronto's Sunnybrook Health Sciences Centre, Bin's main areas of interest lie in thyroid and head and neck pathology. Her nominators describe her as "so awesome," praising her skills on social media and as an educator.

Bruce Fenderson

Bruce is Professor of Pathology, Anatomy, and Cell Biology at Philadelphia's Thomas Jefferson University.

He is interested in mechanisms of morphogenesis and malignancy, exploring how cells develop and transition to a cancerous state, and he has a strong focus on education – from the basic sciences to specialist pathology, including authoring a textbook to assist with preparations for board review.

Carolyn Compton

"Without a doubt, the most stunning thing that I have witnessed in my career is the exponential advances in technology development that have provided pathologists with the power to interrogate biospecimens on a molecular level and provide unprecedented insights into biology and pathobiology," says Carolyn Compton, Professor in School of Life Sciences at Arizona State University, and Chief Medical Officer at the National Biomarker Development Alliance.

Cesar Augusto Alvarenga

Cesar currently works at the Instituto de Patologia de Campinas in São Paulo and was praised for his patient-focused care across a variety of cases. He has held observerships in thyroid pathology at IPATIMUP and in soft tissue pathology at Brigham and Women's Hospital. The most unexpected thing he has encountered? "A difficult diagnosis of a rare granular cell angiosarcoma in a context of previous benign and malignant reports."

Chandra Krishnan

Chandra is Vice President of Clinical Pathology Associates.

Recalling a humorous moment from his first-year residency at Stanford, Chandra says, "An OR nurse asked me to pick up a colon tumor immediately. I stopped what I was doing and rushed down the long hall for this rite of passage. Only, when I came to the OR, nobody was present. Only an orderly mopping the floor around a blue absorbent pad. I asked where the surgeon was and what was the issue at hand with the specimen. The orderly replied, 'Nothing. Just pick up this colon from the floor and take it away.'"

Christina Arnold

"To know pathology is to love pathology," says Christina. "Going to work is like going to an art museum every day—the beautiful colors and pictures and patterns hold the diagnosis and only pathologists can decode the message."
Christina works in the Gastrointestinal and Liver Division at The Ohio State University and serves as the Vice Chair of the Education Committee for the Rodger C. Haggitt Gastrointestinal Pathology Society (GIPS).

Cristina Magi-Galluzzi

"The pathologist of the near future will have at her/his disposal an array of novel technologies (molecular diagnostics, genetics, genomics, proteomics, digital pathology, in vivo microscopy, artificial intelligence) to help provide accurate, timely and relevant information useful in making diagnoses, predicting outcome, guiding appropriate treatment and monitoring therapy response," says Cristina, Director of Genitourinary Pathology at the Cleveland Clinic Pathology and Laboratory Medicine Institute, and Professor of Pathology at Cleveland Clinic Lerner College of Medicine of Case Western Reserve University.

Dana Razzano

"I went into pathology with the goal of contributing solutions to the challenges faced in global health, specifically as it relates to laboratories in low resource settings throughout the world," says Dana. Although early in her career, as Chief Resident of Anatomic and Clinical Pathology at New York Medical College at Westchester, she's definitely striving to make big changes in the field through her Pathology Resident Wiki.

David Harrison

David is Professor of Pathology at the University of St. Andrews, with Honorary Chairs in Edinburgh, Glasgow, and Florida.

As well as Honorary Consultant Histopathologist in NHS Lothian and Designated Individual with oversight of human tissue in research. His research interests cover quantitative pathology and the determination of cell fate after injury. When asked what his proudest moments are, David says, "I'm always seeking to appoint people better than me, and usually succeeding!"

David Wells

David is Head of Pathology Services Consolidation with NHS Improvement.

His peers nominated him to The Power List for leading some of the largest and most specialist laboratory services in the UK, and he still strives to move the field forward. David says, "I hope to bring diagnostic services to the fore in medicine. I want to use my current and future roles to support better, more timely diagnosis of patients through pathology services that are effective in their use of clinical and scientific teams."

Doris-Ann Williams

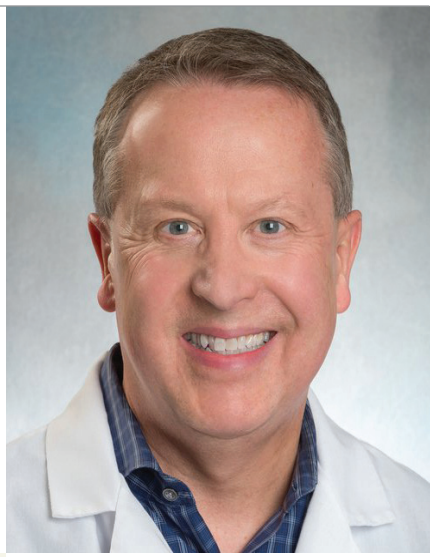
Doris-Ann is Chief Executive of British In Vitro Diagnostics Association (BIVDA).

In 2011 she was awarded an MBE. Now, she has been nominated to The Power List by her peers for being at the forefront of laboratory medicine for 40 years.
When asked what advice she'd give her younger self, Doris-Ann says, "To have more confidence in my abilities. It took me until I was in my early thirties before I really challenged myself to step outside my comfort zone, but now I have the experience to know I can cope."

Edmund Cibas

Edmund is Professor of Pathology at Harvard Medical School and Director of Cytology at Boston's Brigham and Women's Hospital.

Formerly President of the American Society of Cytopathology, he now directs his institution's cytopathology fellowship program and co-directs Harvard's annual postgraduate "Advances in Cytology" course, a task he has undertaken for nearly 30 years. Edmund is also co-author of "Cytology: Diagnostic Principles and Clinical Correlates," and co-editor of "The Bethesda System for Reporting Thyroid Cytopathology."



Emanuel Rubin

Emanuel is the Gonzalo E. Aponte distinguished Professor of Pathology of Anatomy and Cell Biology at Thomas Jefferson University.

Over his career so far, Emanuel has accrued many awards, including the F.K Mostofi Distinguished Service Award of the United States and Canadian Academy of Pathology, the Lifetime Achievement Award from the Research Society on Alcoholism, the Robbins Distinguished Educator Award from the American Society for Investigative Pathology, and many more. Now, he adds The Power List 2018 to his already vast roster.

Esther Youd

Esther is a histopathologist based in South Wales. She is Clinical Director of Pathology and RCPath Wales Regional Council Chair, with a specialist interest in autopsy pathology – particularly in sudden cardiac death and maternal death.

Esther is inspired by, "Lots of opportunities to help others; being an advocate for a bereaved family, and the light bulb moment from a trainee when they 'get it.'"

Faheema Hasan

Faheema is a Pathologist MD and enthusiastic teacher with special interests in oncopathology, hematology, and hemato-oncology. Faheema's peers nominated her because of her astonishing efforts to create educational material of exceptional quality, both for trainees and experts. She says, "The most important barrier in developing countries is the lack of resources, like molecular techniques. Most of my lectures and posts aim at updating my fellows and readers on the latest techniques and the substitutes available in a low-resource setup in order to maximize diagnostic accuracy and improve patient care."

Fred Bosman

"The most interesting aspect of my long career has been the opportunity to work with, and for, a wide range of smart, interesting, and mostly very agreeable professionals, many of whom have become good friends. Interacting with them has contributed significantly to who I am today," says Fred, whose most recent position was Professor and Director of the University Institute of Pathology at the University Medical Center of Lausanne, Switzerland. Having retired from his 40+ year career in gastrointestinal pathology, he now sits on the editorial boards of numerous international journals, editing textbooks and advocating for more integration of various laboratory medicine disciplines.

Gene N. Herbek

Gene is Medical Director of Transfusion Services at Methodist Hospital and Methodist Women's Hospital Laboratory.

He is former president of the College of American Pathologists (CAP), an institute he's been actively involved with for more than 24 years. Gene also launched CAP's See, Test & Treat program, which provides free breast and cervical cancer screenings to under-served women in the US.

George Kontogeorgos

"Education has been my first priority during the last 10 years I have served the International Academy of Pathology (IAP)", says George, President of the IAP. His advocacy for the importance of pathology education has only grown stronger over his career. George's personal philosophy on the topic? "It is time for an educational revolution, in order to give power to all and make education in pathology possible everywhere."

Harald Stein

One of the world's foremost cancer investigators, Harald's contributions to the field include the identification of three new types of lymphoma, as well as the discovery of numerous immunohistochemical markers and characteristics of lymphomas. Unsurprisingly, Harald is also co-founder of the International Lymphoma Study Group, and he is Emeritus Professor of the Charité University Medicine Berlin, Chairman of the Berlin Reference Center for Lymphoma and Hematopathology, and Director of the Institute for Pathodiagnostik Berlin.

Han van Krieken

"In the next few years, pathology will – even more than now – be the key to innovation in medicine. Without pathology there's no precision medicine," says Han, a pathologist with special expertise in the fields of hemato-pathology and the pathology of the GI tract. He is Rector Magnificus Professor at Radboud University and on the Supervisory board at Anthony van Leeuwenhoek Hospital/The Netherlands Cancer Institute. Han believes, "The introduction of artificial intelligence will enhance the potential of pathology, but only when pathologists develop their communication skills."

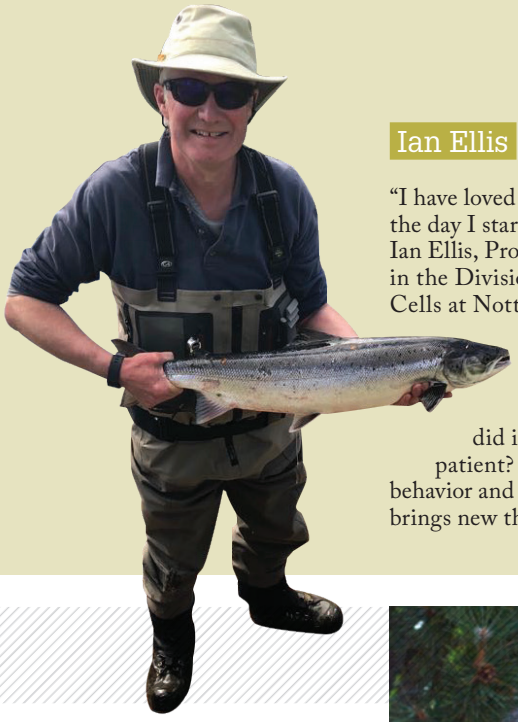
Hilary Humphreys

A man of many responsibilities, Hilary serves as Head and Professor of Clinical Microbiology with the Royal College of Surgeons in Ireland and as Dean of the Royal College of Physicians in Ireland's Faculty of Pathology.

Clearly not one to shy away from duty, he also leads the country's National Pneumococcal Reference Laboratory and recently served as Chair of the Department of Health's National Clinical Effectiveness Committee. Hilary's work focuses on understanding and preventing healthcare-associated infections.

Ian Cree

Ian is a pathologist based at the International Agency for Research on Cancer (IARC) in Lyon, where he's Head of WHO tumor Classification, responsible for the WHO Blue Books. His research career has been based on the investigation of disease mechanisms to improve diagnosis and treatment, particularly for cancer.



Ian Ellis

"I have loved being a pathologist since the day I started on January 1, 1980," says Ian Ellis, Professor of Cancer Pathology in the Division of Cancer and Stem Cells at Nottingham University. "Being able to look at cells and tissues inspires me to ask questions: Why does this cell or tumor do that? How did it start? How will it affect the patient? How can we change its innate behavior and cure the patient? Every day brings new thoughts, surprises, and ideas."

Ian Fry

A clinical biochemist by specialty, Ian has dedicated his career to the successful delivery and modernization of pathology in the UK's National Health Service. Two decades ago, he began developing the network that is now Berkshire and Surrey Pathology Services (BSPS), working to ensure its future sustainability. "He has pushed the boundaries when others wouldn't or couldn't," says one nominator. "This has helped to pave the way for others to follow in his path."

Ivan Damjanov

Ivan is currently a Professor of Pathology at the University of Kansas School of Medicine, where he has worked for 24 years. His nomination stems from his inspiring approach to teaching, and helping boost the status of pathology in Croatia.

When reflecting on one of the lighter moments in his career, Ivan recalls, "A medical student evaluation of my yearlong teaching was reduced to four words: 'Silly, funny, old man.' It still makes me chuckle!"

Jason Hornick

Jason is Professor of Pathology at Harvard Medical School, Pathologist at Brigham and Women's Hospital, and Consultant in Pathology at Dana-Farber Cancer Institute.

His sources of inspiration? "The critical role surgical pathology plays in cancer care; translational pathology research that identifies new biomarkers to improve diagnostic reproducibility and clinical practice; and training pathology residents and fellows in surgical pathology."

James Musser

With a focus on host-pathogen interactions, James and his laboratory use advanced techniques and collaborations to examine the molecular basis of infection, particularly with group A *Streptococcus* and *Mycobacterium tuberculosis*. James holds multiple titles at Houston Methodist Hospital and Weill Cornell Medical College, including Chair of the Department of Pathology and Genomic Medicine and Director of the Center for Molecular and Translational Human Infectious Diseases Research.

James O. Westgard

James is an Emeritus Professor in the Department of Pathology and Laboratory Medicine at the University of Wisconsin Medical School.

His work in clinical chemistry included the development of method validation protocols and led to the introduction of the Total Error concept as a measure of analytical quality. James has been a leader in adopting industrial quality management in medical laboratories and in retirement he continues to work on the design and optimization of statistical QC procedures.

Jason Jarzembowski

Jason serves as Vice Chair for Pediatric Pathology and Associate Professor at the Medical College of Wisconsin and Medical Director of Pathology and Laboratory Medicine at Children's Hospital of Wisconsin.

We asked Jason what his proudest achievement is and he says, "It would be teaching and mentoring people at all levels - students, staff, residents, fellows, and faculty – and watching them learn, grow, and find their professional niche so they can help care for patients in a way that is personally meaningful to them."

Jerad Gardner

"Pathology is headed beyond the paraffin curtain and out of the laboratory!" says Jerad, Associate Professor of Pathology and Dermatology at the University of Arkansas for Medical Sciences in Little Rock. "We will still work in the lab, of course, but our non-pathologist colleagues, our patients, and the public will get to know who we are and why we are important, thanks to the many pathologists who publicly represent our specialty so well on Twitter, Facebook, Instagram, and other social media." Nominees have described Jerad as the 'pied piper of pathology' for his outspoken advocacy of the field.

Jeroen van der Laak

Jeroen is Principle Investigator and Associate Professor of Computational Pathology at the Department of Pathology of the Radboud University Medical Center in Nijmegen.

His research focuses on the use of machine learning for the analysis of whole slide images. Jeroen was nominated for leading the largest research group in Computational Pathology, steering the technical developments of the field in the right direction while remaining close to the clinical pathology practice.

John Goldblum

John is Chairman of Cleveland Clinic Department of Pathology and Professor of Pathology at Cleveland Clinic Lerner College of Medicine at Case Western Reserve University.

He says, "My major career focus has been – and will continue to be – doing whatever I can to contribute to the success and growth of the Department of Pathology at Cleveland Clinic to ensure we do the best possible job for our patients, and make working here as rewarding as possible."

José Aneiros-Fernández

José was nominated for his efforts in the area of computational pathology. An anatomical pathologist at the Hospital Universitario San Cecilio with a focus on dermatopathology and digital pathology, Jose can often be found on Twitter sharing fascinating cases and news about the latest advances in his areas of interest.

Joseph Maleszewski

Joseph is Professor of Pathology and Medicine at Mayo Clinic.

"Never has there been a more exciting time to be a pathologist," says Joseph. "The molecular genetic era has ushered in a vast array of new technologies which we are learning to leverage to better understand disease and create more accurate and expedient diagnoses while incorporating traditional techniques as well. As it always has been, diagnosis is everything. As the consummate diagnosticians in medicine, our work is central to developing care plans in nearly every patient."

Kieth Kaplan

Keith is an Executive Board Member of the American Pathology Foundation and a member of the College of American Pathologists.

Keith's peers nominated him for his digital pathology advocacy, having implemented the first worldwide telepathology program with AFIP which connects 25 hospitals spanning across three continents with patient care, using robotic microscopes.

Kamran Mirza

Kamran is an Assistant Professor of Pathology and Laboratory Medicine and Medical Education at Loyola University Stritch School of Medicine in Maywood, Illinois.

His research interests cover acute respiratory distress syndrome, lung transplant pathology, prognostic IHC markers for lymphoma and leukemia, appropriate laboratory test utilization and innovative approaches to medical education.
Kamran was nominated by his peers for his tireless work in opening up the dialogue between pathologists and their non-pathology colleagues, helping bridge the communicative gap between pathology and other medical fields.

Lance Sandle

Lance has served Trafford, UK, as Clinical Audit Chair, Clinical Director, Deputy Medical Director, and Interim Medical Director. Since 1986, he has been Consultant Chemical Pathologist at Trafford General Hospital (part of Manchester University Foundation NHS Trust).

Reflecting on his past experiences, Lance says, "Take every opportunity to teach pathology to tomorrow's doctors and scientists. They will need this knowledge to look after you as you get older and if you don't teach them, no-one else will."

Lara Pijuan Andujar

Lara is Consultant in Pulmonary Pathology and Cytopathology at Hospital del Mar in Barcelona, Spain.

Her interests lie in molecular diagnosis and immuno-oncology in lung cancer and working in the training of national pathologists in the interpretation of PD-L1 as lung tumor biomarkers.
"The proudest achievement in my career is being involved with oncologists in the update of the national guidelines in lung cancer biomarkers," says Lara. "Working together, we can give the best treatment option to our lung cancer patients."

Laura Guerra Pastrián

Laura is a Junior Assistant Gastrointestinal Pathologist in La Paz University Hospital, Madrid, and was nominated for her role as an enthusiastic Twitter leader in gastrointestinal pathology.

Highlighting one of the most humorous moments of her career, Laura says, "During our training we were so delighted when someone brought food to the residents' room that we printed and set up a big poster: 'Please, feed the pathologists,' in an old Zoo Park typography. It was so nice when the clinicians obeyed!"

Lauren Schwartz

Lauren is Assistant Professor of Clinical Pathology and Laboratory Medicine at the University of Pennsylvania School of Medicine. Her subspecialty concentrations are gynecological - and genitourinary pathology.

"I am continually amazed at how much I enjoy working with trainees at all levels of their training!" says Lauren. "It is truly incredible to feel as though you are continually teaching and learning. I cannot imagine practicing any other field of medicine. Pathology is the perfect fit for me."

Liron Pantanowitz

Liron is a Professor of Pathology and Biomedical Informatics at the University of Pittsburgh, Vice Chair for Pathology Informatics at the University of Pittsburgh Medical Center (UPMC), Director of Cytopathology at UPMC Shadyside, and Director of the Pathology Informatics Fellowship at UPMC.

"I am proud of many things I have accomplished in pathology. However, I am most proud of my role in founding the open-access Journal of Pathology Informatics," says Liron. "Prior to the establishment of this journal, very few pathology informatics articles were published in the pathology literature, if any at all."

Luis Humberto Cruz Contreras

Luis is a Pediatric Pathologist at Hospital Materno-Infantil in Irapuato, Mexico.

"I feel that pathologists have the privilege of helping other human beings, not only at the scope; we are responsible for sharing knowledge and bringing pathology closer to patients," says Luis. "I always keep in mind that every slide has the potential of changing patient life. Every slide holds a microscopic world full of beauty and every slide is a chance to do a better job."

Malak Abedalthagafi

Malak is a Georgetown, UCSF, and Harvard-trained physician-scientist in Clinical Pathology, Anatomical Pathology, Neuropathology, and Molecular Genetics Pathology. She is also Founding Chair of the genomics research department and Primary Investigator of the Saudi Human Genome Lab at Jing Fahad Medical City Research Center in Riyadh.

If Malak had the opportunity to give advice to her younger self, she'd say, "Take breaks regularly and don't feel guilty about it."

Mariam Amrani

Mariam is Co-ordinator of the research team ONCOGYMA dedicated to gynacologic and breast oncology, with competencies in surgical pathology, cytology, immunohistochemistry, and in situ hybridization.

Mariam has been nominated for her leadership in anatomical pathology. When it comes to advising young pathologists, Mariam says, "Always be optimistic, perseverant, patient, joyful, and thankful."

Manuel Salto-Tellez

"Who would have predicted years ago that molecular diagnostics, precision medicine, cancer immunotherapy and artificial intelligence would redefine the future of modern pathology?" says Manuel, Chair of Molecular Pathology at Queen's University Belfast (QUB), Director of QUB's Precision Medicine Centre of Excellence, and a Consultant Histopathologist and Molecular Diagnostician. His advocacy and work on digital pathology and morpho-molecular diagnostics across Spain, Germany, The Netherlands, The UK, and USA has, no doubt, helped that future of modern pathology.

Manuel Sobrinho-Simões

Voted number one on The Pathologist's 2015 Power List, Manuel never considered a career outside medicine. He has studied and worked around the world, zeroing in on thyroid and gastric cancers, and established the Institute of Molecular Pathology and Immunology of the University of Porto, which he still leads today. Manuel has held dozens of leadership positions and has been awarded the Grand Cross of the Order of Prince Henry and the Royal Norwegian Order of Merit.

Marc Ladanyi

Marc is Chief of the Molecular Diagnostics Service and William J. Ruane Chair in Molecular Oncology at Memorial Sloan Kettering Cancer Center in New York.

With research focusing on the genomics and molecular pathogenesis of sarcomas and lung cancers, he aims to uncover potential diagnostic biomarkers and treatment targets using next generation molecular techniques. Marc co-directs MSK's Genome Data Analysis Center and helped develop the MSK-IMPACT tumor genome sequencing test.

Marilyn M. Bui

Marilyn is an Academic Pathologist practicing at Moffitt Cancer Center, with expertise in sarcoma pathology, cytopathology, breast cancer biomarker testing, and digital pathology.

We asked Marilyn about her proudest achievement: "My ability to embrace imperfection and adversity, balance work and life, show compassion and support to others, and continuously transform with modern medicine in order to deliver the best patient care as a pathologist."

Marina Ines Narbaitz

As President of the Sociedad Argentina de Patología, Marina is bringing the next generation of pathologists to the field of molecular pathology.

"She is transforming our scientific society," says one nominator, "allowing professionals from anywhere in the country to participate in educational activities." She was also praised for her skills in hematopathology, her teaching ability, and her commitment to her patients and to the growth of pathology in Argentina.

Mario Plebani

Mario, who is Chief of the Department of Laboratory Medicine and Professor of Clinical Biochemistry and Clinical Molecular Biology at the University-Hospital of Padova, was nominated for his wide experience and renown in the world of clinical laboratory medicine. A holder of multiple leadership roles, Mario has published nearly 900 papers and over 900 abstracts. He is a fierce advocate for quality control and error reduction in diagnostics and laboratory medicine.

Marion Wood

Marion is Co-Lead for the "Getting it Right First Time" Pathology Project Workstream and she's been a Consultant Clinical and Laboratory Hematologist for 25 years.

We asked Marion to give advice to her younger self, and she said, "Understand the potential benefit of finding and working with a mentor. I very much ploughed my own furrow and only saw late in my career how having an experienced 'critical friend' to act as a sounding board and guide could support and encourage at times of challenge."

Michael Misialek

Michael, Associate Chair of Pathology at Newton-Wellesley Hospital, says, "The most interesting moment in my career was doing an autopsy several years ago on a young man who died of metastatic lung cancer. He was a non-smoker and was among the first patients ever to be identified with an ALK translocation and was enrolled in the first trial in the world for ALK targeted therapy, for what would later be approved as Crizotinib. The findings would advance our knowledge of targeted therapy resistance. I consider him a hero and early pioneer of precision medicine. He taught me the role pathologists play in precision medicine."

Melanie C. Bois

"When I decided to become a pathologist, people chastised me for hastening my own retirement by going into a field that would soon be overtaken by Technology," says Melanie, Assistant Professor of the Department of Laboratory Medicine and Pathology at Mayo Clinic. "It's been quite the contrary. I've been heartened that our field has embraced these novel methodologies (rather than being defeated by them) to enhance traditional diagnostic techniques, further our understanding of disease, and positively affect patient care and treatment."

Melissa S. Pessin

Melissa is the Chair of the Department of Laboratory Medicine at Memorial Sloan-Kettering Cancer Center.

Her research interests include diagnostic test development and appropriate laboratory test utilization. Melissa says, "I think that the patient's demand for more rapid results and easily viewing those results is going to drive changes in both testing technology and the format in which results are provided."

Michael Laposata

Michael is Professor of Pathology and Chair of the Department of Pathology at the University of Texas Medical Branch-Galveston.

We asked Michael to advise upcoming medical students on why they should join pathology. "If you want to be involved in the diagnosis of large numbers of cases within your special interest, not just the few you might see in clinic on a certain day, you should become a pathologist. This will allow you to quickly learn about the simple and the complex cases, and provide essential diagnostic information to treating healthcare providers who need your help on many cases."

Michael Roehrl

Michael casts a wide net across the field of diagnostic medicine, with interests ranging from gastrointestinal pathology to analytical science. He is a pathologist at Memorial Sloan Kettering Cancer Center and directs his institution's Precision Pathology Biobanking Center. His own laboratory is focused on discovering proteomic biomarkers via mass spectrometry and studying the effect of genomic alterations on the proteome.

Michael Wells

Michael is Emeritus Professor of Gynecological Pathology at the University of Sheffield and former Honorary Consultant to Sheffield Teaching Hospitals.

At present he is employed by both Leeds and Bradford Teaching Hospitals. Michael has published more than 230 original papers, book chapters, and review articles. When asked to give one piece of advice to his past self, Michael says, "Try not to worry so much, particularly what others think of you, and don't be so hard on yourself."

Miguel Reyes-Múgica

"One of the most interesting things in my career as a Pediatric and Developmental Pathologist is how human societies reproduce cell societies. They cluster together unified by a common language, be that Spanish, English, neurotransmitters, gene signaling pathways or cytokine cross talk," says Miguel. He is Professor of Pathology at the University of Pittsburgh School of Medicine, and Marjory K. Harmer Endowed Chair in Pediatric Pathology and Chief of Pathology and Head of Laboratories at Children's Hospital of Pittsburgh.

Muhammad Ahsan

Muhammad is a Lecturer to Medical Students in the Pathology Department at Sahiwal Medical College, Pakistan.

He gained medical experience in the US as a visiting medical student in the Department of Dermatopathology and Department of Anatomic & Clinical Pathology at Ichan School of Medicine at Mount Sinai. Muhammad has been nominated for his active social media presence and co-founding #PathTweetAward.

Nicholas Reder

Nicholas is Acting Instructor of the Department of Pathology at the University of Washington Seattle.

Here, he offers guiding words for upcoming medical students interested in the field: "As a physician-scientist, pathology offers a unique opportunity: every day that I spend on clinical service, I am making observations that motivate my research projects. Every day that I spend in the lab, I am constantly thinking about how my research can affect my clinical practice and ultimately improve patient care. It's hard to imagine a specialty that offers a better balance of patient care, science, and great colleagues!"

Nicholas West

Nicholas is University Clinical Academic Fellow in Molecular and Digital Pathology at University of Leeds, and Honorary Consultant in Gastrointestinal and Molecular Pathology at Leeds Teaching Hospitals NHS Trust.

Nicholas says, "One of the most interesting things is getting to visit pathology laboratories around the world and see how pathology practice differs internationally – across the UK, mainland Europe, the US, Russia, and Japan. I can then bring home the best practice to hopefully improve our approaches locally."

Nicole Riddle

Nicole is currently providing services at Tampa General Hospital.

"I always tell my medical students to do an elective in pathology because it is a little-known gem of medicine," says Nicole. "We have a part in so many patients' care and are so crucial to them getting the right treatment. Yet, though I 'see' 45-60 patients a day, they will patiently wait for me on my desk while I attend meetings, teach lectures, or take care of the occasional family event. We reach the most patients while having the most flexible time."

Pallavi A. Patil

Pallavi is an Anatomic & Clinical Pathology Resident Physician at Brown University.

She has been nominated for her work on the CAP economic affairs committee, extensive mentoring work as resident director, and her research on prognostic/predictive markers and immune microenvironments.
Speaking about her future goals, Pallavi says, "I would like to work towards more population awareness of pathology and its prominent role in patient care, and tapping into the utmost potential of pathology towards screening, enhanced diagnostics, and treatment options."

Pedram Argani

"After 20 years of practice, I still learn new things and am excited to come to work each day," says Pedram, Associate Director of Surgical Pathology at Johns Hopkins. "There are new clinical cases to humble me, new genetic tools that solve puzzling cases from years before, and new entities to discover."
Pedram also serves on the editorial board of The American Journal of Surgical Pathology, Modern Pathology, The International Journal of Surgical Pathology, and Advances in Anatomic Pathology.

Pembe Oltulu

Pembe is Assistant Professor in Pathology at Necmettin Erbakan University, Meram Faculty of Medicine, Turkey.

Her interests revolve around dermatopathology, hematopathology, and education and training through social media. Pembe was nominated by her peers for being a role model for the pathology community, sharing insightful educational content online and welcoming newcomers to the field.

Peter A. Ward

Peter is Godfrey D. Stobbe Professor of Pathology at the University of Michigan Medical School.

When asked about his proudest achievement, Peter says, "We have long been interested in the complement system and the powerful C5a anaphylatoxin. Over the past several years, we have shown the C5a interacting with its receptors during infectious sepsis plays a key role in the features of human sepsis: lethality, high levels of cytokines, chemokines, and histones – all of which are linked to multiorgan failure."

Peter Isaacson

Known for his cancer studies and the discovery of several new types of malignant lymphoma, Peter is now Emeritus Professor of Histopathology at University College London. Among others, he co-discovered the mucosal-associated lymphoid tissue lymphoma and its association with *Helicobacter pylori*, which means that this particular form of the disease can often be cured by antibiotic treatment alone.

Peter W Johnston

Peter is a Consultant Histopathologist at NHS Grampian and Depute Postgraduate Dean at Scotland Deanery.

He's also the lead for hematopathology at NHS Grampian, an instigator of the East of Scotland Lymphoma Review Group, and Co-director of the University of Aberdeen Center for Healthcare Education Research and Innovation. Peter is currently involves in curriculum redesign at the Royal College of Pathologists.

Philip Quirke

Philip is Yorkshire Cancer Research Centenary Professor of Pathology, and Head of Pathology and Tumor Biology, at University of Leeds School of Medicine. He is also Honorary Consultant and NHS National Institute for Health Research Senior Investigator in Histopathology and Molecular Pathology.

Philip's nomination stems from setting up several schemes to support academic pathology in the UK and internationally.

Pranav P. Patwardhan

Pranav currently works in the Department of Pathology at Seth G S Medical College, Mumbai.

He was nominated for disseminating information to fellow pathology residents and trainees via social media.
"I hope to contribute further to pathology education," says Pranav. "I believe that every student or resident should develop his or her own algorithmic approach to any histopathological case or scenario. I try to encourage this temperament among the students by sharing my own algorithms. It is my dream to get affiliated to a medical school as a faculty in the future to contribute to pathology education."

Rachael Liebmann

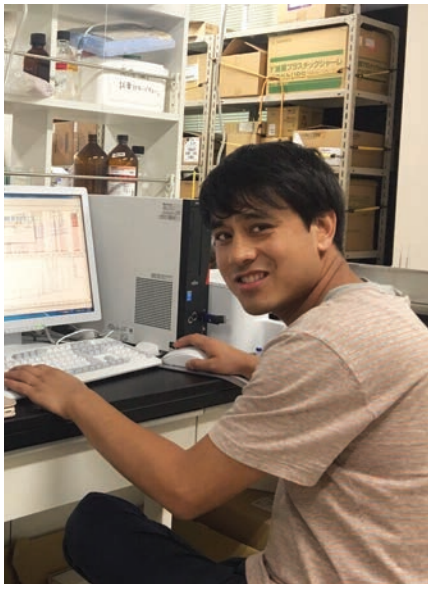
Rachael is Vice President of the Royal College of Pathologists (RCPath), plus she established and led RCPATH Consulting. She also serves as a Secondary Care Representative on a Clinical Commissioning Group in Essex and UK Medical Advisor to the Telemedicine Clinic.

Rachael was nominated for her influence in lab medicine pathology and her role in ensuring that pathologists' voices are heard in political circles.

Rohit Jain

Rohit is an Honorary Consultant at Santokba Durlabhji Memorial Hospital, Jaipur, and founder Secretary of Practicing Pathologists Society, Rajasthan.

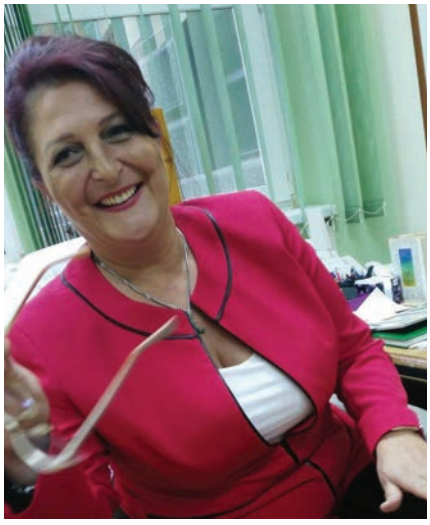
He was nominated by his peers for fighting dishonest practices in the field. Speaking about his future goals, Rohit says, "I want the eradication of 'quackery' in the practice of pathology in India. It's an audacious task but I will keep working for it till my last breath."



Rojeet Shrestha

Rojeet is Assistant Professor in the Faculty of Health Sciences at Hokkaido University, Japan.

His inspiration is drawn from, "The great pieces of work that our senior scientists had left us." Rojeet's nomination stems from him winning the 2017 IFCC Young Investigator Award, which recognizes academic and professional development/scientific achievements in Clinical Chemistry and Laboratory Medicine.



Sanja Milenkovic

Sanja is Lecturer of Postgraduate Studies at Medical Faculty Belgrade and Medical Faculty Kragujevac, and Associate Professor of General and Oral Pathology, Faculty of Dentistry Pancevo, Serbia. Her research interests focus on brain tumors and neuromuscular diseases.

A favorite anecdote from Sanja's career: "My four-year old daughter was in kindergarten and was asked, 'Is your mother a doctor?' She answered, 'No! She's not a doctor. She's a pathologist! My mum cures dead ones and she is a policewoman for doctors.'"

Sanjay Mukhopadhyay

"By far the most unexpected and interesting thing I've encountered in my career is the enormous reach and impact of social media," says Sanjay, Staff Pathologist at the Cleveland Clinic. "The ability to make friends with, educate and learn from thousands of pathologists worldwide in real time and free of charge on a daily basis is simply staggering."

Saul Suster

Saul is Professor and Chairman of the Department of Pathology & Laboratory Medicine at the Medical College of Wisconsin.

When asked about the possible future of the field, he says, "I believe pathology still has a significant and vibrant role to play in the future of healthcare as we are ideally positioned to interpret the molecular-genetic revolution we have at hand, and integrate its findings into the morphologic context of disease. Pathologists should take the lead in this regard and not allow this emerging field to be taken over by other specialties."

Shashidhar Venkatesh Murthy

Shashidhar is Adjunct Professor of Pathology & Post-graduate Research Fellow in Medical Education at Manipal Medical College, India.

He is also Associate Professor and Head of Pathology in the School of Medicine at James Cook University. Shashidhar's nomination was for his teaching work in the field, and developing a post-graduate program in pathology at Fiji National University for all Pacific Island countries.

Xiaoyin "Sara" Jiang

Sara is an Assistant Professor of Pathology at Duke University, and Associate Director of the Duke Biorepository and Precision Pathology Center.

Her areas of research and expertise are cytopathology and surgical pathology of the head and neck and endocrine system.
"We've made some DIY ultrasound training phantoms, using some unusual materials", says Sara. "So probably buying and playing around with things like hot dogs, gelatin, and silicone to come up with custom phantoms has generated some of the funnier moments in my career!"

Sinchita Roy-Chowdhuri

Sinchita is the Director of Molecular Cytopathology at MD Anderson Cancer Center, with interests in pulmonary cytopathology, fine-needle aspiration diagnoses, and molecular diagnostics in solid tumors.

If she had the opportunity to give advice to her younger self, Sinchita would say, "Do not rush to get somewhere, but learn to enjoy the journey. Be open to change (aka possibilities), strive to do your best each day, and always be prepared to ask for help. The best way to be prepared for tomorrow is by doing your best today."

Simon Herrington

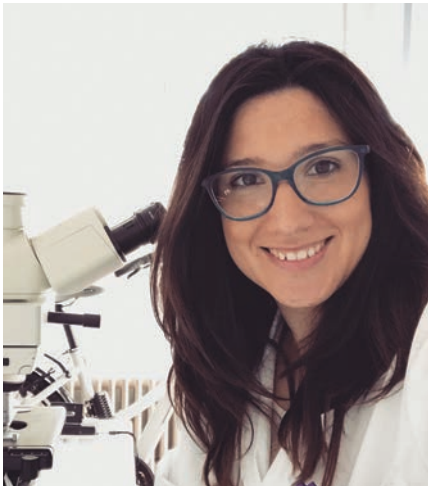
"I would like to continue to promote pathology as an essential component of research, education and clinical practice," says Simon, Chair of Molecular Cancer Pathology at the University of Edinburgh. He's also a Consultant Pathologist, specializing in gynecological pathology, and sits on the Board of Worldwide Cancer Research and is past president of the International Society of Gynecological Pathologists.

Steven Billings

Steven is Professor of Pathology at the Cleveland Clinic, where he co-directs the dermatopathology section. His research interests have led to numerous articles and book chapters, as well as co-authorship of a textbook on inflammatory skin diseases. Although he sits on the USCAP Board of Directors and has a passion for pathology education, "the most important reason for his nomination is that he is an amazing mentor and an approachable attending," say nominators.

Suzy Lishman

"Pathology has always been a dynamic and exciting specialty, but I anticipate that development will be even more rapid in the near future," says Suzy Lishman, CBE, a Consultant Histopathologist at North West Anglia NHS Foundation Trust and the immediate past President of the Royal College of Pathologists. "Technological advances including molecular pathology, digital microscopy, and artificial intelligence will facilitate collaboration, reseatch, education, and patient care. It's a great time to be a pathologist!"



Tania Labiano

Tania is a Pathologist Subspecialized in Cytopathology and Breast Surgical Pathology at Complejo Hospitalario de Navarra, Pamplona, Spain.

She's an active member of the Spanish Society of Pathology (Development of Talent in Pathology Project - DESTAPA) and the Spanish Society of Cytopathology as a regional voice.
"Every patient is unique and cherished for me," says Tania. "I think it is important to create a good environment that facilitates feedback between health professionals in order to keep us motivated and provide excellent patient care."

Valerie Fitzhugh

Valerie is Associate Professor of Pathology and Laboratory Medicine at Rutgers New Jersey Medical School.

Valerie's peers nominated her for promoting pathology and being an advocate of the field, both in the classroom and on social media.
We asked Valerie what inspires her in her career, and she says, "The patients Pathologists have an amazing opportunity as physicians in the cornerstone of medicine to help so many people. The patients inspire me to continue to give my all in their care and in my work."

Victor Tron

Victor Tron is Chief/Medical Director of Laboratory Medicine at St. Michael's Hospital and St. Joseph's Health Centre, Toronto.

If he could give his younger self some words of wisdom, Victor would say, "Get out of the lab and 'engage' treating clinicians and others. Focus on the value of lab medicine outside of the pure diagnostic realm. You are a medical doctor!"

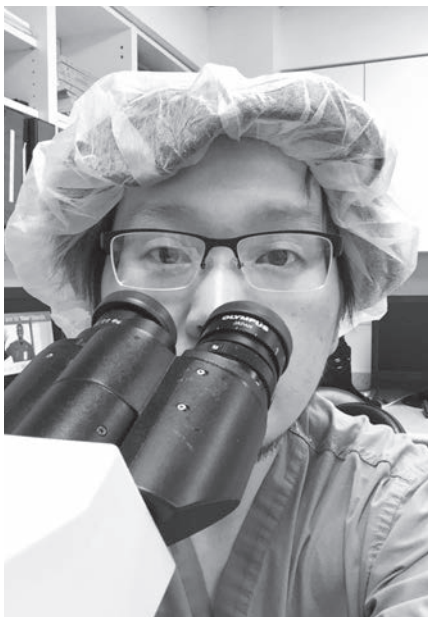
Yael Heher

"Pathology and pathologists are central to every part of medical care: diagnosis, prognosis, and even treatment," says Yael, Assistant Professor of Pathology at Harvard Medical School and Director of Quality and Patient Safety in the Department of Pathology at Beth Israel Deaconess Medical Center. "Whether you're a blood banker, a molecular or cytogenetic pathologist, a pediatric renal pathologist, a microbiologist...our subspecialties are infinitely interesting, always growing and changing, and we have limitless and exciting opportunities."

William C. Faquin

William is the Chief of Otolaryngologic Pathology at the Massachusetts Eye and Ear, a subspecialist in Head and Neck Pathology and Cytopathology at the Massachusetts General Hospital, Boston, and Professor of Pathology at Harvard Medical School.

"I am inspired by the sense that, as pathologists, our work is bettering the lives of patients through diagnosis and innovative discoveries," says William.



Woo Cheal Cho

Woo is currently Chief Resident in Anatomic and Clinical Pathology at Hartford Hospital, USCAP ambassador, and CAP Residents Forum delegate.

We asked Woo about his proudest achievement so far. "I would say that was when I received Ludwig J. Pyrtek M.D. Research Paper Distinction Award this year, which is perhaps one of the most prestigious awards (with the longest history) given by the University of Connecticut and Hartford Hospital. I am also proud of being accepted to MD Anderson Cancer Center (my dream place for fellowship) followed by being chosen as Chief Resident last year."

Zubair Baloch

Nominators called Zubair "an inspiration for pathologists," citing his strong record of authorship (over 150 peer-reviewed publications, chapters, and monographs), his teaching (including lectures, workshops, and short courses), and his influence on social media, particularly on Twitter. Currently Professor of Pathology and Laboratory Medicine at the University of Pennsylvania, Zubair's expertise lies in thyroid pathology – exemplified by his work on the development of the Bethesda Thyroid FNA Classification Scheme.

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Better Biomarkers for AD R&D

Priming diagnostics for the future of Alzheimer's disease research and treatment

By Carlo Medici

Alzheimer's disease has been a minefield for recent drug development, marked by a series of clinical trials whose failures suggest that therapeutic interventions will need to be directed earlier in the disease process. How much earlier? Well, before the onset of dementia – in fact, ideally before any symptoms manifest at all. Complicating the search for drugs to treat the disease is the fact that, in most instances, the symptomatic decline in affected individuals is slow. For a clinical trial to show a definite effect on cognition, it may need to run for many years. At this point, though, such clinical trials are some way in the future. First, to identify and ultimately treat the disease at a pre-symptomatic stage, we need valid biomarkers for Alzheimer's disease. Biomarkers are critical to stratifying and monitoring patients for clinical trials in drug development. Then, once treatments are available, biomarkers are needed to screen patients and confirm diagnoses in the clinic – and also to properly direct the use of drugs and track responses to therapy.

The current situation in Alzheimer's disease research is similar to one that, until recently, existed in the field of multiple sclerosis (MS) – another disease where the clinical diagnosis is frequently neither sensitive nor specific for the pathology. In MS, magnetic resonance imaging (MRI) is now invaluable for detecting and monitoring brain lesions associated with demyelination, which often present far earlier than clinical symptoms. Once the detection of such lesions via MRI of the brain became well-accepted as a biomarker for disease diagnosis and monitoring, drug research advanced quickly to the point where, today, there are 16 approved disease-modifying drugs for MS (not to mention many more that are used off-label to manage severe relapses or to treat specific symptoms).

These twin factors – realization of the need for early therapeutic intervention in Alzheimer's disease and the complexities of drug development under a scenario where clinical diagnosis is inadequate – have led the US Food and Drug Administration (FDA) to propose a biomarker-based approach to defining the illness that could guide new drug development efforts. In February 2018, the agency issued a new set of draft guidelines (1) that indicate its openness to a drug approval pathway based on surrogate biomarker measurements – signals that indicate a drug candidate is working as intended, even before cognitive benefit can be measured. The FDA believes that such a biomarker-driven approach could provide a new foundation for studies to find drugs that help treat, or even prevent, the onset of symptoms in people who are unknowingly in the early stages of Alzheimer's disease. Once a drug is approved, the new draft guidelines suggest the developer would then need to conduct further studies to confirm that it offers a benefit – in particular, an effect on cognition. A biomarker-based approach like this is not a radical idea; statins were developed based on cholesterol lowering as a biomarker even as research continued to establish the drugs' long-term benefit on cardiovascular disease and heart attacks.

Which biomarkers?

Experts today recognize that the pathophysiological changes that ultimately result in Alzheimer's dementia are the result of a multifaceted process that begins many years before symptoms appear. Affected individuals advance along a seamless continuum from asymptomatic to severely impaired. Although the pathology of Alzheimer's disease is still not completely understood, there are three general groups of biomarkers with recognized associations to the disease:

1. *Biomarkers related to beta-amyloid plaques*

   Amyloid plaques form in the brain when beta-amyloid protein fragments (Aβ) clump together and build up between cells. Some experts believe the most damaging form of Aβ may be smaller aggregates of a few pieces, rather than the larger plaques themselves. Such small aggregates may block cell-to-cell signaling or activate immune cells that trigger inflammation in the brain.

   A number of experimental drugs targeting the formation of amyloid plaques have failed in clinical trials, causing some to question the role of amyloid as an essential part of the disease process. However, extensive human genetic evidence exists to support the importance of amyloid in Alzheimer's disease pathology. Familial Alzheimer's disease

At a Glance

- *Thus far, drug development for Alzheimer's disease has not seen great success*
- *Clinical trial failures suggest we must catch and treat early – but at the moment, we have no effective way to detect pre-symptomatic disease*
- *We need valid biomarkers for Alzheimer's disease, not only to detect it, but also to stratify patients and monitor treatment success*
- *Even with fluid biomarkers showing early promise, brain imaging of disease and treatment response will remain essential*

and Down's syndrome (in which affected individuals have a high risk of developing a type of dementia that closely resembles Alzheimer's) are both associated with genetic abnormalities that increase the formation and deposition of Aβ. In sporadic Alzheimer's disease, it is well known that ApoE4, associated with a higher risk of the disease, decreases the clearance of Aβ. Moreover, the A673 mutation in the amyloid precursor protein (APP) is known to reduce the cleavage of APP by beta secretase into Aβ42, thus decreasing the risk of Alzheimer's (2,3).

2. *Biomarkers related to pathologic tau protein and aggregated tau "tangles"*
   Tau proteins regulate the assembly and structural stability of microtubules in the neurons. In Alzheimer's disease, tau becomes abnormally phosphorylated, which causes the pathologic tau molecules to twist and aggregate into "tangles." These tau tangles disrupt the microtubules' transport function so that nutrients and other essential materials can no longer move through the cells, which eventually die.
3. *Biomarkers of neuronal degeneration or neuronal injury*
   Although not specific to Alzheimer's disease, a number of potential biomarkers related to neurodegeneration or brain inflammation are under study as potentially useful markers for Alzheimer's research and drug development. These biomarkers are useful for helping to understand disease progression and severity, but must be used with caution because they are also associated with other brain pathologies.

Only Aβ and pathologic tau are specific indicators of Alzheimer's disease and could be considered as potential biomarker definitions of the disease. For this reason, the National Institute on Aging and the Alzheimer's Association have proposed a biomarker-based definition of Alzheimer's involving these indicators for research purposes (4), rather than defining the disease based on clinical symptoms. Additionally, although many interesting potential biomarkers are under study, only Aβ and tau are either available or close to available for practical use in clinical trials of potential disease-modifying drugs for Alzheimer's disease – or for potential future use in clinical medicine. Given the likely need to intervene in the pathologic processes that result in Alzheimer's dementia well before symptoms emerge, and the failure to date of potential treatments focused solely on Aβ and amyloid plaque formation, it is likely researchers will need to develop a multiple-biomarker approach to Alzheimer's diagnosis, drug development, and the measurement of response to potential treatments.

Brain imaging and Alzheimer's

Positron emission tomography (PET) is an imaging modality that uses radioactive tracers to examine targeted tissue and organs. The FDA has approved three PET tracers for the imaging of Aβ in the setting of Alzheimer's disease: florbetapir, flutemetamol, and florbetaben. PET imaging of brain amyloid deposits can successfully detect Alzheimer's pathology even before cognitive symptoms emerge – and, conversely, the lack of such deposits enables Alzheimer's disease to be ruled out as a likely cause of cognitive problems, speeding the search for other reasons for a patient's symptoms.

Amyloid PET scans are already playing an important role in clinical research. A positive cortical amyloid PET scan is now required prior to patient enrollment in many drug trials, thanks to several studies showing that over 60 percent of patients diagnosed with Alzheimer's based on clinical assessments were actually amyloid-negative on PET scan (5–10). The appropriate role of amyloid PET scans in clinical medicine is less clear-cut, and is the subject of the ongoing Imaging Dementia – Evidence for Amyloid Scanning (IDEAS) study to assess the clinical usefulness and impact on patient-oriented outcomes of brain amyloid PET scanning in patients with mild cognitive impairment or dementia of uncertain cause (11). The study, which has enrolled over 18,000 patients, is expected to generate sufficient data to assess whether amyloid imaging has a positive impact on patient outcomes and thus should be reimbursed by Medicare and other third-party payers. The IDEAS study is also expected to lay the groundwork for the type of information regulators and payers will need when considering coverage for future Alzheimer's biomarkers.

Despite its current utility in clinical research, amyloid PET has significant drawbacks that are likely to limit its widespread use in clinical medicine. PET scans employ radioactive tracers that expose patients to the equivalent of approximately 40 to 70 chest X-rays during a single scan. As a result, patients can only safely undergo this procedure a limited number of times, making PET unsuitable for tracking disease progression or response to treatments over time. PET imaging is also an extremely expensive procedure, with an average cost of US$6,000 or more, which makes it prohibitively costly for patient screening. Moreover, PET scans require the use of cyclotrons (unavailable in the majority of medical centers worldwide), making them a difficult procedure to access.

MRI is widely used for the imaging of soft tissues, and is currently the standard imaging test for brain disorders. MRI offers several advantages over PET in that does not expose patients to radiation, offers higher resolution scans, and is significantly lower-cost (less than 20 percent of the per-scan cost of PET). Additionally, MRI equipment is widely available throughout the world, with 10 to 20 times as many scanners available as PET cyclotrons. Structural MRI has long been used to examine brain atrophy in the course of diagnosing and monitoring the progression of Alzheimer's disease – but structural changes have not historically been useful in clinical diagnosis. Why? Chiefly because the structural changes (in particular, brain atrophy) noted on conventional MRI scans are not exclusive to Alzheimer's disease. Such structural changes can be used to distinguish clusters of patients, but are not necessarily useful for individual patient diagnosis. Additionally, significant loss of brain tissue on conventional MRI would be detected late in the course of the disease, when treatment would be less likely to help.

One industry/academic partnership is working to develop intravenous contrast agents for the MRI imaging of Aβ and tau. The technology is based on liposomal nanoparticles, carrying a ligand and an MRI contrast agent, that bind precisely to their targeted brain protein. The researchers expect to initiate clinical trials of the Aβ

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MRI agent in 2019. Because the platform involves no radiation, it could permit frequent longitudinal imaging of patients, enabling the monitoring of disease response and progression over time – particularly critical in the clinical assessment of new therapies. In addition, such an MRI-based diagnostic agent would make widespread screening for early disease feasible.

A fluid transition

The first fluid biomarkers reflecting Alzheimer's disease pathology were identified in cerebrospinal fluid (CSF) in the 1990s: Aβ42, total tau, and phosphorylated tau. These biomarkers are reported to have greater than 95 percent sensitivity and greater than 85 percent specificity to the disease. CSF analysis also provides a measurement of the equilibrium level of a given protein at a single time point, because CSF content reflects the net result of rates of both protein production and clearance. Unfortunately, CSF biomarkers have several downsides. For one, they provide indirect information; their analysis implies, rather than specifically measures, brain pathology. For another, the lumbar punctures required to sample the fluid are painful and invasive. These difficulties have spurred considerable research aimed at finding suitable biomarkers in blood or plasma for a simple, low-cost, minimally invasive Alzheimer's disease screen.

Advances toward a simple blood test have been reported on several fronts. Research published in early 2018 by scientists from Japan's National Center for Geriatrics used mass spectrometry to ionize and scan blood plasma from more than 300 people for a particular peptide or amino acid linked to Aβ (12). The researchers found that the amount of amyloid they detected in blood predicted – with over 90 percent accuracy – the degree of cognitive problems faced by each of the subjects tested. In addition, the blood test results correlated to amyloid measurements in the subjects' CSF and to PET brain scans of amyloid deposition. Even more recently, a German research group found that changes in the structure of plasma Aβ might foretell Alzheimer's disease. The researchers used infrared spectroscopy to measure the ratio of β-sheet to α-helical forms of Aβ in plasma, and found that they could distinguish prodromal Alzheimer's disease from healthy individuals (13). In longitudinal studies using this approach, healthy people who tested positive for β-sheet forms were nearly eight times more likely to be diagnosed with Alzheimer's disease within the next eight years. Although research looks positive, we'll need further studies before we are able to establish Aβ as a stable blood-based biomarker.

A protein related to neurodegeneration, neurofilament light (NfL), is also showing strong potential as a blood-based biomarker for Alzheimer's disease and other conditions (such as traumatic brain injury) marked by similar tissue damage (14). Dying neurons release proteins into the brain, some of which – including NfL – can be found in trace amounts in blood. Researchers have found high levels of NfL in the blood of people with Alzheimer's disease and mild cognitive impairment (8). Rising plasma NfL levels over time have also been associated with worsening cognitive scores and brain atrophy. Although NfL is neither sensitive nor specific enough to be employed on its own as a marker of Alzheimer's disease, it has been able to distinguish Alzeimer's from mild cognitive impairment and from healthy controls with a performance equal to that of Aβ or tau in CSF. Furthermore, blood NfL measurements have accurately predicted disease progression, making it a potentially useful biomarker for patient enrichment in clinical trials, longitudinal studies of drugs aimed at slowing cognitive deterioration, or clinical trials of drugs that target neurodegeneration.

Biomarker diagnostics in the real world

Brain imaging modalities are already validated as biomarkers of Alzheimer's disease. Tests based on biomarkers found in blood and CSF have not yet reached that status, and no blood- or plasma-based tests are commercially available. However, the availability of such blood tests could be a big step forward for drug development, making it much easier to recruit, screen, and track patients' responses to experimental drugs. Ultimately, the utility of such technologies will depend on a number of factors: the setting in which they are used, the required test accuracy, the tests' cost, and their general availability. Once approved treatments for Alzheimer's disease are available, a blood or plasma test could also enable the widespread screening of older individuals, allowing those with positive biomarker tests to be sent for a more specific confirmatory diagnosis via imaging.

Eventually, the field of Alzheimer's disease research and clinical medicine may come to resemble that of oncology, where the diagnosis of "cancer" is recognized as including a variety of disparate malignancies, and drug development and prescription is increasingly based on the specific biomarkers expressed by an individual patient's tumor. The ability to discern the cause of a patient's cognitive decline based on biomarkers of specific pathologies could change our understanding of Alzheimer's disease in the same way, moving us away from the current blanket diagnosis and toward a spectrum of pathologies that lead to cognitive impairment. The availability of such a precision medicine approach to Alzheimer's disease diagnosis and treatment could only lead to earlier diagnosis and intervention and ultimately better outcomes.

Carlo Medici is chief executive officer of Alzeca Biosciences, Houston, USA, a company developing novel advanced imaging agents for the early diagnosis of neurodegenerative diseases, including Alzheimer's disease.

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Opening Doors With Omics

Sitting Down With… Oliver Fiehn, Director, NIH West Coast Metabolomics Center, Paul K & Ruth Stumpf Endowed Professor in Plant Biochemistry, UC Davis Genome Center, California, USA.

What was your route into science?

I was always interested in understanding how things worked; I was curious and serious, and asked a lot of questions – not what you would call an "easygoing" child! In high school, I discovered that I had a passion for chemistry. When I finished my PhD in 1997, I wanted to go into industry, but there was high unemployment in the sciences in Germany at that time – 2,000 graduate chemists for every few hundred industry positions. I got a postdoc position at the Max-Planck Institute in Potsdam and came to find metabolomics particularly fascinating. After a short time, I became group leader. So that was my trajectory – a chain of reactions…

What fascinated you about metabolomics?

On my first day, my boss said, "Don't ignore the small peaks." Abundance doesn't equate to importance; compounds at very low concentrations, such as hormones, can have huge effects – as can high abundance compounds like glucose. That's the concept of metabolomics – looking at the whole picture, trying to understand what it means and unraveling biological technologies along the way. It is asking an open-ended question, which always leads to new discoveries and opens doors. And it is simply a lot of fun!

How has the field changed in the last 20 years?

In the beginning, we were mainly hunting low-abundance peaks (or peaks in general) and didn't think that much about quantification, harmonization and standardization. Then, 10 years ago, we started the Metabolomics Standards Initiative. Now, we can feed metabolomics data into databases, and compare and contrast findings across studies. No one study tells you the truth; you have to find multiple lines of evidence and compare them in meta-analyses – that's how you figure out the functions of different compounds. The field has become more serious these days, more established, and – I hope – more useful for clinical and biomedical research.

Could you give an example of the modern approach?

My group found diacetylspermine – an acetylated version of spermine – in blood for the first time ever, and discovered that it is indicative of people who will get lung cancer within the next six months. We carried out two independent clinical trials, each with 300 people, and found very high significance. Of course, it needs to be replicated in further cohorts, but it was an important finding.

Another significant discovery was the so-called FAHFA lipids, by Barbara Khan at Harvard. This is a new class of compounds that influences and directs insulin sensitivity and insulin resistance, so it is important in metabolic syndrome, and in the development and progression of diabetes. Again, more research needs to be done – that's the case with all scientific discoveries; after the initial excitement, you need to dig deeper.

You manage a big group…

I am director of the West Coast Metabolomics Center, a consortium of different laboratories at UC Davis. I directly manage two of those labs; one is my own research lab, where we work with postdocs, visiting and project scientists, PhD students and cheminformatics specialists. The second is a service laboratory, with 13 full-time staff who manage the 17 mass spectrometers, and process over 25,000 samples a year, for more than 400 studies. These are two different entities, but both are important. I would never call the service lab team technicians; they are scientists, dedicated to pursuing analytical chemistry in a rigorous manner, and ultimately trying to help people. It is a shame that it's so hard to publish method validation work in analytical journals – they only want new methods, not robust ones, which is strange to me. Analytical chemistry methods have to be proven and validated to be robust.

"It's the best job in the world – and I'm very grateful to society for allowing me to do it."

How does working as a scientist in California compare to Germany?

The culture is more "thriving" here; it is more vibrant, open-minded and energetic. We have absolutely fantastic scientists at Davis, and I love working here – it's fabulous.

What is your biggest source of inspiration?

I am a member of the Molecular and Cellular Biology Department and my lab is located in the Genome Center, so I am surrounded by biologists. I'm also a member member of the Comprehensive Cancer Center in Davis. It means my inspiration comes from actual biological and medical questions. For example, we recently received a grant from Columbia University to research chronic fatigue syndrome. I think if we take analytical chemistry seriously, we can really have an impact on people's lives. That's what drives me.

What are you most thankful for in your career?

My freedom. I can follow my own ideas – I'm my own boss, and I can pursue my vision and favorite topics in metabolomics. It's the best job in the world – and I'm very grateful to society for allowing me to do it.

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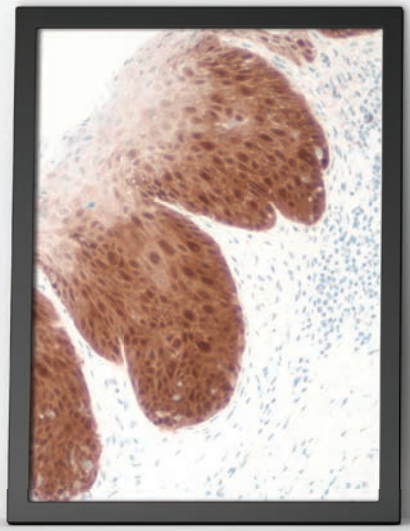

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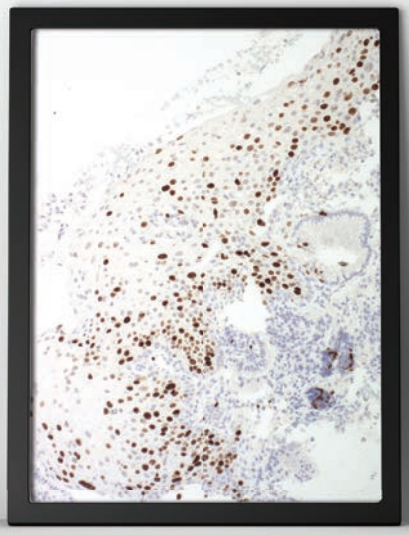

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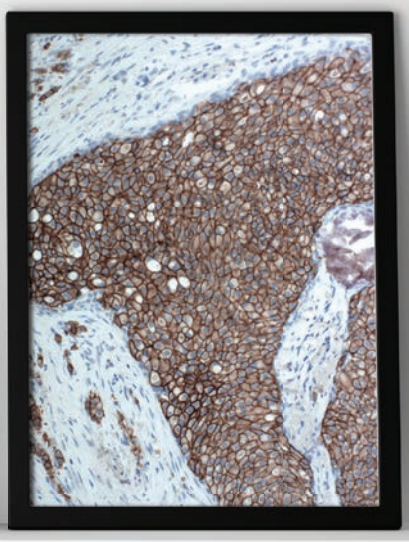

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