FEBRUARY 2019

Upfront
Better diagnosis of Kaposi’s sarcoma
08

In My View
How consolidation helps laboratories
12 – 13

In Practice
Color calibration for slide scanners
30 – 33

NextGen
Spatial arrangements of immune cells
36 – 39

When Pathology Turns Predatory
… and how you can avoid becoming a victim
18 – 27
Redefining Reference Standards
www.horizondiscovery.com
A 49-year-old man presented with a testicular mass.

Based on your diagnosis, which of the following histologic findings incurs a worse prognosis?

- Anaplastic change
- Anaplastic change and sarcomatous change
- Sarcomatous change
- Germ cell neoplasia in situ

Answer to last issue’s Case of the Month…

B. Osseous choristoma

Osseous choristoma, a well-circumscribed mass of viable lamellar bone surrounded by fibrous connective tissue, may occur as a sessile or pedunculated mass mostly on the posterior dorsum of the tongue, near the foramen cecum (1,2). Most develop in females in the second or third decade, and the treatment of choice is surgical excision.

References

Submitted by Joana dos Santos, Anatomical Pathology Resident, Unidade Local de Saúde de Matosinhos, Hospital Pedro Hispano, Matosinhos, Portugal.

To register your guess, please go to http://tp.txp.to/0219/case-of-the-month

We will reveal the answer in next month’s issue!
Contents

03  Case of the Month
07  Editorial
   It's a Dog-Eat-Dog World, by Michael Schubert

On The Cover

Like a shark after a swimmer, predatory groups pursue pathologists for profit

Upfront
08  One TINY Step at a Time
09  MDLUX2: Drawing a Fuller Picture
10  Monitoring the Microbiome
11  Steps Forward in Cancer Screening

In My View
12  Using her own experience as an example, Bamidele Farinre emphasizes the benefits of consolidation.
13  Aaron Schieving discusses the dangers of prion contamination and how laboratory medicine professionals can avoid it.

From the ASCP
15  Achieving Excellence Requires a Multifaceted Approach
    To advance laboratory science and medicine, we need flexibility, innovation, and open-mindedness.
Report

16 Building a Better Biopsy
Using cfDNA synthetic plasma reference standards to improve liquid biopsy.

Feature

18 When Pathology Turns Predatory
Is our “publish (and present) or perish” mindset causing pathologists and laboratory medicine professionals worldwide to fall victim to predatory journals and conferences?

In Practice

30 A Call for Color Calibration
Histopathology is increasingly moving toward digital imaging, but Richard Salmon warns users to make sure colors are accurately represented.

NextGen

36 Watch This Space!
Some lung cancers rapidly recur, whereas others never do. A new approach uses tumor-infiltrating lymphocytes’ spatial arrangements to predict recurrence risk.

Profession

42 Lessons Learned, with Andrew Feinberg
We learn from one of the leaders paving the way to a greater understanding of epigenetics – what we can do, what we have yet to learn, and what we may one day be able to do.

Sitting Down With

50 Benjamin Garcia, Presidential Professor of Biochemistry and Biophysics and Director of Quantitative Proteomics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, USA.
Xpert Breast Cancer STRAT4 paves the way for standardized, fast, and reliable ER/PGR/HER2/Ki-67 mRNA assessment.

Used in conjunction with GeneXpert® technology, Xpert Breast Cancer STRAT4 simplifies breast cancer biomarker assessment through semi-automated sample preparation, automated RNA isolation, reverse transcription, and amplification by real-time PCR and detection. The entire process happens within a patented cartridge-based system.

**Xpert Breast Cancer STRAT4:**
- Enables flexibility, simplicity, and random access for a streamlined workflow 24/7
- Offers a more objective solution compared to conventional IHC and FISH testing
- Unequivocal and easy to interpret results
- Delivers excellent concordance with recognized standards


CE-IVD. In Vitro Diagnostic Medical Device. Not available in all countries. Not available in the United States.

Vira Solelh | Maurens-Scopont 81470, France | PHONE +33 563 82 53 00 | FAX +33 563 82 53 01
It’s a Dog-Eat-Dog World

Does the “publish or perish” mindset create a space for predators to flourish?

I was recently invited to be a keynote speaker at a diagnostics conference. Shortly before that, I received an invitation to submit my thesis (or any other manuscripts I’d written since) to a prestigious science and medical publisher. And before that, I was asked if I would like to participate as an invited speaker at an ophthalmology-themed event. It seems my career as a leading scientist is taking off – or is it?

Our cover feature this month deals with predatory journals and conferences (page 18). Although the piece addresses their effect on pathology and laboratory medicine, similar vultures circle above every field of scientific and medical advancement. Why? In part because many careers are built on prestige; having a range of publications can bring name recognition – valuable currency in an age when most research is built on collaboration. In part because academia is largely built upon the “publish or perish” mindset, which makes journal articles and conference appearances a key part of pay increases, promotion, and tenure. And perhaps in part because some researchers find it more difficult than others to make their voices heard – for instance, those who work in resource-limited settings; those not fluent in English, the language of most publications and events; or those whose work focuses on obscure or difficult-to-fund subjects. Given these pressures, it’s no surprise to find publishers and conferences who target these vulnerable academics.

For many, these predatory groups confer no real benefit. Articles published in for-profit journals often receive negative, rather than positive, attention. Speakers associated with predatory conferences may lose stature in academic circles – and may, in the future, find their identities used to promote further predatory events of which they have no knowledge!

We can all unhappily discuss the harm that such groups can do to academic communities, and what each of us can do to avoid falling prey to them. But we must ask ourselves: are these predators the problem – or are they a symptom? If our academic communities have built an environment where such publications and conferences can flourish, is there something fundamental that must change? And if so… where do we begin?

Michael Schubert
Editor
Kaposi’s sarcoma (KS) presents a diagnostic challenge even in optimal healthcare settings. This is because presentation can be extremely heterogeneous, and there are many clinical entities which mimic KS morphologically. Accurate diagnosis, which conventionally requires experienced dermatopathologists, is critical to avoid unwarranted chemotherapy – and to ensure correct therapy for mimicking conditions. But histopathologic diagnosis is not always possible in resource-limited settings, such as sub-Saharan Africa, where KS is one of the most common cancers among adults. In these settings, clinicians must often diagnose KS only via macroscopic observation and, unfortunately, this is often incorrect. Even where pathology is available, lengthy turnaround times in interpretation often render the findings useless.

To remedy this, a team led by David Erickson, an engineer from Cornell University; Ethel Cesarman, a pathologist from Weill Cornell Medical School; and Jeffrey Martin, a medical epidemiologist from the University of California, San Francisco designed and tested a portable device that can be operated without electricity and may prove useful for KS diagnosis: the Tiny Isothermal Nucleic acid quantification sYstem – TINY, for short (1).

In this system, a small biopsy of the affected skin is taken under local anesthetic. DNA is then extracted from the biopsy and tested for the presence of Kaposi’s sarcoma-associated herpesvirus (KSHV) DNA via a reaction known as loop-mediated isothermal amplification (LAMP). Because LAMP does not require the temperature cycling of the polymerase chain reaction (PCR), it can be performed via a variety of energy sources and does not need the same stable source of electricity required for PCR. Indeed, what makes TINY unique is its ability to collect and store energy from any source, including the sun – even in the midst of intermittent cloud cover.

In preliminary testing, TINY is showing promise for its ability to diagnose KS. The multidisciplinary research team is now working alongside Aggrey Semeere, a clinical researcher in Uganda, to test the device in large numbers of patients with suspected KS. They are also seeking ways to keep its cost low. “Obviously, we need to make this as inexpensive as possible,” says Semeere. “There is little point on working on such a project if we cannot make it affordable.”

References
MDLUX2 has a bold overall mission: to improve the treatment outcomes of cancer patients in Luxembourg, with a particular emphasis on rare and complex cancers (1). Continuing on from a previous initiative, the program also aims to determine whether or not molecular diagnostics are feasible and cost-effective as a routine part of cancer care; at the moment, such tests are not paid for by public health insurance, so MDLUX2 is vital in establishing their value to patients.

“Bringing small-scale local healthcare initiatives to the national level requires a lot of time, meticulous preparation, and the engagement of all possible stakeholders to ensure sufficient funding and the successful implementation of such projects,” explains Nikolai Goncharenko, Coordinator of the Institut National du Cancer. Goncharenko is enthusiastic about the new program because it will provide all patients with equal access to modern molecular cancer diagnostics. “The program will make cancer therapy in Luxembourg more personalized. Knowing the mutations and/or protein expression of particular molecules will help the tumor boards and treating physicians select the most appropriate treatment option for each individual cancer patient.” Additionally, by bringing the program to the national level with the support of private funding, the organizations involved – the Institut National du Cancer, the Fondatioun Kriibskrank Kanner, and the Integrated BioBank of Luxembourg – should be able to secure future public funding for further initiatives. At least, that’s the hope of Goncharenko and his colleagues.

The program’s diagnostic solution combines DNA and protein analyses. “It profiles solid tumor samples by sequencing 75 genes linked to approved targeted therapies,” says Goncharenko—but because sequencing analysis only partially reveals the identity of the tumor, proteins are also evaluated using IHC, microsatellite instability (MSI), and tumor mutational burden (TMB) to assess immunotherapy response. The testing even checks for unusual and damaging splicing in mRNAs and measures the methylation of gene promoters. By combining all of these analyses, investigators hope to establish a complete genetic profile of the tumor that can be used to predict response to targeted therapies, immunotherapies, and classic chemotherapies. Patients can also allow their samples and associated data to be biobanked for future research projects, supporting further advances in cancer research in Luxembourg and around the world.

References
Monitoring the Microbiome

Can gut microbiota help improve the diagnosis and management of esophageal cancer?

Esophageal cancer is the sixth most common cause of cancer-related death worldwide despite the introduction of innovative surgical, chemotherapeutic, and radiological interventions. The high mortality rate is largely attributed to the large number of patients presenting with established disease, signaling a need for improved diagnostic tools to accurately dissect individual risk. To improve the odds, a research group led by Loris Lopetuso from Catholic University of Rome, Italy, delved into the pathogenesis of esophageal adenocarcinoma (EAC), asking: what drives the transition from normal esophageal epithelium to Barrett’s esophagus (BE) and EAC? And can we detect a unique signature that might allow us to spot the changes early (1)?

Previous studies have demonstrated that gut microbiota can play a crucial role in digestive tract health, including in several gastrointestinal diseases and various types of cancer. Culture-independent molecular techniques now facilitate the identification of bacterial actors that could represent significant markers of increased cancer risk. The researchers found a higher level of bacterial diversity in patients with EAC than those without (including a relative abundance of Bacteroidetes species but a relative paucity of Firmicutes in the cancer patients) – an unexpected finding, according to Lopetuso, who notes that intestinal diseases are typically linked to a lack of bacterial diversity. Further differences in the bacteria present separated the microbiota of patients with EAC and those with BE.

“Taken together, our data indicate that BE and EAC mucosal samples can be differentiated by specific characteristics of the gut microbiota; changes to the gut microbiota could represent a predisposing factor for BE – making it the closest precursor of EAC not only histologically, but also microbiologically,” Lopetuso says.

Genetic tests already exist to characterize BE and EAC, and to predict the progression of disease. “Now, though, we have found that specific microbial markers can further differentiate the two conditions, increasing our powers of prediction,” says Lopetuso. Identification of the microbial communities associated with carcinogenesis is of crucial importance in terms of finding risk factors and could potentially guide surveillance protocols. If coupled, genetic and microbial markers may help detect EAC at earlier, more treatable stages. Moreover, they could reduce the need for repeated surveillance procedures on large numbers of patients who never progress to cancer.

Reference

1. LR Lopetuso et al., “Characterization of esophageal microbiota in patients with Barrett’s esophagus and esophageal adenocarcinoma”. Presented at the 26th UEG Week; October 20–24, 2018; Vienna, Austria.
Steps Forward in Cancer Screening

From an ultrathin fingertip blood flow monitor to falling cervical cancer screening rates, we round up the hottest news in pathology and laboratory medicine

Screening Shortages
Cervical cancer screening rates in the US could be far lower than national data suggest (1). A Mayo Clinic study found that fewer than two-thirds of women aged between 30 and 65 were on track with cervical cancer screening in 2016. Even more concerning are the statistics for younger women; just over half of those between 21 and 29 were up to date. Combined, the statistics suggest that true figures may be well below the 81 percent screening compliance rate self-reported in the 2015 National Health Interview Survey.

The Eye of the Microneedle
Despite the great diagnostic potential of interstitial fluid, our inability to gather sufficient quantities has hampered its use for clinical analysis – until now. A new technique that uses microneedles to draw relatively large amounts of the fluid opens new doors in the quest for rapid, painless, and minimally invasive draws. These tiny, hollow needles could be effective for rapidly measuring exposure to chemical and biological warfare agents as well as diagnosing disease (2).

Under the Radar
An alarming number of cancer patients have acute or chronic hepatitis B or C that goes undiagnosed, according to research from the SWOG Cancer Research Network. In 3,051 cancer patients tested between 2013 and 2017, 6.5 percent had acute hepatitis B, 0.6 percent had chronic hepatitis B, and 2.4 percent had hepatitis C. Although this reflects infection rates across the general US population, 87.3 percent of those with acute hepatitis B, 42.1 percent with chronic hepatitis B, and 31 percent with hepatitis C were undiagnosed prior to the study screening. The study concludes that community care clinics should universally screen for hepatitis B and C to help cancer patients avoid liver failure, kidney disease, and other complications (3).

Fingertip Diagnostics
An ultrathin, flexible plastic film can act as a highly sensitive sensor of blood flow when attached to a fingertip (4). The wearable medical device is composed of conductive organic molecules and uses infrared detectors to respond to blood flow characteristics within milliseconds. So far, the device has been shown to accurately measure heart rate; however, the development team believe that, with increased sensitivity, it can serve as a pulse oximeter.

Don’t Worry About a Test
Genetic tests for breast cancer are becoming increasingly complex – and multigene panel tests introduce a greater degree of uncertainty when interpreting results. But does this ambiguity cause patients to worry about their risk of cancer? Not according to a new study of patients treated for early-stage breast cancer between 2013 and 2015. Of the 1,063 women asked, 11 percent said that cancer worry had a high impact on their life and 15 percent worried often or almost always. Interestingly, the study found no difference in the amount of worry patients experienced, regardless of whether they received the multigene panel test or an earlier version that only tested for BRCA1 and BRCA2 genes (5).

References
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

A Win-Win-Win Situation

Consolidation can improve pathology services for administrators, laboratory staff, and patients

By Bamidele Farinre, Specialist Biomedical Scientist in the Department of Microbiology, Virology, and Infection Control at Great Ormond Street Hospital, London, UK

My hospital specializes in pediatric medicine, which means that our patients — and thus our jobs — are unique. The lab at Great Ormond Street Hospital (GOSH) offers a wide range of specialized clinical laboratory services to both support the tertiary services our hospital provides and to act as a specialist referral center for institutions around the world. For me, that involves carrying out routine and specialist analytical testing on patient biological samples to help clinicians diagnose, treat, and monitor recovery from infectious diseases. My colleagues and I use tailor-made equipment and technologies to test a vast range of biological samples, including extraordinarily small sample volumes from some of our youngest patients.

Our department — Microbiology, Virology, and Infection Control — started as two separate entities, but we have now consolidated our molecular diagnostics into a single service. Within that service, our microbiology lab operates 24 hours a day, seven days a week; the virology lab operates during normal working hours, but also offers a weekend out-of-hours service for the prevention, investigation, and control of healthcare-associated infection in patients and staff. Why did we decide to consolidate? To enhance our turnaround times, increase our testing repertoire, and provide a more robust service to benefit our patient population.

And we have achieved all of these things. We have a variety of routine tests available from broad-range 16S (bacterial) and 18S (fungal) sequencing to viral neurological PCR screening of cerebrospinal fluid. Moreover, we are constantly developing new methods of investigation to make best use of diagnostic innovations. This year, for instance, our virology department researched the use of cutting-edge RNAseq for deep sequencing of brain tissue. We hope that this will help us pinpoint the exact viruses and bacteria causing life-threatening brain infections in children, ensuring that they receive rapid and appropriate treatment. The success of this research will provide us with a unique platform to review samples from across Europe, and we hope it will revolutionize how doctors treat encephalitis.

Pressure on pathology services to consolidate, reconfigure, or modernize is nothing new. Lord Carter’s 2006 and 2008 reports — independent reviews of NHS pathology services in England — recommended consolidation of services “to improve quality, patient safety and efficiency (1).” At the same time, it is important to recognize that pathology is a diverse group of clinical specialties; what works for one discipline may not work for another. Some pathology
services must be located close to the patients and healthcare professionals who rely on them, whereas others can be combined to serve larger areas. In our case, to ensure high-quality service while reducing costs, consolidation was the right decision.

But that’s not to say it was easy. The consolidation of our molecular microbiology services was a resource-intensive project that required a dedicated team and the support of both management and operations teams. It was a challenge to simultaneously change multiple aspects of our work (logistics, processes, facilities, equipment, IT infrastructure, and staffing) and we – the staff – were understandably somewhat hesitant. To that end, it was important for our integration to have four main objectives: i) to maintain and improve customer service across networks, ii) to derive economies of scale and cost benefits, iii) to control for and minimize risk during and after the transition process, and iv) to minimize the disruption and impact on staff.

After a transition period, I can comfortably say that the outcome has been positive. Our clinical scientists are now best located for effective results; we can collaborate easily with subspecialty experts; we have research and development opportunities; we can plan for training and succession; overall, our service is larger and more resilient than ever. I feel that, because our service is clinically led and our focus is on providing valuable services to our patients, consolidation was a success – and it has improved our turnaround times, allowing us to work not just more, but better. The service costs less to run, it’s easier to spread workloads and share the burden, and our patients receive accurate results quickly: a win-win-win situation.

References

Protecting Patients from Prions

We must ensure that biological products are free from contamination – or we risk transmission of a fatal disease to a patient

By Aaron Schieving, Director of Sales and Marketing at Lifecycle Biotechnologies, Fort Worth, USA

With the evolution of science, the world is increasingly benefiting from the amazing lifesaving and life-enhancing medical products developed and commercialized today. As new drugs, biologics, and devices come to market, the regulatory landscape evolves alongside them. Because these products are used on patients, it is critical to ensure they are safe – which can mean a number of different things, all of which should be built into the design of these products well before manufacturing begins. The companies developing these products devote significant care and attention to the products they make, but contamination can occur with any product at any time – even one manufactured under current Good Manufacturing Practice and a robust Quality Management System. Although this statement is true for all...
In January 2008, the US health system authorities began to receive isolated reports of hypersensitivity reactions in hemodialysis patients. Symptoms included hypotension, facial inflammation, tachycardia, hives, and nausea. Initially, inquiries were focused on the filters and lines used in dialysis; however, the research carried out by the Centers for Disease Control and Prevention proved that all known cases had in common the use of sodium heparin. In February 2008, the manufacturer withdrew all batches of the product— but there were still reports of allergic reactions, including some fatal cases. After monitoring by the US Food and Drug Administration (FDA), fatalities associated with the use of sodium heparin returned to the usual figures. The next month, the FDA published the discovery that the heparin—which was highly contaminated—had been purchased from a single supplier, who in turn sourced the heparin from its Chinese factory. They determined that the contaminant was in the heparin material before it reached the supplier—but because the Chinese factory sourced its raw heparin from small suppliers, it could not be fully traced. The deficiency led to extensive revisions of the unfractioned heparin monographs of both the US and European pharmacopeias—and it provided a hard lesson that lead to much stricter control and better understanding of how contamination risks can be mitigated.

Potential human donors of such products bear no lighter a burden. They must be screened to determine their eligibility to donate, and to ensure that the human cells and tissues to be transplanted are free from communicable disease agents. Once a person is deemed eligible to donate, the tissues and cells consented for donation are recovered to be transplanted and processed. If a potential donor is not free from risk factors for—and clinical evidence of—infection with a relevant communicable disease, they may be ineligible to donate their tissues and cells. This is a critical step at the beginning of the lifecycle of the HCT/Ps we use today. Why, then, after this required screening and testing, would you risk introducing one of these communicable diseases back into your tissues and cells? The question may sound absurd; however, the risk is real, especially for prion diseases like bovine spongiform encephalopathy (BSE) and its human variant, Creutzfeldt-Jakob disease (CJD).

In an ideal world, we would eliminate the risk of contamination of human- and animal-derived products by avoiding their use—but that simply isn’t possible; some materials either require, or are cost-prohibitive without, such products. These may include proteins, enzymes, and amino acids; biotechnological products like serums, blood products, and vaccines; or even primary packaging materials like gelatin capsules (which are particularly susceptible to BSE/CJD). Even when a product involves no such materials, there may still be a risk of BSE/CJD contamination if they share equipment or facilities with biologically derived products. It’s important for diagnosticians to bear this risk in mind when dealing with patients experiencing unexplained neurological symptoms—and it’s important for labs that produce such materials to ensure that there’s no risk of contamination when those products are provided to patients.

If the use of animal-derived products is at all avoidable, I suggest that maintaining an animal-origin-free facility is the best way to eliminate the risk of contamination entirely—and to hold suppliers to the same standard. To do otherwise is to welcome the risk of contamination into your laboratory. The pharmaceutical industry is taking precautions to eliminate and mitigate this danger, but academia and other industries have not followed suit. As consumers and patients, we must educate ourselves on the risks associated with these medical products—and, if necessary, we must demand higher standards to ensure our patients’ safety. We must ask questions about the medical products we and our patients use and demand that they be produced safely and with as little risk of contamination as possible. Just think of the alternative if we don’t ask—patients may end up with a degenerative, ultimately fatal brain disorder. The choice is simple.
When studying cytopathology in the early 1980s, we were taught that the causative agenda for cervical cancer was *Chlamydia trachomatis*, among other epidemiological factors. Of course, today, we know that to be completely inaccurate – but it was a long road to acquire the scientific evidence needed to finally link high-risk human papillomavirus (HPV) virotypes to cervical cancer. What tools were missing? We needed advances in technology, such as Southern blot and PCR, to detect viral DNA integrated within host DNA. We needed that data to correlate with cellular changes indicating that malignant transformation was likely to occur. It was nearly 20 years later that Harald zur Hausen won the Nobel Prize for determining that HPV was the causative agent of cervical cancer. Today, the virus can be detected by internal closed system PCR amplification and, within hours of analyzing the epithelial sample, we can determine if the patient is at high risk of cervical cancer. That gives the clinician the information they need to remove the precancerous lesion before it transforms into a malignancy – a clinical game-changer for the patient.

Moving from one consensus opinion to another, especially in a discipline as broad as ours, requires flexibility, innovation, and open-mindedness. You don’t have to be a researcher to appreciate how important these concepts are to management and administration in the clinical pathology laboratory. Achieving excellence in our laboratories requires a multifaceted approach focusing on people, policies, and practices. Laboratories need to be up-to-date on the regulations and accreditation bodies that govern our industry. Pathologists and laboratory scientists need to be aware of the latest clinical care guidelines so they can implement changes in procedures if necessary. Laboratory administrators, managers, and staff need to be proficient in conflict management and emotional intelligence to create a happy and productive workplace culture. And, on top of everything else, we must all continue to prioritize training, competencies, and continuing education. After all, advances in diagnostic techniques are only impactful if we are trained in both the theory behind the tests and their practical use.

As laboratory professionals, it is our responsibility to constantly acquire new skills. Providing the very best care for our patients means we must not only keep up with the current paradigm, but also commit to implementing the latest innovations and anticipating new gold standards of diagnostics. Our practice changes as our knowledge base expands, and it’s up to us to make sure that knowledge base is as broad as it can be. It might feel impossible at times but, as practitioners dedicated to the highest level of patient care, we must be up for the challenge.
Building a Better Biopsy

Combating the challenges of liquid biopsy with cfDNA synthetic plasma reference standards

By Lisa M. Wright, PhD

Medical professionals in the cancer sphere are all familiar with solid tumor testing for patients. And although valuable, these procedures are also painful, invasive, and costly in multiple ways. Liquid biopsy – the approach of examining fluid samples, usually blood, for biomarkers – holds many advantages over solid tumor testing. It is less invasive for the patient and has improved levels of sensitivity to detect low-frequency somatic driver mutations. In oncology, pathologists often examine circulating free DNA (cfDNA) for markers that indicate the presence of cancer, its molecular characteristics, and the tumor’s susceptibility to treatment.

The industry is pushing to make liquid biopsy the go-to method of collecting clinical DNA samples for oncology genotyping. Liquid biopsies can be taken at the point of diagnosis for routine monitoring during treatment, enabling practitioners to rapidly detect the appearance of resistance mutations that might indicate the need for a change of therapy. One day, liquid biopsy could even be used for preventative cancer screening in the general population. The ultimate goal is to facilitate earlier diagnosis and better treatment outcomes.

As with any new technology, using cfDNA for diagnosis via liquid biopsy has its challenges. Common technical hurdles include:

1. **Sample handling**
   Liquid biopsy workflows involve additional sample handling steps. For example, clinical labs that have been handling robust FFPE blocks for many decades are now faced with processing blood samples, which have shorter shelf lives and require multiple extraction steps. Each step must be properly validated to ensure it does not introduce errors into the final results.

2. **Reliability of results**
   Liquid biopsy assays must operate at much lower limits of detection than previous FFPE-based sequencing. As a result, the technology needs to be rigorously tested to ensure it can accurately call variants down to between 0.1–5 percent allele frequency without calling false positives.

3. **Sample variability**
   Human plasma naturally displays high lot-to-lot variability, making it difficult to control and implement a consistent protocol for your diagnostic assay. Inconsistencies in the clinical blood draw and immediate blood storage process, which can vary between phlebotomists and hospitals, can introduce further sample variation. Controlling for this variation and introducing a consistent protocol is essential for the success of wide-scale liquid biopsy adoption.

The two big challenges

1. **Limit of detection and false positive error rates**
   A key challenge in using cfDNA to detect cancers early is the extremely low quantities of cfDNA in patients’ blood. So how can we be confident in our lower limit of detection and ensure that we’re not seeing false positives? The answer: an appropriate reference standard. Using a reference standard with a range of precisely defined allelic frequencies can help determine a true limit of detection and reduce the risk of false positives.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant</th>
<th>Allelic Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5%</td>
</tr>
<tr>
<td>EGFR</td>
<td>L858R</td>
<td>5.0</td>
</tr>
<tr>
<td>EGFR</td>
<td>ΔE746-A750</td>
<td>4.9</td>
</tr>
<tr>
<td>EGFR</td>
<td>T790M</td>
<td>4.9</td>
</tr>
<tr>
<td>EGFR</td>
<td>V769-D770ins</td>
<td>5.0</td>
</tr>
<tr>
<td>KRAS</td>
<td>G12D</td>
<td>5.1</td>
</tr>
<tr>
<td>NRAS</td>
<td>Q61K</td>
<td>4.9</td>
</tr>
<tr>
<td>NRAS</td>
<td>A59T</td>
<td>5.2</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>E545K</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Table 1. Comparing human and synthetic plasma as reference standards for cfDNA assays.
In this example dataset, the reference standard informs the user that i) the reliable limit of detection for this cfDNA assay is 1 percent allelic frequency, and ii) they are calling a false positive for NRAS A59T.

When you run a reference standard before a patient sample, you can be sure of the limit of detection for your assay. It also allows pipeline optimization; you can recalibrate and amend your workflow to counter any false results, which gives you confidence when handling real patient samples.

2. The variability and instability of human plasma
Using human plasma as a control for your cfDNA assay comes with numerous challenges (see Table 1). Yes, human plasma matches your patient sample behaviors, but this does not always outweigh the challenges that come with using it as a reliable control for diagnosis.

Our approach to testing:
1. 400 ng of cfDNA was spiked into 1 mL of human or synthetic plasma and stored at -80°C.
2. cfDNA was extracted using a Circulating Nucleic Acid kit (Qiagen); extraction efficiency was measured with Qubit BR Reagents (Molecular Probes).
3. Total AKT1 gene copies were quantified by ddPCR (Biorad).

Take control of your workflow
Having well-characterized cell line-derived reference standards that closely mimic real patient samples, with clinically relevant variants defined by a gold standard mechanism like droplet digital PCR (ddPCR), allows new liquid biopsy assays to be properly validated. Users can:
• check that their workflows accurately detect all of the variants in the control material at the correct allele frequencies without calling false positives
• validate and control for the introduction of errors during the DNA extraction procedure
• ensure that the design of their liquid biopsy sequencing assay functions effectively with no amplicon dropout (liquid biopsy assays need to sequence from smaller fragments of DNA than was previously required in fresh tissue or FFPE assays)

Horizon has developed a range of cell line-derived cfDNA reference standards to help develop, optimize, monitor, and control the accuracy of new patient tests. These materials contain a range of actionable variants in key cancer genes at well-characterized allele frequencies as determined by ddPCR. The variants are located within genomic DNA and have an average fragment size of 160 bp.

Find out more at tp.txp.to/horizon/cfDNA

Our cfDNA material in synthetic plasma helps users to monitor the entire liquid biopsy workflow from DNA extraction to interpretation of results, giving labs confidence in the accuracy of their test.

Find out more at tp.txp.to/synthplasma

What’s next?
The ability to examine and support cancer patients using liquid biopsy is hugely exciting. It promises to make genetic analysis more accessible with only a simple blood draw, and it encourages more frequent testing in all aspects of cancer management – pre-disease preventative monitoring, diagnosis, treatment, tumor evolution, resistance management, and long-term remission surveillance and check-up. For both laboratory professionals and the patients they serve, liquid biopsy with appropriate reference standards is the way to a brighter future.

Dr. Wright is Diagnostics Business Unit Leader at Horizon Discovery plc.
When Pathology Turns Predatory
ANATOMY OF A PREDATOR

How to navigate the dangerous world of predatory journals and conferences in these “publish or perish” times

By Benjamin Mazer

• Predatory journals and conferences often take advantage of academics pressured by the common “publish or perish” mindset
• These groups often overcharge those presenting or publishing without delivering the scientific rigor and stature they promise
• To avoid falling victim to predatory groups, always check journals’ and conferences’ credentials (ideally with respected researchers you know personally) and examine predatory publishers to ensure your identity is not used without permission
• This kind of predation is a symptom of a larger problem; we need to reconsider how academic science and medicine are incentivized

Academia’s “publish or perish” mindset is one that drives productivity and competition. And that can be a good thing – inspiring hard work, broad collaboration, and rigorous scientific quality control. But sometimes, it can lead to the opposite – a sense of urgency in publishing and presenting that may make some look less carefully at the journals and conferences accepting their work. This, in turn, opens the door to predatory organizations who take advantage of the perceived urgency.

What are predatory publishers?

A predatory publisher is a for-profit company that uses minimal to no traditional peer review (despite often advertising a rigorous review process) and accepts nearly all submissions (for which it
may charge exorbitant fees). Beyond simply lacking scientific rigor, predatory publishers use deceptive practices meant to increase the credibility of their offerings. They will use the names, biographies, and photographs of prominent scholars without permission, falsely claiming that they are journal editors or conference speakers. If a scholar has knowingly submitted an article to even one journal or spoken at even one conference associated with these predatory publishing networks, their name and likeness may be – unbeknownst to them – disseminated throughout the network to advertise unrelated productions.

The creation of “predatory” journals and conferences in science and medicine is raising new questions about the scholarly publishing process. What is the value of scholarly publication in the Internet era? How are scholarly publications being used as secondary measures of influence and academic success? How effectively are we distributing the costs, labor, and profits associated with scholarly publishing?

Predatory publishers are also an unintended consequence of the rise of electronic journals and open-access publishing, two increasingly mainstream methods that are still dominated by legitimate players. Electronic publishing substantially lowers the barriers to entry into academic publishing due to its lower costs. Open-access publishing also shifts the burden of paying for journals from large libraries to individual scholars. Predatory publishers feel they can more easily manipulate these new consumers, who may have less experience with academic transactions than professional librarians.

**Predatory publishing networks**

Though there appears to be a seemingly endless supply of new open-access titles, each a slight variation on our sober academic vocabulary, most are actually part of a single Indian predatory publishing network owned by Srinubabu Gedela (1). This network generated US$11.6 million in revenue in 2016, according to Bloomberg. Although profitable, this represents only a tiny fraction of the more than $24 billion scholarly publishing market.

Gedela and related individuals and companies have been charged with fraud by the US Federal Trade Commission (FTC), and a federal court has placed a preliminary injunction against the companies (3). The FTC charges make plain the risks these publishers pose to researchers:

> “The defendants deceptively claim that their journals provide authors with rigorous peer review and have editorial boards made up of prominent academics when in fact, many articles are published with little to no peer review and many individuals represented to be editors have not agreed to be affiliated with the journals.”

The FTC’s complaint alleges that the defendants do not tell authors submitting papers for publication that, after their online journals accept an article, the defendants charge the authors significant publishing fees and often do not allow authors to withdraw their articles from submission, making their research ineligible for publication in other journals.

The FTC also alleges that, to promote their scientific conferences, the defendants deceptively use the names of prominent researchers as conference presenters, when in fact many of those researchers had not agreed to participate in the events.”

According to the summary judgment motion (4) filed by the FTC last May, Gedela’s network of companies includes the OMICS Group, iMed Publications, Conference Series LLC, Meetings International, Allied Academies, EuroSciCon, and Pulsus Group. Hundreds of journals and conferences are produced from this network of subsidiaries. Most are new publications; however, Gedela has also been purchasing older publishers to gain credibility. The Pulsus Group and Andrew John Publishing, for example, were originally respected Canadian publishers that are now part of this network, leaving Canadian scholars concerned (5) about academic “hijacking.”

The OMICS group publishes multiple pathology-related
Examining these journals, you will find publications by pathologists at many well-respected academic institutions. Each journal will list multiple editors, many of whom are prominent in our field. Some of these pathologists may not be aware at all that their names are being used for this purpose. Others may have consented to being listed as editors, but may not have been fully aware of the deceptive practices that these journals consider standard operating procedure.

**Predatory pathology conferences**

Pathology is no more immune to predatory publishing practices than any other area of medicine or science. I was motivated to write about this topic for our community after seeing tweets by influential individuals and organizations about the “17th International Conference on Pathology & Cancer Epidemiology,” a conference run by OMICS subsidiary EuroSciCon.

Among the sponsors listed for the conference was The Pathologist magazine – which, despite being a relatively new publication, has quickly gained respect within the pathology community and even formed a partnership with the American Society for Clinical Pathology. I contacted the editor of the magazine to learn more about their potential conference sponsorship and learned that,
although the magazine had knowingly made an agreement with the conference, they were not aware of its predatory nature and have discontinued the relationship. This pattern is a good example of additive deception; a conference that advertises untrue affiliations with respected speakers and organizations may appear falsely legitimate to further speakers and potential sponsors – who will then enter into genuine agreements, risking their own reputations by accidentally liaising with predatory groups.

Examining the website and program brochure (7,8) for the conference, we can see some hallmarks of predatory conferences:

- Sessions run the gamut of loosely related subdisciplines, with topics ranging from dermatopathology to plant pathology to psychopathology – an absurd combination.
- Past speakers at other conferences make up a large portion of the promotional materials, a tactic meant to increase perceived legitimacy and optimize search engine placement.
- Photos of related conferences show, at most, a few dozen participants, despite so many purported topics and speakers listed on the website and in the program.
- Content is disorganized, poorly edited, and clearly drawn from stock text.

I reached out to one pathologist I know who was listed as a “renowned speaker” in the program brochure of this upcoming predatory pathology conference. He was not, in fact, participating in the conference and had no prior knowledge that his likeness was being used to advertise it. It’s clear from experiences like his that, despite FTC intervention, these predatory groups’ deceptive practices continue unchecked. In 2013, University of New South Wales biologist Richard Edwards memorably blogged about his negative experience at an OMICS-sponsored scientific conference (9), describing an event “bordering on farce.” After examining these marketing materials and seeing similar practices still taking place, I have no reason to believe his experience would be much different at a predatory pathology conference today.

Not the victims’ fault

The science presented in predatory journals and conferences is often legitimate and high-quality – and that is exactly the pernicious nature of these outfits. Predatory publishing’s deceptive practices can reduce scholars’ credibility, and that of their scientific work by association.

It is possible that a minority of people who publish in predatory journals and speak at their conferences are aware of their true nature – and they wish to use the lack of rigorous review to enhance their CVs. I do not intend to cast aspersions on even these behaviors. I have heard senior pathologists complain, over and over again, that in academic medicine there is increasing pressure to publish frequently, while protected time for scholarly work is shrinking. Traditional publishing
also remains slow and cumbersome, and legitimate open-access journals often charge very high publication fees. If we want to avoid the knowing use of predatory publishing, we must confront the misaligned incentives our system is creating.

Forensic implications

In an editorial in the journal Forensic Science, Medicine, and Pathology, forensic pathologist Roger Byard has raised an important point about the risk predatory publishing poses to forensic pathology in particular, due to its potential legal ramifications.

“In forensic circles there has always been a problem in dealing with aberrant theories that are at odds with the mainstream literature. In the past, this material was often introduced into court without the imprimatur of peer-reviewed, or any, publication. It is now possible with the advent of predatory journals, however, that even the most bizarre theories with inadequate or no scientific validation could be published. To the courts, these papers would appear to be no different to those published in legitimate journals, and without a clear knowledge of a particular journal’s reputation and process, may be difficult to exclude. My concern is that predatory journals may be used in future to legitimize fringe and Pathologists Residents Forum Executive Committee, which runs its own conferences for pathology residents. This article is written in my personal capacity, and is not affiliated with any organization or my employer.

Benjamin Mazer is Resident in Anatomic and Clinical Pathology in the Departments of Pathology and Laboratory Medicine at Yale-New Haven Hospital and the Yale School of Medicine, New Haven, USA.

References

WHEN PROGRESS BECOMES PREDATION

Predatory publishing can lead to academic ruin, especially for developing countries

By Yaman AlAhmad, Ibrahim Abdelhafez, Faruk Skenderi, and Semir Vranić

“Pseudojournals” – predatory journals or publishers – abuse the academic system and community solely to gain profit. They do so by charging for the publication of questionable scientific content, devoid of standard editorial procedures like peer review. These journals operate globally, but their deleterious effects on the academic environment are felt most keenly in developing countries, where local researchers who publish in such journals build careers and gain tenure based on their publications, but fail to advance their scientific and medical skills. On the other hand, these journals may also attract honest but inexperienced researchers who find their article “hijacked” after submission – no longer permitted to withdraw it, but subject to pressure to pay the fee for publication.

How to spot a pseudojournal

Predatory journals disguise themselves in different ways. Some of them operate in the “borderline” zone, balancing legitimate and for-profit practice, but still consistently and notoriously publish low-quality or even fabricated articles without conducting any peer review. Unfortunately, there are no firmly established criteria to help distinguish a predatory journal, particularly a “borderline” example, from a low-quality but legitimate one.

In more pronounced cases, it is easy to tell. At first sight, these journals use titles similar to legitimate journals, or label themselves as American, British, or originating from another scientifically sound nation despite being based in a completely different location. At the same time, they display false, misleading, or irrelevant scientific metric indices. Usually, information on the pseudojournals’ editorial policies is vague,
limited, incomplete, or altogether missing. The contents are especially revelatory; such a journal publishes everything it gets, regardless of its aims and scope, and sometimes even crossing the boundaries between branches of science, as with the Journal of Medicine, Radiology, Pathology and Surgery. Published articles lack basic editing and the layout is usually poorly done. These journals are almost never covered by PubMed/MEDLINE, Scopus, Web of Science, or the Directory of Open Access Journals (DOAJ).

In more discreet cases, it is not easy to recognize predatory journals. They look deceptively like legitimate ones, with fitting titles, appropriate articles, and professional-looking layouts. Some of these journals even manage to become members of authoritative associations dealing with editorial and publishing best practices – a fact they then misuse to improve their reputations. In addition, some of them have their contents covered by PubMed or Scopus – which not only makes it more difficult to spot the fakes, but also creates “noise” in the literature and spreads irrelevant, trivial, or wrong information while making it more difficult to locate and identify true science. Of note, in our research revealed that only one predatory journal was listed in a reputable database (1). However, we do not know how many of them have applied and may be accepted for inclusion in reputable databases.

Another common feature that should raise suspicion of a predatory journal is its focus on authors – for instance, advertising or overemphasizing rapid peer review, database coverage, journal metrics, and emails with non-selective calls for papers. In contrast, legitimate journals put emphasis on scientific content to attract readers. Nevertheless, sometimes a more detailed analysis of the journal is necessary to rule out its potentially predatory nature, including looking at the reputation of the editor-in-chief and the journal’s validation by databases or authoritative bodies. Sometimes, even a simple Google search for the journal can reveal other people’s experiences that may assist determining its legitimacy.

The scope of the problem

The impact of predatory journals is astonishing – far more severe than it appears at first glance. They affect not only individual authors, but can have a negative or even ruinous impact on the academic environments of entire countries. Developing countries have limited scientific infrastructure and human resources. Unfortunately, without equivalent scientific resources, many researchers in these countries cannot reach the level of research quality and importance required to publish extensively in reputable journals, so these countries usually have loose criteria for academic tenure. Nevertheless, they have adopted the academic organizational structures of developed countries, including the “publish or perish” mindset that makes authorship essential for an academic career. This is where predatory journals come in to fill the gap.

This setting creates a vicious cycle leading to extreme detriment of under-resourced academic communities. Inexperienced or incompetent researchers publish in pseudojournals, use those publications to rise through the ranks of academia, and train the next generation of researchers in the same methods. Eventually, the scientific potential of such a community could be devastated.

These journals also pose a significant challenge to individual laboratory professionals. In particular, young and inexperienced researchers might be tricked into contributing to predatory publications. This can have a deleterious impact on their academic and professional careers. Consider that the misfortune of publishing in a predatory instead of a legitimate journal could result in a failure to fulfill the requirements for a doctoral thesis – or that relying on results from an inadequately peer-reviewed publication could mean a waste of months or even years of scientific work. For those whose academic work has a direct impact on patients, illegitimate journals might even lead to a negative effect on patients’ health.

Our research has shown that the number of predatory journals in pathology is approaching the number of legitimate pathology journals listed in Science Citation Index Expanded and the Web of Science. If this trend continues, it is expected that pseudojournals may outnumber the legitimate ones at some point in the future. Our next step is to look into the prevalence of predatory journals in laboratory medicine to determine whether or not the threat is equally great – and to help raise awareness and build reliable tools for identifying these journals.

Open access: a risk and a benefit

Like any other revolutionary development, open-access publication can be – and has been – misused. However, we do not believe that open access itself is to blame for the rise of predatory journals. In fact, open access is definitely the way of the future, especially in areas where researchers may not be able to afford multiple expensive subscriptions. The availability of legitimate, peer-reviewed information facilitates research dynamics and the overall progress of science and medicine. The academic community widely recognizes the importance of open access, and many institutions support their researchers in publishing with open-access journals. And the benefits extend to authors as well as to readers; many prefer open access because it means their papers are immediately available for reading and citation, thus increasing the author’s reputation and disseminating knowledge faster. No wonder, then, that an increasing number of reputable publishers are offering open-access options to their contributors. Nevertheless, we believe that predatory journals are damaging the open-access model – once again, with a more pronounced effect in developing countries.
As the issue of predatory publishers is brought to the forefront, the academic community will need to adopt quality control criteria that can clearly differentiate between predatory and legitimate journals – particularly in the countries that are most severely affected. Eventually, such precautions will improve the publishing landscape for both academia and legitimate publishers.

In search of publication

Many researchers may find that they are pursued by predatory publishers, who ask them to submit manuscripts. And many more will likely come across these publishers online while seeking appropriate venues for future articles. How can legitimate academics protect themselves from danger? In addition to the criteria mentioned earlier, they should request the advice of senior colleagues and fellows – a task made much easier by social media; science and medical professionals all over the world can share information about pseudojournals almost instantly.

It’s also important to question what you find, just as you would any scientific result. Have I ever read an article from this journal? Have I seen it cited in other legitimate publications? Have any of my colleagues or collaborators published articles in this journal? If all of the answers are negative, or if any of the journal’s characteristics raise suspicion of a potential predatory nature, you should definitely apply the criteria used in our study (1) to ensure that your article is not being submitted to a pseudojournal.

A plethora of excellent and legitimate open access journals enable the free and unrestricted sharing of scientific and medical knowledge. Before deciding whether or not to submit your research to any of them, you should carefully evaluate the journal’s impact factor (as provided by Journal Citation Reports, Clarivate Analytics) and indexing status – especially given that even legitimate journals, if recently launched, may lack an impact factor and may not be indexed in the major bibliographic databases. Notably, important information may be obtained from sources such as the World Association of Medical Editors (WAME) (2) and the Committee on Publication Ethics (COPE) (3), which are dedicated to promoting best principles and practices in publication ethics – including those related to research and publication misconduct. A coalition of scholars has also developed an online tool known as “Think. Check. Submit.” (thinkchecksubmit.org) to help scientists identify trusted journals in which to publish their research. When contributing to our collective knowledge, researchers would be well served to familiarize themselves with the basic principles of academic publishing and indexing using the above sources. Such knowledge is your best defense against academic predation!

Yaman AlAhmad is a medical student at the College of Medicine, Qatar University, Doha, Qatar.
Ibrahim Abdelhafez is a medical student at the College of Medicine, Qatar University, Doha, Qatar.
Faruk Skenderi is an academic pathologist at the University of Sarajevo, Sarajevo, Bosnia and Herzegovina.
Semir Vranić is an Assistant Professor of Pathology and a Union for International Cancer Control Fellow at the College of Medicine, Qatar University, Doha, Qatar.

References
Advance Your Career and Improve Your Skills with ASCP Certificate Programs

ASCP offers a broad selection of online certificate programs that have been developed to support the ongoing professional needs of pathologists, laboratory professionals and residents. These programs are a convenient way to stay sharp and learn new skills. Review the certificate programs and see how they can help advance your career!

Comprehensive and Inclusive Leadership Training for the Laboratory Medicine Team

Hone your leadership skills at your own pace with 12 on-demand courses offering CME/CMLE/SAMS credit! This program teaches participants to adapt their behavior, communication skills, and leadership styles to be effective in a variety of workplace situations. Through an advanced self-assessment program, participants gain insight into their current viewpoints on leadership topics, identify areas of growth and use the knowledge gained to develop advanced leadership skills.

The Best Training Resource in Laboratory Management Today

Created for pathologists, residents and laboratory professionals, LMU is a customizable program for individuals planning on moving into management positions or seeking to advance their management skills.

The Most Complete Pathology Informatics Education Program You Will Find

Take the lead to improve lab productivity and move your lab to the next level with this unique self-paced online certificate program. The program is designed for individuals participating in laboratory informatics initiatives to enhance quality diagnosis, throughput and patient safety.

www.ascp.org/certificate-programs
Advance Your Career and Improve Your Skills with ASCP Certificate Programs

ASCP offers a broad selection of online certificate programs that have been developed to support the ongoing professional needs of pathologists, laboratory professionals and residents. These programs are a convenient way to stay sharp and learn new skills. Review the certificate programs and see how they can help advance your career!

www.ascp.org/certificate-programs

Comprehensive and Inclusive Leadership Training for the Laboratory Medicine Team

Hone your leadership skills at your own pace with 12 on-demand courses offering CME/CMLE/SAMS credit! This program teaches participants to adapt their behavior, communication skills, and leadership styles to be effective in a variety of workplace situations. Through an advanced self-assessment program, participants gain insight into their current viewpoints on leadership topics, identify areas of growth and use the knowledge gained to develop advanced leadership skills.

The Most Complete Pathology Informatics Education Program You Will Find

Take the lead to improve lab productivity and move your lab to the next level with this unique self-paced online certificate program. The program is designed for individuals participating in laboratory informatics initiatives to enhance quality diagnosis, throughput and patient safety.

A JOINT COLLABORATION BETWEEN ASCP AND APF

The Best Training Resource in Laboratory Management Today

Created for pathologists, residents and laboratory professionals, LMU is a customizable program for individuals planning on moving into management positions or seeking to advance their management skills.

In Practice

Technologies and techniques
Quality and compliance
Workflow

30–33
A Call for Color Calibration

Digital imaging is the way of the future, but those images are of little use without accurate color representation.
A Call for Color Calibration

Why digital slide scanners must be correctly calibrated to yield trustworthy results

By Richard Salmon

Many laboratories are moving into digital imaging – scanning slides, viewing them on computer monitors, and using software-based tools to assist with analysis. But there’s an understandable hesitation from some pathologists, who ask: “How can we be sure that the digital image we see is truly representative of the slide?” In particular, with histopathology’s need for accurate staining, how can practitioners be assured that nothing is being lost or inaccurately represented in the digitization process?

Guidance from the US Food and Drug Administration (FDA) has recommended color calibration for whole slide imaging (WSI), just as it does for many other digital systems. There is substantial variation in color between digital slide scanners, a fact the FDA recognizes, and standardization of color can increase the validity, reliability and quality of WSI.

Color calibration seeks to ensure color fidelity throughout the imaging process. The goal? To provide the pathologist – who may be looking at an image scanned in their own lab or one scanned a lab across the globe – with the confidence that the colors they see are representative of the true colors of the tissue sample and are not altered by the scanning process. This gives pathologists confidence that they are working from ground-truth data.

But what exactly is color calibration – and why should we trust it to provide a true representation of tissue slides?

Bringing color fidelity to biomedical imaging

Digital pathology scanners (often referred to as WSI scanners) are computer imaging devices for the in vitro examination of biopsy, cytology, and tissue specimens. They are capable of all sorts of tasks – scanning, digitizing, compressing, storing, retrieving, and even enabling the viewing of high-resolution, high-magnification digital medical images. Most pathologists are aware that digital pathology has only recently come into its own (go back 10 years and it was far less common than it is today). Histology laboratories have shown reluctance to move away from the age-old microscope and into the digital space. Why? At least in part, their hesitance was due to the absence of color fidelity regulation and image quality assurance in WSI systems.

Global transition to WSI systems has been gradual, with key regulatory bodies, such as the FDA, requiring better color fidelity alongside other factors that determine diagnostic reliability. In addition, the FDA believes that software analysis of images from WSI systems will be very important in the future and has therefore indicated that the analysis

At a Glance

- For histopathologists, it is vital to ensure that digital images of stained tissue accurately represent the original slides
- Color calibration for whole slide imaging can verify accurate color representation
- Calibration is a complex issue, especially given the variations between different scanners and imaging software
- A physical, slide-based device may offer a good approach to universal calibration

"Histology laboratories have shown reluctance to move away from the age-old microscope and into the digital space."
Figure 1. Different color representations of the same alcian blue-stained WSI scan. On the far left is the original image with no color correction; the three images to the right show the same scan with different color profiles applied. Images were captured on the same 12 MP camera, either from a calibrated monitor or down a microscope eyepiece. The act of digitally representing data such as this suffers from the paradoxical lack of color management for “truth” with the chosen digital medium; however, the use of the same camera for all figures is the closest available control.
software should be treated as a separate module in the medical approval process (1). And that is only achievable if the colors in the image being analyzed are consistent and correct from one version of the same WSI system to another, and from one vendor’s WSI systems to those of another.

But color calibration and standardization is complex. A significant degree of color variation exists between different WSI systems, and the method by which WSI systems observe color is different from the way the human eye does. All of this means that images need to be processed to interpret these differences.

The path to standardization
How can we ensure that the colors of scanned specimens are the same when digitally presented to a pathologist as when viewed down a microscope? And how can we ensure that those colors are the same regardless of the systems on which they are scanned, stored, and viewed?

To make sure WSI systems produce images with an accurate replication of the stains used, one approach the FDA suggests is color management using a unique slide-based device. The FDA’s WSI guidelines (1) state, “The WSI system should be tested with a target slide. The target slide should contain a set of measurable and representative color patches. Ideally the color patches should have similar spectral characteristics to stained tissue.” The document also describes the need to create three datasets: truth, intended color, and output color – a responsibility that I propose should lie with both the vendor (to ensure that products are accurately calibrated prior to market) and the user (to ensure that systems remain calibrated and validated for ongoing diagnostic accuracy). Essentially, this means obtaining a measure of the “true” color of a stained sample and comparing it with the output of a WSI device to identify the device’s effect on color representation through the digitization process.

Creating a “truth” dataset is critical to the whole process and requires the use of specialist equipment calibrated to internationally accepted standards. Of equal importance is the precision of the color profile this calibrated equipment generates, which is why color calibration specialists work to International Color Consortium (ICC), Commission Internationale de l’Eclairage (CIE), and ISO standards.

What difference does it actually make? Color calibration to device-specific ICC standards takes WSI scan fidelity to another level. Figure 1 shows an alcian blue-stained tissue section as viewed down the microscope alongside three different representations of the same scanned image on the same calibrated display monitor. The first corrected image is from a scanner with only standard white balancing applied – a color correction that is likely to vary between scanner models in relation to differences in illumination source. The next is shown with only RGB standard values applied. The final image displays the tissue with the scanner-specific ICC color profile applied. The color shows clear variation in intensity across all three images. Applying the RGB profile improves the color representation of the scan; however, it can’t compare with the improvement obtained by applying the ICC color profile, which most closely matches the original tissue as viewed through a microscope.

Looking to the future, applying ICC color profiles to WSI technology will also aid in the application and validation of artificial intelligence (AI) algorithms for automated diagnostics. The algorithms are then able to create, make decisions on, and work from data files to process digital pathology images across disparate locations and scanner types. For AI algorithms to be universally applicable and medically reliable, we will need rigorous validation and quality assurance of images fed into automated diagnostics – including stringent control of color management to ensure image fidelity. The application of color management using a slide-based device has proven its potential for ubiquity across WSI platforms and offers a subtle and integrable solution to this “pathology of digitization within digital pathology.”

Richard Salmon is Product Manager – Life Sciences at FFEI, Hemel Hempstead, UK.

References
As tumor profiling using DNA sequencing rapidly gains importance in pathology, more laboratories are adopting NGS and more pathologists are looking to NGS data to deliver precision medicine in their clinical reports. However, adopting NGS is not easy. Avoid the pitfalls. Know best practices. Attend our eSeminar Series:

Unlocking Precision Medicine: with NGS Tumor Profiling – From Sample to Report

The future is now for NGS and pathology. Are you ready?

1: NGS wet-lab workflow guidelines
Unlocking the FFPE block upstream and building confidence in downstream data

2: Demystifying big data in NGS cancer pathology
Bringing state-of-art data interpretation and reporting within reach of routine pathology labs

3: The next generation in NGS Data Analysis
From data analysis basics to unleashing your inner informatician

Register Free at:
https://thepathologist.com/agilent/
Watch This Space!
How can we predict which lung cancers may recur and which won’t? Examining the spatial arrangements of tumor-infiltrating lymphocytes may yield insight.
Patients with early-stage lung cancer have a head start from a diagnostic point of view. But once their disease has a name, it’s important to press that advantage by giving them the right treatment as soon as possible. However one of the critical problems in early-stage lung cancer is predicting whether or not patients will benefit from aggressive chemotherapy. In other cancers, predictive assays allow clinicians to identify which patients will receive added benefit of more aggressive chemotherapy; unfortunately, there are no such tests for lung cancer – the most fatal cancer worldwide. My colleagues and I recently discovered that the arrangement of tumor-infiltrating lymphocytes (TILs) is a prognostic signature of early recurrence in early-stage lung cancer. Subsequently, we developed an automated technique that uses their spatial architecture to predict patient outcomes.

Looking into space
Much of my career has involved linking computer-aided diagnostics with digital pathology, including the application of methodologies and algorithms for the analysis of digital pathology slide images. Over the last 8–9 years, our focus has shifted a little; we wanted to move away from using computational pathology as a form of decision support for the pathologist, and instead explore how computational pathology could play a direct role for the clinician. More specifically, we wanted to help oncologists modulate therapy and manage patient treatment. At the moment, we are attempting to use computational algorithms in conjunction with digital pathology images to find predicting the chance of disease recurrence is vital; up to 55 percent of patients relapse within the first five years.

At a Glance
• The number of tumor-infiltrating lymphocytes (TILs) is associated with patient outcome in early-stage lung cancer
• A new automated method uses the spatial arrangement of TILs to predict which early-stage patients will benefit most from chemotherapy
• The prognostic signature separates patients by risk of disease recurrence and uses a deep learning approach to analyze digital pathology images
• Predicting the chance of disease recurrence is vital; up to 55 percent of patients relapse within the first five years

“We developed an automated technique that uses [TIL] spatial architecture to predict patient outcomes.”
patterns that inform us about the aggressiveness of disease. We hope that these will ultimately help us predict potential responses to therapy. In this respect, our goal has evolved from merely supporting the pathologist to striving to develop companion diagnostic tools for disease risk stratification and treatment response assessment, making decisions easier for the oncologist.

I've been particularly interested in the concept of spatial nuclear architecture for a long time, especially in the context of grading breast and prostate cancer. The idea really took off when we started looking not only at the shape and number of immune cells, but also at how their spatial arrangement and architecture could be used to improve the grading of breast and prostate cancer, and therefore benefit the pathologist. It's already well known in lung cancer that TIL number plays an important role in determining prognosis and treatment response. But, because there is a subjective element to the manual counting of TILs, the challenge has always been trying to address issues with inter-reader variability. For that reason, the first ambition of our project was to use the spatial architecture of TILs to aid pathologists in counting. In addition, we also wanted to use the spatial arrangement of features to forecast prognosis and disease recurrence in early stage lung cancer patients.

It turned out that spatial arrangement was extremely important; in fact, significantly more so than the manual enumeration of TILs. These features clearly separate the patients who are at high risk of disease recurrence (and who would therefore likely benefit from adjuvant chemotherapy following surgery) from those who are at a lower risk of recurrence and may not need adjuvant chemotherapy. The spatial architecture of TILs was prognostic in every one of our data sets, providing good validation of our initial hypothesis that arrangement and architecture are critical.

Dipping into deep learning
At the moment, deep learning is the go-to technology for many aspects of digital pathology. We used targeted deep learning to find the TILs and cancer nuclei initially, but the subsequent spatial features and architecture were captured using a non-deep learning methodology known as a handcrafted feature approach (which we adopted to imbue some domain knowledge into the process). One of the most critical aspects to me as a bioengineer is that there has to be feature and model interpretability; there has to be some degree of intuition built into the classifier. That's why, for me, the most satisfying part of this research is that it resonates with something we already know about morphology of the disease: that TILs are important.

I believe this combination of transparency and intuition is going to be a critical facet of clinical adoption. One of the challenges with deep learning is that, sometimes, it doesn't quite provide that transparency, and I have my concerns that a lack of intuition and interpretability could potentially impede clinical adoption. Before clinicians make a call as to whether or not chemotherapy is needed, they are going to want to know exactly what's "under the hood." And that's why I find our approach so satisfying – because it

“It turned out that spatial arrangement was extremely important; in fact, significantly more so than the manual enumeration of TILs.”
resonates with what we know about the domain and has intuitive appeal.

A vital aspect of the success of our test lies in making it simple for the end user – the oncologist. In essence, we’re providing a risk score that gives the oncologist easy access to clinically actionable information, so we want to minimize the need for training and learning.

Space for progression
We’ve already established that we have a prognostic signature, and we believe that it will be validated in the future as predictive of the potential added benefit of adjuvant chemotherapy. We are striving to begin clinical trials that will look at patients previously treated with surgery or surgery plus chemotherapy. Of those who were treated with surgery, we want to show that we can identify which patients had a higher risk of recurrence and would have benefited from adjuvant chemotherapy. Additionally, of the patients treated with surgery plus chemotherapy, we will attempt to identify the low-risk patients who may not have needed chemotherapy.

I think the signature also carries significant implications for other therapeutic modalities. There is currently a great deal of excitement surrounding immunotherapy, and there has been much interest in trying to understand

“We’re providing a risk score that gives the oncologist easy access to clinically actionable information.”
whether patients who have more TILs will exhibit a better potential response to immunotherapy than those with fewer TILs. We have managed to show that the TIL spatial arrangement signature from diagnostic biopsy images also predicted how well patients would respond to immunotherapy. Taken together, these results suggest that our prognostic signature could help identify not only patients who stand to benefit from adjuvant chemotherapy, but also patients who stand to benefit from checkpoint inhibitor immunotherapy for lung cancer.

In terms of a timeframe for our vision, I believe we have a good shot at deploying in clinics within 18–24 months. Once we have managed to prove that our prognostic signature is predictive, we must obtain regulatory approval from the US FDA. The beauty of our approach lies in the fact that we’re not destroying any tissue because we only use digital slides, so our validation studies shouldn’t be too time-consuming. Indeed, we believe the technology can be approved via a somewhat less onerous regulatory pathway.

Going global
The fact that our concept potentially spans multiple different disease indications is very appealing. Joel Saltz and his group from Stony Brook recently wrote an excellent paper that looked at the spatial location of TILs within the tumor and stroma, and found that TIL position was prognostic across multiple types of cancer. In cancers such as ovarian cancer and triple negative breast cancer, the role of TILs has been linked with disease outcome and prognosis. Therefore, although we’ve developed the signature using lung cancer, we absolutely intend to apply and validate it across multiple disease stages and sites. For me, the most exciting part of this research is that it demonstrates the possibility for finding sub-visual signals and patterns in routinely acquired hematoxylin and eosin (H&E) stain slides, which could help guide pathologists and oncologists in the future.

Although we’re working in a relatively new area of research, the impact that digital and computational pathology could have on global health is huge – and that’s very exciting. Expensive molecular companion diagnostic tests have a big market in Europe and North America, but large parts of the world are simply unable to afford these tests. Consider that, because our computational pathology approach can be carried out from an image alone, analysis can be performed for anyone with a specific cancer anywhere in the world. The local pathologist or oncologist would simply upload an image and analyze it with the algorithm to render a prediction – an immediate change to the way cancers are diagnosed, staged, and treated throughout the world.

Anant Madabhushi is the F. Alex Nason Professor II of Biomedical Engineering at Case Western Reserve University, and Director of the University’s Center for Computational Imaging and Personalized Diagnostics, Cleveland, USA.

References
2. X Wang et al., “Interaction of Tumor Infiltrating Lymphocytes and Cancer Nuclei Predicts Response to Nivolumab in Non-Small Cell Lung Cancer (NSCLC)”. Presented at the International Association for the Study of Lung Cancer’s (IASLC) 19th World Conference; September 23–26, 2018; Toronto, Canada.
Meet…
… the researchers overcoming the obstacles of bench-to-bedside research

Explore…
… the technologies and techniques driving robust, cutting-edge life science

Connect…
… with the scientists, engineers and clinicians, who work together to improve global health

Visit…
… www.thetranslationalscientist.com
Meet…

… the researchers overcoming the obstacles of bench-to-bedside research

Explore…

… the technologies and techniques driving robust, cutting-edge life science

Connect…

… with the scientists, engineers and clinicians, who work together to improve global health

Visit…

… www.thetranslationalscientist.com

42–45
Lessons Learned, with Andrew Feinberg
What has a decades-long career in epigenetics revealed about the nature, and the future, of the field?
Lessons Learned, with Andrew Feinberg

From Cornell to Westminster Abbey, Feinberg has traveled a compelling career path. Here, he describes his journey and offers his thoughts on the future of epigenetics.

The importance of collaboration

I started out as a kid interested in mathematics and computers. I took a year of college math at Cornell the summer after my junior year of high school, then worked at IBM Research after my senior year. I really thought that was what I’d end up doing. I never saw myself wanting to do biology and absolutely never thought about medicine, but, during my sophomore year at Yale, I picked up a catalog out of curiosity and noticed a five-year program at Johns Hopkins that led to a medical degree after only two years of university. I applied on a whim and, while working in France that summer (for IBM again), I received a telegram from my father saying that I had been accepted at Hopkins and he had sent in a deposit. There weren’t any discussions about it, and he said I could change my mind. But I thought it sounded good, and his judgment was probably better than mine at 19 – so that’s how I became a teenaged medical student.

Throughout my career, I’ve always had an instinct for finding really good teachers and collaborators, and I think that has been one of the most important advantages I’ve had. I had the good fortune of meeting eventual National Institutes of Health (NIH) director Bernadine Healy when she was a resident and I was a second-year medical student. She used to see me in the pathology lab, trying to learn to recognize tissues and diseases late at night, and she offered to tutor me through it. I just about managed to pass the course, which involved memorizing slides and subtle differences in tissues – a tough task for someone who can barely recognize peoples’ faces!

Another great colleague of mine was Sam Barondes, and it was with him in the late 1970s, as a postdoc, that I first thought about epigenetics. Together we worked on Dictyostelium, the slime mold; we were trying to solve the problem of differentiation to understand the fate of its cells. There are two types of slime mold cells: vegetative and sporulating. I figured out a way to achieve density separation of pre-spore and pre-stalk cells and label them differentially before reconstituting them into a vegetative state, or “slug.” When the cells differentiated again, we were amazed to see that they remembered their former identity. It was clear to us that they had some kind of “memory” of their future, which is an epigenetic trait, and this idea of epigenetic plasticity stayed with me throughout my research career. That’s the idea that eventually led me to conduct research into cancer epigenetics.

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

At a Glance

• Working alongside great mentors and collaborators enables different perspectives to combine, helping solve complex problems
• Epigenetics is a relatively young but rapidly evolving field that must be incorporated into the broader medical research picture
• The National Institutes of Health are one of the great triumphs of western civilization, but more funding should go to “high-risk, high-reward” projects
• Because of the strong relationship between early life exposure and what happens to that person later in life, it is important to take an integrated view of the life cycle

After medical school and some clinical training, I did a second postdoc in the early 1980s with Bert Vogelstein. We specifically tested the epigenetic hypothesis of cancer for the first time and discovered altered DNA methylation in human colorectal cancer compared with matched normal mucosa. As a Howard Hughes Investigator at the University of Michigan, I continued these studies. I found another great collaborator, Michael Debaun, a pediatric hematologist at Washington University at the time, and we set up a clinic for patients with Beckwith-
Profession

Wiedemann syndrome (BWS), a congenital disorder that leads to Wilms tumor of the kidney. We showed that loss of imprinting of IGF2 specifically causes pre-malignant lesions in all BWS patients with this abnormality, and half of them develop cancer – a 500-fold increase in risk. Without this epigenetic change, though, patients are not at increased risk. It was the smoking gun that showed that epigenetic changes can cause cancer even in the absence of genetic mutations.

My epiphany

I got a lot of skepticism for my early work on epigenetics, especially by conventional “hardcore” transcription factor researchers. However, my persistence in epigenetics and a lot of evolutionary biology study on my own resulted in what I like to facetiously call my “epiphany,” because it happened in Westminster Abbey. Prior to that, I had been trying to understand how epigenetics could contribute to understanding the puzzle of missing heritability of disease – that is, that common variants do not explain most of the genetic risk. I couldn’t work out how epigenetic traits were transmitted through many generations, which was a common view at the time, but ran counter to my studies of the powerful reprogramming in the genome we see for imprinted genes. I was in London with my son enjoying some of the sights when it occurred to me: maybe there’s a role for stochasticity in
human disease. It sounds like a scene from a movie, but I was standing in front of Charles Darwin’s grave in November 2009 because a sign outside Westminster Abbey announced that it was the 150th anniversary of *On the Origin of Species*. Next to Darwin’s grave is Isaac Newton’s grave, and you are not allowed to stand on it. Just above Newton’s grave is a plaque in honor of Paul Dirac, one of the founders of quantum theory in physics, which introduced stochasticity above conventional Newtonian physics. There was no such plaque in front of Darwin’s grave, and the absence caused me to realize that stochasticity could be important if the environment often changes. My idea was that multicellular, phenotypically complex organisms that evolve in a sporadically changing environment might develop genetic variants that themselves cause epigenetically mediated phenotypic variability. This would provide a selective advantage – for example, if organisms have a growth advantage in an environment with abundant nutrients, but then those nutrients become scarce for many generations, and then continue to switch back and forth between the two extremes. It occurred to me at the same time that this epigenetically mediated stochasticity could also underlie tumor cell heterogeneity, which is what had gotten me interested in cancer research years earlier in the first place. This idea would imply that there is a cellular mechanism for switching epigenetic stochasticity on and off, perhaps by the compartmentalization of large chromatin regions that contain varying degrees of intrinsic noise. This stochasticity could be helpful when cells need to change their phenotypic state, such as in the epithelial-mesenchymal transition in normal repair mechanisms after injury. However, they also might be aberrantly and constitutively reactivated in cancer, enabling the tumor to adapt epigenetically to a changing environment.

“Epigenetics stands right at the center of gene-environment interaction, and I believe it has a huge role to play in predicting and mitigating human disease.”

High risk, high reward

Epigenetics is a branch of genetics that I used to follow in its entirety, but now it has grown to the point where I just can’t keep up with all of it. I think it’s wonderful to live in a state of some degree of ignorance, because it forces me to keep asking questions. My response to that is to read widely and frequently, but also to be prepared for unexpected ideas to appear from nowhere, just waiting for me to grab them and start working through them – “How do I test it out? What do I do?” I find this process extremely exciting, but also a little scary – especially as grant reviewers generally want you to have a substantial amount of preliminary data before they will support your ideas. I understand why they take that approach and I agree with it; they have to make sure the money is well-spent and scientific rigor is upheld. However, I’m constantly grateful that the NIH also supports innovative research. The NIH is, in my view, one of the great triumphs of our government, and its contributions to humankind are incalculable. In its portfolio, I believe that “high-risk, high-reward” research is crucial; we should look for more ways to increase it, particularly in areas where individual institutes may not be able to fund some of the big trans-disciplinary ideas on their own and can collaborate with other institutes to identify potential breakthrough projects.

I also hope for epigenetics to be incorporated more formally into big human disease risk studies. Epigenetics stands right at the center of gene-environment interaction, and I believe it has a huge role to play in predicting and mitigating human disease. In the future, we might be able to make epigenetic predictions about everyday life; for instance, by determining what an individual’s diet should be to maximize health. Epigenetics is also important in viewing the life cycle in an integrated way. There is a strong relationship between prenatal and early life exposure and what happens to an individual later in life, and it may not be limited to a single generation. Most importantly, epigenetic diagnostics and therapy may be used to tailor environmental exposure, and to deliver precision medicine to both genetic and epigenetic targets to improve human health.

Andrew Feinberg is Bloomberg Distinguished Professor of Medicine, Biomedical Engineering, and Mental Health at the Johns Hopkins University School of Medicine, Baltimore, USA.
Efficient specimen identification with the Signature Slide Printer

The Signature Slide Printer by Primera Technology, designed for use in pathology and histology labs, significantly increases the lab’s efficiency while helping to reduce the risk of specimen misidentification by directly printing onto slides, even in color. It can easily be integrated into existing LIS or can be purchased as a standalone system. http://dtm-medical.eu
LVEM 25 Low Voltage Transmission Electron Microscope

The LVEM 25 is a perfectly suited instrument when it comes to imaging pathologic thin sections, providing well-contrasted and highly detailed images. The compact and easy-to-operate LVEM 25 is designed to be installed where electron microscopy is needed most, creating seamless and efficient workflows.

www.lv-em.com

FioNA™ – Fine Needle Aspiration Simulator from Sawbones

Sawbones Fine Needle Aspiration Simulator (FioNA™) helps physicians, medical students, cytotechnicians, and nurses practice and refine their fine needle aspiration skills. With FioNA™, users can now safely practice puncturing, aspirating material, and preparing cytology smears: procedures that today are commonly practiced without previous training experience and on live patients.

www.sawbones.com/fine-needle-aspiration-model-fiona.html

The Sapphire™ chip

Crystal Digital PCR is Still’s next-generation technology for absolute quantification of nucleic acids. Using cutting-edge microfluidic innovations, this technology integrates the Digital PCR process in a single consumable. With Crystal Digital PCR, the combination of powerful image analysis and intuitive visual inspection offers an unmatched level of confidence in the digital pcr measurement, yielding data you can truly trust.

www.stillatechnologies.com/naica-system/

Milestone SealSafe - Vacuum system for biospecimen management

Need a solution to improve your diagnostic results due to unpredictable pre-analytical? SealSafe is a vacuum system that provides the flexibility to receive specimens from the O.R. in fresh or in a monitored fixative condition. More standardization with no more exposure to formalin fumes! To learn more visit Milestone at USCAP.

www.milestonemed.com

We listened. We learned. Now we lead.

EKF Diagnostics has developed Quo-Lab, a semi-automated HbA1c analyser, in conjunction with industry experts to deliver a product that meets the requirements of NGSP certification and CAP EQA criteria. Quo-Lab is setting new standards in HbA1c measurement.

www.ekfdiagnostics.com/

Faster decisions with Olympus’ DP74 camera

The DP74 brightfield and fluorescence camera: 60 fps live imaging, 20.7 MP resolution, and faithful color reproduction. A smart Position Navigator keeps track of your location and returns to previous positions, an anti-whiteout function makes the live image instantly available after every objective change, and automatic adjustment for low-emitting fluorescent samples delivers rapid motion and clean still images.

www.olympus-lifescience.com
Analyze all key biomarkers for EGFR, ALK, BRAF, and ROS1 kinase inhibitors, and many more currently in clinical trials, from one sample, in one report, in 4 days.

It's time for Oncomine Dx Target Test—the right choice for your patients.

Immunology Diagnostic Service Update
How to incorporate new tests and technology, improve quality and accuracy and nurture relationships

With immunology diagnostic service updates that you can’t afford to miss, this unique one day conference will bring you together with your peers to focus on how to incorporate new tests and technology, improve quality and accuracy in your immunology service plus how to nurture relationships and improve clinical practice.

Book your place today and benefit from the chance to investigate:
- The practicalities of applying assays to new diabetes antibodies
- Lupus (SLE) Extractable Nuclear Antigen (ENA) Antibodies assays
- Should we stick with immunofluorescence or switch to new testing technologies?
- ANCA testing guidelines for vasculitis
- Ensuring accurate interpretation and validation of results
- Driving forward quality assurance and best practice in your immunology service
- What makes paediatric immunology testing different to adult services?
- What information and support do GPs need from immunology services?

For further details visit [www.sbk-healthcare.co.uk](http://www.sbk-healthcare.co.uk)

SPECIAL DISCOUNT FOR The Pathologist READERS:
Quote AL1926 and receive £110 OFF (This offer cannot be used in conjunction with any other offer.)
With the ongoing development of precision oncology and more and more biomarkers entering routine clinical testing, a true end-to-end IVD solution, consolidating everything into one streamlined workflow, is needed in more pathology laboratories. The Oncomine Dx Target Test, based on next-generation sequencing (NGS), is now available in Europe and offers just that—46 gene targets, including biomarkers associated with approved and investigative targeted therapies, all from one test, in one workflow, and in four days.

Among the biomarkers tested are not only \textit{EGFR, ALK, ROS1} and \textit{BRAF} but also \textit{cMET, NTRK1/2/3, RET, ERBB2}, and others, currently in clinical trials.

Based on technology proven in many clinical oncology research trials, such as NCI MATCH, the Oncomine Dx Target Test can deliver results from a minimal FFPE tissue sample with a success rate over 93 percent, which makes it suitable for routine patient sample testing.

It comes as part of a complete, end-to-end solution including bioinformatics and application service, so even if your laboratory has no experience with NGS, you do not need to worry about additional expertise. Our clinical application specialists team will take care of you.

\textit{Learn how your lab can enter the NGS era. Now, NGS is here for everybody.} [https://www.oncomine.com/dx/testing-methods-eu](https://www.oncomine.com/dx/testing-methods-eu)

\textbf{Oncomine Dx Target Test – an IVD NGS solution for every lab}

It’s time for Oncomine Dx Target Test—the right choice for your patients

Analyze all key biomarkers for \textit{EGFR, ALK, BRAF,} and \textit{ROS1} kinase inhibitors, and many more currently in clinical trials, from one sample, in one report, in 4 days.

\textbf{https://www.oncomine.com/dx/testing-methods-eu}
The Epigenomic Explorer

Sitting Down With… Benjamin Garcia, Presidential Professor of Biochemistry and Biophysics and Director of Quantitative Proteomics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, USA.
Congratulations on receiving the 2018 Biemann Medal for your contributions to elucidating the histone code! It’s an amazing honor. Every person who has received this award has been an incredible pioneer in the field and has made significant contributions. I am overwhelmed to have my name on the same list as theirs, and to continue deserving my place on that list, I feel that I must still achieve more!

When you said “it takes a society to raise a scientist” in your acceptance speech, what did you mean?

In any field – and especially in science – we achieve very little alone. To become independent, rigorous scientists with the vision to ask and answer important questions, we must be trained and mentored, supported and encouraged. I definitely couldn’t have become the scientist I am without that support. Even now, I’m not doing it alone; I have a fantastic research group with scientists at all levels and from all backgrounds.

Many minority groups are underrepresented in science. How can we change that?

As a young scientist, not seeing people like you at faculty level can be discouraging. It’s a catch-22. We don’t have enough senior scientists from underrepresented groups, so the next generation may not think it’s an achievable goal. I cannot change the whole field, but I can work hard to bring diversity to my own lab. Diversity isn’t just a worthy goal in its own right, but hugely beneficial to our work – the most creative and productive times in my group have been when the lab was at its most diverse.

Who have been your most influential mentors?

During my undergraduate studies at the University of California, Davis, I met Carlito Lebrilla, who has been an amazing mentor – from the first day we met right up to the present. I came into his lab as part of a summer undergraduate research program, knowing nothing about analytical chemistry; he engaged with me and held me accountable. I really felt that I was part of the group. He also introduced me to several well-known scientists who went on to become mentors to me, such as Jack Beauchamp, for whom I worked at Caltech. In graduate school, I worked with Donald Hunt, studying tandem mass spectrometry of complex biological mixtures. It was amazing to be around a scientist of that caliber – very few people have the vision he has. He is a great mentor and knows exactly how much flexibility and freedom to give you. By that stage, more was becoming known about histone modifications, but it was all bottom-up mass spectrometry looking at a few modifications at a time. I knew we needed to take a broader approach, so I applied for a postdoc in Neil Kelleher’s group. Neil is an incredible, infectiously enthusiastic scientist, and it was the perfect training with him – both in top-down proteomics and in running a group. Lastly, David Allis (Rockefeller University), who won the Lasker Award for his chromatin research, has been a collaborator, mentor, and friend for a long time as well.

Why did you choose to focus on histones?

Quite simply, because they are such amazing proteins. I’m fortunate that the fields of proteomics and epigenetics have taken off and I’m at the crossroads of both. But I didn’t have a master plan; I just kept studying what I was interested in, without thinking too hard about what would be “fundable” in future or whether I’d be able to build a career.

What upcoming projects are you excited about?

Fifteen years or more since the role of histone modifications in controlling gene expression was first suspected, we have certainly made progress, but there are still many unanswered questions. I’m excited about taking our fundamental knowledge and applying it to health and disease by reprogramming a diseased epigenome with small molecule inhibitors or histone-modifying enzymes. I truly believe that is a feasible long-term goal. I use the analogy of a computer: the computer hardware is your genome, but no computer works without the software to control it, and the epigenome is that software. If a virus infects your computer, you can often combat it by resetting the computer to its original state. I think we’re going to be able to do that in human disease states.

“The most creative and productive times in my group have been when the lab has been at its most diverse.”

What do you hope to achieve in your career?

I won’t judge my ultimate success on the scientific breakthroughs I make or the awards I receive – gratifying as it is to be recognized by my peers. Instead, when I look back on my career, I will judge myself on the impact I have had on others. Seeing those I have trained and mentored take their place as leaders across multiple fields would be more satisfying than any award I could ever receive.
Experience
The Power of Advanced Automation...

Designed to meet the needs of all IHC laboratories.
VALENT is a uniquely open and flexible IHC staining platform that provides ease-of-use, full automation, high-throughput, and the quality staining results your lab requires.

Unmatched Open System Versatility
The open design of VALENT supports the transition of your laboratory's custom IHC protocols to fully automated, walk-away workflows: saving valuable staff time.

High-Throughput Performance
VALENT breaks the 30-slide barrier with true parallel processing of 48 slides simultaneously, boosting laboratory throughput with minimal user interaction.

Learn How VALENT Can Automate Your Lab: biocare.net/pathologist

Biocare Medical is a global leader in solutions for cancer research and diagnostics. We provide world-class reagents and a comprehensive suite of advanced instrumentation for IHC, molecular and histology testing. Our advanced platforms of semi and fully-automated instrumentation are designed to meet every need from high throughput clinical diagnostics to flexible research requirements.

www.biocare.net  ·  Order Online 24/7  ·  800 · 799 · 9499