JANUARY 2019 # 50

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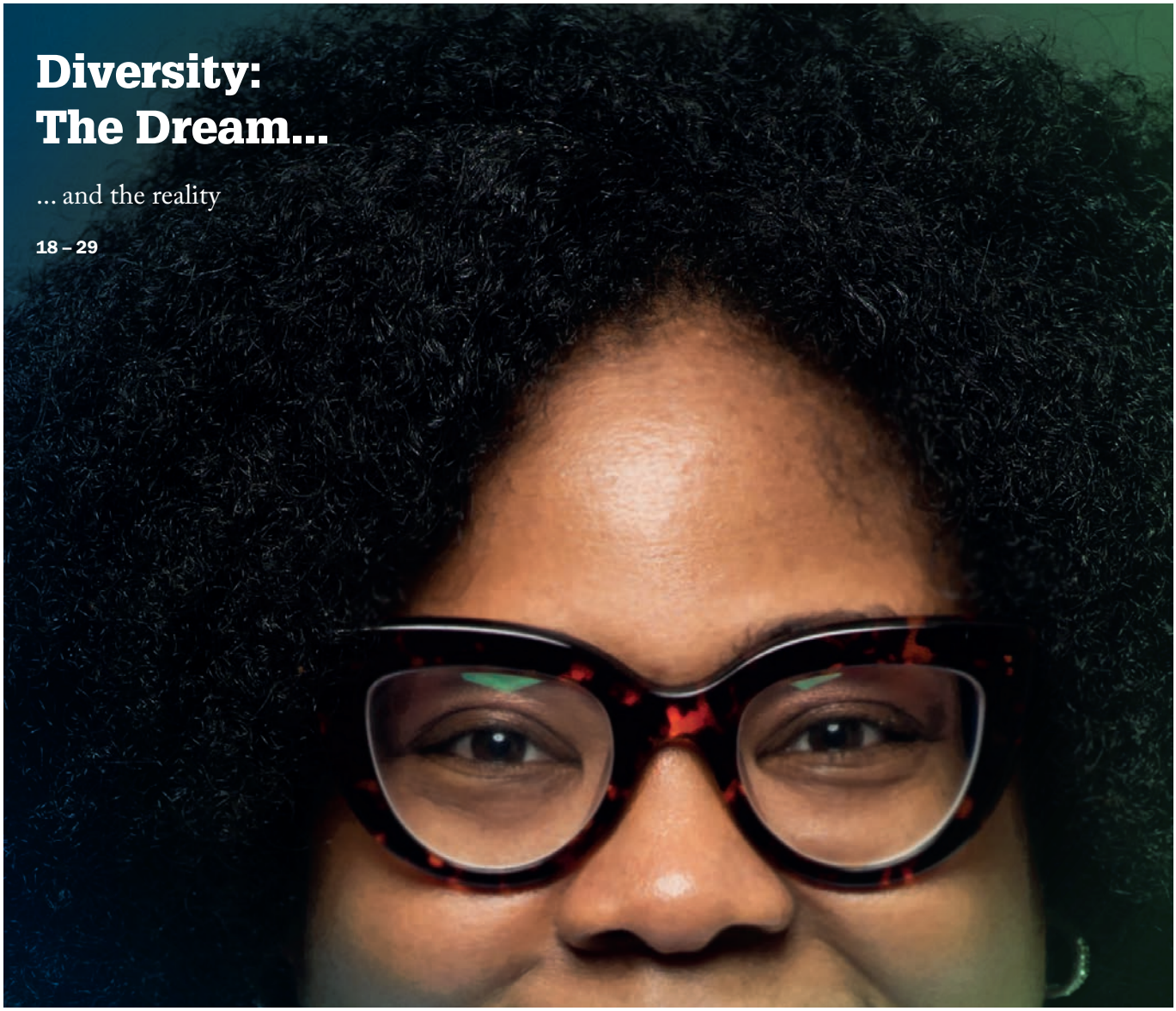

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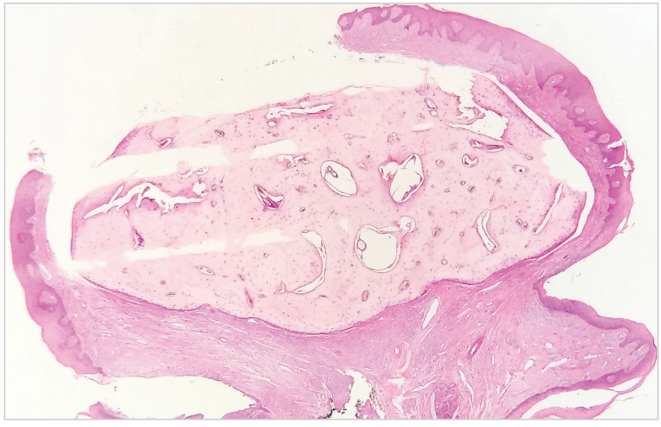
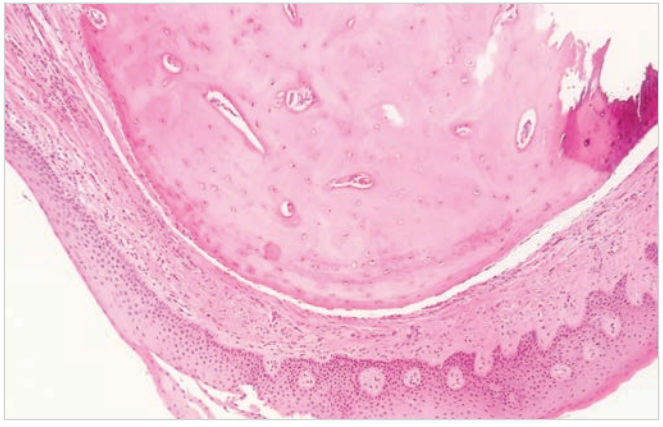
Case of the Month





A 50-year-old woman presented with a single painless lesion to the left side of the base of the tongue. Gross evaluation revealed a nodular lesion measuring 0.7x0.5 cm that was whitish and firm.

What is your diagnosis?

a Pleomorphic adenoma

b Osseous choristoma

c Peripheral ossifying fibroma

d Oral torus

Answer to last issue's Case of the Month…

B. Particulate matter aspiration

The images posted last month showed pathologic findings diagnostic of aspiration of microscopic particulate matter into the pulmonary parenchyma (1). The tissue reaction in this case – a combination of organizing pneumonia and granulomatous inflammation with foreign body giant cells – is typical. The aspirated material shown was a combination of microcrystalline cellulose (colorless) and crospovidone (purple, coral-like). These particles are more commonly encountered in patients who inject oral pills intravenously (talc granulomatosis), but in those cases they are found within the interstitium around small blood vessels (2). Less commonly, these particles can enter the lung due to aspiration of oral pills. The presence of organizing pneumonia is a clue to the correct diagnosis, as is the location of the material adjacent to bronchioles.

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Submitted by Sanjay Mukhopadhyay, Staff Pathologist, Cleveland Clinic, Cleveland, USA.

To register your guess, please go to http://tp.txp.to/0119/case-of-the-month
We will reveal the answer in next month's issue!

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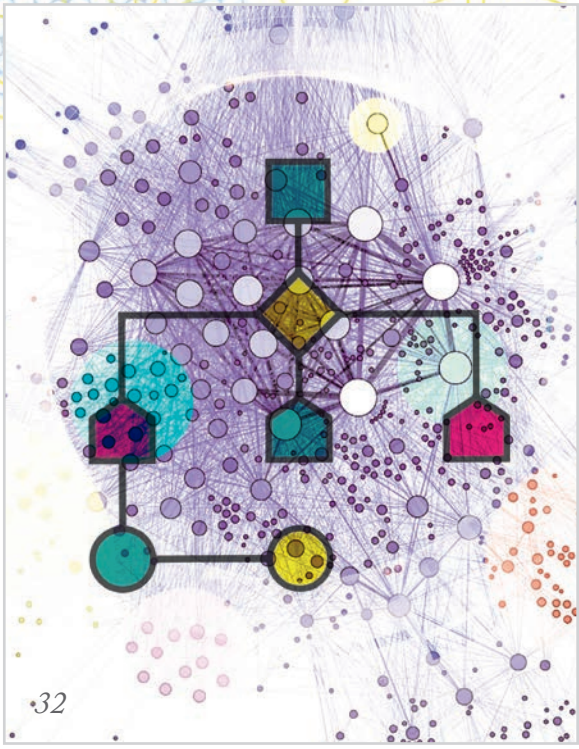

On The Cover

A photograph of Valerie Fitzhugh – champion of diversity in pathology and laboratory medicine

NextGen

Features

Profession

In Practice

Sitting Down With

the Pathologist

ISSUE 50 – JANUARY 2019

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General enquiries:
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+44 (0) 1565 745200
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Distribution:
The Pathologist (ISSN 2055-8228), is published monthly by Texere Publishing Limited, Booths Park 1, Chelford Road, Knutsford, Cheshire, WA16 8GS, UK
Single copy sales £15 (plus postage, cost available on request info@texerepublishing.com)
Non-qualified annual subscription cost is £110 plus postage

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A View to the Future

Laboratory medicine is leaping ahead – so where will it go next?

Welcome to the start of another year! I'm sure I'm not the only one among us who, every January, wonders where the time has gone. And yet, a glance at the world around me adjusts my viewpoint.

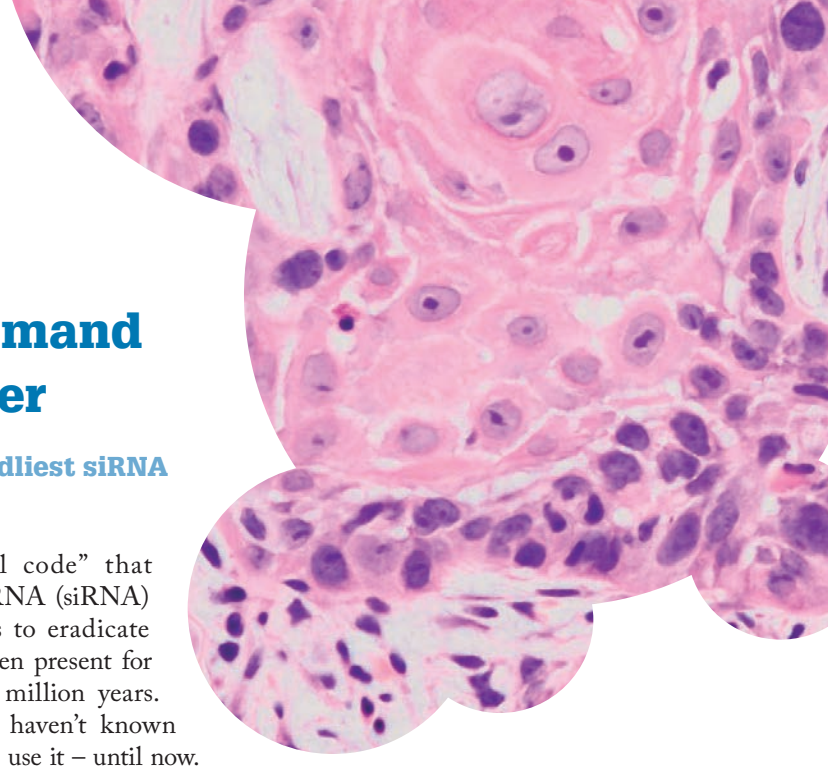
In fact, science and technology are moving along so quickly that it's hard to believe some changes have taken place in only a year. We have brand-new, high-resolution photographs of the surface of Mars. We have artificial intelligence whose reading comprehension exceeds that of humans. We have cloned monkeys, grown human ova in the laboratory, identified skeletal stem cells, completed the 100,000 Genomes Project, and even produced (with significant uproar from the scientific community) the world's first genetically edited babies.

Clearly, laboratory medicine has played a large part in the scientific advances of the past year – albeit perhaps not on Mars. But where do we go from here? With the pace of scientific advancement rapidly increasing, what are the next steps?

In 2018, we saw the start of the first trials using CRISPR-based T cell modification to fight cancer. We saw the advent of liquid biopsies that can detect multiple common cancers even before symptoms emerge. We mapped the complete connectome of the fruit fly and identified multiple potential therapies for neurodegenerative diseases. We launched the Earth BioGenome Project, an ambitious, decade-long initiative that aims to sequence all known species on Earth. Will those promising starts bear fruit in the near future?

When I speak with researchers about their up-and-coming projects, the strongest message they send is hope – for the future of their patients, for their discipline, and for science and medicine as a whole. New discoveries seek to spare patients pain and discomfort, increase their chances of a long and healthy life, and reduce the mental, physical, and financial toll of ill health among a growing, aging population. So I put the question to you (and invite your responses at edit@thepathologist.com): where do you think pathology and laboratory medicine are going in 2019 and beyond? What do you think the next important advance will be? And how can individual practitioners help forward the goals of the field?

Michael Schubert
Editor

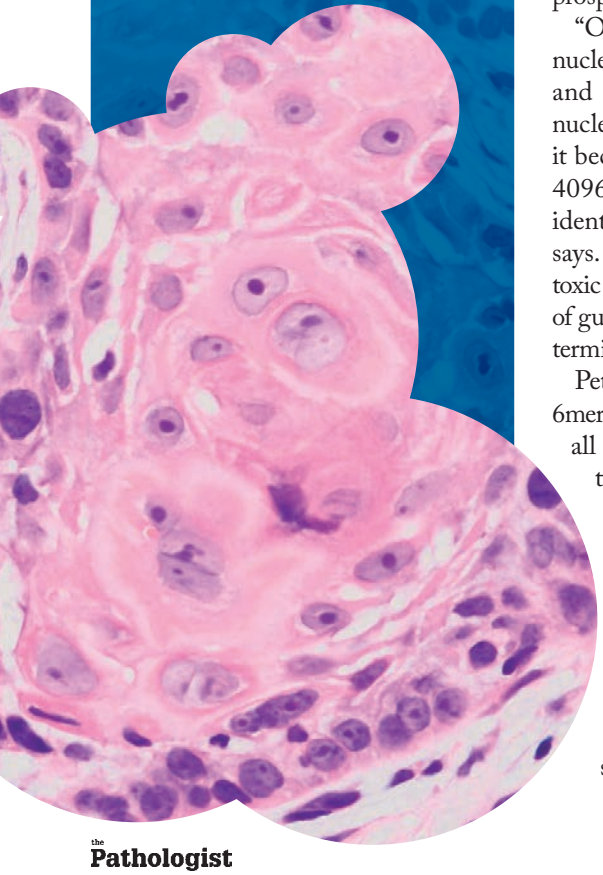


Upfront

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



Kill Command for Cancer

What's the deadliest siRNA sequence?

The "cellular kill code" that small interfering RNA (siRNA) molecules harness to eradicate cancer cells has been present for an estimated 800 million years. Unfortunately, we haven't known what it is or how to use it – until now. The deadly code has now been found to result from just six nucleotides – between positions two and seven in a sequence of 19 – known as the 6mer seed sequence. Marcus Peter, Professor of Cancer Metabolism at Northwestern Medicine, Chicago, USA, led research into the siRNA nucleotide sequence. And he is now understandably excited by the prospect of targeting cancer.

"Once we knew that it was just six nucleotides responsible for the toxicity, and that there are only four possible nucleotides for each of these positions, it became clear that we could screen all 4096 possible 6mer combinations to identify the deadliest kill code," Peter says. The researchers found that the most toxic composition to cancer cells consisted of guanine enrichment toward the 5' end, terming the sequence "G-rich."

Peter continues, "We believe the G-rich 6mer is not only toxic to cancer cells, but all cells of the body, regardless of their tissue of origin. Our data suggest that healthy cells are protected from the mechanism by an extremely high expression of microRNAs (miRNAs) that carry non-toxic 6mer seeds. When cells become cancerous, they downregulate these non-toxic miRNAs, rendering them susceptible to the 6mer seed's toxic mechanism." Analyses suggest that mature miRNAs have evolved over time to avoid guanine at the 5' end of the 6mer sequence, preventing the killing of healthy cells – but some naturally occurring tumor-suppressive miRNAs have taken the opposite tack, preserving a G-rich 6mer seed that can eradicate cancer cells.

Cancer cells were unable to develop resistance to the toxic mechanism both in vitro and in vivo, making it a highly effective kill code. "Based on these findings, we can now design artificial miRNAs to make their toxicity as high as possible, even to the point where they are more toxic than the ones designed by nature," says Peter. But despite their "micro" size, drug delivery will represent a challenge: "These RNAs are actually quite large compared with small molecule drugs. To have a real impact, we need to find ways to get them into every single cancer cell. We are working on a number of ways to achieve this; we are seeking industry partners that can help us take our concept to the next level."

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Catching the Bug

A rapid test for influenza could prevent patient isolation and save money

The winter months are notorious for wreaking havoc with our immune systems – and draining resources in already overstretched hospitals. Incidence of influenza rockets during the cold season, affecting 5–10 percent of adults and 20–30 percent of children every year (1). Now, a rapid, PCR-based molecular test can diagnose 43 strains of influenza A and B and seven strains of respiratory syncytial virus (a leading cause of respiratory disease) within 20 minutes (2). By applying real-time PCR to a nasopharyngeal swab sample, the test could significantly reduce the unnecessary occupation of hospital beds and lead to more effective treatment for patients.

Fran Brooke-Pearce, a Clinical Nurse Specialist for Infection Prevention and Control, trialed the test at Kingston Hospital, and says it has been a positive addition to the way patient flow is managed. "We previously had to wait up to two days for influenza results, meaning that patients with suspected influenza were isolated even if they didn't have the virus. As well as now being able to determine quickly whether a patient has influenza, we can often discharge patients who test positive on the same day, once other risks have been ruled out," says Brooke-Pearce. "It has enabled us to keep more bays open on our wards and fully use the beds that we have available."

During the Kingston Hospital trial of the test, only 479 of 1,526 suspected influenza cases came back positive, meaning that 65 percent of patients with suspected (but unconfirmed) influenza could be discharged or admitted without unnecessary isolation. Another UK hospital that trialed the test estimates that it will save around £142,555 over the course of a flu season – albeit before accounting for the cost of the tests (under £50 each).

Given that the test can be used in nontraditional settings, such as emergency rooms and physician offices, it has potential as a rapid point-of-care diagnostic, which could help prevent the unnecessary prescription of antibiotics.

But does the new test come at the cost of accuracy? Not according to Brooke-Pearce. "We carried out a number of laboratory tests in parallel with this test and found 100 percent accuracy, which means that we can diagnose, treat, and discharge patients with flu accurately and much more quickly than before."

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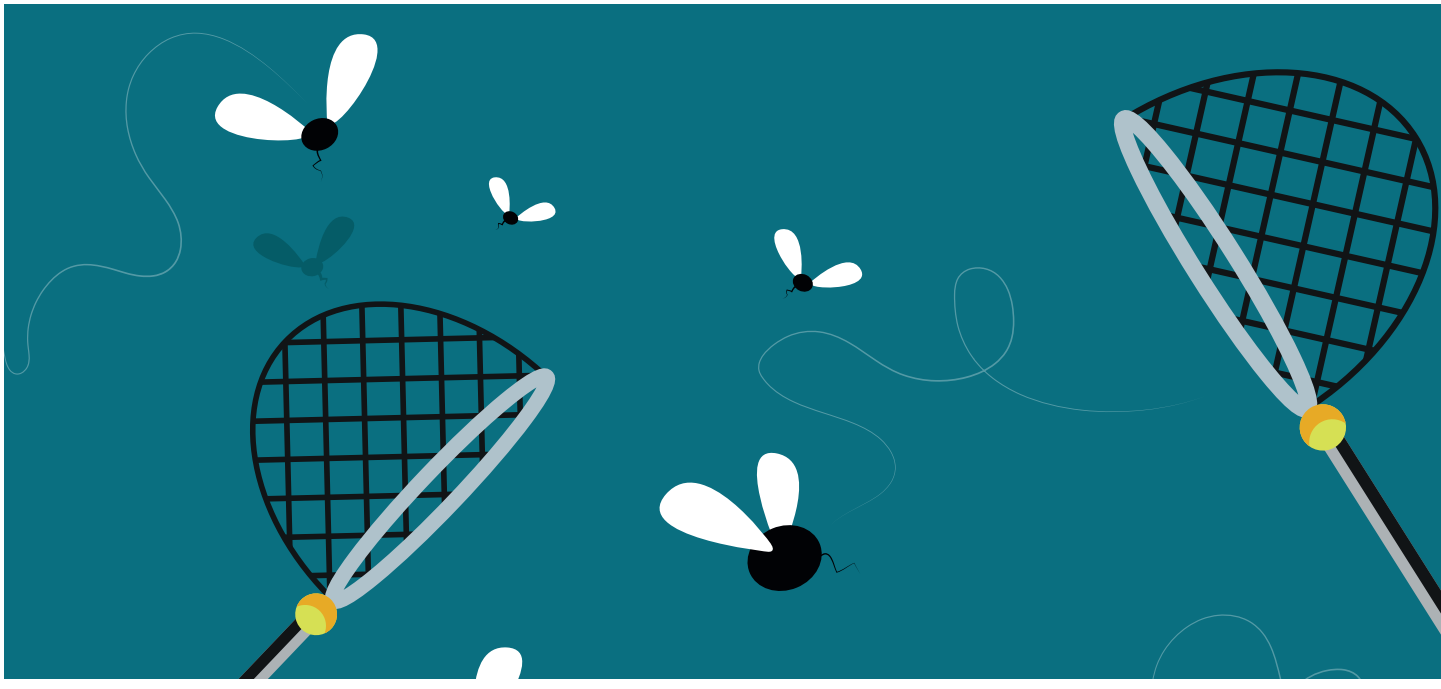
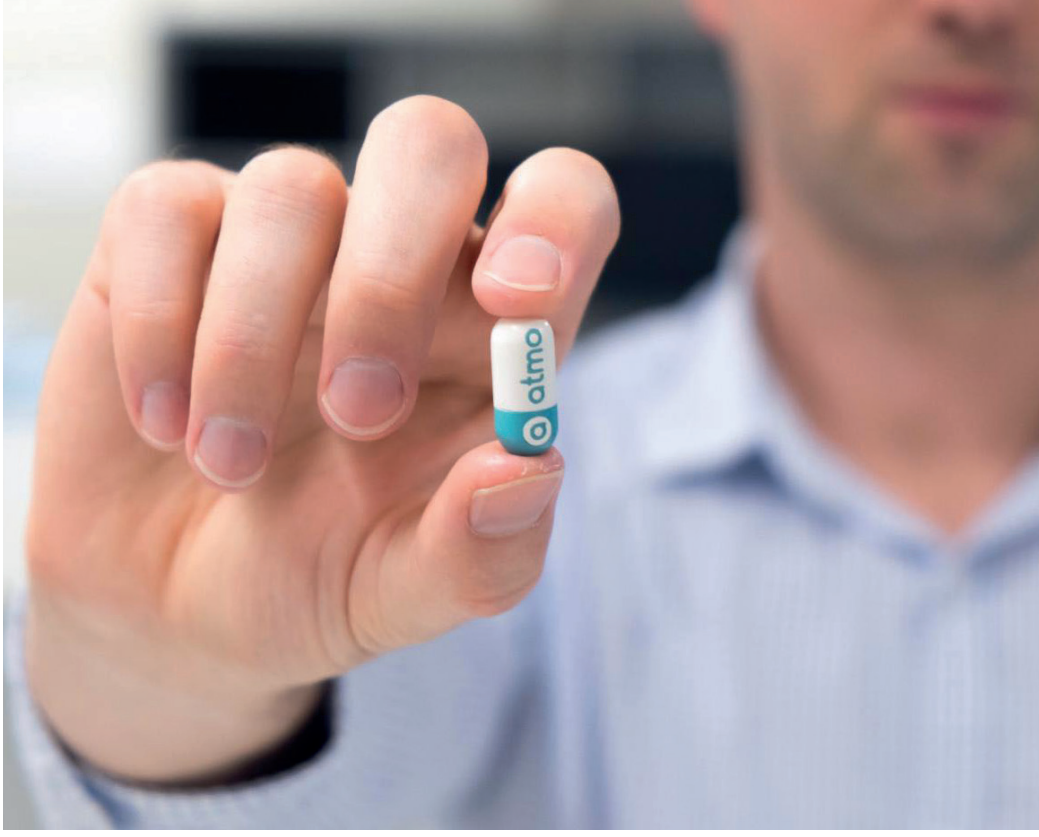


An Analytical Pill

Measuring gaseous biomarkers to help diagnose and monitor gut disorders



Digestive disorders are common, and their symptoms are often incontrovertible – certainly to the tens of millions of patients worldwide who suffer from them. Diagnosis, however, is rarely so clear, which is why nearly one-third of all patients with gut disorders are unable to put a name to their condition. But a new device – an electronic capsule that can measure gaseous biomarkers and transmit the information wirelessly to waiting physicians (1) – may improve upon the accuracy of existing tests.

Kouroush Kalantar-zadeh, co-inventor of the capsule and Lead Scientific Advisor for the company set to commercialize it, explains: "In most cases, unless there is a visual marker like a wound or inflammation, prevention, diagnosis, and monitoring tool options are very limited for gut disorders." It was an encounter with a gastroenterologist that inspired the new device; Kalantar-zadeh was initially asked to make existing breath tests more accurate, but concluded that the indirect measurement made the task impossible. Instead, he decided to create a capsule that patients can swallow – one that can directly sense and measure gases such as hydrogen, oxygen, and carbon dioxide – within the digestive system.

"The capsule, designed by engineer Nam Ha, moves along the gut after ingestion and leaves the body with the natural motility of the gastrointestinal tract – generally within 24 to 48 hours," Kalantar-zadeh explains. The capsule transmits data every five minutes to a handheld monitor the patient carries, which in turn sends the information via Bluetooth to a mobile phone for online monitoring or cloud storage. "So far, we have shown accuracy of near 100 percent in measuring hydrogen as a biomarker. In comparison, breath test accuracy is significantly lower." Kalantar-zadeh emphasizes that accuracy of gas measurements directly translates to accuracy in the prevention, diagnosis, and monitoring of gut disorders from malabsorption to inflammatory bowel disease. Soon, he hopes, the device will enter mass production and begin improving the lives of digestive disorder patients everywhere.

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(Digital) Center of Attention

Investing in the future of UK pathology with a network of technology centers

As the digital revolution continues to sweep across the field of laboratory medicine, five new digital pathology centers will open in the UK in 2019. The aspiration? Helping hospitals reduce manual reporting and increase the number of digital scans and biopsy images. The £50 million investment in the centers – located in London, Oxford, Glasgow, Leeds, and Coventry – comes from the UK government and business partners, and will provide the National Health Service (NHS) with the infrastructure and training for scanning equipment.

Some pathologists remain skeptical about the field's digital future, but the centers aim to emphasize the need to keep laboratory professionals at the forefront of new technologies. "NHS pathologists will play a key role in the co-development of new tools within these centers, along with engagement and outreach work to the wider pathology community," says a spokesperson for UK Research and Innovation (UKRI), the organization that allocated the funding. "Development of the centers has been led by active pathologists, and ongoing collaboration with leading professional bodies will play a key role in their success."

Spearheaded by leading medical companies, the centers bring together teams that will use artificial intelligence to develop the image analysis tools that UKRI believes are the future. "The ultimate aim is to achieve a wholly digital service. However, this ambition is still some way off, and it's clear that there is work to be done with the pathology community to ensure that their needs and aspirations are met by any digital future. These centers will hopefully enable that journey to begin in earnest, in partnership with NHS pathologists and patients."

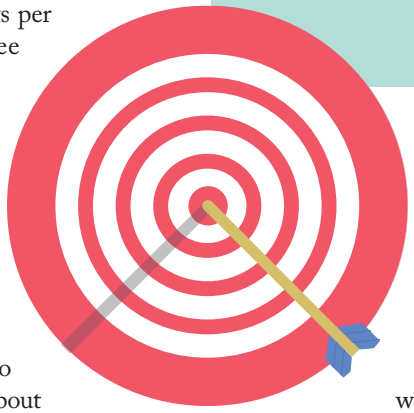
Another goal of the centers is to have an impact on the future recruitment of pathologists. The UKRI says, "We hope that this type of high-profile investment in the field will help to showcase the rich rewards and opportunities of a career in pathology. The centers will provide an integrated training environment for early-career clinicians with an interest in pathology."

Quick Hits

Discover the latest in pathology and laboratory medicine with this roundup of short news stories

Diagnostic Tests Triple

The use of diagnostic tests in the UK has increased rapidly over recent years – an average of five tests per person, per year, three times more than 15 years ago. From 2000 to 2016, there has been an 8.5 percent increase in diagnostic test usage each year, which researchers suggest may reflect a greater expectation among patients to participate in decisions about their care (1).



Building an Organ

A three-dimensional "organ on a chip" that allows continuous, real-time monitoring of cells has opened up new opportunities for understanding disease. The device accurately mimics the growth of cells within the body and can be modified to generate multiple organ types that can help simulate the efficacy of different treatments. The biomimetic platform, which has been used to grow epithelial and fibroblast cells that form tissue-like architectures, uses a sponge electrode to provide a natural environment for cells (2).

Tracing Tumors

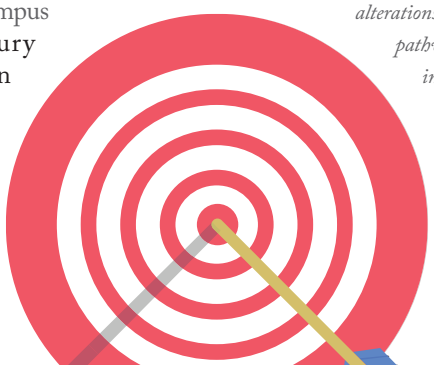
A new radiotracer that targets the c-Met receptor – a signaling pathway that contributes to tumorigenesis in non-small cell lung cancer – could improve diagnosis of the disease. The 99mTc-HYNIC-cMBP tracer showed much higher uptake in tumor cells with high c-Met expression than in those with low c-Met expression, and revealed the tumors on nuclear imaging scans within half an hour. This, coupled with reduced radiation exposure because the tracer is more quickly eliminated from the body, makes it more promising than current tracers (3).

Behind the slides

As the UK celebrated its 10th annual National Pathology Week in November, Robert Gordon University in Scotland marked the occasion by opening its doors to around 50 children from schools across the region. Budding scientists aged 14 to 17 attended "Science Secrets of the Hospital Lab" educational sessions that exposed them to histology, microbiology, and hematology as they attempted to solve a clinical puzzle.

Mapping the Hippocampus

Traumatic brain injury (TBI) – a common occurrence in domestic sports – often results in hippocampal dysfunction that ultimately leads to cognitive decline and the escalation of other neurological disorders, such as Alzheimer's and Parkinson's disease. New research to map out the hippocampus in its first cell "atlas" has found that TBI affects a range of previously undefined cell populations and alters gene co-expression across different types of cells. These results indicate the presence of new therapeutic target pathways and hidden pathogenic mechanisms (4).



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Biomarkers on the Brain

Steve Clifford describes a new chromosome signature associated with favorable outcomes in medulloblastoma patients

Medulloblastoma – the most common malignant childhood brain tumor – originates in the cerebellum and comprises various disease entities that differ in their characteristic mutations and biological profiles. The most effective current treatments for medulloblastoma are based on multi-modal surgery, radiotherapy, and chemotherapy. Despite the adaptation of treatment intensity to reflect disease risk, quantification of that risk is imprecise. About 60 percent of all patients – termed the standard risk group – receive essentially the same treatment. This subgroup, which is characterized by the absence of high-risk features, such as metastatic disease and large-cell histology, has a five-year survival rate of 75–85 percent. How could we improve upon those numbers? One possible solution was to search for ways of better personalizing treatment within this standard-risk group. In an attempt to discover a more precise biomarker of disease risk, we performed a large-scale genomics study. The result? A chromosome signature associated with greater patient survival.

Using data from the most recent pan-European medulloblastoma trial, we identified a group of patients whose tumors were characterized by multiple whole-chromosome aberrations associated with an excellent prognosis. Clustering and biostatistical methods enabled us to establish the combination of chromosome defects that best predicted favorable outcomes in the standard risk category, indicating those who would benefit from a reduction in treatment intensity. Ultimately, the "favorable risk" patients who possessed the signature exhibited a 100 percent survival rate.

Conversely, patients without the chromosome signature showed a five-year survival rate of only 60 percent, placing them in a higher risk category. For these patients, it's possible that treatment intensification is the best course of action. We estimate that stratification using chromosome biomarkers could facilitate the assignment of 150–200 patients per year in Europe to a "favorable risk" group, reducing the number of standard risk patients receiving intense treatment.

We now aim to validate this signature in further clinical trials before taking it to the clinic. To detect the signature, neuropathologists can use various methods – for instance, interphase FISH with specific chromosome probes, single nucleotide polymorphism arrays, and array comparative genomic hybridization, all of which are becoming more commonplace in medulloblastoma diagnostics. Pathologists will also need to identify non-*WNT*/non-*SHH* molecular subgroups of medulloblastoma, as these don't fall within the standard risk category.

Our study has identified around half of all standard risk patients who could potentially benefit from less intensive therapies. The next step will be to run trials that test whether their favorable prognosis is maintained once therapy intensity is reduced – a goal that could alleviate neurological late effects, such as reduced growth and IQ.

References

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In My View

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

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

Contact the editors at edit@thepathologist.com

Smarter, Faster Sepsis Testing

Point-of-care diagnostics for sepsis would catalyze early intervention

By David Ludvigson, President and CEO of Nanomix, Emeryville, USA

Sepsis robs millions of people of their lives each year, but because its symptoms overlap with those of several other medical conditions, even well-trained medical professionals can have trouble recognizing it. Unfortunately, this confusion contributes to the condition's high mortality rate; every hour of delayed treatment increases the patient's risk of death by 8 percent (1). It is estimated that sepsis may affect over 30 million people around the world each year, causing as many as six million deaths (2). In some countries, it is one of the leading causes of death among patients who die in hospitals. And although sepsis most often occurs among patients who are already hospitalized for kidney, lung, or urinary tract infections and other problems, it can just as easily arise in the community setting, where the likelihood of a timely diagnosis is even lower.

There are a number of fronts where we must make progress to improve patient outcomes related to sepsis. At the most basic level, clinical lab professionals can participate in efforts to raise awareness among the public of the signs and symptoms of sepsis. If more people understood the condition and knew what to look for among their neighbors and loved ones, suspected cases of sepsis would likely get medical attention sooner. Other improvements must happen within clinical labs and in the research and development departments of diagnostic developers. Already, teams are working hard to design better sepsis diagnostic tools that can help clinical teams determine whether drug-resistance markers or other pathogen-specific traits are relevant to treatment selection.

> *"There are a number of fronts where we must make progress to improve patient outcomes related to sepsis."*

But there is another critical area that tends to get less attention from the clinical lab and diagnostic communities: point-of-care (POC) triage testing. Although classifying the causative pathogen is important, the very first question – the one that will give patients the best chance at survival – is whether or not the patient actually has sepsis. A simple yes-or-no test that could be performed right away, whether the patient is in the hospital or being picked up at home by an ambulance, would dramatically improve the speed with which antibiotics could be

administered to prevent a sepsis patient from getting worse.

The introduction of such a POC triage test would entail a significant shift in the way the diagnostics community thinks about sepsis testing; instead of having just one test designed to identify the pathogen, we would need a two-stage testing protocol. The first stage would quickly reveal important information about the patient's condition and spot the onset of sepsis. The second test would essentially be what's available now: a more advanced test, performed in a clinical laboratory, that provides in-depth data about the pathogen and its drug resistance profile.

A POC test that provides sufficient evidence of sepsis would allow first responders to get patients started on this treatment hours or even days sooner than if they had to wait for hospital admission and clinical laboratory testing. Indeed, typical treatments for sepsis include antibiotics and fluids, which are quite effective at beating back sepsis – at its earliest stages.

For optimal results, though, the POC triage test would have to generate results incredibly quickly, during the narrow critical care window – half an hour from when the first symptoms of sepsis manifest – during which patients have the best chance of recovery with standard treatment. In other words, the POC test would have to produce actionable results in just 10–15 minutes to have an impact on patient outcomes.

A triage test for sepsis would have the added benefit of easing the burden of generating rapid results for hospital labs, allowing them to focus on the more complex pathogen identification tests without the pressure of knowing that patients are going without treatment until results are returned.

You may not be surprised to hear that a portable POC test for sepsis is currently in development and being evaluated in clinical trials. Measuring lactate, procalcitonin, and C-reactive protein – three well-documented biomarkers of sepsis – it generates results with better sensitivity and specificity than lactate-only tests.

In my view, the two-stage testing model is a better route forward. It enables emergency teams to offer early intervention while still engaging hospital laboratorians for more sophisticated strain identification testing to further hone antibiotic selection. Just as early administration of clot-busting drugs has revolutionized outcomes for stroke victims, the ability to treat patients in the initial stages of sepsis could make this common condition far less deadly.

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Pathology Recruitment Down Under

Medical student education and recruitment in pathology, "Australasian style"

By Eve Propper, Events and Sponsorship Manager at the Royal College of Pathologists of Australasia, Surry Hills, Australia

As pathologists and laboratory medical professionals, it's our job to ensure that our profession continues to thrive – and that most definitely includes encouraging and educating the next generation. But how do you begin when most science students are unaware of their career options in laboratory medicine? What do you say to medical students who aren't familiar with pathology's role in patient care? It's clear that the first step is to introduce these students to the field – and where better to do so than at a conference designed for sharing knowledge and insight?

"What do you say to medical students who aren't familiar with pathology's role in patient care?"

Pathology Update is the key annual

scientific meeting for the Royal College of Pathologists of Australasia (RCPA) – an organization with training programs across Australasia, including Australia, New Zealand, Hong Kong, Singapore, Malaysia, and Saudi Arabia, and the support of over 2,800 fellows and 700 trainees. Rotating between Sydney and Melbourne, Pathology Update features every discipline of pathology and laboratory medicine separately (allowing the 1,200 delegates to choose their preferred streams and sessions) but, each day, all of the disciplines and faculties come together for a plenary session.

What makes the meeting unique is its strong focus on promoting pathology by actively engaging science and medical students. Especially in view of changing trends in medical education, which have reduced the visibility of pathology as a specialist medical discipline, it's vital to ensure future generations of pathologists and scientists. And that's why the Pathology Update Overseeing Committee and the RCPA Board of Directors made the decision to invite medical and science students to attend the annual conference. By showcasing the disciplines of pathology and laboratory medicine and by highlighting the current diverse scope of practice in pathology, we hope to reach out to future pathology medical and science trainees, helping to avert a workforce crisis.

Not only do we welcome them, but we provide them with assistance to attend our meeting. The RCPA offers 25 full complimentary scientific and social registrations to Pathology Update and another 25 reduced-rate registrations to medical and science students from Australia and New Zealand. These medical and science student grants are promoted directly through Australian and New Zealand academic universities and institutions. Interested students simply need to complete a registration form to explain briefly why they would like to attend Pathology Update and what benefits they hope to gain by attending. The applications are (anonymously) assessed by our Director of Education and Education Advisor and the top 50 applicants provided with grants. As a separate award, the RCPA provides travel and accommodation grants for medical and science students who identify as Indigenous, Torres Strait Islander, or Maori. We also invite students who have completed projects in pathology-related areas to submit posters for presentation at Pathology Update.

"The reaction from students is positive; some find attendance so rewarding that they apply to attend successive meetings!"

On the first morning of the meeting, all student grant recipients are invited to a "Welcome Breakfast" to get to know each other and the representatives of the RCPA. The session is informal, but includes a brief introductory talk about pathology and the RCPA, and highlights suggested sessions. And, to break the ice, all students are photographed by state or territory with Debra Graves (RCPA's CEO) and attending pathologists.

Throughout the conference, science and medical students are identified by dots on their name badges so that they can easily recognize each other and so that existing RCPA trainees can identify and interact with them. We understand how overwhelming it can be for students to attend a specialty conference! That's why we also have the Education Advisor keep track of the students and contact them each day to make sure they're having the best possible experience. We encourage students to attend Pathology Update in its entirety, including social functions such as the welcome cocktail party, annual awards and admission ceremony, and celebration. The educational aspect of Pathology Update is important – but the social networking aspect is no less so. Networking and socialization are a huge part of life in medicine and this is a good introduction. After all, it's how young trainees and senior fellows can offer advice to guide and influence students.

The reaction from students is positive; some find attendance so rewarding that they apply to attend successive meetings! But, for a more objective measure, we also monitor the progression of each cohort; approximately 20 of those who attend Pathology Update as scholarship recipients each year sit the RCPA Basic Pathological Sciences examination. And about five trainees who join the RCPA training programs each year are previous Pathology Update scholarship recipients – direct evidence that our approach is having a beneficial effect.

The introduction of the Medical and Science Student Grants to attend Pathology Update has been a popular initiative amongst interested students. Even those students who pursue careers in other medical specialty disciplines tell us that they have benefited enormously from their exposure to, and engagement with, enthusiastic pathologists at our annual conference. In my view, every organization could benefit from a similar program – as would the potential pathologists of the future.

Making a Difference, One Laboratory at a Time

A visit to Tanzania that could change the lives of 10 million patients

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

This past fall, several colleagues and I traveled to Tanzania to attend ribbon-cutting ceremonies at Muhimbili Hospital in Dar es Salaam and at Kilimanjaro Christian Medical Center in Moshi. These proceedings represented over a year of planning, coordination with other organizations, partnerships with industry, and the dedication of dozens of staff members all working toward the same goal: improving cancer diagnostics in Africa.

Currently, cancer rates are increasing in sub-Saharan Africa. Around 650,000 people develop cancer there each year, and over half a million people die annually from the disease. More than a third of these deaths can be attributed to cancers that are preventable and/or treatable if detected early. It's the "early detection" part of the equation that the ASCP, along with the American Cancer Society and our partners in industry, are working to solve.

In the United States, there are 5.7 pathologists per 100,000 people (1); in Tanzania, those numbers are closer to one pathologist per 1.3 million people (2). Although equipment is needed, it is useless without vital experts to interpret the slides and provide a diagnosis.

When we conducted site visits at these laboratories in December 2017, we saw the need firsthand. Both facilities combine to serve an area that is home to over 10 million people; however, each hospital only has a handful of pathologists on staff. We concluded that both hospitals would benefit from primary diagnostics and immunohistochemical services – but, without the addition of telepathology capacity, neither would be effective at meeting the needs of millions of patients.

Telepathology serves other purposes as well: training, access to whole slide imaging archives, and consultation on difficult cases. We determined that both pieces – diagnostics and telepathology – were vital to achieving mutual goals. To make that happen, memoranda of understanding had to be negotiated and signed by all parties; ASCP worked with the telepathology vendors to get the equipment ready before shipping; and teams from both entities traveled to Tanzania for onsite installation and training.

But the story didn't end with the provision of equipment, training, and additional personnel. We also worked closely with their staff to provide vital downstream leadership education through our ASCP Leadership Institute; the program, which was developed specifically for pathologists and laboratory professionals, had to be fine-tuned so that it was culturally appropriate within Tanzania.

When the ASCP committed itself to the lofty goal of "providing access to cancer diagnostics in Africa," we knew it would entail an enormous amount of effort by thousands of people for a decade to come. What we didn't fully realize was how gratifying it would be to see all our work come to fruition. Together, we look forward to seeing what 2019 – and beyond – will bring. The heart of our membership has never been stronger.

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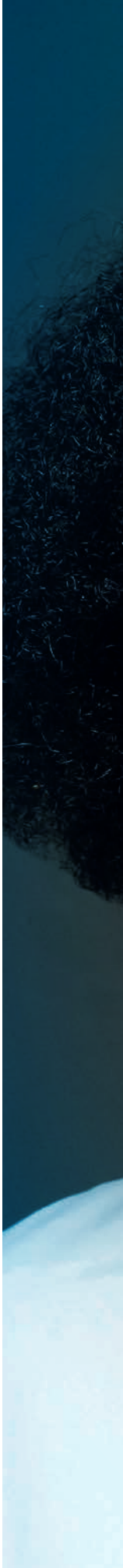
DIVERSITY: THE DREAM... AND THE REALITY

We celebrate our differences in pathology and laboratory medicine, but how can we become as diverse – and as accepting – as we aspire to be?



THROUGH MY EYES

The experience of a Black woman in pathology

By Valerie Fitzhugh

When I began medical school in the summer of 2000, I was sure I wanted to be a surgeon. I was coming off a two-year stint as the captain of the Rutgers women's fencing team. I was a four-time varsity letter winner in the sport. My path was already very unusual for a black woman, but I was proud of what I had accomplished. My background and interest in sports led me to what I thought was a very natural interest in orthopedic surgery.

I went through my coursework and did well, despite losing my mother to metastatic colon cancer in the early part of my second year. By the autumn of 2003, I had done a research elective and three acting internships in orthopedic surgery. When I submitted my application to 89 residency programs, I felt pretty confident about my chances. While I waited,

though, something interesting happened. In January of 2004, I did a student elective in forensic pathology. I was amazed at how those physicians put all the pieces together to figure out exactly how a patient died. This experience was not my first clinical interaction with pathologists; in my first acting internship, I would often accompany the orthopedic oncologists to anatomic pathology to read the frozen section slides with the pathologist. It was positively exhilarating to watch her render diagnoses. But seeing as I was going to be a surgeon, none of this mattered – right?

Wrong. In March of 2004, on a crisp Monday afternoon, I – like residency hopefuls all over the country – hurried to the nearest computer to check my email. I saw the message from the National Residency Match Program, a program we in the United States lovingly refer to as "The Match." I got as far as, "We regret to inform you…" and that was all I needed to read. I spent much of the following hour crying on the shoulder of my favorite emergency physician. Over the following 24 hours, I re-evaluated what I was going to do with my life. I knew I had enjoyed my brief interactions with pathologists, and I was fascinated by – and completely in awe of – what they were able to do for their patients. I wondered if my awe and fascination was enough for me to make a career out of it. After much consideration, I decided to give pathology a chance. The next day, I sent my application to pathology programs all over the country. I received several offers, but chose to begin my training at Albany Medical Center.

I went to New Jersey Medical School in Newark, New Jersey, a very diverse medical school; I was used to seeing faces that looked like mine. But when I began my residency in pathology, there were almost no black faces – something I hadn't even considered. One of my co-residents was a black woman, but there were no black faculty (or, indeed, any other black people) in the department. After my first year, I returned to my medical school to complete my residency. While I was a student, there was one black faculty member, a woman, in the department – but by the time I returned, she had retired; two black women were co-residents, but no black faculty. When I became a fellow at a very large academic center in a major city, I was the only black fellow. Two black women were residents – but, yet again, zero black faculty.

It is appropriate at this juncture to note that I've said nothing about black male pathologists in my training. I spent time with three during my forensic pathology rotation. I have not had the honor or pleasure of training (or training with) a black male pathologist, although I have mentored one black male student who went on to train in pathology. I know others exist – I am friends with several – but in academia, we just don't see them as often as other groups – including black women.

> "THIS BRILLIANT YOUNG WOMAN LEANED IN AND ASKED ME, 'WHAT IS IT LIKE TO BE THE ONLY ONE?'"

After completing my training, I returned once again to my medical school alma mater, this time as a member of the faculty. Nearly a decade later, I am still the only black woman on the faculty. That has not gone unnoticed by applicants to our residency training program. Several years ago, I was interviewing an applicant – a black woman – who was incredible. Indeed, she was far and away the best applicant we had seen during the cycle, and I would have loved to have her join our program. She asked if it was okay to ask me a question. Of course it was, because we love it when applicants ask questions! And then this brilliant young woman leaned in and asked me, "What is it like to be the only one? You're the first black attending I've met on the interview trail." My answer then remains my answer now: it is hard. Allow me to give you some examples of how hard it can be.

Once, I was having a seemingly lighthearted conversation with two other people. The conversation was centered on the exclusivity of a group within a particular organization – one with which we were all familiar. One participant mentioned that no one gets into the inner circle with the exception of a select few. That same participant then looked at me and said, "They don't have any black people, though, and everyone loves you. You can be their token." The third participant, who had said almost nothing up to this point, looked at the first speaker in complete disbelief. I felt the blood rush into my face with anger as I excused myself and left the room. What is "tokenism?" Tokenism is the practice of making a shallow attempt at appeasing a group by including a person of that group (often an underrepresented minority) into a select circle.

The colleague clearly either did not understand or did not care that it is offensive to imply that I would be allowed into the inner circle simply to stand there, smile, and be black. Worse, what was implied – though not stated – is that my skin color was the only thing worth recognizing.

My existence is that of a double minority: a black woman. Because of this, I have encountered people who question whether or not I deserve to be in the spaces I work in. I've been asked pointedly if I was an affirmative action hire. I can imagine how an insensitive person with no home training would ask such a question. After all, as I stated earlier, I continue to be the only black faculty member in my department. Clearly, that must be because they need a black person – and, by hiring a woman they can fill two quotas at once. Believe it or not, I was hired based on my ability and commitment to patient care!

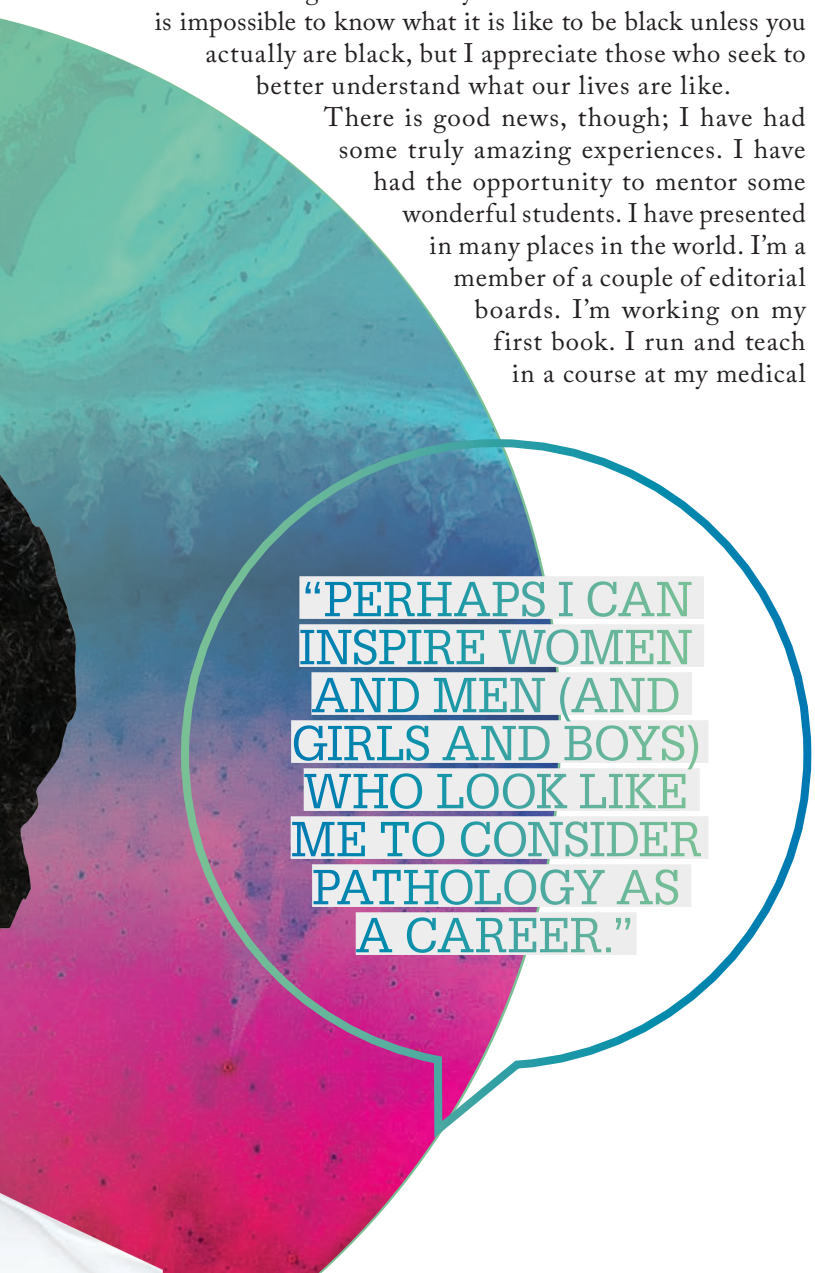
It's also hard to hire that which does not exist in large numbers. Black people are one of the least represented ethnic groups in pathology in the United States; only indigenous Americans have less representation. In the 2017 and 2018 Medscape Pathology Compensation Reports (1,2), there were so few black respondents that our salary data could not even be published. How can we expect departments to hire more black pathologists when we're not entering the specialty in the first place?

Imagine an existence where you have to work two or three times harder than your peers to prove to others that you are just as good as they are. Imagine experiences where your efforts to explain that you've been mistreated by someone because of the color of your skin are dismissed as being merely your perception, rather than reality. Microaggressions and gaslighting are easier to face when you're not facing them

"HOW CAN WE EXPECT DEPARTMENTS TO HIRE MORE BLACK PATHOLOGISTS WHEN WE'RE NOT ENTERING THE SPECIALTY IN THE FIRST PLACE?"

alone – and, in my professional world, I often face them alone. I was discussing this piece with a friend and colleague as I was writing it and she said something profound: "I have no idea what your world is like. This piece you're writing is important. Because, as close to you as I am, I still don't know." I hear what she is saying. As a woman who has been asked to discard garbage while wearing scrubs in the hospital (and, by the way, our cleaning staff doesn't wear scrubs), I am grateful for the opportunity to share my experiences. I am certain I have colleagues of color who have been through worse professionally than I have. I also recognize the opportunity I have been given with this piece. Although there are people who condemn my blackness, there are many more allies who seek knowledge so that they can learn and understand. It is impossible to know what it is like to be black unless you actually are black, but I appreciate those who seek to better understand what our lives are like.

There is good news, though; I have had some truly amazing experiences. I have had the opportunity to mentor some wonderful students. I have presented in many places in the world. I'm a member of a couple of editorial boards. I'm working on my first book. I run and teach in a course at my medical school involving the musculoskeletal and integumentary systems. I have the honor and pleasure to teach in many other courses at all levels of the medical school curriculum. I've chaired the medical school's curriculum committee over the last several years. I've accomplished all this despite the challenges I have faced as a black woman in pathology, not because of them.



"PERHAPS I CAN INSPIRE WOMEN AND MEN (AND GIRLS AND BOYS) WHO LOOK LIKE ME TO CONSIDER PATHOLOGY AS A CAREER."

And stories like mine aren't limited to pathology; on Twitter, we use a hashtag, #BlackWomenInMedicine, to celebrate our triumphs and successes. We use it to call attention to ourselves and to remind others that we do exist – that we're not unicorns. Social media is not always kind either (I have been racially trolled), but we are able to use it to come together in a common space and show the world that we are an important piece of the medical landscape. Diversity and inclusion are of the utmost importance in medicine. Although pathology desperately needs more diversity, it will not exist until we improve recruitment. I'm committed to improving recruitment of underrepresented minorities in pathology by starting to attract them as early as possible. Perhaps I can inspire women and men (and girls and boys) who look like me to consider pathology as a career.

Hearing the difficulties I've faced, you may be tempted to ask if I would choose pathology again. My answer is a resounding yes. I have been incredibly fortunate in my career. I have the awesome responsibility of helping people every single day, even if most of those people don't know I exist (which is okay). I'm not looking for immediate gratification; my gratification lies in arriving at the correct diagnosis for my patients so that they can get the treatment they need. My subspecialty has allowed me to travel the world. I get to teach and mentor amazing medical students. I have an amazing network, much of which I have gained through my interactions on social media, as well as through publishing and speaking. It may not always be easy to be "the only one," but I would not change any of the experiences I have had – and I invite others to join me on this amazing journey.

Valerie Fitzhugh is Associate Professor in the Department of Pathology, Immunology, and Laboratory Medicine at Rutgers New Jersey Medical School, Newark, USA.

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THE DREAM OF DIVERSITY

Increasing the African-American presence in pathology

By Angelina Knott, Robin Suggs, and Timothy Craig Allen

"…who makes friends with black males in today's world?"
— Gregory A. Threatte (1)

Diversity versus inclusion

Pathology has long been a diverse profession – but is "diversity" really enough? In our opinion: no. We must strive to be not only diverse, but also inclusive. Inclusion, "[f]ully and respectfully involving all members, regardless of gender, religion, race, color, sexual orientation, national origin, age, or physical ability, in the activities and life of the organization (2)," fulfills the promise of diversity. Diversity – for example, with respect to issues related to people of color – provides for proactive retention and recruitment efforts, ensures some representation at all levels, and addresses differentiation between groups. In contrast, inclusion actualizes diversity; it calls for critical mass at all levels, the inclusion of people of multiracial identity, and two-way mentoring across racial lines (3). "The challenges are to broaden the definition of diversity to include all social identity groups, to understand that an inclusive culture for all members of the organization is a must and to convey the links between leveraging diversity, a culture of inclusion, and organizational success (4)."

In an article on diversity and inclusion in medical schools, Jennifer Tsai said, "Hospitals and medical schools are training their eyes on the numbers. But these institutions focus so much on the quantitative proof of diversity that they're missing their failures to safeguard inclusion (5)." And yet, all is not lost. Pathologists can assist in the quest for inclusion – not least because we are, and have been for many decades, a strongly diverse profession.

But although pathology currently has measurable diversity, it doesn't reflect the community. African-Americans are historically underrepresented in medicine (in fact, in 2015, African-Americans represented just 6 percent of medical school graduates, a number unchanged over at least four years [6]). The same population is markedly underrepresented in pathology to the point where one African-American pathologist, prominent on social media, has described herself as "almost a unicorn (7)." It is ironic that, although the Constitutional amendment and federal laws governing diversity and the United States Supreme Court decisions interpreting them, come from situations involving African-Americans, pathology still has so little African-American representation. Our discipline will never be able to proudly claim it has complete diversity and inclusion without an African-American pathologist presence that reflects the community.

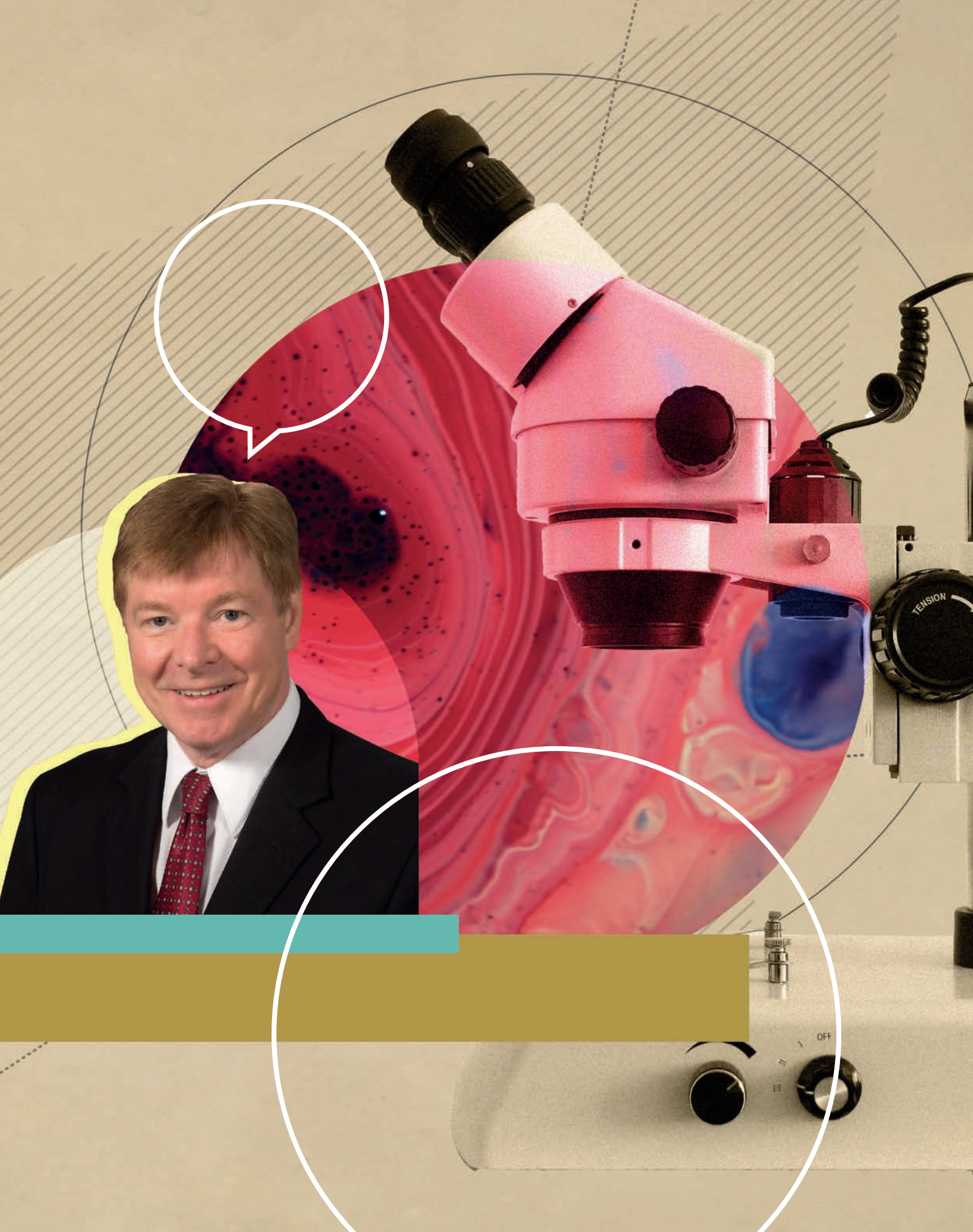
"ALTHOUGH PATHOLOGY CURRENTLY HAS MEASURABLE DIVERSITY, IT DOESN'T REFLECT THE COMMUNITY."

Increasing the presence of this population in pathology cannot be done easily or quickly. "If all reasonably possible outreach is undertaken and the pool of applicants with the potential to be interviewed do not include minorities and women, then it is reasonable to conclude that there is likely a significant deficit of qualified and available minorities and women (i.e., a severe 'pipeline problem')… (8)." Unfortunately, the problem is not limited to pathology; medicine as a whole has far too few minorities in its pipeline, and African-Americans are hit particularly hard.

Why is there a pipeline problem?

Growing up in rural America is rooted in traditions. Historically, African-American families have raised their children to do what is safe and trusted. In their communities, it truly takes a village to raise a child. But all too frequently, opportunities aren't communicated – or may even be thought of as "not fitting" for an African-American child. In such an environment, families recommend that their children


“PATHOLOGY STILL HAS SO LITTLE AFRICAN-AMERICAN REPRESENTATION.”


TENSION
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choose careers they think are achievable and will provide a stable, reasonable wage. Rural African-American children are frequently raised to seek jobs that will make them "honest, hardworking people." It is also considered important to find a career that doesn't require a long training period – ensuring that it will quickly provide a source of income as an adult.

These careers – teaching, nursing, military service – are certainly laudable, but the self-imposed glass ceiling remains. African-American families in rural America rarely recommend that their children consider becoming physicians, and certainly not pathologists. Generally, neither do teachers and counselors. Schools perpetuate the "safe" options through Career Days and choice sheets. Being a doctor is the dream reserved for well-to-do families, often ones in which there are already physicians. And for many African-American children, the battle is even harder: they often attend underperforming schools and deal with multiple negative socioeconomic determinants. Some may even be completely unaware of the medical profession, much less believe that they themselves would be capable of succeeding in it.

"THESE CAREERS – TEACHING, NURSING, MILITARY SERVICE – ARE CERTAINLY LAUDABLE, BUT THE SELF-IMPOSED GLASS CEILING REMAINS."

A head start on a solution

We believe that success will require pathologists' lifetime mentoring of young African-Americans who have been identified as talented. In particular, we are starting to work with fourth-graders: nine- and ten-year-old children. Many of these children have never experienced the kinds of opportunities we take for granted, and know little about medicine (and certainly nothing of pathology). We need to go to them and talk directly to them – but we also need to be careful how that outreach occurs. It's neither right nor effective to simply visit these children's communities, load them down with facts, and then leave. Rather, pathologists need to partner with African-American men and women – existing members of those communities – to build bridges to those fourth-graders. Local community leaders (clergy, school guidance counselors, teachers, principals) could connect pathologists to the children we want to reach.

But even working with those bridging members falls short of the ideal. What we need more than anything else is African-American role models – pathologists that a child can say "look like me." These pathologists could mentor multiple children through an occasional telepresence, while others (not necessarily of the same race) could develop a lifetime mentoring relationship that will serve the student through high school, college, medical school, residency, and beyond. Strong and consistent mentorship from an early age can provide support, guidance, and transformational opportunities for African-Americans in medicine, ultimately decreasing the current stark deficit of qualified and available minority medical school applicants, doctors, and pathologists.

The African-American community has always embraced the philosophy that "it takes a village to raise a child." For pathologist mentors to be successful, they need to adopt that philosophy as well. To guide these students – and ultimately produce great pathologists – not only they, but also their communities, must be supported. Understandably, African-American children may want to see a pathologist who "looks like them" to prove that they could actually realize the dream of a medical career – but the involvement of those pathologists does not diminish the importance of the responsibility we all share for mentoring those children through the process of obtaining a medical degree and beyond. When we communicate this new career option to the parents of fourth-graders, we have to include a clear outline of the mentoring relationships we hope will last a lifetime. And once these programs are in place and the benefits begin to show, I think that other schools and communities will want to become a part of this endeavor.

Facing the obstacles

There is likely to be pushback. Some believe that "enough" has already been done to help African-Americans – but that belief ignores the reality of many African-American families. For example, a housekeeper at our institution recently shared that her daughter was graduating from high school. She reminisced that, when young, her daughter would "joke" about becoming a doctor one day. Whether or not the child meant it sincerely, the housekeeper did not support that dream or motivate her daughter because she didn't believe it was possible; she thought there would be too many obstacles to overcome. In her words, "They'll never let her make it." This lady wanted the best for her child – but, at the same time, she was unwittingly imposing her own childhood experiences upon her daughter and thereby limiting her.

Today, "they" are not going to keep a child from making it; "they" no longer exist. But "their" ghost hovers in African-American parents' memories, influencing their children's choices. Imagine a child who has no dreams because he harbors no hope. Or a child who dreams, but sees no way those dreams can ever become a reality. Or one who dreams, only to be told, "You can't do that." Imagine the staggering loss of potential. And that's why early mentorship is so important – because it can expand the horizons of young African-Americans in a strategic and targeted way before their paths are set in stone.

And it's pathologists themselves who are the key to expanding those horizons. We must understand these perspectives if we are to help African-American children find their way to pathology. We need to engage with them and support their excitement in pursuing this new, precious career option – being a pathologist! It's a responsibility that will require extraordinary, lifelong dedication, but it is an opportunity that pathologists – innately caring physicians – should relish.

"… as a physician, a professor, and/or a director, you are of unquestioned authority to most young people. Believing in someone, before they have had a chance to believe in themselves, can be decisively important; not just to them as individuals, but to us as a society (1)."

> "IT'S A RESPONSIBILITY THAT WILL REQUIRE EXTRAORDINARY, LIFELONG DEDICATION, BUT IT IS AN OPPORTUNITY THAT PATHOLOGISTS SHOULD RELISH."

"… everyone should find a young black [child], make a friend, and then believe in them…"
— Gregory A. Threatte (1)

Angelina Knott is Department Business Administrator of the Department of Pathology at the University of Mississippi Medical Center..

Robin Suggs is Project Manager II of the Department of Pathology at the University of Mississippi Medical Center.

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

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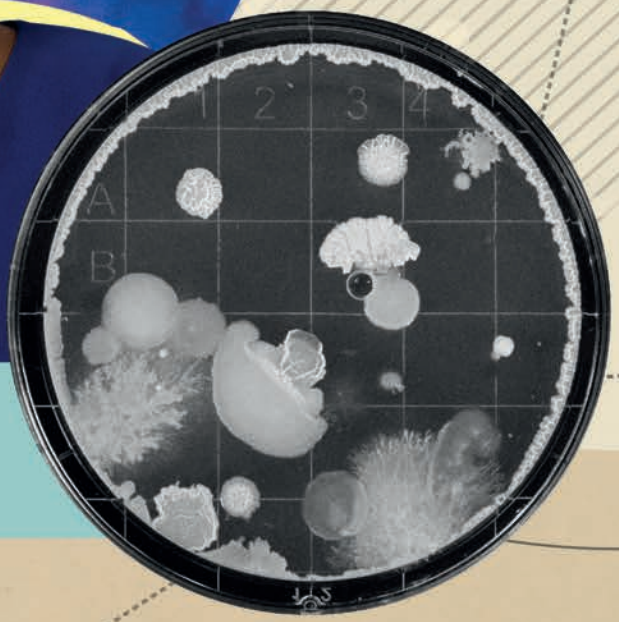
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American Society for Clinical Pathology

Partners for Cancer Diagnosis and Treatment in Africa

Volunteer as a telepathologist and share your unique expertise with clinicians around the globe.

Through the placement of cloud-based digital pathology systems in target countries, ASCP can assist local medical staff in obtaining rapid, accurate diagnoses for the countries' populations using teams of 15 ASCP volunteers (across specialties) per country. This initiative will benefit efforts to promote earlier diagnosis and appropriate oncology treatment to provide both palliative and curative care.

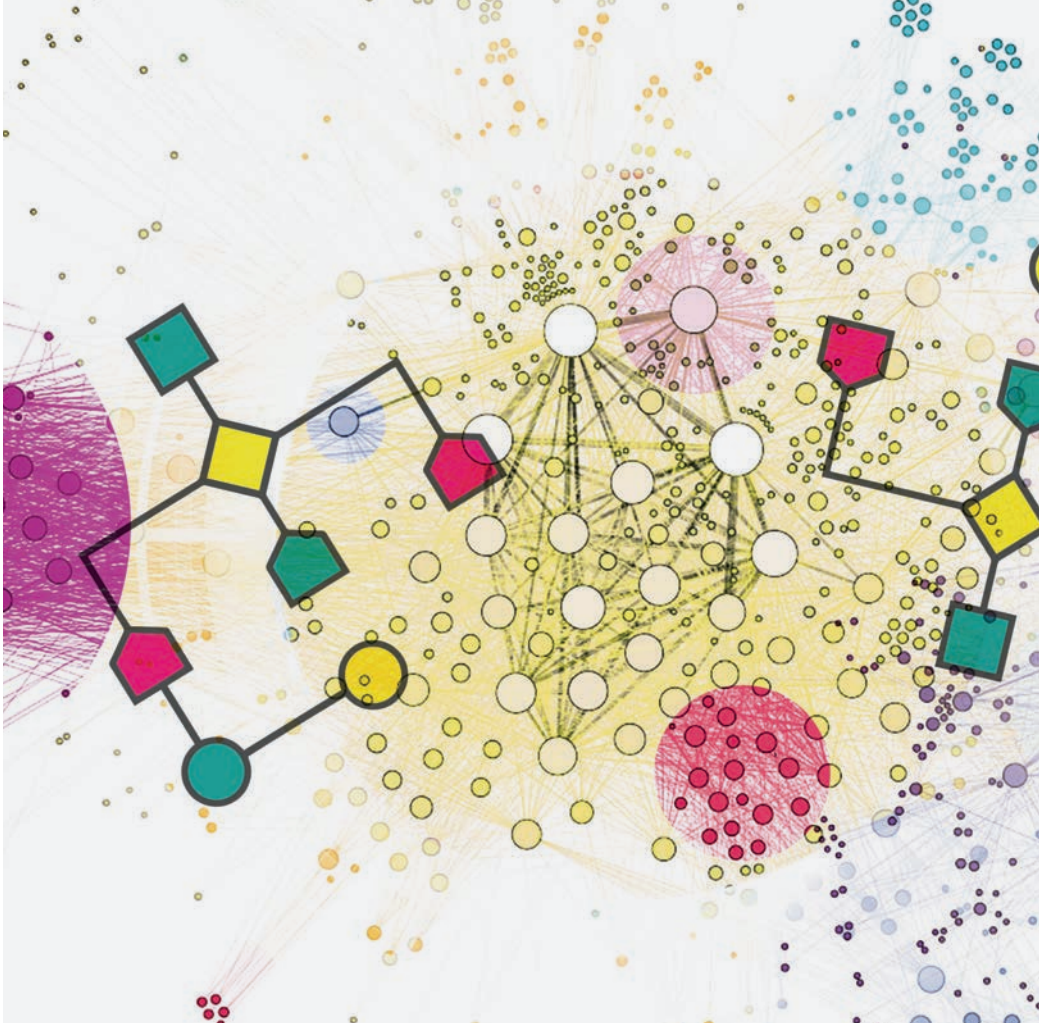
ASCP is currently seeking:

- Volunteers who can work as a team with two to three other colleagues to participate in monthly to quarterly, online telementoring sessions in the areas of histology, quality, management, and diagnostic pathology.
- New to slightly used standard histology equipment.

Visit **www.ascp.org/globalimpact** to find out how to volunteer or donate!

In Practice

Technologies and techniques
Quality and compliance
Workflow



The Art of Algorithms

How can an algorithmic approach to diagnosis strengthen the practice of pathology?

By Pranav Patwardhan

Every pathologist knows that there is an element of art to the science of diagnostics. Not every disease presentation is typical. Sometimes, an important finding is barely captured on the edge of a slide, or buried in a patient's clinical history. Other times, an abnormality in a biopsy may lead you to not only a primary diagnosis, but also an unrelated second observation. But with so much information to corral, how can you progress logically through the steps from sample to diagnosis, and how can you ensure that you are taking note of every important finding along the way?

I recommend that every pathologist and trainee develop an algorithmic approach to the slides and samples we see every day. And although I create algorithms for my own use in the clinic, my main motive in sharing them – and in writing this piece – is to stimulate my colleagues and trainees in the discipline and help them develop an analytical approach to pathology.

But what exactly are these diagnostic algorithms? And what features make them complete, meaningful, and useful in training and in our daily practice.

At a Glance

- *An algorithmic approach to diagnosis promotes a logical, sequential, and organized thought process*
- *Diagnostic algorithms can be handy resources and allow pathologists to share their knowledge easily*
- *They are especially useful for trainees, who can not only make use of existing algorithms, but also learn to create their own*
- *Such algorithms move from history and clinical information all the way to immunohistochemistry and molecular diagnostics*

Foundations of an algorithm

To develop a diagnostic algorithm for any lesion or tumor, it's important to establish your first steps. Just as the evaluation of any slide should begin with a few simple questions, your approach to any case begins with the gross examination and the clinical details you receive from the operating surgeon. Different key points in the history and clinical exam may be important for different organ systems, so relevant positive and negative findings are commonly placed at the first level of any algorithm I make.

For example, in the evaluation of a central nervous system tumor, the patient's age and the site of the lesion should be the first things you ask about; they can give you specific hints as to what you might expect to find in the microscopic evaluation. A lateral ventricular tumor should make you think not only of the common ventricular tumors, but also of subependymomas, subependymal giant cell astrocytomas (SEGAs), and central neurocytomas. If you also know that the patient has a history of tuberous sclerosis, you should start your microscopic evaluation with a strong probability of SEGA in mind. Meningeal and posterior fossa-based tumors are also cases in which the site may lead you to a diagnosis even before you see the slide under the microscope.

When dealing with a bone lesion or tumor, the age of the patient, the site of the lesion, and the radiological information should be the first steps in your algorithmic approach. If you're working on an algorithm for hematolymphoid malignancies, you should consider physical examination findings like hepatosplenomegaly, lymphadenopathy, back pain (in a suspected

"As you're examining a tissue sample, you must keep in mind new diagnostic entities with greater prognostic significance or treatment relevance."

plasma cell dyscrasia), and peripheral blood smear evaluation. By now, you may have noticed a pattern: clinical details and supportive radiological information are the two key factors that should inform the initial steps of an algorithm for any pathological lesion.

Once that information is established, gross examination is the logical next step. New residents are often fascinated by the advent of immunohistochemistry (IHC), molecular pathology, and other novel approaches – but may sometimes miss minute details on the gross. Systematic gross examination in organs like the adrenal glands can be very rewarding. There, bilateral multifocal lesions will make you think of metastasis; a single, well-circumscribed nodular lesion will lead you toward a diagnosis of adenoma; a dusky brown color of the tumor will point to pheochromocytoma; and anything large, hemorrhagic, or necrotic will make you think of adrenocortical carcinoma. Relatively well-circumscribed cystic lesions with only a few hemorrhagic areas mixed with yellowish-white tissue will hint at the possibility of myelolipoma or angiomyolipoma.

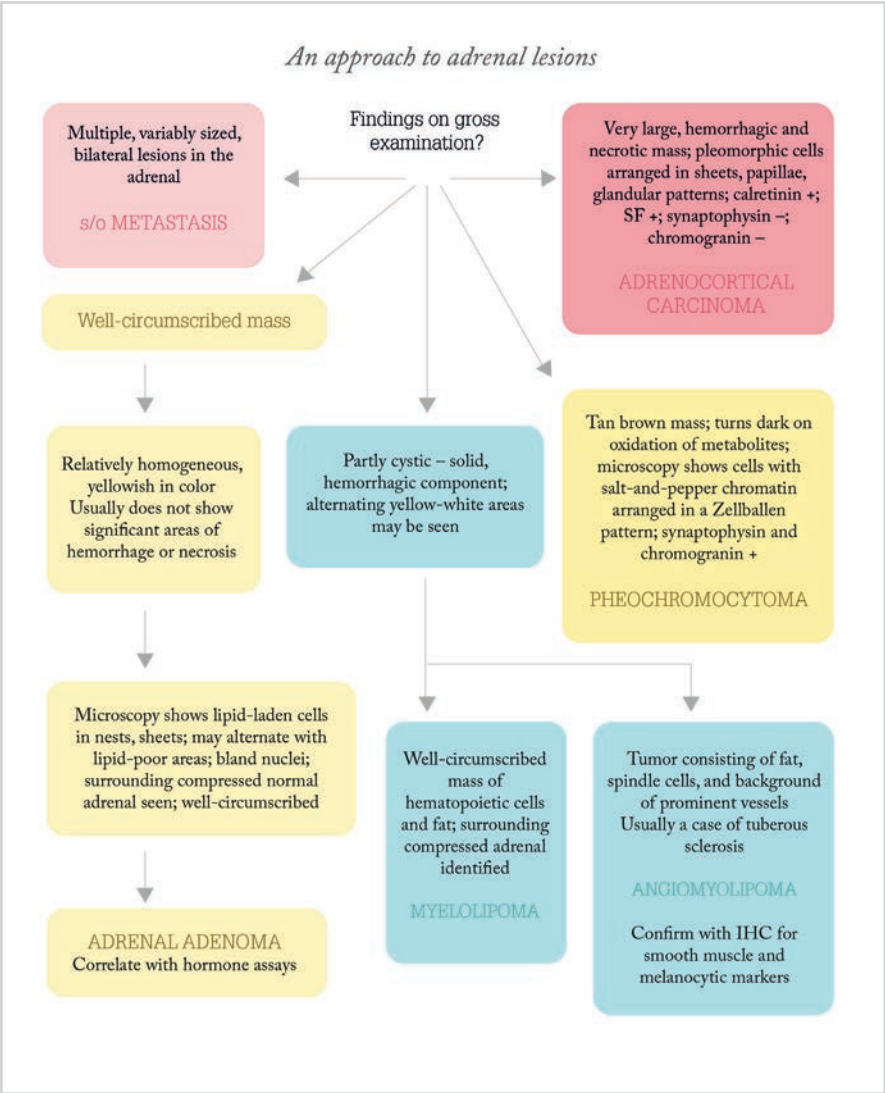
The "2C"s and "2S"s of gross examination – color, consistency, size, and shape – are the key points to take away from the exam. Gross clues are important in diagnostic algorithms for nearly all organ systems, but they hold particular importance in genitourinary, ovarian, and gastrointestinal pathology. Fine needle aspiration findings should also be included in the algorithms for hematolymphoid malignancies and tumors of the thyroid and salivary gland.

No stain, no gain

Microscopic examination still benefits from classic H&E staining, which continues to provide diagnostic insights. As you're examining a tissue sample, you must keep in mind new diagnostic entities with greater prognostic significance or treatment relevance; differentiating between two tumors formerly considered a single entity could have a vast impact on the patient's treatment or expectations.

This step in the algorithm is not to be taken lightly. Pathologists should consider each cell component – nucleoli, nuclear membrane, chromatin, cell inclusions (if any apart from the surrounding vasculature), inflammatory infiltrates, and mitosis – when narrowing down a differential and a final diagnosis. A good example is when differentiating oncocytomas from chromophobe renal cell carcinomas on the basis of nuclear membrane irregularity and perinuclear halo.

Special stains and their interpretations should be included in the algorithms whenever relevant; for example, in liver biopsy interpretation, bone marrow examination, or suspected pituitary adenoma. It's also good practice at this stage to add histological details on H&E that may be associated with a particular genotype or mutation. A few examples:



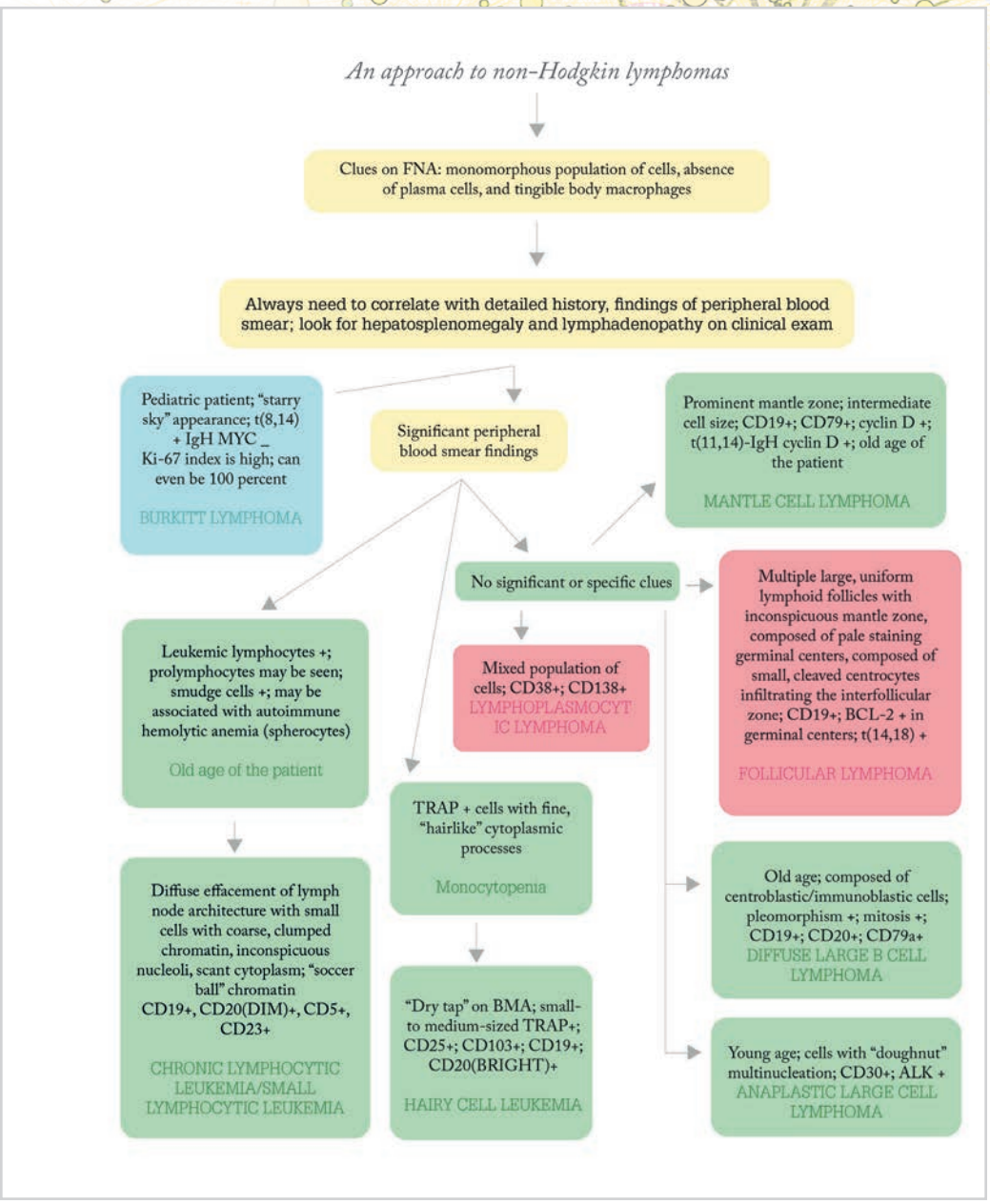
- Tumor cells in hereditary leiomyomatosis and renal cell cancer show eosinophilic nucleoli with a peripheral halo, arranged in a type 2 papillary pattern.
- Colorectal carcinomas in cases of Lynch Syndrome are more likely to show tumor-infiltrating lymphocytes and less likely to show dirty necrosis, characteristically described in intestinal adenocarcinomas.
- Amyloid or calcification in a pituitary adenoma would suggest a prolactinoma, paranuclear fibrous bodies a somatotropic adenoma, and Crooke's hyaline change in the surrounding normal pituitary a corticotroph adenoma.

These histological clues can point you toward particular genetic or functional subtypes of tumors and help correlate your histological findings with the molecular diagnosis later on. In situations where molecular testing may not be feasible, they enable you to provide at least some guidance to surgeons and oncologists.

It's at this point – not before – that pathologists should begin to consider immunohistochemical and molecular diagnostic details. Although the use of these assays is inevitable in many scenarios, it can be difficult – especially for trainees and new pathologists – to fully understand their relevance without the previous steps. This, then, is the key to the algorithmic approach: it must first lead you to a narrow differential diagnosis on the basis of the history, gross, and H&E microscopic evaluation, and then guide you to the relevant IHC and molecular studies for a conclusive diagnosis wherever possible

A good IHC evaluation should ask four questions: i) Which cells take up the marker?, ii) Which component of the cell shows positivity?, iii) What is the pattern of that positivity?, and, most importantly, iv) Are your markers working on your internal controls? All of these points are vital to the final step of your diagnostic algorithm.

Additionally, if the IHC or molecular characterization of your tumor is complex, I recommend a separate algorithm or "sub-algorithm" for this step. The diagnostic evaluation of lymphomas, for example, is somewhat complex. It helps pathologists, especially those new to the discipline, understand the significance of each marker in turn. Let's say you have a case of B cell lymphoproliferative disorder in which H&E evaluation suggests a diagnosis of chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). Your algorithm would recommend first evaluating CD5 and then CD23. Positivity of both markers indicates CLL, whereas a negative CD23 result suggests mantle cell lymphoma. If both markers are negative, the algorithm should recommend testing others (such as CD10, CD25, or CD103). In this example, the diagnostic process is a relatively common diagnostic process – but you can create and use this kind of sub-algorithm in any similarly complicated case.



When conducting these analysis, always bear in mind that the stroma – the "climate" of the tissue on the slide – can sometimes lead to an unrelated diagnosis if you observe it closely. For instance, in a duodenal biopsy, the absence of any plasma cells should make you think of common variable immunodeficiency (CVID); diffuse generalized hyaline arteriolosclerosis should alert you to the possibility that the patient might be hypertensive; ulcerative or exudative lesions with "volcano"-like inflammatory infiltrates should make you think of pseudomembranous colitis! Nowadays, whenever I make a checklist for duodenal biopsies, I invariably include a point on CVID after I finish describing the luminal features (including parasites like Giardia) and mucosal changes (which may point to issues, such as celiac disease).

An educational tool

These "personal diagnostic algorithms" are useful for any pathologist at any career stage, but I find them particularly valuable for residents and trainees. Why? Because working in this way helps them to develop an analytical approach toward any case evaluation. It fosters a thought process that uses logical, sequential reasoning to arrive at a final diagnosis – exactly what we intend to achieve when we train new students. The eye cannot see what the mind doesn't know!

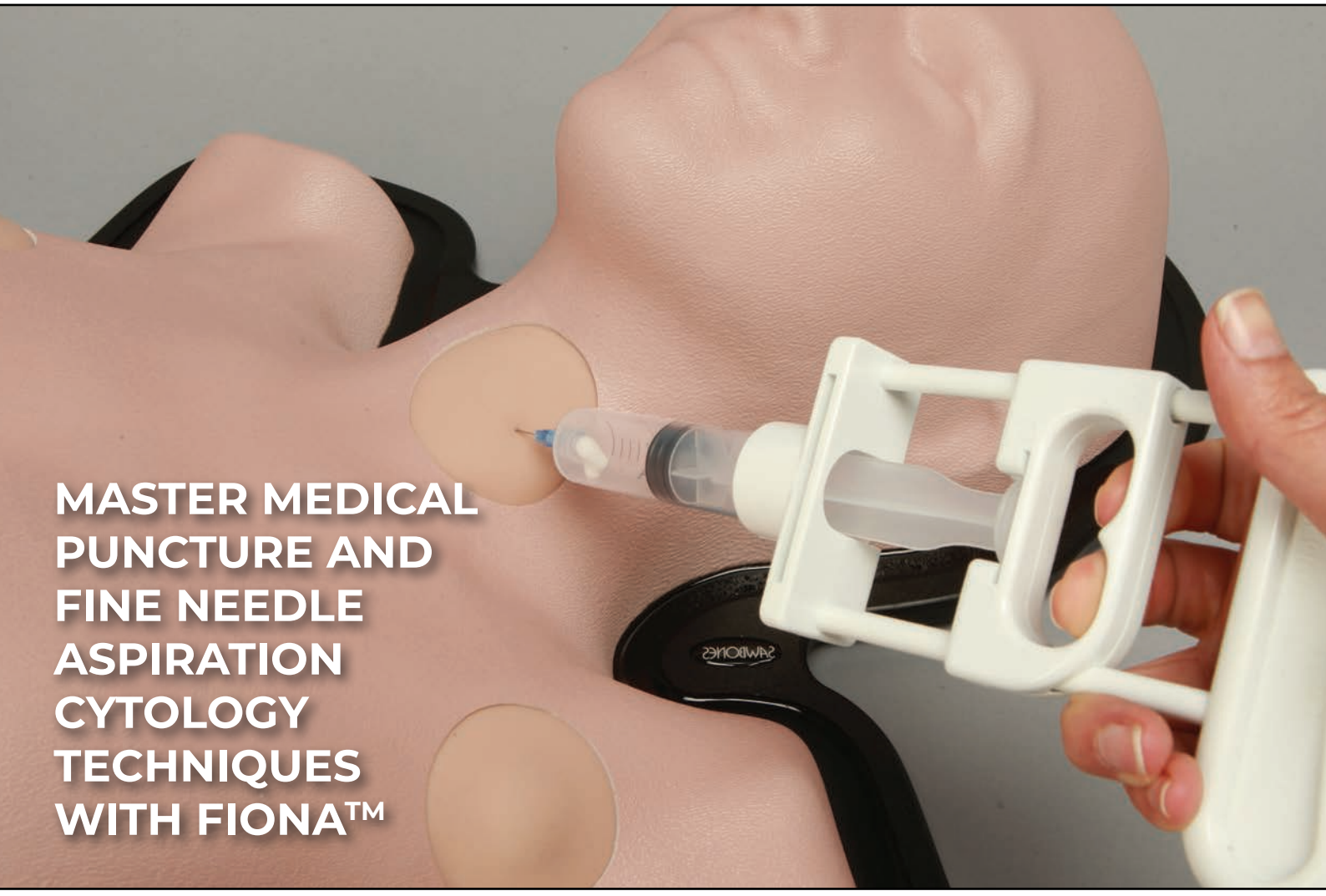
Though the details at times appear complex, I encourage all of my colleagues to develop a sharp eye for the "catchy" diagnostic points of any lesion they encounter, whether in real life or in the literature. Always think about how you would differentiate those entities from other similar ones. And, if the knowledge you pick up is not already present in the literature, it may be a valuable resource for dissemination amongst your peers.

The diagnostic algorithms we build up using both published data and our own experience are extremely useful tools for us, and for those we train to follow us. I share my algorithms with my trainees, but I also urge them to create their own, which not only provides them with the tools themselves, but also with the thought processes that arise from pursuing a logical approach to diagnosis. Remember that all of histopathology is based upon a simple, algorithmic principle:

- Is the tissue normal or abnormal?
- If it is abnormal, is it neoplastic or non-neoplastic?
- If it is neoplastic, is it benign or malignant?
- If it is malignant, is it primary or secondary?

And, of course, don't forget the value of a good report after you've put in the work to reach a diagnosis. Frame it carefully, word it well, and make sure that the final report is just as logical as your diagnostic process!

Pranav Patwardhan is a pathologist in the Department of Pathology at Seth Gordhandas Sunderdas Medical College, Mumbai, India.



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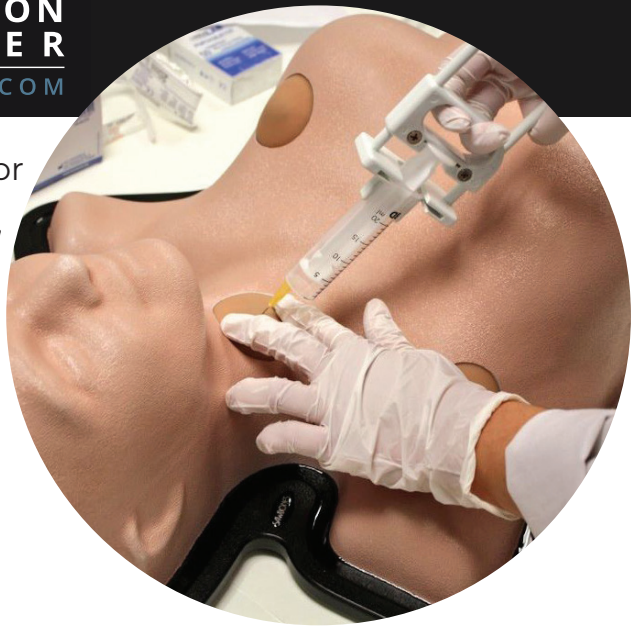

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Pathologist-Centric AI

Machine learning may be the way of the future – but pathologists will remain a central component of artificially intelligent systems

By Holger Lange and Cris Luengo

Most people have some understanding of artificial intelligence (AI) – but what exactly does it mean in the context of pathology? A pathology AI system is a computer program that assists pathologists in their work or provides automated pathology. The key capability of such a system is to analyze digital slide images using image analysis and "machine learning" – another buzzword! Machine learning is the process of learning a task (for instance, providing a diagnosis or a score) or a sub-task (such as classifying cells into different cell types) from data. There are many approaches in machine learning, including decision trees, random forests, and deep learning. You may have heard of some of these – in particular, the latter.

At a Glance

- *Machine learning is attracting increasing hype in the pathology sphere, especially in the realm of deep learning*
- *Deep learning has its pros and cons – as do other approaches to pathology AI, such as decision trees*
- *The key is to design a pathology-centric system that relies upon both human and computer input for full accuracy and effectiveness*
- *In the near future, such pathology-centric systems can assist us in providing better patient data, care, and outcomes*

Deep learning

In recent years, we've seen a great deal of hype around deep learning. It's a process that has overcome major challenges in computer vision, allowing us to implement feature detection successfully where image analysis algorithms failed. A deep learning network can learn highly complex visual features from image data, achieving performance that may even equal that of a human expert. Deep learning requires huge amounts of data and significant processing resources. But recently, with the increase of processing power and, in particular, the use of GPUs, it is now possible to train deep learning networks successfully.

The first deep learning network to achieve a major breakthrough was AlexNet, which in 2012 significantly outperformed all previous approaches on the ImageNet challenge (a large visual database designed for object recognition software research). Since then, more efficient, higher-performing systems have been introduced – and, because pathology is a visual task, it is more than understandable that deep learning is now coming to pathology as well. In 2016 and 2017, Grand Challenges in Biomedical Image Analysis (CAMELYON 16 and CAMELYON 17) were run to encourage the development of programs to detect cancer metastasis in lymph nodes. Both challenges were clearly dominated – and won – by deep learning. These are complex programs, which explains both their high performance and the difficulty of designing them. It's no longer just about finding the right

hyper-parameters; now, creators must design new network topologies. It's not just a science, but also an art!

Because of this complexity, many applications begin by reusing existing designs that have been proven in other applications. For example, the winner of CAMELYON 16 reused and modified GoogleNet, which won the 2014 ImageNet challenge. But because pathology applications are different from general-purpose image recognition tasks, laboratory professionals could gain a lot by handcrafting an appropriate net topology for pathology applications – especially focusing on cell data.

Decision trees

It's only in recent years that academia has started to use digital slide images, but today, academicians are driven by the deep learning hype. It has great potential in situations where feature detection presents a challenge for traditional image analysis, but it comes at a price. The data sets used to train deep learning algorithms are expensive, there's always the risk of bias from the training data, and there is no transparency in the decision-making process. Why did the machine classify one group of cells as benign and another as malignant? With deep learning, it can be hard to know.

Decision trees are like hierarchical flowcharts – a structure humans tend to find both intuitive and transparent. Their advantages include:

- no data normalization,
- proper handling of missing data,
- heterogeneous data (numerical, ordered, and categorical),
- intrinsic feature selection,
- multi-class,
- multi-output, and
- fast predictions.

"Decision trees sound perfect for use in medical devices – but can they deal with the complexity of analyzing digital slides?"

Decision trees sound perfect for use in medical devices – but can they deal with the complexity of analyzing digital slides? A natural extension that provides a more complex machine learning approach uses "random forests." These share the same advantages as basic decision trees; they do lack transparency in the decision process, but the important features can still be identified. Before deep learning took the world by storm, random forests had success winning competitions used to evaluate different machine learning approaches.

The key problem for any pathology AI system is the variation between different patient types. In a disease state, no two patient samples look identical. To distinguish between different cell types – a task any machine learning system has to accomplish – we must observe that the same cell type can have different, and sometimes even contradictory, characteristics in different patients.

Figure 1 shows two patients that

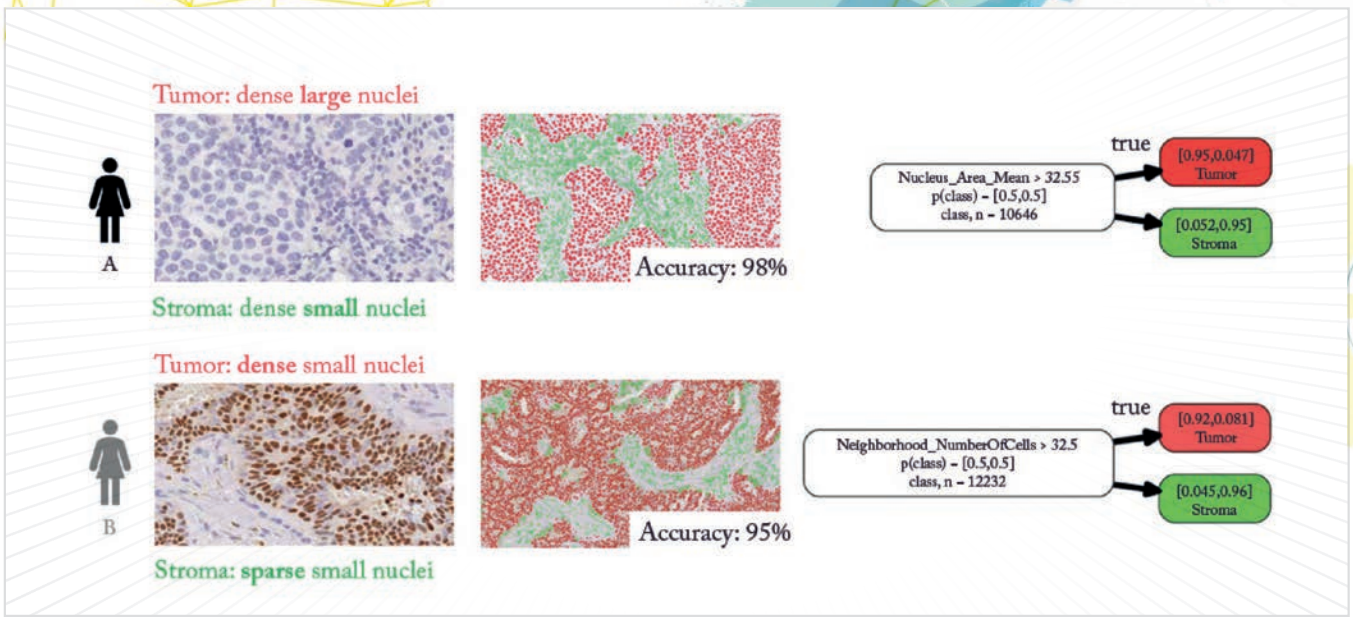


Figure 1: Two patients whose tumors exhibit contradictory cell characteristics

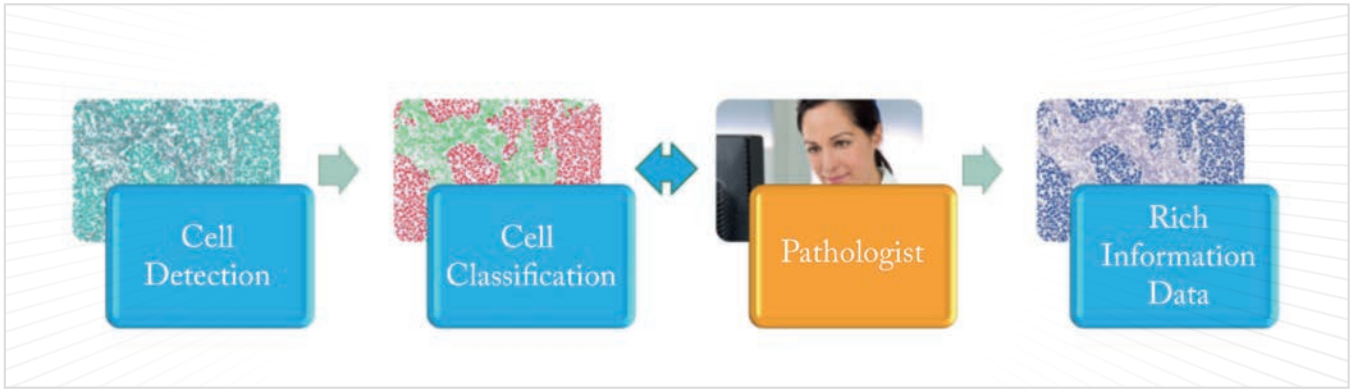


Figure 2. The structure of a pathology-centric AI system.

illustrate the concept of contradictory characteristics: patient A's stroma cells have the same characteristics as patient B's tumor cells. If we create a machine learning system trained only on patients with the same cell characteristics as patient A, it will fail when it encounters a patient like B, illustrating the potential bias that can originate from the data used for training. To ensure that the machine learning system would be able to learn the characteristics of all patient types properly, we need a lot of training data. Getting a machine learning system from 90 percent performance to 95 or even 99 percent becomes exponentially harder as remaining exceptional cases are hard to come by.

Now, when we create a machine learning system trained on patients belonging to a variety of patient types, the system would have to learn somewhat contradictory data. We would need to use a complex machine learning approach that could learn highly complex visual features with different contexts. Obviously, deep learning would be the right tool for that job – but its lack of transparency will eventually lead to legal and regulatory hurdles as pathologists and their AI partners make medical decisions that put human lives at risk.

A new diagnostic AI

In pathology, there is no critical need to use machine learning to learn the visual features in a histology slide. We are not looking at arbitrary objects in an uncontrolled environment; we are

looking for cells that a) are of a certain size, b) have three cell compartments – nucleus, cytoplasm and membrane – and c) can only be stained by a small number of stains with distinct colors.

Traditional image analysis does a good job of detecting cells and measuring the wealth of information on a histology slide. But what do we do with that information once we have detected the cells and logged all of the biology-motivated information? A machine learning system that uses multiple "patient type"-specific classifiers and is based on cells, not pixels, requires no training data, yields excellent performance and provides transparency into the decision process! Here is how it works:

1. When we encounter a patient that belongs to a new type, we create a new "patient type"-specific classifier. A pathologist, using their expertise, identifies a few example regions for the different cell types (for instance, tumor and stroma) and trains a new classifier "on the fly" that is then used to classify all of the cells on the slide. Proper controls are implemented by having the pathologist verify proper classification of the cells. New example regions are added and the classifier retrained until the pathologist is satisfied with the cell classification.
2. With any new patient, we first select the best classifier from all existing "patient type"-specific classifiers and use it to classify all of the cells on the slide. A simple, robust method that nicely illustrates the selection of the best classifier is to have a pathologist identify an example region for one or more cell types and select the classifier that provides the best performance on those regions. When the pathologist verifies the classification of the cells, they may decide that it is not good enough, which means that the new patient belongs to a new patient type and a new classifier needs to be created (go to step 1).
3. It's clear that, if we were to create different classifiers for different patient types, a simple decision tree using just a single feature with a single threshold would provide excellent performance and easily interpretable decisions. The results obtained by machine learning match nicely with what we see by eye (the separation between tumor and stroma cells based on nuclei size in patient A and on density of cells in patient B). Limiting machine learning to a specific patient type and using cell data simplifies the problem considerably. It can yield excellent performance with simple approaches like decision trees, which consist of easy-to-understand hierarchical flowcharts and only require data from a few regions for training. The training is ultra-fast and can be done "on the fly" in an interactive, iterative workflow. A decision tree based on biology-motivated features provides easily interpretable data and a meaningful grouping of patients by type.

A pathologist-centric system

A pathologist-centric AI system (see Figure 2) semantically segregates tissue analysis into three distinct parts: a) cell detection, b) cell classification, and c) measurements that provide rich information. It's at the junction between classification and rich data that pathologists provide their expertise and the proper controls for the system in a natural way.

Traditional image analysis is good at detecting cells because the imaging process is very controlled and the image contains only tissue prepared using a controlled process. Computer vision is an area where deep learning has achieved major breakthroughs over the last few years, so deep learning algorithms can be used for meaningful cell detection. And, because pathologists have been looking at cells on histology slides for over a century to make their assessments, a cell-based representation of AI data allows pathologists to understand and interact with the system intuitively. Markup images of the cells on a slide contain all of the available histological information – making them the perfect abstraction layer for a pathology AI system.

Cell classification is a critical step that any pathology AI system needs to accomplish; it ultimately determines the complexity of the machine learning approach and our ability to understand the decision-making process. As noted, we propose a "patient type" machine learning approach based on cell data, wherein pathologists contribute their expertise by using example regions for the different cell types to train patient type classifiers. This approach provides full transparency into the decision-making process. Of course, the pathologists must also serve as controls to verify cell detection and classification!

With those elements properly verified, the measurements that provide rich information for tissue can then be viewed as simple computer algorithms. This is the final step, but no less key than those that go before it. After all, this is the data we use to develop specific diagnostics, companion diagnostics, and prognostics for our patients – and we need these things to enable big data for pathology. It's our hope that, in the near future, pathologists and AI systems will work together for better data management and patient care!

Holger Lange is Chief Technology Officer at Flagship Biosciences.

Cris Luengo is Director of Image Analysis at Flagship Biosciences, Westminster, USA.

Floppy Disks to Diagnostics

Technology has come a long way in the past 20 years... and the next 20 will be equally exciting

By Clare Verrill

Many of you may remember a childhood spent with floppy disks, Atari joysticks, and computers whose operating systems were nothing more than green words glowing on a black screen. Graphical interfaces were still years away, and the idea that a computer might be able to assist with something as complex as medical care was still a twinkle in science fiction writers' eyes. Yet in our lifetimes, we've gone from that fantasy to the point where we have to consider just how much, and in what ways, we can trust computers as diagnostic aids. It's an exciting journey and one I'm privileged to be taking, but a journey that comes without obstacles is rare indeed!

Analog beginnings

My career as a pathology consultant began in 2008 when I completed my training. After three years working at the Royal Bournemouth Hospital, I relocated to Oxford, where I am now a specialist urological pathologist.

I initially joined the National Health Service (NHS) in Oxford as a consultant pathologist but, after a couple of years, I was invited to build a research group at the University of Oxford. As part of my work on prostate cancer with the Oxford Biomedical Research Centre, I was exposed to artificial intelligence (AI) and the building of algorithms. The process fascinated me – few people really know how much work goes into an algorithm to bring it up even to research grade, let alone make it viable for clinical practice. It's through that experience that I recognized the need to build an infrastructure from the ground up on which to pin the algorithms my colleagues and I were developing.

Although I have no formal training in digital and computational pathology, I did most of my growing up in the 1980s, when computers were just starting to come into people's homes. I used to sit with my friends and load up computer games, first on tape and then on disks. My family had one of the first disk computers to enter the market, so you can see I've always been tech-savvy! I'm amazed at how quickly we've gone from 5" floppy disks that would inevitably crash before they loaded to the kind of technology that can help us diagnose patients' diseases and save their lives.

Early applications

I use digital pathology a lot in teaching – for instance, to set up online teaching portals where I can present a variety of interesting cases and include text sections that explain each case and provide answers. I recently taught the British Association of Urological Pathologists' testis course that way; instead of lugging a bag of slides across London (and hoping that they all arrived at their destination intact), I uploaded my seminar to a secure, cloud-based site, and participants viewed all of the relevant and anonymized cases on that "virtual microscope." I find it really exciting – and certainly much more efficient (and pleasant) than transporting physical slides.

"My institution has now made significant moves into the digital space for primary clinical reporting."

My institution has now made significant moves into the digital space for primary clinical reporting. We have installed slide scanners in our laboratory, as well as around the region, so that we can take digital referrals from other hospitals. At this point, we've finished retrospective validation in some subspecialties and are now "live" for digital reporting for medical renal, hematopathology and testicular cases. The entire team at Oxford University Hospitals NHS Foundation Trust is very excited that we are changing the way that pathology is practiced in the Oxford and the UK for the better. I'm optimistic that we will see benefits for patients in terms of quicker turnaround times and greater flexibility to work with colleagues across the region, giving them – and us – expedited access to expert opinion. And, for the pathologists, I anticipate more flexibility to work offsite and access cases remotely and securely – for example, when urgent diagnosis is needed.

At a Glance

- *Many pathologists today have little formal training in digital technologies, but use a lifetime of experience to get to grips with new advances*
- *At the moment, digital pathology offers great benefits in teaching and long-distance consulting*
- *Soon, algorithms and artificial intelligence may even assist in the diagnostic process and provide novel insights for patient benefit*
- *Digital pathology is not without its obstacles, but nonetheless, its future looks bright*

"Digital pathology can help us make more efficient use of the resources we have."

Urological pathologists, like many subspecialists, have seen a significant increase in our workloads over recent months – not just numbers of cases, but also in terms of their complexity. There are only so many of us trained in this particular field so, at a certain point, there is no more "people power." Many hospitals now find themselves in this situation, so we have to begin looking for ways to work smarter, rather than simply harder. Digital pathology can help us make more efficient use of the resources we have.

To validate case reporting at Oxford according to Royal College of Pathologists guidance, we've defined a number of small pilots to establish feasibility, determine the pipeline, and work out any issues we encounter along the way. Once we've done that, we'll snowball this into bigger specialties and begin using it more widely. I've taken the approach of not running before we can walk to make sure the processes are safe; hence the smaller pilots. We want to demonstrate to our pathologists and biomedical scientists first, that this can work, and second, how we might do it on a small scale so that we can scale it up rapidly, which we are planning to do over the next 18 months. We'd rather get the team on board by demonstrating that this works than dictate to them what we're going to do, so I'm trying to gradually win their hearts and minds. Luckily, I have a supportive team who are all excited about the digital pathology revolution. We've implemented a steering group, we have an exciting research program with an

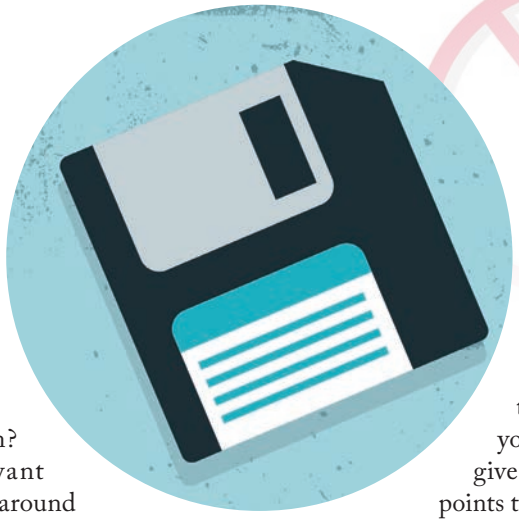
engineering collaborator, Jens Rittscher, and we're developing algorithms that might be of use in the near future. I've been fortunate to work with such keen early adopters; this really is a team effort that I couldn't have achieved alone.

Addressing uncertainties

I believe digital pathology is not only an exciting opportunity for the laboratory; I also think it has the potential to reinvigorate academic pathology. For me, the idea is intriguing because the efforts involved – building algorithms, setting up digital infrastructures – also highlight the value of the professionals in our field. For instance, it's impossible to develop useful algorithms without involving pathologists, so we are given the opportunity to apply our expertise in a novel way. And it's interesting to unpick the diagnostic process when I'm building algorithms, because a lot of what we do is pattern recognition. You may know a lymphocyte on sight, but the computer doesn't, so you have to ask yourself, "What are the features? How can a machine 'brain' conclusively identify this object?"

On a practical level, I recommend that laboratories looking to enter the digital pathology sphere tap into the knowledge of those who have already done it. Such a transition involves a great deal of research, especially with respect to procurement. By talking with someone who has already undertaken a similar task, you can save a lot of time. I also recommend involving your IT department early – and you should keep an eye out for hidden costs that seem to come slightly further down the line as you work out the practicality of transitioning to digital.

Digital deployment naturally involves some capital outlay and developing a strong business case is quite complex – after all, the cost savings come from a variety of different places. Staff time is saved, for instance, but incrementally rather than as an easy to define single block. The argument I rely on most often? Quality! We want to decrease turnaround times, reduce the chances of error (because the barcoded workflow reduces the likelihood of mismatched cases), increase quality around network working and flexibility, and provide better access to second opinions.



Another argument that works quite well in a large academic center like Oxford is the development of clinical trial portfolios. Digital pathology platforms enable us to create a library of cases with easily accessible images; central review of patient slides or image analysis for new prognostic markers is much more efficient (with the appropriate consent, of course). You don't have to scrabble around in the archives searching for old slides that might be missing or misfiled.

In short, it's harder for decision makers to say "no" to a technology that offers speed, safety, and quality.

A digital future

For the generation of younger pathologists coming through the system, I think that digital pathology and image analysis will make the field exciting. The next generation is much more likely to fully embrace the technology and use it to change pathology. I expect that we'll start to use AI and image analysis tools to support our work. And though algorithms may replace some of our current tasks, I don't feel threatened. I believe they'll more likely take over the simplest duties, so that we can focus on the more complex tasks that rely on human instinct as well as intelligence. For instance, you might oversee a prognostic algorithm, but that doesn't mean it will do the entire job for you; rather, it will give you a set of data points that you will need to verify you are happy with to incorporate into your report along with the information you generate yourself. Pathologists' roles may shift to include more supervision of complex algorithms and AI, but it will still be humans who have the final word.

AI, and digital pathology in general, will do more than just remove tasks from our workflow; they'll stratify our work into what needs immediate attention and what doesn't. What requires extra testing? What needs a human eye to make a final diagnosis? I also think that pathology will increasingly feed into big data models; rather than having the pathology report as a standalone entity, it will be part of a pipeline and will be seen alongside the patient's other results (from clinical examination, sequencing, and so on). Features extracted from the pathology images and report will be fed into that overall pipeline, which will lead to advanced predictive models. And that's where I think pathology will fit into the big picture – as part of a multi-modal patient assessment.

The pathologist's new clothes

Going forward, I expect that most – if not all – pathologists and biomedical scientists will need to have a working knowledge of IT. It's likely that you're going to need to embed that into the training for new pathologists, much in the way that molecular pathology is now included. Why? Eventually, pathologists will be taking responsibility for the

"If a lab becomes fully digital, it will churn out terabytes of data and it won't be long before it runs out of storage space."

outputs of algorithms in their reports and, to do that, we need to have a basic understanding of how each algorithm generated that output – or at least understand the steps that have led to that result, so that we can make sure it's valid. Otherwise, how can we take responsibility for it?

I think everybody, both trainees and existing consultants, will need to upskill. I also think there will be a place for a new subspecialty within pathology wherein people are trained to a higher level in these new technologies – "pathology informaticians" or something along those lines. Some institutions in the United States already have a designated specialist who takes responsibility for deploying digital platforms and setting up algorithms. I can see other countries taking a similar tack in future years.

Unfortunately, no amount of training will help if there simply aren't enough laboratory medicine professionals to take on the amount of work we'll be facing in the coming years – a workload that is steadily increasing as more and more pathologists approach retirement. Digital pathology will help us make better use of the workforce we have. That applies to aspects such as optimizing the diagnostic pathway, but also to tasks as simple as searching through stacks of glass slides to find the specific ones needed for a meeting or a case presentation.

Strengths… and weaknesses

The strengths of digital pathology are obvious. It's exciting, it's cutting-edge, and it will enable workforce flexibility to patient benefit. I think it will particularly help in more highly specialized fields that need geographic cross-covering because of the small number of pathologists trained in those fields. My subspecialty, uropathology, is one that benefits greatly from digital and telepathology; others, like renal pathology, will probably see similar benefits. I also predict that the routine creation of library images will underpin personalized medicine, research, and clinical trials going forward. And, of course, the potential reductions in errors and turnaround time are great strengths.

At the moment, though, the volume of data these platforms generate is a problem with no clear solution – to me, anyway! If a lab becomes fully digital, it will churn out terabytes of data and it won't be long before it runs out of storage space. Some laboratories are moving to off-site storage or low-cost cloud options, but it remains to be seen what's best and most secure. I also see interoperability between platforms as a problem – although most companies are working to improve this. I think one of the main issues is that, when you're trying to make a purchase in this area, it's difficult to put all the information together. You have to turn into a bit of a procurement and finance whiz to push the order through.

Finally, on a more general level, I think we'll need to have extensive conversations about consent, patient and public involvement, and the building of algorithms. Just as digital pathology and AI are taking off, the General Data Protection Regulation (GDPR) has been implemented across Europe. We need to take a step back, look at what GDPR allows, and interpret that for digital pathology so that we can fully understand our responsibilities.

These weaknesses are not insurmountable, but they will require a strong focus and investment to overcome. Some of them must be fixed by industry – like the interoperability issue – whereas others, such as data storage, need to be fixed by institutions in collaboration with industry. I hope that centers that have already embraced digitization and found solutions to these problems will share what they've done so that others can follow in their footsteps. Other issues must be addressed on a national or even international level; for instance, those tackling consent, data protection, or public involvement. It's true that there are a lot of grey areas at the moment, but all great modernizations begin with unanswered questions. We're getting there!

Clare Verrill is Associate Professor in Pathology with Nuffield Department of Surgical Sciences, University of Oxford, and Consultant in Cellular Pathology (Uropathology) at Oxford University Hospitals NHS Foundation Trust, Oxford, UK. She is co-lead for the Testis Genomic Clinical Interpretation Partnership (GeCIP) as part of the 100,000 Genomes Project.

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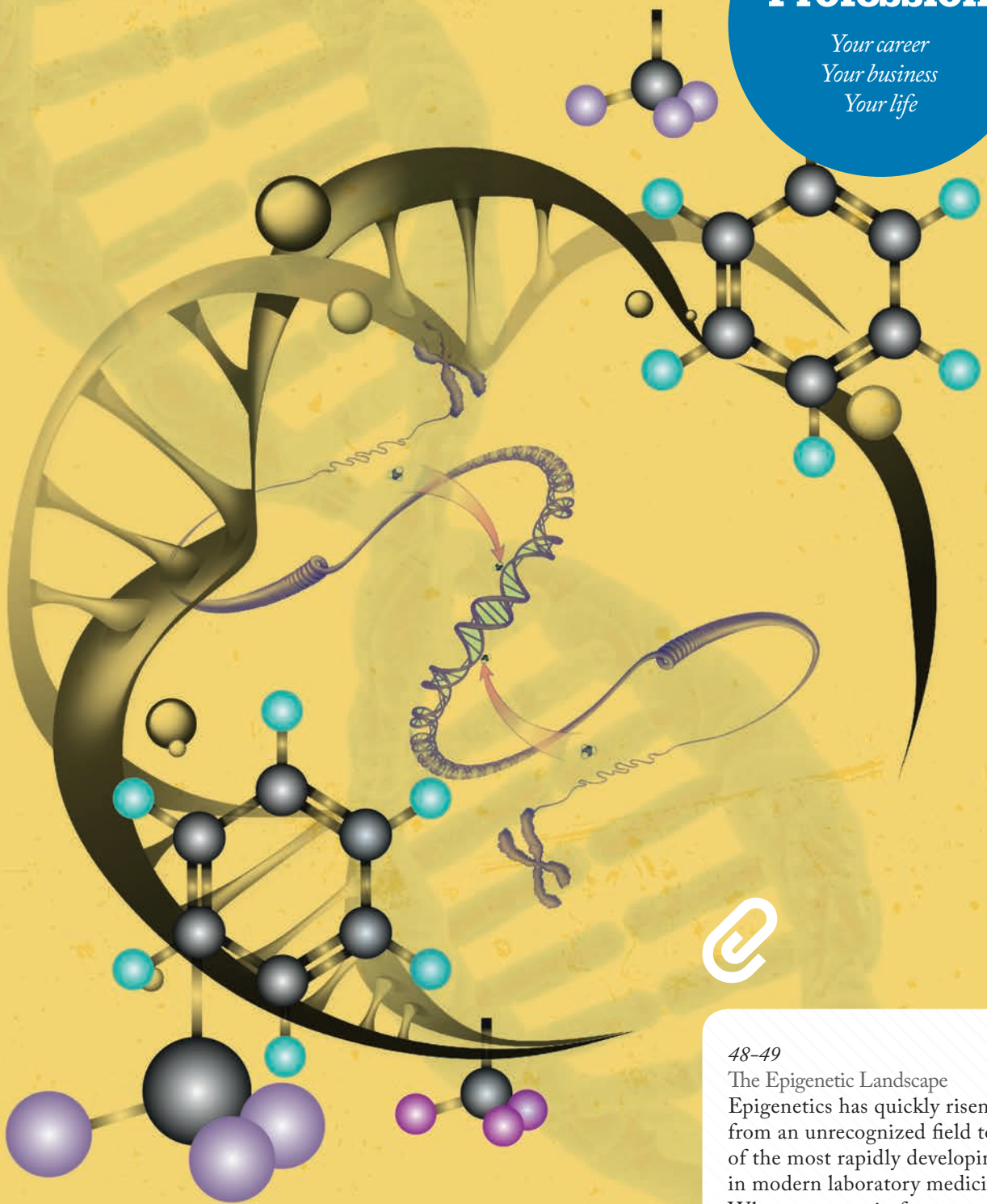

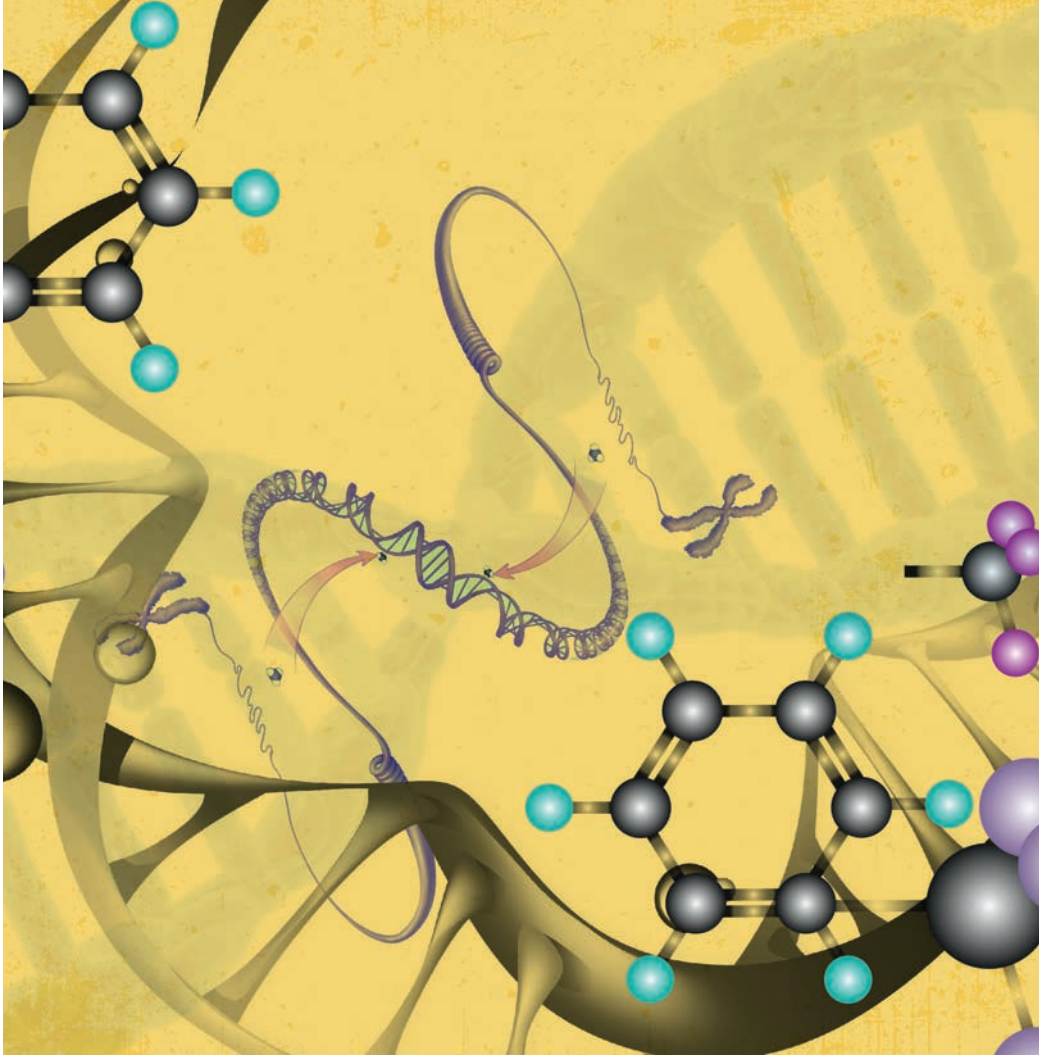

The Epigenetic Landscape

To build a complete picture of disease origin, epigenetics must be part of the equation

By William Aryitey, with Andrew Feinberg

When it comes to investigating the origin of a disease, it's common to first look into the realm of genetics – but a vital piece that can help us tackle complicated puzzles is often missing: epigenetics. Although still a relatively young field, research proving its significance in understanding disease origins has led to growing interest.

"Whole journals have sprung up on the issue of epigenetics," says Andrew Feinberg, Professor at Johns Hopkins. "It's a very young field, so there are many new things coming up, and people are still finding their way around and developing the best ways of investigating." The development has been facilitated by big changes in technology and mathematics, fields in which Feinberg started his career. He believes that, even though rapid growth has led to teething problems (for example, incomplete information), there's still a great deal of useful knowledge to be gained.

At a Glance

- *Epigenetics is vital to building a complete picture of disease pathogenesis*
- *The field is young, but extensive research has elucidated its crucial importance in disease*
- *When investigating heritable or potentially heritable disease, it's vital to consider epigenetics as well as genetics*
- *Only by studying epigenetics and gene–environment interactions can we fully understand, diagnose, and treat complex diseases*

Early days of cancer epigenetics

Not everyone agrees, however. Despite the strides being made in epigenetics and the increasing research supporting its importance in disease, there are still many scientists who disagree on the field's usefulness. Feinberg welcomes the criticism and says, "There's a joke that circulates about epigenetics being an 'epi-phenomenon.' It's healthy for people to push back and make the epigenetics community focus on clarity, what's uniquely epigenetic, and also how epigenetics and genetic alterations relate to each other."

This skeptical reaction to epigenetics was very much the case in the early days of cancer genetics, because of the spectacular advances in the purely genetic understanding of oncogenes, for example. But Feinberg and others felt that epigenetics provided a functional context to the understanding of cancer biology because of its strong relationship to gene expression and because cancer, in many ways, represents normal gene expression gone awry.

Feinberg and Vogelstein's first experiments on altered DNA methylation in human cancer took place in the early 1980s and showed that these epigenetic changes were ubiquitous across tumor types and occurred from the earliest stages of malignancy. From there, Feinberg went on to study Beckwith-Wiedemann syndrome (BWS), a congenital overgrowth disorder that increases the risk of a form of pediatric kidney cancer known as Wilms tumor. With collaborator Michael DeBaun, he showed that the several hundred-fold increase in cancer risk in BWS is caused by an epigenetic abnormality, loss of imprinting, present at birth (1). Wherever the imprinting defect was present, it caused a precancerous condition in the kidney –

the smoking gun showing that epigenetic changes can cause cancer.

Painting a landscape

"Conrad Waddington coined the term 'epigenetic landscape,' which was the concept of a pluripotent cell committing to different lineages, becoming progressively more differentiated, like a ball rolling in several different potential pathways down a curvilinear landscape," says Feinberg. "That was a metaphorical point Waddington brought up, but what my colleagues John Goutsias, Garrett Jenkinson, and Elisabet Pujadas, and I have derived is a real epigenetic landscape using principles of statistical physics that embody stochasticity. (2)" In effect, cells take different epigenetic routes to reach their final differentiated states – routes that can be altered by the effects of heredity, external factors, and randomness. This epigenetic variability is leading to new diagnostic and predictive measures that embody variance, not just mean changes – for example, in DNA methylation.

Feinberg and his colleagues have also branched out into studying the epigenomics of common disease more generally. "Dani Fallin, an epidemiologist at Hopkins, and I started to investigate the idea that maybe the epigenome is the funnel through which gene-environment interaction takes place to cause disease," he says. "People don't usually get cancer, or most other diseases, based entirely on genetic risk. I think that idea of a purely genetic origin is generally too limiting in genetic testing and in projects looking for risk markers for disease." To prove his point, they worked on studies exploring the epidemiological aspects of autoimmune and neuropsychiatric disease (3). He says that this line of research is still in its early stages in his and many other laboratories, but there are already important clues emerging, linking prenatal environmental exposure to epigenetic changes in the fetus, and linking hereditary genetic changes to epigenetic alterations affecting gene function in adults.

"It's important to think about the life cycle in a more integrated way, like prenatal or early-life exposure. We need to see how the epigenome fits into that. More and more data suggest that early-life, prenatal, and even parental exposure is important to what happens in adult life – which is not the same as Lamarckian inheritance, with which I largely disagree," says Feinberg. "Dani Fallin and I, along with my son Jason, who works with Dani, showed a link between paternal sperm DNA methylation changes and autistic features in children born to mothers who had already delivered a child who developed autism (4)." He notes, "This could be caused by a prenatal exposure, or by a genetic predisposition affecting DNA methylation. Most importantly, the work needs to be independently replicated by other groups to know if it holds up."

Expanding horizons

There are many elements to consider when it comes to funding disease research, but Feinberg believes that investigators often overlook epigenetics. Given the massive potential benefit the field could offer, he feels that epigenetics could be incorporated more formally into the overall study of human disease risk. We need to think about gene-environment interaction in particular, and how epigenetics stands right at the center of the two in terms of predicting and mitigating human disease."

Feinberg's work has continued to show the relevance of epigenetics; an investigation with Christine Iacobuzio-Donahue demonstrated that pancreatic cancer progression is linked to metabolism (3). Feinberg explains, "In that paper, we show that the metastases in pancreatic cancer are driven by genomic regions of change from heterochromatin to euchromatin. These regions show increased plasticity of gene expression, which allows for natural selection of the metastases in the absence of any driver mutation. We've proven that metastatic progression is driven by epigenetic changes that arrived within those primary lesions."

As epigenetics grows and gains more traction in terms of its epidemiological value, there's still a lot of room for knowledge – but that information won't help patients unless more researchers are available to the field. Feinberg concludes, "I can't emphasize enough the importance of cross-disciplinary training of young people going into genetics, epigenetics, and epidemiology. Because epigenetics is a comparatively young area, it is important that its practitioners of the future learn both the strengths and limitations of the field, as well as the statistical tools to distinguish the difference."

Andrew Feinberg is Bloomberg Distinguished Professor of Medicine, Biomedical Engineering, and Mental Health at the Johns Hopkins University School of Medicine, Baltimore, USA.

Curious for more? See next issue for "Lessons Learned, with Andrew Feinberg."

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Delivering the Digital Revolution

Sitting Down With… Darren Treanor, Diagnostic Digital Pathology Lead for The Royal College of Pathologists and Consultant Liver and Gastrointestinal Pathologist at Leeds Teaching Hospitals NHS Trust, UK

What first piqued your interest in digital pathology?

On the digital front, I had always enjoyed computing. Even during medical school, it was something that I did on the side as a personal interest. When I first came to Leeds, I enrolled in a part-time computer science degree. Then, in 2003, we received a Department of Health funding pilot for digital pathology – a combination of my two interests. This visionary scheme aimed to find out whether digital technology had a place in pathology. It did, of course, so then I did a PhD in digital pathology and helped create the Powerwall.

What is the Powerwall?

Digital pathology scanners existed 15 years ago, but viewing slide images on computer screens was far inferior to doing so under a microscope, so pathologists were (rightly) rejecting the technology. Instead of filling your field of view with a very high-quality image in the same way as a microscope, early digital systems could only provide a tiny (one-megapixel) display at slow speed – one frame per second. For comparison, most modern animation is done at 24 frames per second!

I was convinced that it was possible to create a better viewer, so I took my ideas to virtual reality specialist Roy Ruddle, Professor of Visualization at Leeds University. I thought a VR headset would be perfect for viewing huge pathology images. And it was good – Roy made a prototype for viewing digital pathology images in 2006. But he told me, "We've got something next door that we think is far better for what you're doing," and opened the door into a computing research lab that contained a 50-megapixel, 28-screen Powerwall. Our images are many gigapixels in size, so a large, high-quality display was much better than a narrow (albeit immersive) view. As soon as I started using it, I knew that it was something really special. We then conducted experiments and found that, with no modifications, the Powerwall was as fast as a microscope.

We knew we were onto something big. Thankfully, a research grant allowed us to test the Powerwall with pathologists, modify it around their needs, and develop software that can display images on a tiny laptop screen, a big computer monitor, or a gigantic Powerwall.

"We pride ourselves at Leeds on our evidence-based approach, and I think we have a realistic view of how many challenges there are to digitizing any lab."

Where do you think digital pathology is heading over the next few years?

We pride ourselves at Leeds on our evidence-based approach, and I think we have a realistic view of how many challenges there are to digitizing any lab. Having said that, the pace of deployment has been astonishingly fast; I underestimated how much it was going to explode over the last few years. I think that, in the UK, we will see lots of regional use – mainly for point-to-point sharing of patients' data to get second opinions – but whole clinical adoption will be a bit slower.

As for AI, it might take some time before there is a "killer tool" that pathologists use for image analysis, but it will definitely come. The reason there is so much excitement at the moment is that deep learning has come along and improved accuracy rates in our domain – from 80 percent (with the older image analysis) up to 99 percent in certain areas (for instance, finding cancer in lymph nodes, a repetitive and arduous task on the microscope). If we can show that these tools are replicating that performance in the real world, there's a huge opportunity for it to become mainstream. We're approaching with cautious excitement because, as a multidisciplinary group with broad knowledge including computing, we understand the strengths and weaknesses of the technology. Luckily, its biggest strength is in clearly defined tasks, such as those where you can tell it to find something specific within an image. Pathology, of course, is full of these scenarios, so it's an exciting opportunity!

How will this push toward digital pathology affect those at the start of their careers?

People shouldn't be afraid of the technology. Some are saying that it will reduce the need for pathologists, or make pathology less interesting as a job. I understand those perceived risks, but if you implement the technology correctly, it will make being a pathologist much more exciting, and you'll achieve a lot more for your patients. Also, the digital revolution brings pathology out of the lab and into the general hospital arena, so I'd reassure people starting out that – with genomics and digital pathology beginning to come together – it's a really exciting time. New pathologists will learn different things to what our generation learned, but that's the nature of medical progress. I'm sure that we will soon look back on our past and wonder how we ever used the microscope for so long.

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