MAY / JUNE 2023 #90

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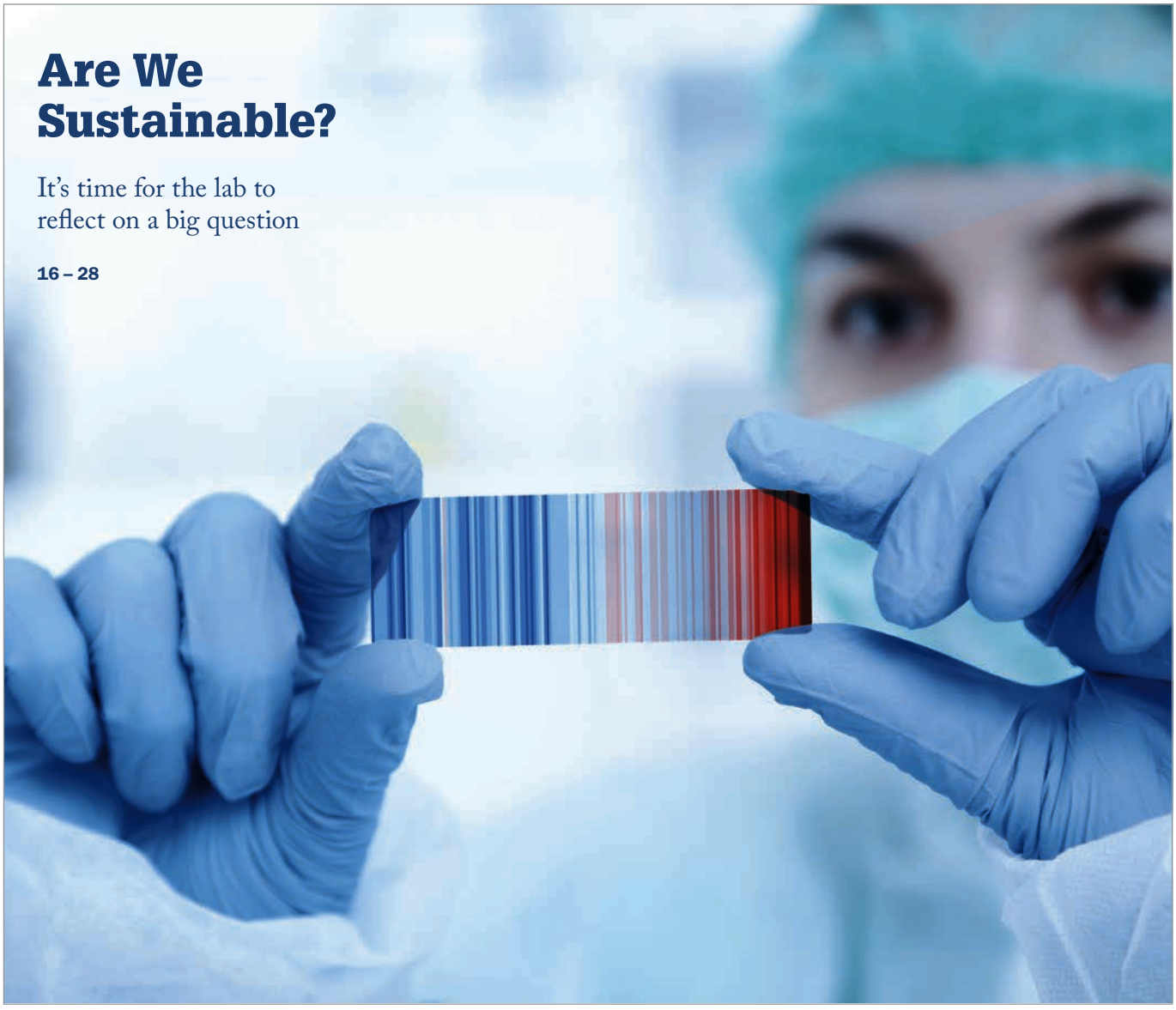

Are We Sustainable?

It's time for the lab to reflect on a big question

Reveal the Resistance

Let Hardy do the detective work

Carbapenem-resistant Enterobacterales (CRE) are a serious threat to public health. Carbapenems are generally administered as a last resort for treating infections caused by Gram-negative bacteria. Most available drugs are ineffective for treatment of CRE, limiting treatment options drastically. CRE have been associated with mortality rates of up to 50% for hospitalized patients. Hardy Diagnostics is committed to make it easy for you to screen for these dangerous bacteria.

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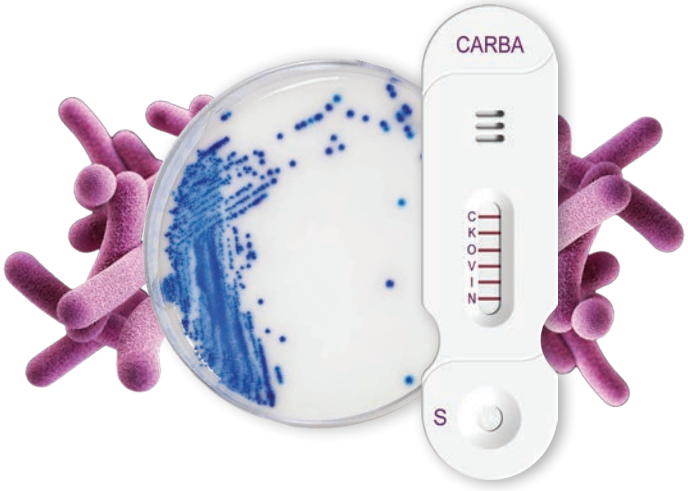

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The Impact of the Lab

Some words on laboratory life in the anthropocene

Those unfamiliar with warming stripes may have a question or two about the cover of this issue. This particular gradient of red to blue won't be like any H&E stain you've seen in the lab, but it is an image with growing popularity.

It's simple: each line of color represents the average temperature of every year since 1850. It doesn't take a meteorologist to spot the encroaching red waves crashing against the shore of the steady, blue status quo – the predictable climate that we depend on to make our planet habitable. It's a devilishly simple image that says – no, screams – we cannot go on as we are. Unfortunately, this temperature tapestry is already created; the only lines that we can influence are those that are yet to be weaved. It's this situation – over a century of inherited climate inaction – that inspired us to produce a feature focused on what we can all do to help make a difference.

Sustainability. It's a word we hear a lot, but what does it actually mean to be sustainable in the laboratory? Is it recycling pipettes? Switching off the lights? How much of the talk on sustainability is serious and how much is just spiel to make us feel better? How much impact does the lab, and healthcare in general, have on our world?

"Are We Sustainable?" This simple question frames content that aims to arm laboratory professionals with the knowledge to take action on climate breakdown and environmental collapse. Throughout this issue (and our extended online feature), you'll find interviews, how-tos, and deep dives on a variety of sustainability topics – everything from eco podcasters to a polemic on greenwashing.

For someone whose world has always been exposed to phrases like "global warming," "climate change," and "anthropocene," the future feels like an increasingly dreaded and uncomfortable thing – but the future is all we have. And I don't know about you, but when (or if) future generations can look back at this period of human history with a sense of hindsight, I'd much rather go down as one of the people who tried to make a difference in my very short stint on this planet.

It's my hope that, with the knowledge and insight found throughout this feature, we can all at least answer the title question. Are we sustainable? Perhaps not. But we can be.

George Francis Lee
Deputy Editor

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Discussing sustainability in the lab
Credit: Shutterstock and Wikimedia Commons

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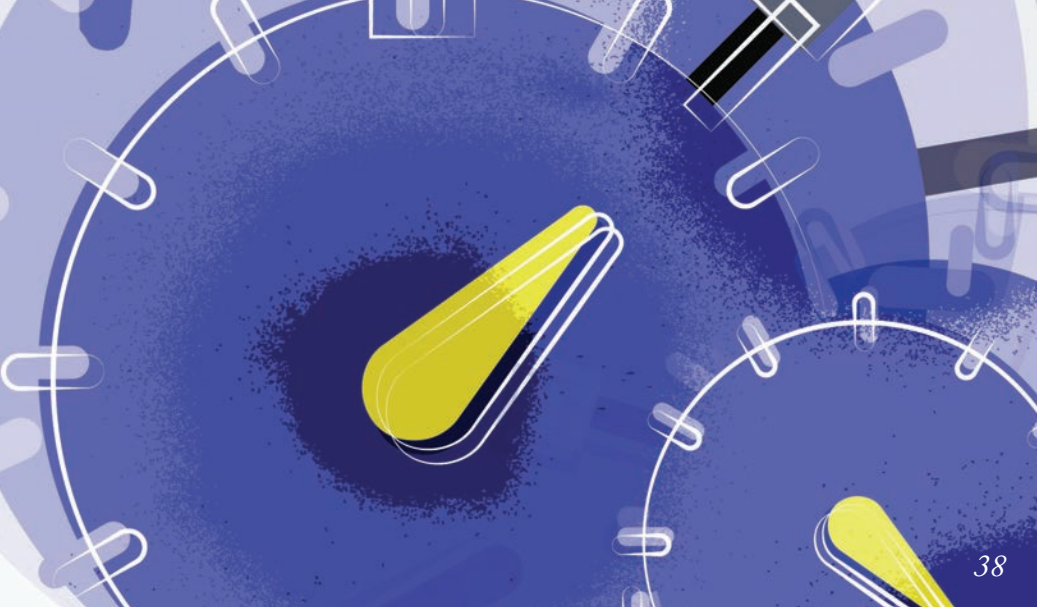

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the Pathologist

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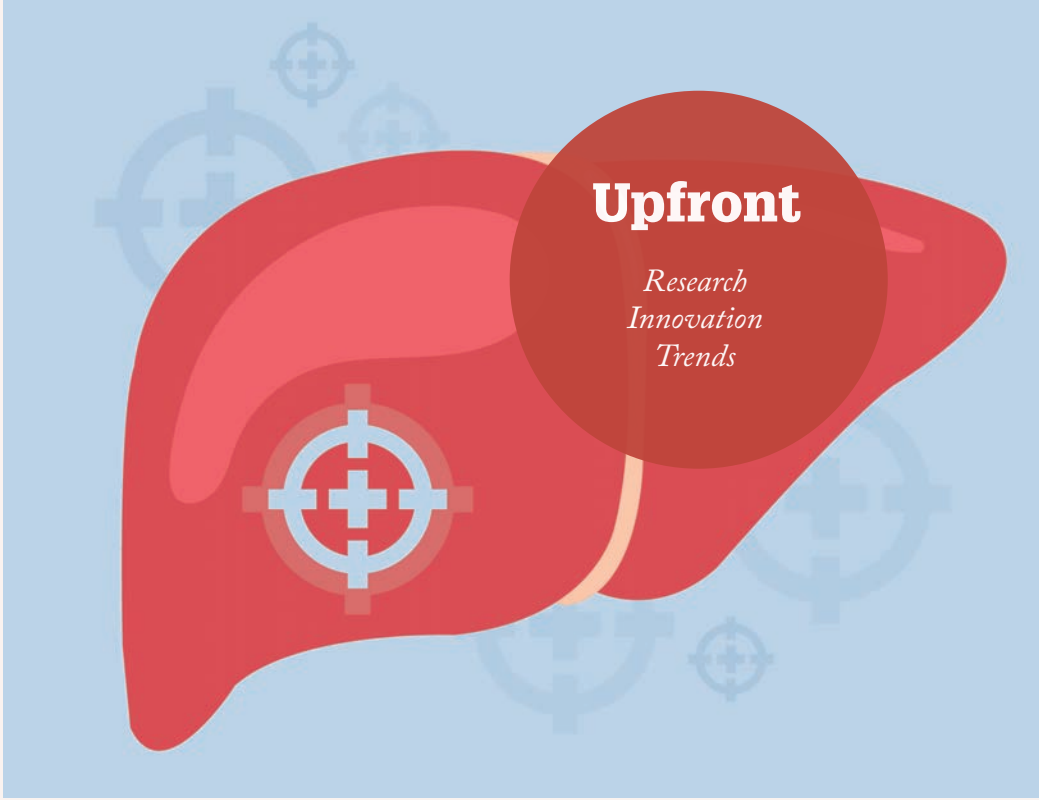


Changing the Narrative

A new clinical target to blunt HCC onset?

Hepatocellular carcinoma (HCC) – the sixth most common cancer type worldwide – is closely associated with environmental and metabolic stressors, such as obesity, type II diabetes (T2D), toxicant exposure, and viral hepatitis. These factors can trigger endoplasmic reticulum stress, and subsequent hepatocyte death – leading to non alcoholic fatty liver disease (NAFLD), including nonalcoholic steatohepatitis (NASH).

"The prevalence of global obesity and T2D has attained the status of a global pandemic," says Feng He, lead author of a study conducted by the Shanghai University of Traditional Chinese Medicine and UC San Diego School of Medicine that has investigated the role of activating transcription factor 4 (ATF4) – a protein historically associated with cancer cell growth (1). But, while investigating the function of ATF4 in NAFLD progression, the team were surprised to discover that it protected the liver against hepatocyte death and tumor formation – making it a potential clinical target for preventing HCC development.

In the study, ATF4 deficient MUP-uPA mice and control mice were fed a high-fat diet to promote NASH-induced HCC. Researchers found that the ATF4 deficient mice had livers littered with surface nodules, increased hepatocyte damage, and necroinflammatory injury – ultimately resulting in advanced liver cancer. Most importantly, they discovered that ATF4 was key in activating SLC7A11 expression – a protein involved in maintaining hepatocyte homeostasis and suppressing ferroptosis, an iron-dependent cell death. In short, ATF4 deficiency enhances the chance of stress-induced ferroptosis and liver tumor formation. The researchers also concluded that the amounts of ATF4 and SLC7A11 were positively correlated in human HCC and livers of NASH patients.

"Developing accurate cancer models to truly mimic human cancer characteristics is always a challenge," says He. However, the research successfully opened new avenues for cancer prevention, and in the future, He aims to not only explore the potential of ferroptosis inhibitors, but also hopes to "uncover the threshold of ATF4 in its function from a cancer protector to a cancer promoter and develop small ATF4 modulators that could be optimized for cancer prevention and cancer treatment."

Reference

1. *F He et al., J Hepatol [Online ahead of print] (2023). PMID: 36996941*

INFOGRAPHIC

Tips for a Sustainable Lab

We talk a lot about making the lab more sustainable, but how do you actually do it? Here's a list of obtainable and scalable tips to lessen your laboratory's impact

Use a fume hood… And close it!

- Encourage thoughtful fume hood management
- Offer points and prizes for departments that achieve goals

Get organized

Collaborate with other eco laboratory professionals. Find like-minded people, meet and discuss barriers and solutions, and try to put pressure on management together.

RESEARCH ROUNDUP

From environmental bacteriophages to cap snatching viruses, we bring you the latest news in infectious disease

Flipping the script.
A study has found multiple areas of concern in profiles of quaternary ammonium compounds (QACs) – a frequently used antimicrobial. Researchers discovered that exposure not only has chronic toxicological effects for vulnerable aquatic organisms, but also has a number of respiratory, immunological, and dermal implications for humans (1).

Making a splash.
Researchers have conducted *Typhi*-specific bacteriophage surveillance in surface water bodies to identify typhoid endemic settings. The low cost tool proved there was a strong link between the presence of *Typhi*-specific phages in the environment and the burden of typhoid fever. The team hopes that environmental bacteriophages can be leveraged for the future collection of data on disease burden (2).

In it for the long run.
New evidence reveals that mRNA vaccines initially produce higher neutralizing antibody (nAb) responses compared with the adenovirus-vectored vaccine, Ad26.COV2.S. However, after a period of six months, follow-up investigations revealed that patients who received the Ad26.COV2.S vaccine showed an increase in neutralization and, overall, had more nABs (3).

Breathe in, breathe out.
Cavity-enhanced direct frequency comb spectroscopy – a novel laser-based technique – has successfully detected SARS-CoV-2 in real-time by identifying volatile molecules in exhaled breath. The researchers hope that the non-invasive method can identify other medical conditions – particularly those with respiratory, gastrointestinal, or metabolic origin (4).

No cap.
Researchers have discovered that the enzyme MTr1 is essential for influenza A and B replication. In a process called "cap snatching," the virus hijacks the cellular RNA molecules of MTr1 for its own replication. The team also found that trifluoromethyl-tubercidin (TFMT) successfully inhibits MTr1 in human lung explants, providing a potential molecule for the treatment of influenza (5).

See references online at: tp.txp.to/0623/whats-new

A Sweet Solution

How altered levels of N-acetylglucosamine and tau protein can detect the development of Alzheimer's disease

A type of sugar molecule – bisecting N-acetylglucosamine (GlcNAc) – could help predict early onset Alzheimer's (1).

233 dementia-free patients were randomly selected from the Swedish National Study on Aging and Care in Kungsholmen. Blood samples were collected between 2001–2004, and the cohort was regularly monitored for signs of memory loss or presence of dementia for a total of 17 years. Both bisecting GlcNAc and t-tau levels in the blood were analyzed at the start of the study and then again six years later.

The team found that GlcNAc was strongly linked to blood t-tau levels, especially in individuals who later developed AD. Further, participants with an intermediate tau/bisecting GlcNAc ratio – compared with participants with a high or low ratio – were twice as likely to develop AD. Although tau and bisecting GlcNAc could not successfully predict AD individually, their combined power – plus APOE gene status – give a boost to diagnostic power.

See references online at: tp.txp.to/0623/sweet-solution

Be smarter about your energy use

- Set timers to turn off machines during downtime
- Use motion-detecting lights
- Shut down computers after use

Check your freezers

ULT freezers see heavy use in the lab. Therefore, they need regular maintenance and checks to ensure energy efficiency.

- Check seals for damage
- Install digital thermometers

Tell your suppliers that you want change

Nothing speaks louder than cold, hard cash. Tell your suppliers that you're looking at alternative sources that use less packaging and promote sustainability. At the same time, research competitors who are willing to accommodate the needs of their customers.

A Breath of Bad Air

How exposure to air pollution causes dormant cells to form tumors

Credit: Wim van 't Einde / unsplash.com

Since the industrial revolution, increasing levels of emissions in our immediate and global atmosphere have, unsurprisingly, had a detrimental impact on our health. But what is surprising is how exposure to these emissions drives the formation of lung cancer. According to the authors of a new study, it is the inflammation caused by air pollution that causes naturally dormant mutations to "wake," activate, and develop into tumors (1).

"These rare cells are normally dormant," says co-author Clare Weeden, researcher at the Cancer Evolution and Genome Instability Laboratory, The Francis Crick Institute, London, UK. "But inflammation triggered by air pollution inhalation wakes them up and increases their likelihood of forming tumors." Interestingly, in the team's experimental model, they found that if inflammation was blocked during exposure to air pollution, tumor development was avoided.

The paper focused on cases of *EGFR*-driven lung cancer – particularly people who have never smoked. "About 10–25 percent of lung cancer cases worldwide occur in people who never smoke," says Weeden, "We have changed how we view lung cancer in people who never smoke and identified one way in which cancer can be triggered in this group – through air pollution exposure."

The team found that air pollution interacts with what they call a "tumor promotion" mechanism – something that was first hypothesized in research of tumorigenesis over 70 years ago. Using mouse models, the team found that air pollutants lead to a deluge of macrophages within the lungs, which then release cytokine interleukin-1β. It's this process that "promotes" the generation of tumors, particularly within *EGFR* mutant lung alveolar type II epithelial cells. The researchers also revealed that *EGFR* and *KRAS* driver mutations were found in 18 and 53 percent of lung tissue samples from a study cohort, respectively.

The researchers hope their findings may lead to new options for cancer prevention – even point us towards a way to reverse tumorigenesis. "The mechanism we identified could lead us to find better ways to prevent and treat lung cancer in never-smokers," says Weedan. "Our next steps are to find who might be most at risk of this cancer and see if there are any novel therapies that might stop cells from growing in response to pollution."

Reference

1. *W Hill et al., "Lung adenocarcinoma promotion by air pollutants," Nat, 616, 159 (2023). PMID: 37020004.*

Midnight for Masks

Are face coverings effective against infection or is their time running out?

Three years into COVID-19, some are questioning universal masking as a necessary precaution. A recent opinion piece in the Annals of Internal Medicine suggests that, event though widespread masking across health care workers was justified, continued use is unnecessary. Masking in all instances, they argue, delivers dwindling returns and negative patient experiences. Moving forward, they recommend management to match other endemic respiratory viruses in healthcare settings.

The paper says future outbreaks and pandemics may see widespread mask use adopted again – but there is a need to educate everyone in healthcare on the rationale of changing policy. In light of the dynamic relationship between humans and infectious diseases – and with our developed understanding of SARS-CoV-2 since 2019, it is time to "deimplement policies," according to the authors. In short, the clock may have struck midnight for universal masking – but for how long?

Reference

1. *ES Shenoy, et al., Ann Intern Med (2023). PMID: 37068281.*

IMAGE OF THE MONTH

Passing Down Pathology

This month's image comes from the feed of Gary L. Keeney where he poses with his first-ever microscope – originally bought over half a century ago.

Credit: Gary L. Keeney Consultant and Professor of Laboratory Medicine and Pathology Mayo Clinic, Rochester, Minnesota.

Do you have a photo suitable for Image of the Month?
Send it to edit@thepathologist.com

QUOTE of the month

"Assuming white European genetics broadly applies to all can ultimately lead to patients being mismanaged."

Quoted from Chauhan's talk at the Genomics and Precision Medicine Expo, 24 May, 2023

One Drop Is All It Takes

Could a new multi omics microsampling platform "Amazonize" healthcare?

Researchers from Stanford University have developed a strategy that combines multi omic profiling from a series of blood samples with physiological measurements from wearable sensors (1). The approach relies on a microsampling device and 10 µl of blood to measure thousands of metabolites, lipids, cytokines, and proteins.

"This analysis gives a much clearer picture of a patient's immune function, inflammation, metabolic markers, and overall health," says Michael Snyder – Stanford W. Ascherman Professor of Genetics at Stanford and corresponding author of the paper. The approach could allow scientists to ask questions about the impact of lifestyle on health; for example, how the persistence of caffeine may correlate with sleep quality or how people respond to a nutrient shake. "Some people had a proinflammatory response and others had an anti-inflammatory response to the exact same shake," says Snyder. He believes that the strategy will lead to more large-scale biomarker discovery, monitoring, and health profiling.

See references online at: tp.txp.to/0623/one-drop

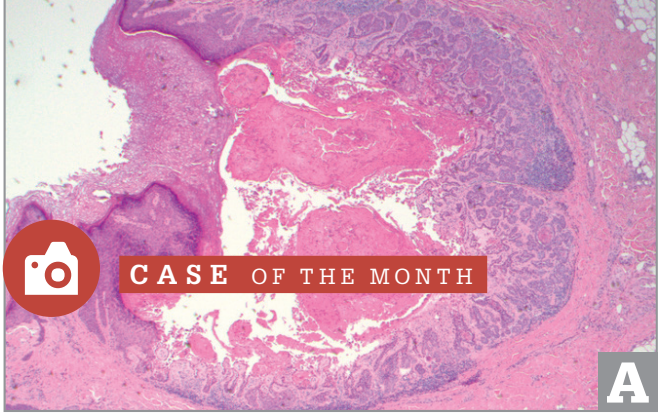


Figure 1. Skin, preauricular nodule, 10x.

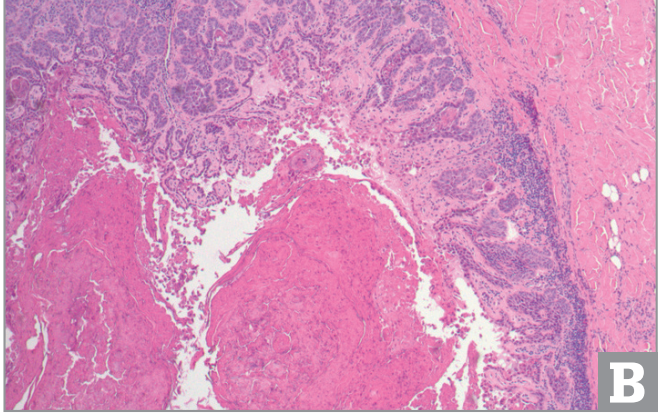


Figure 2. Skin, preauricular nodule, 20x.

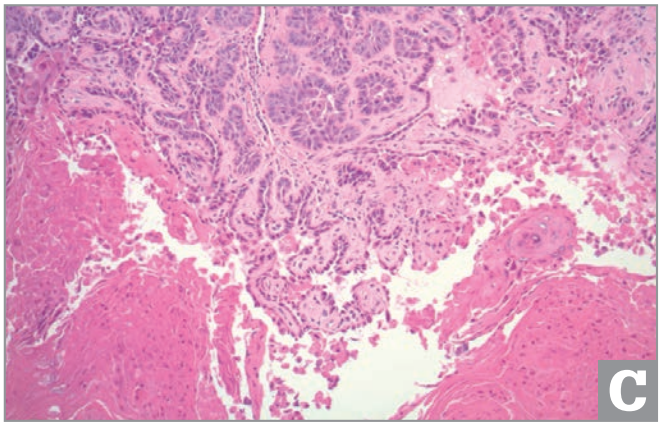


Figure 3. Papillary structures, 40x.

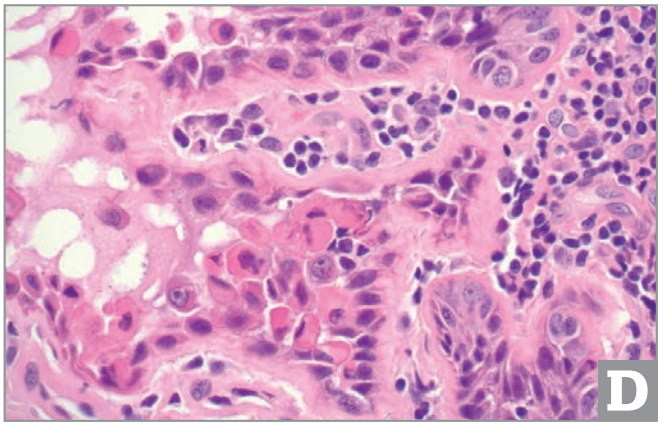


Figure 4. Dyskeratosis, 40x.

A 60-year-old male with a history of nonmelanoma skin cancer presents with a bothersome preauricular nodule.

Based on the morphologic findings, what is the diagnosis?

a) Squamous cell carcinoma
b) Warty dyskeratoma
c) Acantholytic actinic keratosis
d) Darier disease

Submitted by Megan C Smith, Vanderbilt University Medical Center, Department of Pathology, Microbiology, and Immunology.

Answer to last issue's Case of the Month…
d) Low-grade oncocytic tumor

Low-grade oncocytic tumor (LOT) of the kidney is a small, circumscribed, tan to brown solid tumor with or without cystic areas (Figure 1). Histologically, it shows compact nests, solid sheets, or a trabecular growth and is composed of bland oncocytic cells with round low-grade nuclei, usually with perinuclear clearing but without membrane irregularity. Often, it has characteristic sharp areas of edema where cells become discohesive, stretched out, or interconnected in short strands.

The nuclei characteristics aid in the distinction of LOT from oncocytoma, which lack a perinuclear halo, and from ChRCC, which have additional nuclear membrane irregularities. The immunohistochemical profile of diffuse cytokeratin 7 positivity with a negative to weak CD117 staining (only rare mast cells), typical of LOT, is also useful. Distinction from SDH-RCC, hybrid oncocytic tumor in the context of Birt-Hogg-Dubé syndrome, or ESC-RCC is generally possible on clinical and morphologic grounds alone, but further immunohistochemical or molecular studies could be warranted.

Submitted by Tiago Oliveira, anatomical pathology resident, and Dolores López-Presa, anatomical pathologist at Hospital de Santa Maria, CHULN – Lisbon, Portugal.

Extended answer and references online at: tp.txp.to/0623/case-of-the-month

To register your guess, please go to http://tp.txp.to/0623/case-of-the-month
We will reveal the answer in next month's issue!

Case of the Month is curated by Anamarija M. Perry, University of Michigan, USA.

Breakthrough in Evaluation of Brain Injury

How biomarkers are changing brain injury evaluation in emergency departments

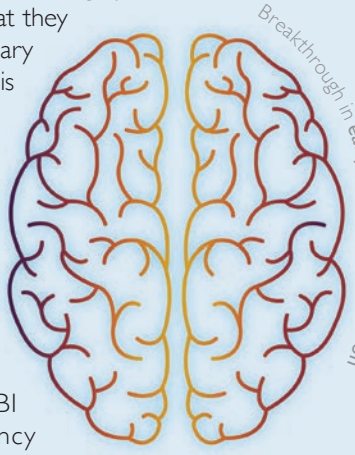
Insights provided by Gemma Álvarez and Martina Pavletić

In recent years, there has been increased interest in using biomarkers of brain injury for the evaluation of patients with mild traumatic brain injury (mTBI) in the emergency department. Many of you will be aware that mTBI can result from a blow or jolt to the head or body, which causes the brain to suddenly move inside the skull, resulting in a variety of potential symptoms, including headaches, fatigue, nausea, anxiety, and irritability. In some cases, mTBI can lead to post-concussion syndrome (PCS).

Currently, computed tomography (CT) scans of the head matched with Glasgow Coma Scale evaluation is the gold standard for evaluating mTBI patients in the acute setting. However, this method has two significant drawbacks. First, it is expensive. Second, approximately 90 percent of patients with mTBI show no tomographic finding (1–4), meaning that they are exposed to unnecessary radiation. Evidently, there is a need to integrate new diagnostic technologies in emergency departments to improve the evaluation and triage methods for the mTBI population.

Adoption and implementation of the use of biomarkers of brain injury for mTBI evaluation in emergency departments has resulted in practice improvements. Álvarez's practice, Hospital Universitario Virgen de las Nieves in Granada, Spain, treats an average of 15 TBI patients per day. Meanwhile, Pavletić's University Hospital Rijeka in Croatia treats between 3–5 TBI patients per day.

At Hospital Universitario Virgen de las Nieves, the use of biomarkers for mTBI evaluation has brought numerous benefits for patients, physicians, and emergency department administration. An objective test that can rule out mTBI not only increases the physician's confidence in making decisions that eliminate unnecessary pathways, but also provides reassurance to the patient. As noted above, the elimination of unnecessary CT scans reduces patient exposure to radiation and saves costs for the healthcare system. Since implementing TBI biomarkers, staff have tested 348 patients, 80 of whom a CT scan was not necessary. This has led to a reduction of unnecessary CT scans by 76 percent, and has saved €12,183. Time is also saved; before the introduction of mTBI biomarkers, the average emergency room wait time for a patient with mTBI was eight hours; now, patients with negative mTBI biomarker results are often discharged, dramatically bringing the average wait time down to three hours.



Similar improvements have been seen at University Hospital Rijeka since it became the first hospital in the region to use mTBI biomarkers. The most notable impact is on patient safety, as the blood test helps reduce scans (and therefore radiation) and prevents unnecessary medication and procedures – factors that are especially important for younger and older patients. Like Hospital Universitario Virgen de las Nieves, the use of biomarkers has also reduced the backlog of CT and MRI scan results, making the evaluation process more efficient for both the patient and physician.

There is a promising future for the use of biomarkers in the area of brain health. Blood biomarkers of the brain are fascinating because they can help us better understand brain injury and how to protect this most precious of organs. We believe that, in the future, the benefits of these blood biomarkers will see application in other fields, such as psychology.

Gemma Álvarez is a doctor who specializes in clinical analysis. She is a member of ibs. GRANADA, and head of the emergency laboratory at Hospital Universitario Virgen de las Nieves, Granada, Spain.

Martina Pavletić is Internal Medicine, Nephrology and Intensive Medicine Consultant, and Head of ED, CHC, Croatia.

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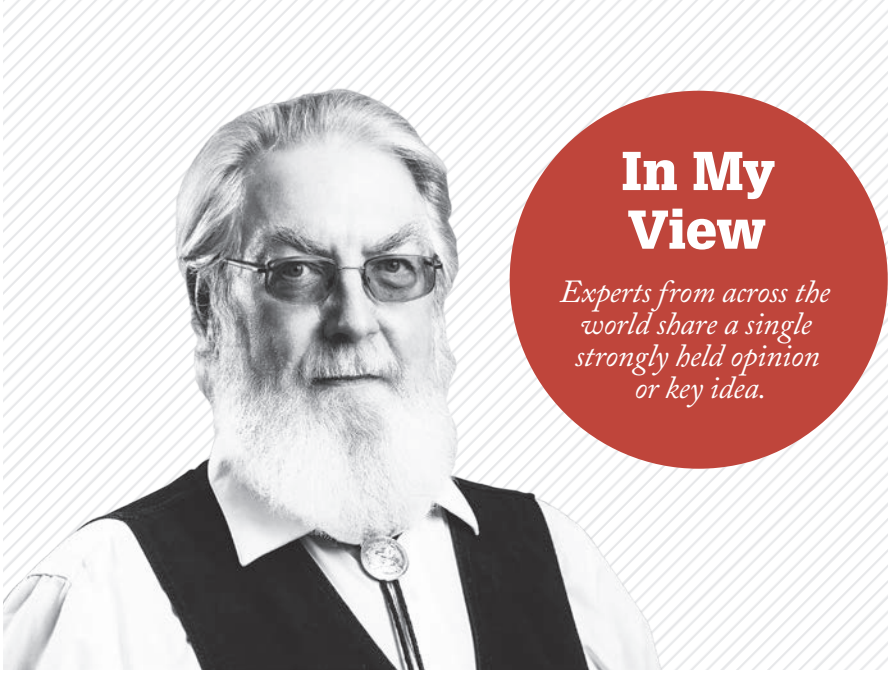

In My View

Experts from across the world share a single strongly held opinion or key idea.

"I Don't Get No Respect!"

What causes burnout in the lab? It all boils down to a single concept: general disrespect

By David Lynn Smith, retired medical laboratory scientist, Perryton, Texas, USA.

I worked in several non-medical labs before working in a hospital. Once there, I spent 30 years in two small hospitals in different states. In all that time, I never encountered a general disrespect like I did in those hospitals – a disrespect that manifested itself both directly and indirectly.

As a health inspector I could shut down entire kitchens for having no warm water to wash hands in. It's important, obviously, because there are germs. But in two hospitals over three decades I never had warm water to wash with. Disrespect. "It's just the lab," they'd say. Not as important as a fast food joint. The technical reason we never had warm water is because the lab was way down at the end of the line – at the end of all the infrastructure.

In any organization, you can measure your likelihood of reward or recognition as the inverse proportion of your distance from the boss' desk. Where is the lab? Down the hall, around the corner, turn left, ring the bell to enter.

Respect does not come from speed or precision of work, as we introverts would like to believe. The test that once took six hours now takes 60 minutes. And the doctor is demanding to know why it's taking so long at 30 minutes. You run a test and get 10.15 mg and the doctor asks you to rerun it and you get 10.16 mg, and they yell: "Well, which one is it?!"

Respect does not come from hard work. I don't know you, but I know you likely work outrageously long hours that could be considered medical malpractice. Truck drivers, like my father, were required by law to have sleep time; it's important to stay sharp. But medical staff are apparently not subject to the laws of biology. We are expected to display perfect performance in high complexity work – without sleep. Medicine is too important to acknowledge medical reality. The doctors assure us that, during training, they all worked six weeks straight without so much as a bathroom break or a single error. Uphill – both ways – so, we shouldn't complain… I once saw a patient nearly die of a simple kidney stone because a doctor was so drunk on sleep toxins that he failed to diagnose what the nurses and lab people saw – and said – was obvious.

But I can already hear the defenders among you decry: "But we have to work those hours because of staff shortages," and "Americans just aren't willing to do the job."

No! Don't allow that! Americans are unwilling to train for a difficult, high-stress, high-complexity job where they will be tantamount abused for wages lower than they can get elsewhere. That's not a moral failing, it's common sense. Immigrants and those from lower incomes work these jobs (and bless our lucky stars that they do) because their alternatives are probably worse.

I did on-the-job training for low wages for years until I was allowed to take the test. I passed it on the first go without going to school. To reflect that I'd become a certified medical technologist, I received a ten cent raise.

To repeat: respect does not come from working hard for long hours. You have probably witnessed it in other fields of work; think of the doofus who hangs around the boss all day and gets a promotion over the person who actually does all the work. It's PR. And hidden away in our windowless cave, where our only contact with other people is sticking needles in them, we don't have good public relations.

People think the hospital is one part doctors and one part nurses, because that's what they see on TV. The doctors draw the blood and do the X-rays and the nurses help them interpret the results. Meanwhile, the best that we lab rats might get is: "Are you one of those blood suckers?" Because phlebotomists, bless them, are all most people see of the lab. Even then, phlebotomy doesn't get respect either.

In truth, none of us ever really leave high school. The doctors are the football team, the nurses are the cheerleaders, and the lab is made up of the geeks and nerds who do their homework. We are the Rodney Dangerfield of the hospital.

So, short of retiring, what can be done? Get out of your cave. Sell yourselves to those above you. Use all the big words you know. You are impressive people. Make sure they know it. Why do you think the police insist on being addressed as "officer," judges as "your Honor," and my old colleagues as "doctor." It's because respect is not given. It's demanded.

Lucky But Not Recognized

Responding to our weekly newsletter, Mariia Ivanova shares her experience as a pathologist born in Ukraine but living and working in Italy

By Mariia Ivanova, Pathologist from Kyiv, Ukraine, currently residing in Milan, Italy.

I enjoy seeing the weekly newsletter from The Pathologist land in my inbox. Besides being full of helpful information and updates, it often raises philosophical questions – offering some food for thought to ponder throughout the day.

Normally, I consider myself a classic, well-mannered introvert – often confounded with extroversion – preferring to keep my opinions to myself, unless explicitly asked. But a recent newsletter titled: "Are You One in a Million?" struck such a chord in me that I had to hit reply. To my excitement, I got a response!

So, it's with great honor and gratitude that I exploit the opportunity to share my story with all of you.

I am not sure if I am one in a million, but an answer to "What unique circumstances are affecting the area you live in?" – well, that is pretty straightforward. I am Ukrainian. Most of you are probably aware of the horrifying events that have been ongoing in my country since February 2022. Fewer are probably aware that this war actually started in 2014 with annexation of Crimea and the instigation of an internecine feud in the east of Ukraine.

But let's talk pathology – because that's what this whole story is really about. Like many countries, Ukraine has always experienced a lack of pathologists and an unequal distribution of the ones that do exist. This is compounded by the impressive size of the country, which is over 233,062 square miles.

We must also acknowledge a persistent stigmatization of our profession. It's not uncommon to hear: "What do you do? Are you even a doctor?". Volunteering doctors (and pathologists too) have left their work and some have fled because their homes have been destroyed and their families were in danger. This is truly heartbreaking.

I was born in Ukraine's capital, Kyiv, into a family of medical doctors. That city – where I studied, graduated, and worked – will forever remain my homeland. In 2014, I was Vice-Dean in Kyiv's National Medical University – the same place I graduated from just a few years earlier. I personally welcomed and integrated hundreds of medical students that fled from destroyed Donetsk and Luhansk medical universities. These young students went on to complete their study in Kyiv several years later and became strong and successful healthcare professionals, but in a very particular way. I personally knew doctors – specifically pathologists – who were forced to leave their hospitals and university departments. We worked side-by-side in the pathology departments at the university and hospital. Some of them never came back to Eastern Ukraine. Some of them were forced to move further under different circumstances.

In 2015, I too moved further afield. But in my case, it wasn't as bad as it may sound.

The war had been going on for a year, but I hadn't fled. I had a good position in one of the biggest Ukrainian hospitals and biggest medical universities, but I started to feel stuck. So, after hearing of an international project on my subspeciality and PhD topic, renal pathology, I moved out from my home country. After that study, I received an offer to join a PhD project in translational research in kidney diseases (the topic of my second PhD), and then, I accidentally found myself married.

Today, I am still living and working in Italy. But there's a caveat; Ukrainian medical diplomas are not recognized in Europe and the US. As a Ukrainian doctor, you have to undergo a long, expensive, and complicated recognition procedure. Some have managed to do it. Some have not – holding out in the hope they might return to their homeland. Even I haven't managed to get recognition yet – despite my residency, an Italian PhD, and my strong desire.

But don't get me wrong; I am happy. I'm working in a fantastic team, doing translational research in oncology at the department of pathology – and in one of the greatest research facilities in all of Italy. But I'm not letting go of my hope to complete the MD diploma legalization process and get back to my professional origin (or, better said, make the most of it).

What I'm really trying to tell with my story is that, besides the lack of healthcare professionals and pathologists, those doctors who fled across the world are now "homeless" in so many senses. Set aside the often overlooked emotional component and imagine yourself in their shoes. You find yourself in a new place, with new rules, and little to no rights. You would like to work, do your job, make a living, and simply be useful – but you can't. For those like me in Italy there is some flexibility; in 2022, the country released a "temporary" recognition of MD degrees for Ukrainians who applied for political asylum. But there are too many nuances in the legislature.

To sum it up, there is an immense loss of resources across the world. Smart, trained, and hardworking people remain outcasts due to bureaucracy and political issues. While the planet declares a lack of certain specialists, professionals like me are prevented from helping to improve those statistics. Thousands of miles from my home, I'm told I can't do the work I was trained to do. And me – I consider myself a lucky one.

Pathology, Pandemics, and Preparation

Will we ever fully move out of the "pandemic mindset?"

By E. Blair Holladay

Not long after the start of the COVID-19 pandemic, pathologists and medical laboratory scientists were already discussing how to handle the next pandemic. It wasn't – and isn't – a question of if we would experience another pandemic – it is when.

That the laboratory played a critical role in the testing, diagnosing, and monitoring of COVID-19 is an undeniable fact. The ways we, as pathologists and medical laboratory scientists, interact with infectious diseases – from examining tissues and fluids of infected individuals, to identifying the root causes of the disease, to running and analyzing the tests that provide diagnosis and ultimately impact treatment – are critical to both stopping the spread of the disease and educating healthcare providers, public health officials, and the general public. The information the laboratory provides is invaluable when it comes to monitoring outbreaks – and potentially stopping more from happening.

There have been many important lessons learned since 2020, both in and out of the laboratory – one of the most significant being the understanding that, without the laboratory, the detriment and havoc that the COVID-19 pandemic brought about to the entire world would have been exponentially greater. What's important to note, however, is that, though the public health emergency of COVID-19 may be over, our role in the laboratory is not.

It's unclear whether any of us will ever fully move out of a "pandemic mindset." How we view healthcare has been forever changed and there is now strengthened emphasis on monitoring outbreaks of diseases in all corners of the world. As members of the laboratory, we understand that monitoring diseases is elemental in mitigating (or outright stopping) one from developing into pandemic proportions. As laboratory professionals who touch almost every patient who seeks care, we are the first line of information and defense when it comes to identifying potential threats, whether locally or globally. We are the ones who embrace our duty to stay informed, learn from the past and innovate for the future, so that we can continue to care for our populations.

Understanding the lessons we've learned from our most recent pandemic will help inform how we approach and lead during the next one. The laboratory's role cannot be underscored enough. If we do not step up to lead – both now and in the future – we do our patients and our health systems a disservice. The COVID-19 pandemic brought new and unforeseen challenges, but the laboratory rose to meet each one with skill and expertise. If – or rather when – we experience another pandemic, we will undoubtedly not only be ready for the challenge, but stronger together in the knowledge that we can lead the world through it.

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SUSTAINABLE?

Sustainability is a word said so often that it often has no meaning. What makes a sustainable lab? Is it even possible? And if it is – how do we do it? With global temperatures and mountains of landfill rising at equal speed, there's no time left to ponder.

We gathered experts to explain how anyone in laboratory medicine – you – can enact change. Big or small, physical or cultural, all kinds of changes are needed to lessen the lab's load on the planet. But before we have answers, we need to ask ourselves some serious questions.

Meet the Scientists Who Care

The hosts of The Caring Scientist: Mission Sustainable podcast give us a peak behind the microphone

By George Francis Lee

We often feel powerless. Politics, climate change, personal strife – perhaps a mixture of all three can keep us deflated. We live in an age where we are acutely aware of the powers above us and the things we cannot directly control. We can easily find out how bad things are – with almost infinite information readily available in our pockets. In this regard, knowledge can be a hindrance to one's health. It's not uncommon for caring, principled individuals to lose hope. When the world is on fire, the caring quickly become crestfallen.

In short, pessimism is abundant. But what's less so is action. It's in this void where Nikoline Borgermann and Adriana Wolf Perez forged The Caring Scientist: Mission Sustainable – a podcast that tackles the unavoidable unsustainability tied into laboratory work. Currently 17 episodes strong, the series has explored the experience of laboratory professionals who are all-too-aware of the impact that their work has on the planet. We sat down with the two founders – and the newest member of the team – learn more about their thoughts on sustainability.

What inspired you to start The Caring Scientist podcast?

Adriana: Nikoline was invited as a guest speaker on another podcast and really enjoyed it. Shortly after, the two of us met for the first time (on Zoom), and we clicked immediately through our shared passion for green labs. We wanted to do something together to raise awareness about sustainability in science, and we figured that a podcast might be a good way to do that!

Why should lab professionals care about sustainability?

Nikoline: Firstly, we're in a climate emergency. All sectors and areas of business must do what they can to reduce the climate impact of their activities. And that goes for labs as well. Secondly, labs leave behind a considerable climate footprint. It really isn't peanuts! We're consuming heaps of energy and water, and we are producing a great deal of waste. Most importantly, we are also consuming a wide range of reagents, chemicals, and equipment – and these things have a massive climate impact. We can't just lean back and point fingers at other industries – labs are part of the problem.

The sustainability focus seems to have somewhat shifted away from the actions of individuals and onto corporations… What are your thoughts?

Nikoline: This is a tricky one! We think it's great if people take individual actions, but, at the same time, it's important that we don't focus exclusively on "the small stuff." For example, when it comes to recycling, we can sort our waste perfectly but that does not mean that it will actually be recycled. This depends on the market, the plastic manufacturers, and the waste haulers' agreements. We need the corporations to reduce their use of plastic as much as possible, and we need them to take responsibility for the plastic they create. It should not be the responsibility of individuals, municipalities, and taxpayers alone to deal with the plastic waste problem. The same goes for other topics – corporations must do their part. The climate and ecological crises call for systemic change and collective action.

I was surprised to hear in one of your episodes that labs produce nearly two percent of the world's plastic – is that really true?

Nikoline: Well, no one has measured all the plastic waste coming out of labs! But, according to estimations based on numbers from The University of Exeter, labs did produce around two percent of the world's plastic waste in 2014 (1).

How much of the plastic use in labs is avoidable?

Adriana: It's important to note that labs are extremely diverse – both in terms of the research carried out and in terms of financial resources. In some labs, there's massive potential to reduce the use of single use plastics. Labs that are financially stable use more single-use plastics than needed. Some simple steps to sustainability include using the smallest possible plastic item that fulfills your needs, downscaling whenever possible, reusing single-use plastics (for example, non-sterile purposes), and using glass or multi use-plastics instead of single-use plastics. In our experience, labs that struggle with finances are generally very aware of these tactics and their resource use in general.

How important are skills like community-building, leadership, and communication in the sustainability journey?

Nikoline: Extremely important! Individual actions won't do the job – we need to act collectively. Also, we can learn so much from each other – in a green lab context and beyond – so it's important that we build networks and that we communicate. Leadership is also crucial. We must take bold and progressive decisions and set ambitious targets – despite not knowing exactly how to get to the end point of our sustainability journey. We simply don't have the time to map these things out before starting. The climate crisis is already here, and we must prevent "really bad" getting "a lot worse."

Is "slow science" an important part of making the lab sustainable?

Nikoline: Yes! Slow science would – in our opinion – solve many of academia's problems. Fast science is what we have now – where we value the number of publications and citations above all else. Currently, the quality of the research, teaching, outreach activities, and the leadership skills are (in the majority of cases) not taken into account when funding or tenure positions are given. Because of fast science, we're seeing serious mental issues in academia and a lot of salami science. Scientists are cutting corners to compete in a fast science world. Irreproducible science is an incredible waste of planetary resources.

What pitfalls should people be aware of when thinking about sustainability. Should we be teaching labs about greenwashing?

Nikoline: Two classical pitfalls are that waste sorting will increase sustainability efforts in the lab and that individual actions will fix the problems. It's great if you sort your waste but please don't stop there. We must reduce the amount of waste (not just sort it), and we must change how and what we consume. At the same time, we must engage with (and put pressure on) manufacturers to reduce the carbon impact of their products. The largest part of a lab's carbon footprint comes from the products that we buy – so clearly, waste sorting isn't changing much. Also, a third pitfall is to believe the manufacturers and vendors when they claim that their products are green. Very often, they have made only minor changes to the products or the packaging which doesn't drastically change the carbon footprint of the product. So yes, it would be great to teach labs about greenwashing. And green lab practices in general, of course.

I love the tips you share at the end of each episode. What are your all-time favorites?

Nikoline: That's a difficult one. We think it's important to combine tips for individual actions and tips that point to more systemic or collective changes. The latter are the most impactful ones, but it can be quite difficult and take a long time to see results – so it's important to combine these with individual actions that are doable and show results right away.

Adriana: One potential favorite is to start a local green group at an institute or center level. It's a really good way to find like-minded spirits with whom you can share ideas and frustrations. And it's easier to push for changes at the institute level, if you are a group.

If you only had someone's ear for 30 seconds, what would you say to encourage labs to start thinking about sustainability?

Adriana: It really isn't rocket science to take green lab actions – and there are many additional benefits! Among others, you can improve your health and safety, while saving time and money. Moreover, we are convinced that – with time – it will be difficult to attract students and staff – or receive funding, if you are not taking green actions in the lab.

Reference

1. *MA Urbina., Nature, 528 (2015).*

Meet the Team

Nikoline Borgermann

My background is in biochemistry and I have a PhD in genomic (in)stability from the University of Copenhagen. Despite enjoying the lab work, I never came to terms with the climate impact of science, so after a short postdoctoral, I began working as an independent, value-driven, green lab advisor. I now work two days a week at the University of Copenhagen as a sustainable labs advisor, and am active with the climate activist group Scientist Rebellion.

Adriana Wolf Perez

I am a biochemist by training, and hold a PhD in Nanoscience from Aarhus University, University of Cambridge, and Novo Nordisk. I have completed research on neuroscience and immunology and have a strong interest in research areas such as biodiversity, climate change, and the circular economy. I now work as a Program Manager and Course Coordinator at the University of Cambridge.

Greening Your Laboratory

How sustainable choices can save both the planet and your budget

By Andy Evans

In a former life, I was an equipment salesperson.

At the time, my focus was on selling premium brands – but my clients were interested in lower-cost items. It's understandable for laboratories to focus on cost savings, but I noticed that many of them were purchasing the same equipment over and over again. I wondered: Is the cheapest equipment really a bargain – or do you get what you pay for?

My investigation began with ULT (-80°C) freezers. A good ULT freezer will cost you about £300 ($350)a year to run in the UK, give or take a little to account for door opening. A cheap one can cost you double that amount! I brought that information to one of my clients – the University of Birmingham – and, within a year, we'd set our first framework agreement for ULT freezers. It was clear that spending a little more money at the outset led to significant cost savings over time. And that principle sits at the core of my work as a laboratory sustainability consultant. In short, I help labs simultaneously minimize both their running costs and their environmental footprints.

Lower costs, greener planet

Can the two coincide? We hear from a lot of labs that they'd like to "go green," but can't afford the expense. One of the big misconceptions about sustainability is that it's "extra" – something new to think about in addition to their usual purchasing criteria. In fact, sustainability means looking at every single cost in the lab and its knock-on effects – and then communicating those costs to the people who control the purse strings. Much of the time, the people who pay for utilities and running costs would contribute to a more sustainable option if they knew it was available. I work with all three levels of laboratory operators: the scientists at the coal face, the people in procurement, and the people responsible for paying the bills and managing the buildings and facilities. If you want widespread sustainability that has a real impact, you have to work with all three types of people in mind.

Recently, I think people have become more conscious of what they're buying. As a result, they're realizing that sustainable equipment tends to last longer and be easier and safer to use. And that, in turn, leads to a willingness to invest a little more upfront in an item with a longer lifespan and lower running costs. A laboratory requires up to 10 times more energy per square meter of space than an office building, so the next generation of green-minded researchers and administrators is focused on bringing together those two key goals – cost consciousness and environmental friendliness.

Waste not, want not

The average lab's most wasteful practices might surprise you.

One of the key areas of wastefulness involves cold storage malpractice. Many laboratorians don't keep an inventory of what's in their refrigerators and freezers – not even a simple label like, "Shelf 2: Reagents" or "Shelf 3: Waste." Without an inventory, door opening times increase, and so does the unit's energy consumption and its running costs. Another factor that is often overlooked is ice buildup. The longer the door is open, the more ice builds up in the unit – which both limits the available space for samples and means the device itself may wear out faster. Finally, many labs still have fridges and freezers without precise temperature control – just a dial that goes from one to five. With no temperature display, your devices may be colder than necessary, which can negatively impact not only energy consumption, but also sample quality and viability. Cold storage is low-hanging fruit for most labs as far as "greening" goes.

Fume hoods are another area in which simple practice improvements can yield huge gains. During audits, I've found that over 90 percent of fume hoods are left open when not actively in use – and a single fume hood can use thousands of dollars worth of electricity per year! In a building with dozens or even hundreds of fume hoods, imagine the expense.

Even the smallest gestures can lead to huge savings. Most laboratories own at least one dry block heater, which is usually kept somewhere between 37 °C and 100 °C. We've measured the energy consumption of these kinds of units. Would you believe that, if you leave one on at 90 °C, it consumes more energy than a 100-liter -20°C freezer? Just by switching off a single dry block heater when not in use, you could make significant savings.

There are two easy ways for labs to become more sustainable. One is to apply best practice at all times in every way possible; the other is to become educated with respect to identifying and procuring the greenest options. Once labs can implement these two improvements, the sky's the limit.

Sustainable standards

How are laboratorians supposed to "go green" when we have no standards for energy efficiency? At the moment, almost all of the data on equipment performance is provided by the manufacturers themselves – and regular use in real-world settings often yields quite different results. People buy equipment in good faith, emboldened by marketing material that assures them they're choosing a green product – a phenomenon known as "greenwashing" (see below). It's easy to make a product *look* green – which is why we need standards to ensure that it actually *is* green.

Not only that, but we need standards that address the practical needs of science and medical professionals. We don't just need to know how much energy a piece of equipment uses; we need to know how it works for us. If you open your freezer door and withdraw a tissue sample, how long does it take the internal conditions to recover from that door opening? If you work in a busy clinical laboratory, that door might open and close every few minutes – so what effect does that have on your energy consumption? How does it affect your samples? You may have bought a "low energy" device – but what have you sacrificed for that low-energy designation?

The great greenwash

If I were issuing one word of caution to laboratorians choosing new equipment, it would be, "Beware of greenwashing." It's one of the biggest threats to sustainability in the lab. Remember that, no matter how a manufacturer presents data on their equipment, it's always marketing material – and there are always marketing tricks. For instance, they might compare their devices with older ones that are no longer competitive, rather than with actual competitors. They might use words like "eco-friendly" without providing evidence. They might use green colors or imagery to lend impact to their messages and make people feel good about buying their products. Always ask for independent verification of manufacturer-provided data – and, if possible, test the equipment yourself.

There are always new products coming out, which means my work is never done.

First, someone will identify a sustainability problem with a product they've been using for years (or even decades!). Invariably, a manufacturer will produce a more environmentally friendly version. For a year or two, that's the only green version available – making it an attractive prospect to buyers. Eventually, because of loss of revenue, other manufacturers will bring out similarly "eco-attractive" products – and they all start fighting over the "green dollar."

At this point, we begin to see things like greenwashing pop up in advertising. We see manufacturers manipulate their product data to give a good impression of sustainability – even if the information is not entirely accurate under real-world conditions. There's no point in buying something that saves energy, saves water, or reduces running costs if it's not fit for

"A laboratory requires up to 10 times more energy per square meter of space than an office building, so the next generation of green-minded researchers and administrators is focused on bringing together those two key goals – cost consciousness and environmental friendliness."

Learn From Past Mistakes

I did some work for an institution who gave me a "wish list" – they told me what kinds of devices they needed and it was my job to locate the best possible products for their purposes and give them a short list of choices. For instance, they wanted a list of the top 10 under-bench -20°C freezers, the top 10 ULT freezers, the top 10 fume hoods, the top 10 safety cabinets…

I made my recommendations based on a variety of factors: energy efficiency, temperature, performance, warranty, service, and so on. For the most part, they went with my top choices – but, for ULT freezers, they did a last-minute about-face. They found a freezer I hadn't recommended that promised extremely low energy consumption and purchased 50 units at a fantastic discount. Unfortunately, it didn't take long before all of the freezers began alarming on a regular basis. Why? The researchers needed to go into their freezers more than once a day – and they weren't returning to -80°C quickly enough because that's what had been sacrificed to achieve those low energy consumption figures.

Within the first year, all 50 units had failed at least once. Ultimately, because appropriate cold storage is so important, the institute invited multiple manufacturers to submit their units for testing under real-world conditions. They've now replaced all of their original freezers with the ones that "won" their test!

Thankfully, there are a lot of good products out there that perform as promised in the lab – but this is a good illustration of why standardization is so essential.

purpose for science. Why buy an affordable freezer with good energy efficiency data, if you can't open the door more than once a day because the temperature is too slow to recover?

Overcoming inertia

A dangerous phrase in science (and life) is, "We've always done it this way." People often default to the cheapest option – understandable, given many labs' limited funds – but it's important to be aware that the lowest purchase price rarely translates to the lowest ongoing costs. I use the analogy of a computer printer. When you buy a printer, you spend less time thinking about the price of the device than you do considering the cost of the ink or toner. Why not apply that principle to everything you buy?

Fortunately, once people are more aware of the options, they do change – and I see it happening more and more. Now, there are schemes and accreditations to encourage people to go green. Funding bodies are starting to ensure that applicants' equipment wish lists include sustainable products. It makes sense – if you're investing thousands or even millions of dollars into a laboratory, you'll want to know that they are only spending that money once. You want them to buy equipment that is efficient, long-lived, future-proofed, and has lower running costs. And that includes consumables, where applicable; you want them to be affordable and readily available. That way, you know the money is being used wisely.

Ask the experts

In the past, I've asked people to write their own sustainable procurement questions. I've had researchers from universities, research organizations, private institutions, even the British Antarctic Survey share their thoughts –

and what I've found is that some of the best, most insightful questions come from people who haven't worked in procurement at all. That may seem counterintuitive at first, but these are the people who have all of their research needs and cost factors and compromises in their heads. They can see the potential impacts of their choices much more easily than someone who isn't familiar with their laboratory or their projects.

Every lab is different. A team of histopathologists will have vastly different requirements to a team of analytical chemists. Basic sustainability principles – energy awareness, carbon awareness, and so on – don't change, but the details – and how you prioritize them – do.

How do you identify the main cost of a particular piece of equipment? For some, it's energy consumption; cold storage and drying cabinets are good examples. For others, it's consumables. A water purification system, for instance, will likely cost more in filters and hoses and wastewater removal than it will in energy – so you have to focus on those expenses. My job isn't just to choose equipment for labs, it's to help those labs learn how to make their own equipment choices. It's a great feeling to meet someone in the morning who has never written a product specification and, by the end of the day, see them not only writing like a professional, but teaching others to do the same.

For full equipment sustainability case studies by Green Light Laboratories got to: https://tp.txp.to/0623/case-studies

Building Your Sustainable Dream Lab

The three pieces of equipment that make all the difference:

1. Fume hood - The first piece of equipment to focus on is fume hoods. I would get fume hoods with high-quality variable air volume controllers to ensure that the lab was always using exactly the power they needed and no more. I would also make sure users followed best practice by closing the fume hoods after use.
2. ULT freezer - I would have a ULT freezer that I had independently tested. I'd want it to have good cooldown and door opening recovery times and I'd want the display to accurately reflect the freezer's interior temperature.

   Unfortunately, a lot of manufacturers will sacrifice temperature performance for better-looking energy consumption figures. When they present their data, the fine print includes temperature variation – which can be as great as plus or minus nine degrees! That means, when the freezer purports to be at -80 °C, it may actually only be at -71 °C. That's great for your running costs, but not for your samples.

   All of my cold storage, from fridges to freezers, would have digital temperature displays and solid drawers. Some laboratorians need to have their freezer doors open for quite a long time, so solid drawers are a wise investment because they significantly reduce the speed at which the temperature rises. I've done my own experiments with long door opening times; the interior temperature of the freezer with no drawers went up by 30 degrees, whereas the freezer with solid drawers saw a maximum increase of only nine degrees.
3. Drying cabinet - I would make sure I had a well-insulated, energy-efficient drying cabinet. Glassware drying cabinets are one of the greatest sources of energy consumption in the lab – so much so that a 100-liter drying cabinet at 75 °C uses 10 times the energy of a 600-liter ULT freezer at -80 °C.

   Because these pieces of equipment aren't complicated, technical, or expensive, they're often overlooked as a potential source of energy wastage. But the older designs are essentially just metal boxes with massive heating elements inside – and they're not particularly safe; if you touch the front (where they lose most of their heat) while wearing plastic gloves, you'll melt them. Manufacturers' stickers melt off. If you stand them on a polyvinyl floor, they crack and destroy the floor. That's how bad they are. Luckily, there are newer systems that use half the energy of older ones – or less. The savings are so vast that, a few years ago, the UK's University of Oxford replaced 155 drying cabinets in one fell swoop to increase their sustainability.

> *"A dangerous phrase in science (and life) is, "We've always done it this way." People often default to the cheapest option – understandable, given many labs' limited funds – but it's important to be aware that the lowest purchase price rarely translates to the lowest ongoing costs."*

Laboratory Sustainability: The Need for Green

A practical deep dive into the world of lab sustainability – and answers to one crucial question: How do we go green?

By Sheri Scott

Climate change has become the "greatest global health threat facing the world in the 21st century" (1). Climate change brings with it a decline of planetary and public health – and the effects we are already seeing on these systems are escalating on a global scale.

In 2015, nearly 200 countries recognized this threat and committed to a global collaboration in the form of the Paris Agreement. The aim? To limit the harm caused by climate change by setting a target to decrease global warming to below 2 °C. The Lancet Countdown came soon after, and was established to follow the 2015 Lancet Commission on Health and Climate Change. The annual Lancet report tracks the global progress of the commission across five key areas (see Figure 1).

The report also highlights the health impacts of climate change and potential health benefits that could result from our accelerated climate action. At the time of writing in 2023, the most recent version of the report (2022) presents a worrying view – the impacts of climate change are worsening. The number of extreme weather events is not just rising but accelerating, heat related deaths among our elderly population have risen by 68 percent over the last 20 years (1), infectious diseases are on the rise, and food security is declining.

As we continue through 2023 and reflect on the status of the economy and cost of living, we may find it difficult to focus on the wider picture of our climate and our planet. As a species, we have an addiction to the use of fossil fuels, which accelerates climate change. Unfortunately (or fortunately, depending on your view), if we are to have any hope of mitigating the worst scenarios of climate change, we need to curb our addiction. You need only look in the 2022 Lancet report to see the view that moving away from fossil fuels can save 1.2 million lives.

The healthcare sector is responsible for 4–5 percent of global greenhouse gas emissions (2); therefore, it has a role of responsibility in the mitigation of climate change, ultimately by substantially reducing its greenhouse gas emissions.

Here, I present an overview of my own healthcare sustainability advocacy and explore what we, as healthcare science professionals, can do to reduce the carbon footprint of clinical laboratory practice. By sharing these insights, I hope to add just one voice to the bigger conversation to help healthcare reach its targets for carbon-zero.

Developing a passion to promote change

As a healthcare scientist currently working in academia, I have developed a passion for environmental sustainability. I have always had an interest in the environment and ecology preservation, recycling where possible, following a vegetarian diet, and ensuring minimal personal impact on my surroundings. However, it was only when I became an academic in a sustainability-conscious university that my passion evolved into action as a sustainability ambassador.

As I developed skills of leadership and teaching, my knowledge for curriculum development grew to encompass the concepts of education for sustainable development (ESD). Sustainability became a consideration for student employability skills, student research projects, and for healthcare scientist continual professional development.

I found that, although the research and academic laboratory environments were actively looking to practice more sustainably, clinical laboratories were behind – despite national efforts to reduce the carbon footprint of healthcare.

I adapted my own laboratory practice and became a sustainability ambassador for the Institute of Biomedical Science and Nottingham Trent University. From there, I went on to facilitate change across UK clinical laboratories. Using expertise gained through 21 years of clinical laboratory practice as a biomedical scientist – and knowledge collected from published research and case examples – I promote positive

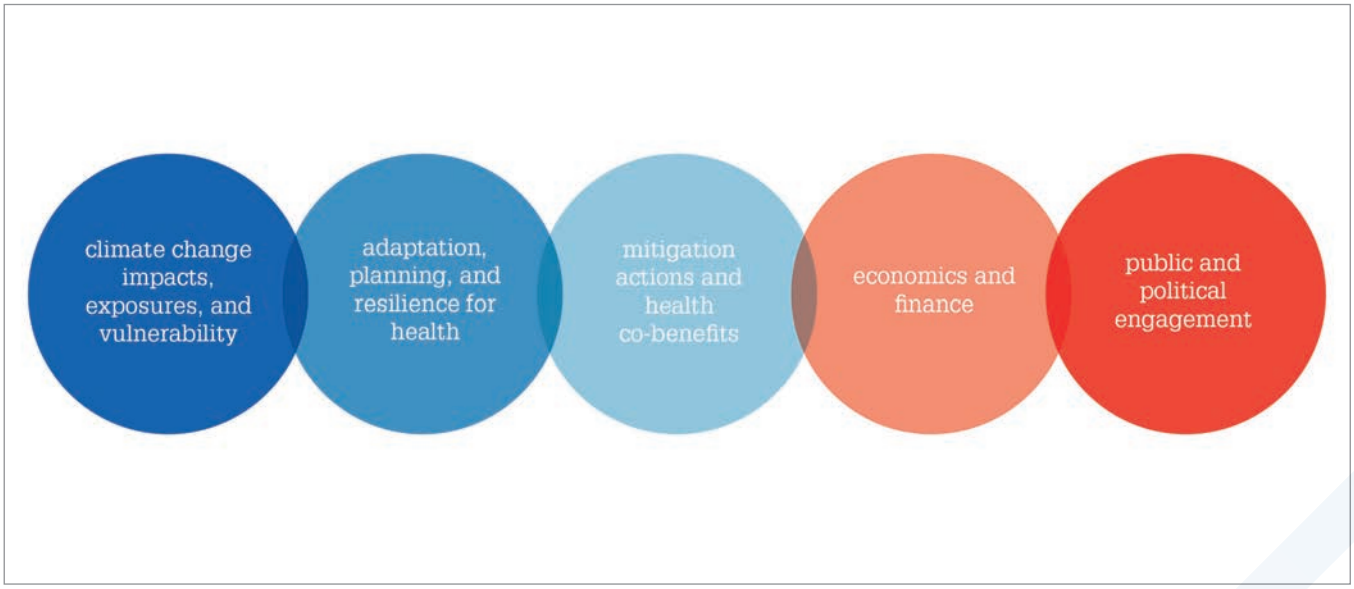

Figure 1. The five keys areas of the annual lancet report (1)

quality improvements in practice to lessen the carbon footprint of healthcare laboratory science.

Current work includes collaboration with organizations, such as Laboratory Efficiency Assessment Framework (LEAF), to develop a clinical laboratory tool, acting as a core member of the European Federation of Laboratory Medicine's Green and Sustainable Laboratory Taskforce, and launching the Centre for Sustainable Healthcare's international network for clinical laboratory professionals – Clinical Labs Susnet. I bring these activities up not as a list of achievements but as an example of how an initial curiosity can blossom into a lifelong vocation. If you find yourself passionate about sustainability, know that the first steps are often the most important.

From fundamentals of laboratory sustainability to case examples of good practice, there are some practical steps that a laboratory (and you!) can take.

A circular economy – reducing the need for Earth's resources

As healthcare facilities increase to match global demand, so does global healthcare waste generation – at an accelerated rate of 2–3 percent (3). Global healthcare waste is fast becoming an environmental concern, and so targeted management and suitable treatment strategies before waste becomes waste are needed to limit the harmful impact. There is a need for healthcare environments to adopt safe mechanisms that segregate, collect, transport, and treat waste before disposal.

In truth, there are many challenges to implementing a healthcare waste management policy. A World Health Organization (WHO) assessment in 2015 highlighted that only 58 percent of the sampled facilities from 24 worldwide countries had proper systems for waste disposal. This deficit results from a lack of budget allocation, lack of workforce skill, and outdated technologies.

If we can adopt changes that reduce resources at the source, the need for treatment naturally decreases – as does the associated carbon footprint and environmental impact of waste accumulation and disposal.

The circular economy – unlike our current "take, make, waste" economy – is a viable solution. The concept is simple: promote the reuse, the repair, and the reconditioning of products. But for a circular model to be adopted, we need management of the sustainable healthcare supply chain. To get there, we will need information collection, supply analysis, discussion and collaboration with suppliers, consideration of service providers, investment by internal and external customers – and, of course, the involvement of end users (4).

For reuse, repair, and reconditioning to work, a clinical

"Climate change affects every single aspect of our lives, and so sustainability should be considered at every single stage of our work."

Short haul flight	156g
Long Haul Flight	150g
National Rail	40g
Medium diesel car	171g
Medium electric car	53g

Figure 2. The carbon footprint of travel per km in 2018 (CO_2e)

laboratory needs to work and share with every other link in the supply chain – including other departments, organizations, suppliers, and local education providers. Sharing resources reduces the need for new production, reselling resources offers possible financial benefits, and reusing equipment in new settings, such as education, not only supports the circular economy model, but provides realistic training opportunities for the future workforce.

Adapting practice: the carbon footprint of travel

Adopting the principles of a circular economy is one of – if not the best – practices to halt the demand on new resources. But the requirement for change goes far beyond the scope of "recycle and reuse." A laboratory needs to look at the practices that directly produce carbon and other greenhouse gases.

According to the NHS England's 2018 report, Reducing the use of natural resources in health and social care, health and care-related travel constitutes approximately 5 percent of all road travel in England each year (5), while transportation accounts for 27 percent of total national emissions across the US (6).

Since 2010, the NHS has reduced its emissions by 30 percent, falling under the Climate Change Act requirements (5); however, when we consider the healthcare-related travel associated with pathology, we need to encompass travel by the patient, the sample, the suppliers, and the staff. Laboratory leaders need to consider promoting a reduction in carbon intensive modes of transport and consider changes in practice that can reduce the carbon footprint of sample and resource delivery.

Healthcare organizations already have numerous initiatives to promote sustainable staff commuting – therefore, we need to consider current processes and their impact. Regular fluctuations in test demand can often lead to urgent "kit" orders, with suppliers receiving multiple requests for single delivery of items, often transported by carbon intensive methods. Looking at the comparison of carbon emissions by differing transportation options (see Figure 2), we can better understand the impact of urgent deliveries.

By encouraging organizations to share kits and consumables when an urgent need arises, we save carbon by eliminating the need for single item, long-distance deliveries.

Sample collection and processing

The widely-understood concept of carbon footprint from travel can also be applied to sample transportation. Collection frequency, transport type, delivery route, and number of samples collected will all contribute to the carbon footprint of the laboratory. To promote evidence-based changes in practice, this data needs to be collated and analyzed to permit evaluation of sample delivery routes.

Furthermore, how we transport the sample to the laboratory is also an area for sustainability consideration. If you consider the production, use, and disposal of sample transport bags, it is easy to see how the laboratory feeds into the plastic waste of healthcare. Globally, 8,300 million tonnes of plastic were produced from 1950 to 2015, with only 7 percent recycled and more than half discarded into landfill or leaked into the environment (7). Although My Green Lab provides us with statistics on laboratory production of plastic (5 million tonnes per year from laboratories), the contribution for healthcare laboratories is unquantified. The move to single-use plastics is fundamental in this plastic waste production, but we can take steps to reverse this practice.

One initiative is the use of sample transport boxes, replacing the single-use sample bag. Samples can be transported in boxes securely and safely, but the switch away from bags also improves confidentiality and reduces the risk of sample loss. A simple change like a reusable transport box can reduce single-use plastics, save time in sample unbagging, and reduce turnaround times – all from a small amount of initial effort.

Using POCT

Point-of-care also has an impact on sustainability. It's believed that the impact of point-of-care testing (POCT) is considerably less than laboratory analysis. This is not only because of the equipment manufacturing process and running emissions, but often as a direct result of the reduced need for patient, sample, and staff transportation requirements. Moreover, one case study explored the use of POCT CRP test in nursing homes (8), finding that application of the test for suspected lower respiratory tract infection safely reduced

antibiotic prescribing compared with usual care in nursing home residents. This suggests that implementing POCT CRP in nursing homes might contribute to reduced antibiotic use. And because the POCT test would relieve the need for laboratory analysis, the approach also brought additional environmental gains.

That said, more robust research is needed in this area to truly quantify the carbon intensity of POCT versus laboratory analysis. When considering POCT implementation, we must also consider the fundamental clinical patient requirements and quality assurance practices. Though we may look for clever ways to reduce our impact, we must always meet safety and quality related regulatory requirements.

Further studies and quality improvement approaches, such as Sustainability in Quality Improvement (SusQI), in healthcare professional development aim to promote evaluations of the patient pathways and the need for laboratory samples (9). In recent years, quality improvement (QI) and sustainable healthcare have become integral to healthcare professional curricula. QI is a fundamental requirement of good laboratory practice and accreditation, and by employing principles of SusQI, a laboratory can achieve sustainability and QI objectives in tandem.

Sustainability in clinical laboratories – getting it right first time

My final thoughts on laboratory sustainability center on the frequency of pre-analytical errors seen in laboratories. Data from numerous studies puts the pre-analytical error rate at around 12.1 percent. A paper by Alcantara and colleagues gathered information on error rates from numerous countries and found preanalytical error rates ranging from 0.15 percent in India to 43.7 percent in Egypt (10). Regardless of these exact figures, conclusions can be drawn that pre-analytical errors contribute to an unnecessary carbon footprint. Some Initiatives, such as the UKs Getting It Right First Time and implementation of the international standard, ISO 15189, reduce the error rate, but there is an urgent need for further education. Mislabeling, sample rejection, and retests are just a few of the pitfalls that phlebotomy practitioners can fall into. But let's not forget the need to educate clinicians on lowering their number of inappropriate testing requests. In all, by reducing the number of samples being transported, processed, and disposed of, true carbon savings and environmental benefits can be realized.

Doing no harm

As responsible healthcare professionals, we need to connect, educate, and share sustainability practices to combat the climate and public health crisis. Leaders need to embed the sustainability agenda into current and future practice, and ensure that sustainability practice education becomes embedded into every single thread of what they do – inductions, professional development resources, and professional qualifications.

> *"As healthcare facilities increase to match global demand, so does global healthcare waste generation – at an accelerated rate of 2–3 percent (3)."*

Climate change affects every single aspect of our lives, and so sustainability should be considered at every single stage of our work.

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Turning Over a New LEAF

Martin Farley discusses the building momentum in laboratory sustainability – and how the Laboratory Efficiency Assessment Framework is aiding environmental action

Awareness about environmental sustainability is growing rapidly of late. Historic increases in energy prices have highlighted the importance of improved insulation – and motivated individuals, companies, and institutions to reevaluate what mitigation measures might be feasible. Beyond energy, the impacts of consumerism and consumption have been quantified – and they may be our greatest challenge yet. There are also increasing efforts to consider and address our dwindling biodiversity. As the world becomes more willing to address climate change, we have inevitably started to look beyond our homes and into our workplaces. For some jobs, the actions available to mitigate environmental impacts might be more feasible, but in the laboratory, it isn't quite as straightforward.

Laboratory facilities are in great demand, with high costs reflecting their energy intensive nature. A single ultra-low temperature freezer can consume more energy than the average UK home, and that doesn't take into account the energy required to ventilate laboratory spaces. Clinical and diagnostic labs – just like many research facilities – are increasingly reliant on single-use consumables. Diagnostic labs can present further challenges compared with research labs because, typically, they will perform fewer processes but at a much greater volume. The processes are often tightly regulated – particularly when they relate to the health of patients.

So what can be done to address these issues? And how can laboratory staff increase their sustainability efforts? Currently, staff are – for the most part – expected to figure it out on their own. Unlike health and safety requirements – which are standardized and easily accessible – environmental standards do not exist for diagnostic labs.

To start, we need to bring people together. The Centre for Sustainable Healthcare has created a network for sustainable clinical/diagnostic labs, with representation from across the UK. This network allows us to come together over common challenges, and quickly seek out solutions. The network also provides case studies which highlight new solutions that provide practical guidance for labs to share and learn from. But how can we ensure that such learnings are fully integrated into the labs? I would argue that the answer lies within frameworks – similar to how we manage health and safety.

At University College London (UCL), I have helped to create and manage the Laboratory Efficiency Assessment Framework (LEAF), which is a certification in the sustainability of laboratory operations. It incorporates all of the idealistic protocols that a lab can take to reduce their impact on the environment. Initially designed for our own research labs, LEAF's quick growth has proven how our sector wants to make active change. Since 2021, over 2,000 labs have registered from over 90 institutions in 15 countries, and LEAF has become the most widely used certification for "green labs." LEAF also contains purpose-built calculators that allow users to estimate the impacts of their actions.

By engaging with the wider community, we have also realized that there are other specialists seeking sustainability guidance, including technical staff working in animal facilities, commercial labs, computational labs, and, of course, diagnostic and clinical labs. We have launched new versions of LEAF to address these areas, and we are currently piloting a version specifically for diagnostic labs. Pilot participants include NHS sites and several commercial diagnostic laboratories. At the end of summer 2023, the course will be completed, and we will adapt LEAF based on the feedback we receive and offer it to the sector by the end of the year.

Our new version of LEAF for diagnostic labs will not remain idle. For example, we have seen that clinical labs face great challenges in introducing reusable consumables. In recognition of this, Eppendorf have released new biobased material in their single-use microtubes. At UCL, we have conducted life-cycle assessments of single-use consumables, and included Eppendorf's new product to measure the extent of carbon reduction. Equally, we have engaged with diagnostic labs to see if they would make the switch. If the outcomes are positive, we will alter LEAF's criteria.

As LEAF has expanded, we have learnt the importance of community and engagement – we must share sustainability efforts and responsibilities. If you're interested in making your lab more sustainable, create a "green group" or simply make sustainability a top priority in an existing group.

Although we don't exactly know how to achieve net-zero emissions in the laboratory, momentum to address the problem is building. Networks, new research, and programs like LEAF are starting the conversation and, though much work needs to be done, a more sustainable future is finally in sight.

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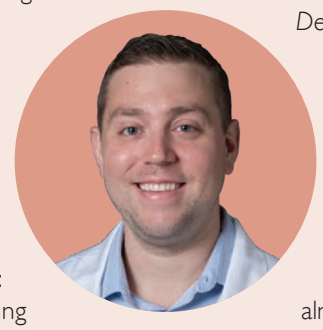
ANALYTICAL INTELLIGENCE

A Tradeoff Decision

How do we decide which NGS technology is the best for detecting fusion variants?

Fusions – whether for approved or investigative therapies – are one of the rarer but important variant targets in precision oncology. Though next-generation sequencing (NGS) has long been established as one of the technologies of choice, especially when there is a need to analyze multiple biomarkers, there is a debate on which of the technologies is "the best". Experts Annarita Destro and Eric Vail share their thoughts on the issue below.



Can you please introduce yourself and your laboratories?

Destro: I lead the diagnostic molecular pathology lab. We analyze a variety of cancer samples every year: the majority of them are lung cancer (around 500); followed by 250 for CRC; 50 for melanoma, 50 for CNS tumors; and roughly 30 each for cholangiocarcinoma, sarcoma, and GIST.

Vail: I'm the director of a clinical molecular pathology laboratory and we perform both solid and hematological tumor molecular analysis on approximately 2200 solid tumor samples and about 1000–1200 heme samples a year. The biggest volume from solid tumor samples is lung cancer, while the rest is a mixture of colorectal, breast, pancreaticobiliary, CNS tumors and others.

Which fusions are clinically actionable today?

Destro: As of today, the actionable fusions are *ALK, ROS1, RET, MET, NTRKs* for lung cancer, *FGFR2* for cholangiocarcinoma, and *NTRKs* for gliomas and sarcoma.

How do you perform fusion detection in routine samples?

Destro: Since 2022 we have been utilizing a 50 gene amplicon-based NGS panel in routine diagnostics.

Vail: We are using 500 gene amplicon-based NGS as a first line testing method, and in some cases, we confirm with fluorescence in situ hybridization (FISH) or anchored multiplex PCR based NGS.

Why have you chosen amplicon based-NGS for first line testing?

Destro: We chose it because it has a highly automated workflow which cannot be found with other platforms. We have a very high sample flow which cannot be sustained without this level of automation. The technology works with almost every type of sample, which gives us an extremely low failure rate – even when the quantity of the sample is really small. For example, between June 2022 and March 2023 we have profiled 471 lung cancer samples, 98.72 percent of which with valid RNA-NGS analysis. Furthermore, 99.78 percent (470/471) had successful DNA analysis, meaning that we are able to provide clinical meaningful results to virtually all our patients. In the past with other technologies we had up to 50 percent failure, including insufficient quantities for analysis. Moreover, most clinically actionable fusions are covered by our panel.

Vail: This technology is very robust. It requires far less material than the other NGS methods, like large hybrid capture-based NGS panels or anchored multiplex PCR based NGS. We routinely run samples with 10ng of nucleic acid (NA) input and have even had success with less than 5ng. This is very important because many real-life tumor samples – roughly 20–30 percent – are of very low quality or quantity. If we were unable to test those, we would exclude large numbers of samples, and ultimately patients, from targeted therapy options.

Any disadvantages?

Destro: There is the occasional technical failure, which can be resolved, and the software analysis may have more than one call for deletions and insertions (due to amino acidic loss following mutation), but they can be manually checked on the original file.

Vail: The disadvantage of amplicon-based NGS is that it cannot detect all fusions, including novel fusions and partners. Some other technologies can do it, but as I said, they require large amounts of material for testing, which is not often available. In an ideal world where every sample was freshly frozen, perfect quality, and large in size, it would not matter. But in real life we have mostly FFPE tissue samples, many of which these methods would not be able to test at all. So, it's a tradeoff decision in the end.

Could you explain further?

Vail: You get extreme sensitivity and specificity with amplicon-based chemistry because you're targeting both partners and can amplify them from very little original content. And the specificity is very high as well – I do not remember a false positive intergenic fusion in the years we've used this technology. But, given the design of the amplicon-based assays, they cannot detect what is not targeted. Some of the sarcoma genes which are very promiscuous are not well covered,

as well as fusions important in pediatric cancers. That's because it's hard to design targeted panels for some of these very low frequency tumors and rearrangements.

Also, they [amplicon-based assays] cannot detect novel fusions. There is a rare but meaningful amount of these and as we expand the knowledge by sequencing more, there will be more of those and they are not covered by the targeted design.

How many novel fusions are typically missed?

Vail: We have all of our validation data, where we used other technologies and cases that were sent out to different laboratories. Also, we have been running FISH *ALK, ROS* and *RET* on more than 1000 lung cancer samples in parallel, and we have discovered just one novel ROS fusion partner. Adding all these data together, we believe the miss rate is less than 1 percent of all solid tumor cases – and as the targeted panels are very well designed for lung cancer samples, it's even less, about 0.1 percent. Is it important for that patient? Yes. But, if we use a different technology that requires high input to detect these rare novel fusions, we might lose 20 percent of patients, or more. So that's the tradeoff. All technologies have some tradeoffs.

It's difficult to establish what the true miss rate is, but we can estimate. We have been running FISH of *ALK, ROS* and *RET* on over 1000 lung cancer samples in parallel, and we have discovered just one novel ROS fusion partner. Combined with data from other labs, we believe the miss rate is less than one percent of all solid tumor cases. And as the targeted panels are very well designed for lung cancer, it's even less, about 0.1 percent. Is it important for *that* patient? Yes. But, if we use a different technology that requires high NA input to detect these rare novel fusions, we might lose 20 percent of patients, or more. So that's the tradeoff. All technologies have some tradeoffs.

How do you detect novel fusions?

Destro: We do not proactively look for them. Being a diagnostic unit, we rather focus on the identification of what is proven to be clinically relevant *right now*. However, I believe that novel fusion identification is important in the clinical and translational research space. In the future we could run alternative approaches like anchored multiplex PCR-based NGS, IHC, or FISH to see if we missed something, especially for negative cases where the patient characteristics (woman, young, never smoker) would suggest the presence of a genetic alteration. However, these other NGS technologies work only on "perfect" FPPE samples, and therefore it would not be the optimal approach to look for novel fusion in more difficult samples like lungs tend to be.

Vail: Our panels have the 5'/3' imbalance assay for *ALK, RET, NTRK 1/2/3*, and *FGFR2*. It looks for over-expression of the fusion partner portion of the gene and under-expression of the gene portion that's lost from the fusion. It works in the sense that the sensitivity is pretty high, however, the specificity is pretty poor for a clinical assay to use as standalone. So, in my opinion it is a screening tool. If it's positive without a concurrent targeted fusion cell, we do a confirmatory assay afterwards. We don't report it on its own, as it might well be negative. We also do and recommend reflex testing with another method for true driver-negative lung cancer samples.

What is important when choosing NGS technology and which is the best?

Vail: Every lab director should look at NA input requirements, sensitivity, and ability to detect novel fusions – all in context of the available workflow automation, the local technical expertise, and labor costs. For our patient population, we have chosen a technology which we believe enables us to test more patients and detect more actionable variants, including fusions. The advantages we discussed outweigh the disadvantages – which we are aware of and have secondary strategies in place to offset.

Destro: It's important to look at: 1) the need to reliably detect gene rearrangement events in all clinical samples, even with little tissue; 2) the level of automation and ability to detect DNA and RNA alterations simultaneously; and 3) whether the workflow is really complete and does not require new special skills. In my opinion, we have chosen the best solution for our routine diagnostic samples: highly automated, 7-day measured turnaround time, and simultaneous DNA/RNA analysis.

"Every lab director should look at NA input requirements, sensitivity, and ability to detect novel fusions – all in context of the available workflow automation, the local technical expertise, and labor costs."

Annarita Destro is Head of Molecular Pathology Department, Humanitas Research Hospital in Milan, Italy.

Eric Vail is Director of Molecular Pathology, Cedars-Sinai Medical Center, Los Angeles, California.

You can find full interview with Dr. Eric Vail including his advice to different types of laboratories and why he is passionate about democratization of genomic profiling at www.oncomine.com/blog

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Molecular Pathology

Graphic revamp. Using human reference genomes always comes with challenges. For one, biases can be introduced, ultimately affecting how researchers interpret the sequences of other human genomes. In a bid to curtail these disadvantages, a paper has proposed the use of a graph-based system called a pangenome to visualize genetic diversity more accurately. The author's example saw better genomic alteration identification than standard thanks to its use of 94 highly accurate and nearly complete genome assemblies from 47 individuals representing diverse ancestries (1).

Renal revelations. To examine the potential of epigenetic biomarkers for diabetes and related conditions, researchers have analyzed type 2 diabetes and possible links to kidney dysfunction. They found that DNA methylation levels were linked to renal function in type 2 diabetes, and previously unknown CpG sites showed associations with baseline estimated glomerular filtration rate. The genes that were near to the CpG sites and included in prediction models were related to pathways associated with kidney disease pathogenesis. Methylation biomarkers could help assess risk in type 2 diabetes and provide insights into the pathogenesis of kidney diseases (2).

Markers… in space! Leveraging recent progress in spatial transcriptomics (ST), researchers have developed an algorithm – SpaceMarkers – that is capable of inferring molecular changes that result from interactions between cells. The algorithm gleans its bioinformation from latent space analysis of ST data and can analyze tumor-immune interactions through a combination of spatial transcriptomics and single-cell RNA sequencing data (3).

An inflammatory comment. The liver tumor mutation LKB1 is strongly associated with deregulated inflation, but the underlying reasons why have not been understood. A recent study, however, has established that inflammatory potential downstream of LKB1 loss is driven epigenetically through deregulated signaling by CREB-regulated transcription coactivator 2 (CRTC2). Researchers identified that LKB1 mutations make cells more sensitive to inflammatory stimuli, leading to increased production of cytokines and chemokines – highlighting a previously unknown anti-inflammatory process that links metabolic and epigenetic states and potential cell inflammation.

See references online at: tp.txp.to/0623/pathology-news

IN OTHER NEWS

In the driver's seat.
Using neuron-specific gene regulatory networks, a study into Alzheimer's disease has highlighted 1,563 neuronal key drivers of the condition. One significant interesting target, JMJD6, displayed significant influence towards Aβ and tau levels (5).

A prime example.
In place of standard mouse models, a team has developed an in vivo system by using a prime editor in the mouse germline. This facilitated more rapid and precise engineer mutations in cell lines and organoids derived from primary tissues – notably those commonly observed in pancreatic cancer (6).

The search for SPOCK2.
Investigation of the SPOCK2 protein in the extracellular matrix and its relationship to pancreatic ductal adenocarcinoma (PDAC) has found that i) it is downregulated in PDAC cell lines, and ii) its expression is increased by demethylation. Moreover, stymied SPOCK2 resulted in cell growth, while high numbers were associated with better patient outcomes (7).

Science That Lasts a Lifetime

Yassmine Akkari discusses the evolution of cytogenetics – and its timeless importance

For decades, cytogenetics has been declared dead. But for as long as I can remember, I have never understood this statement. In my mind, cytogenetics is the science of chromosomes – and how can a science die?

A quick google search brings up many different definitions of the word "cytogenetics." These include "the study of inheritance in relation to the structure and function of chromosomes," "a branch of genetics concerned with how the chromosomes relate to cell behavior, particularly during mitosis and meiosis," and "a branch of biology focused on the study of chromosomes and their inheritance." Nowhere in these definitions does it imply that this area of genetics is linked to a particular technology or that it has a limited lifetime.

While discussing this matter with colleagues, it became apparent that the concern over the "longevity" of cytogenetics lies in the fact that genetics has progressed into genomics, and by focusing on sequence variation and advanced sequencing technologies, we have neglected the principle of chromosome science and the importance of understanding chromosome behavior.

The technologies that we use to interrogate chromosome structure have evolved throughout history and the testing landscape of cytogenetics has changed dramatically. Cytogenetics has taught us that there are 46 chromosomes in normal human cells and has allowed us to distinguish chromosomes based on their banding patterns. These advances legitimized the birth of clinical cytogenetics and acknowledged the burden of chromosome aberrations in human disease. Just as the detection of single nucleotide variants has evolved from Sanger sequencing to next-generation sequencing, the detection of chromosome alterations has evolved from G-banding to FISH to chromosomal microarrays to – perhaps in the very near future – optical genome mapping (OGM) and whole genome sequencing (WGS) (see Figure 1).

Our genomic community now faces a lack of understanding on the behavior of DNA in health and disease at the chromosome level – the view at 30,000 feet. We are experiencing a decline in interest from future geneticists on the importance of understanding this science.

Why? Because it appears that looking at a G-banded karyogram is an archaic practice and doesn't allow for the single-nucleotide resolution that is afforded by advanced molecular methods. The real question is: Are all human diseases driven by single nucleotide variation? The answer is no. Is G-banding a technology that allows for a well-established view of the genome at a single-cell level? The answer is yes. So, what's the problem?

The problem is that we didn't fight to continue education on the science of cytogenetics. In 1993, the human genome project promised the field an unprecedented understanding of human health and an explosion of interest occurred in genomic sequencing. Though this project advanced the discovery of the genes involved in mendelian disorders, there was also a parallel line of discoveries in the world of oncology: targeted therapy. These two waves of genomic advances allowed for interventional clinical management and therapies for both constitutional and somatic disease, and enriched the medical community with molecular technology-focused teaching curricula. While this legitimized genomics as a bona fide medical specialty, cytogenetics was overlooked. We started experiencing a shortage in professionals who had expertise in cytogenetics and witnessed the decrease in national programs dedicated to cytogenetics training. This, along with the rumor that cytogenetics was dead, discouraged younger generations from receiving training in the field, further accentuating the lack of innovation and appreciation (see Figure 2).

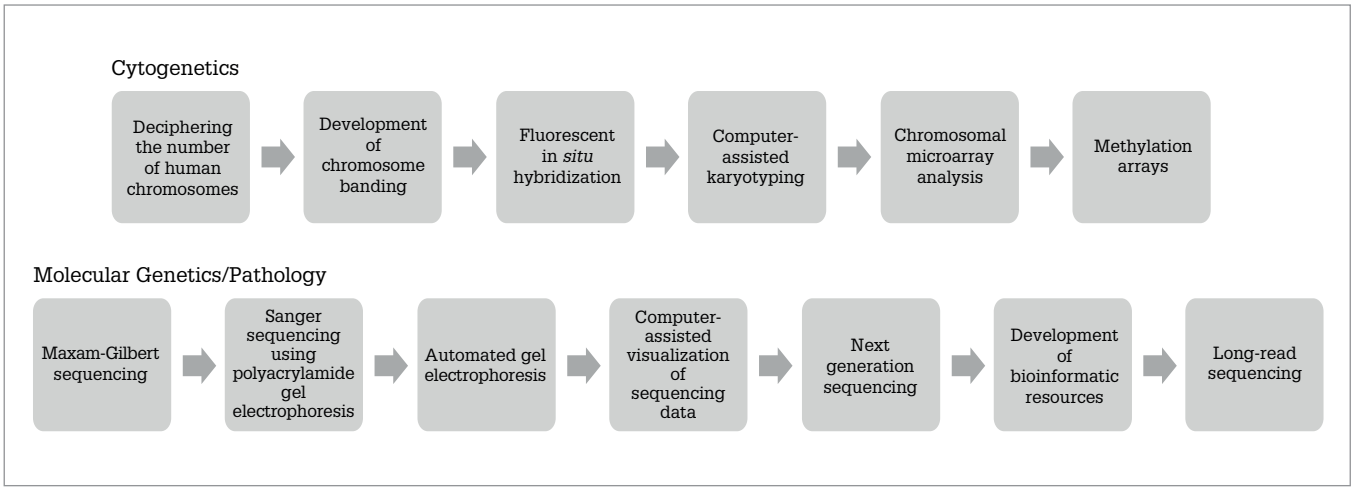

Figure 1. Parallel Technology Evolution: Cytogenetics and Molecular Genetics

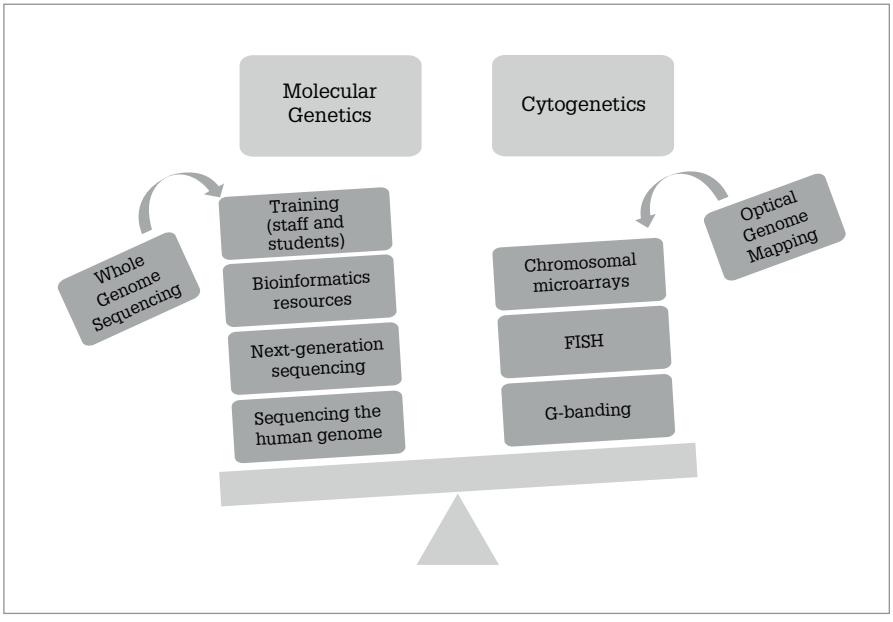

Figure 2. Paradigm Shift

Ironically, despite a decrease in the number of cytogenetic trainees (both at the director and technologist level), the workload in cytogenetic laboratories never wavered. Many had predicted a decrease in prenatal cytogenetic workload because of the wide adoption of non-invasive prenatal screening or a decrease in cytogenetic analysis of a child in the NICU. These changes did not materialize. Further, in this era of limited healthcare resources, do we really need to perform WGS to confirm the diagnosis of Down syndrome?

Slowly but surely, we have started to realize that a good molecular geneticist/pathologist needs to fully understand chromosome structure and function. As we start to derive information about chromosome copy number and structural rearrangements from sequencing technologies, we are becoming more cognizant of the need to learn cytogenetics. For example, with NGS sequencing, it is important to appreciate that, if one sees a deletion on one end of a chromosome and a duplication at the end of another chromosome in a child with congenital anomalies, it may be an unbalanced recombinant from a balanced translocation. It is crucial to understand and schematically visualize the preceding meiotic event. Why? Because it will have a profound impact on our ability to provide accurate determination of recurrence risk.

Certainly, we must pause and appreciate the immense advancement in genomics. This progress touches on sequence variation, chromosomal structural rearrangements, epigenetic processes, and the effect of clonal heterogeneity. But it is equally important to understand that cytogenetic technologies are also evolving, and that the implementation of the new and upcoming OGM and WGS will benefit from cytogenetic interpretation.

In conclusion, cytogenetics remains extremely important, and reciprocal training and education on both ends of the DNA technology spectrum (whole chromosomes to methylation and single nucleotide aberrations) will allow true breakthroughs in genomic science.

Yassmine Akkari is Senior Director, Clinical Laboratory, The Steve and Cindy Rasmussen Institute for Genomic Medicine, Nationwide Children's Hospital and Professor, Department of Pathology, The Ohio State University College of Medicine, USA.

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ADD-144004-EMEA-EN 04/23

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Foundation

Infectious Disease

The end of an era. In a media briefing on May 5, 2023, the World Health Organization's (WHO) Director-General Tedros Adhanom Ghebreyesus said, "Yesterday, the Emergency Committee met for the 15th time and recommended to me that I declare an end to the public health emergency of international concern. I have accepted that advice. It is therefore with great hope that I declare COVID-19 over as a global health emergency." The pandemic is still very much a global health threat, Adhanom Ghebreyesus warns, but the announcement means that countries can now shift from dealing with COVID-19 as an emergency to managing it like other infectious diseases (1).

Too much, too soon? Speaking of announcements, on May 11, 2023, WHO declared that mpox is also no longer a PHEIC, citing the 90 percent decrease in reported cases over the past three months, compared with the previous three (2). Mpox's emergency status has helped raise awareness of the neglected disease – despite already being endemic in several countries across Africa – and shift vital resources to tackling the global outbreak. However, speaking to Nature, WHO emergency committee members Dimie Ogoina and Boghuma Titanji disagree with the decision to strip its PHEIC status, saying the decision may divert support from governments and public-health leaders in African countries such as Nigeria (3).

Easing up. In 1983, gay and bisexual men were banned from donating blood in the US; now, 40 years later, the FDA has finalized recommendations for assessing blood donor eligibility using risk-based questions to reduce the risk of transfusion-transmitted HIV (4). Regardless of sexual orientation, sex, or gender, every donor will be asked the same series of individual, risk-based questions to glean their eligibility. In 2022, the American Red Cross declared a national blood crisis and, as of May 12, 2023, 32 percent of community blood centers across North America had only 1–2 days worth of blood supply, and 14 percent only had one day's worth (5). The new guidance could cast a wider net on how many people are eligible to donate blood, while ensuring safety standards for the blood supply are upheld.

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A Diagnostic Dilemma

Sepsis places a significant burden on healthcare and can be challenging to identify early – is there a way to ease the pressure?

By Richard Brandon, Co-Founder and Chief Scientific Officer at Immunexpress, Queensland, Australia.

Sepsis takes a heavy toll on society, causing millions of fatalities worldwide per year and costing upwards of US$50 billion yearly in the US alone. Sepsis can develop from viral, bacterial, and even fungal infections, but bacterial infections are by far the most common cause – accounting for more than 80 percent of sepsis cases. The term is a manufactured one, and medical definitions have evolved over time; however, fundamentally, what is referred to as "sepsis" is a severe, dysregulated host immune response to infection. This severe response can be life-threatening, and the lack of tissue and organ oxygenation typically seen in sepsis can lead to organ failure and acute kidney injury.

When a sepsis patient arrives at the emergency room – a common path to medical care for these patients – they often present with a vague set of clinical signs, including altered mental capacity, pain, rapid heart rate, and rapid breathing. Because the symptoms may resemble other conditions, such as heart failure and stroke, clinicians face an immediate diagnostic challenge, but they must identify sepsis under significant time pressure; after all, outcomes depend on how quickly treatment can be administered.

One traditional method of identifying sepsis is to pinpoint the infectious agent causing the response which, as mentioned, is typically bacterial. This requires culturing and identifying the microbe – a process that can take hours, days, or in some cases, weeks. During this time, the patient is often treated with antibiotics. However, taking such a proactive approach can have deleterious consequences because antibiotics can cause adverse side effects, while their overuse or misuse contributes to the ever-growing problem of antibiotic resistance.

On the other hand, operational approaches monitor a set of clinical parameters to assess the probability and severity of sepsis; for example, the quickSOFA (qSOFA) score identifies high-risk patients for in-hospital mortality using measures of respiratory rate, blood pressure, and mental state.

"This approach could form the basis for a rapid, accessible, and widely applicable test."

However, it is not used to diagnose sepsis, but rather to predict patient mortality. There are other parameters that could have application in diagnosing sepsis, such as blood cell width and elasticity or levels of procalcitonin or C-reactive protein, but these may actually be indicative of inflammatory processes related to non-sepsis causes.

Given that sepsis is fundamentally a dysregulated immune response, it may be fruitful to directly measure the underlying process: dysregulated immune gene expression. In addition to accuracy and the ability to discriminate sepsis from other conditions, this approach could form the basis for a rapid, accessible, and widely applicable test. Having access to such a test could address the variation in sepsis incidence and outcomes among countries, with regions such as sub-Saharan Africa currently shouldering the highest burden.

Critical to this accessibility is ease of sampling. Early studies in a horse model of sepsis (endotoxemia) provided proof of concept that gene expression analysis of white blood cells in a peripheral blood sample could be used to identify the early stages of sepsis. This provided the foundation for further clinical studies and investment to identify specific biomarkers of human sepsis. Peripheral blood biomarkers and their measurement using gene expression analyses are now widely used in the diagnosis of infectious disease and cancer. The clinical utility of this approach is its ability to provide rapid, accurate, and early identification so that clinicians can respond quickly to sepsis.

Infectious diseases are a significant human health issue in their own right, but one cannot overlook the downstream consequences of the host's own dysregulated immune response in causing negative health outcomes. Rapid and accurate sepsis diagnosis can improve patient outcomes while helping to avoid adding to the growing problem of antibiotic resistance. With several new technologies entering the market, earlier diagnosis of sepsis is becoming a more achievable goal every day.

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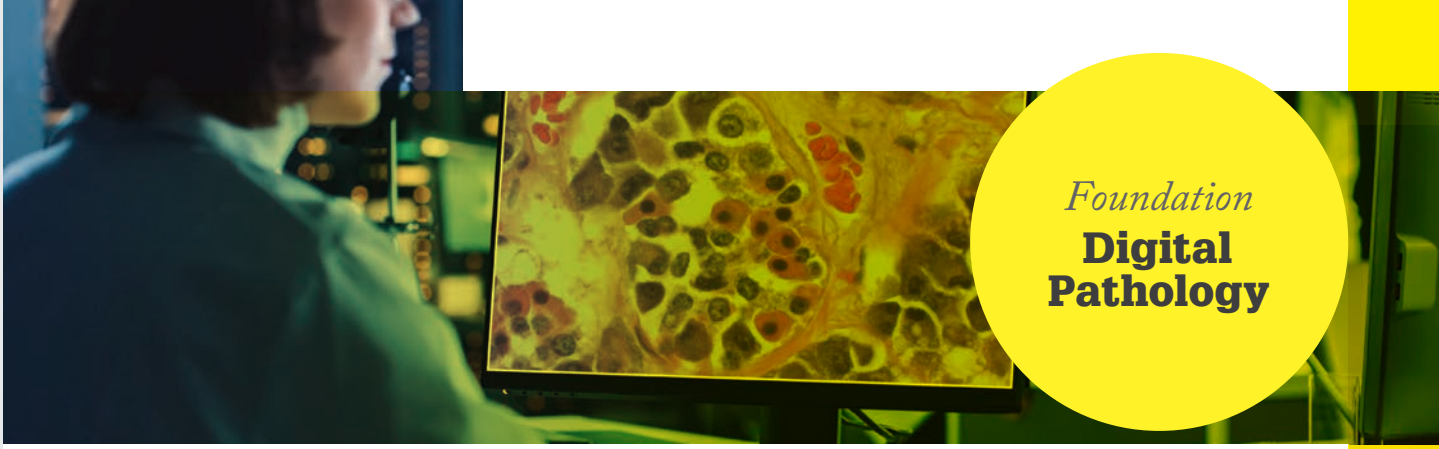

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Foundation
Digital Pathology

Overcoming Digital Disparity

A few simple steps can make AI-enabled digital pathology a reality in the developing world

By Talat Zehra

The benefits of digital pathology are well known. However, there are obvious challenges hindering implementation – particularly in the developing world – which makes up more than two thirds of the world's population. Low- and middle-income countries (LMICs) are the hub of world tumor cases and endemic disease. According to GLOBOCAN, the annual incidence of cancer cases in 2020 was 19.3 million (1). It is estimated that these numbers will reach approximately 28.4 million cases in 2040 – a 47 percent rise from 2020.

It's also well known that there is a significant shortage of pathologists around the globe, but it is the LMICs that suffer most with the burden of disease. This disproportion is rapidly increasing – as is the prevalence of malignant tumors.

Clearly, a great diagnostic dilemma is arising. And it's clear to me that the adoption of digital techniques in the field of pathology is crucial to improve patient care and management of disease – especially in LMICs.

The challenges

Financial constraints are the largest challenge in LMICs. The cost of digital microscopes, whole slide scanners, and AI-based software are beyond the budget of many low resource organizations. And large data sets demand powerful computing and likely access to cloud systems, which also don't come cheap – especially when considering the need for adequate data security. Clearly, reliable digital technology needs solid IT infrastructure, which is not guaranteed.

Other barriers also exist. Regulatory challenges can pose a problem in some regions because only a few whole slide scanners have FDA approval that can be used for primary diagnosis. And then there are more personal barriers; pathologists are familiar with conventional microscopes, and the switch to digital pathology may take a lot of getting used to.

Finally, more large validation and proof of concept studies are needed before digital pathology can be integrated wholesale.

The solutions

The challenges do not prevent resource-constrained organizations in LMICs from starting their digital journey. For example, resources from open-source organizations – many of which offer free access to their whole slide image archives – can be used. Alternatively, microscope-connected cameras can easily acquire digital images, negating the need to navigate the technical hurdles of downloading huge data files. Experts can photograph a region of interest for a particular pathology, annotate them, and essentially create a data set using their own patients. These digital snapshots are small compared with whole slide images, whose size is usually in gigabytes. After the slides have been annotated, the images can be used to train automated AI models in image analysis software. Though it's true that commercially available tools are expensive, open source software options do exist, including QuPath, Orbit, DeepLIIF, and many others.

Recently, we used the open-source software DeepLIIF on Ki-67 immunohistochemistry images. This cloud-native software with user-friendly web interface can quantify Ki-67 positive tumor cells in different tumors and at different magnifications. We used diagnosed cases of breast cancer at 10x resolution, validated the software for Ki-67 quantification, and then compared manual versus automated quantification. The consensus was statistically significant. The software was easily compatible with digital images. With the help of this assistive tool, pathologists can perform size gating (to differentiate tumor/stromal cells) and adjust the intensity of positive tumor cells while also selecting – or excluding – regions of interest.

In other words, pathologists can make disease models without the need for high-tech scanners, large hard drives, or high-speed Internet. By making data digital, pathologists can predict the outcome of disease using data science, opening new horizons for precision medicine. The role of technology vendors will be crucial for technical support, but slowly, with these steps, we can achieve full digitization of pathology in the developing world.

Talat Zehra is Assistant Professor and consultant histopathologist at Jinnah Sindh Medical University, Karachi, Pakistan.

See references online at: tp.txp.to/0623/digital-disparity

It's a People Thing

Digital adoption won't go anywhere if the technology is seen as an inconvenience

By Prasanth Perugupalli

New technology can be powerful – but how far does it get if people don't want to adopt it? Find out in part three of our six-part "Barriers to Adopting Digital Pathology" series.

The adoption rate of any new technology is dependent on how much positive impact it offers and how much it resonates with its users. This reality was evident in the early days of mobile payments, which took over two decades to mature because of various factors, including clunky software that caused usability issues, practical limitations caused by phone batteries dying halfway through the day, and misunderstanding about the security of mobile payments.

Two key factors that determine mass adoption of any new technology are trust and ease-of-use. Technological advances will resolve reliability issues over time, but it is imperative that people can use the tech without difficulty. There are many technology users in a pathology lab: laboratory technicians who prepare the specimens, make slides, and organize them for review; pathologists who consider all the facts of a case and establish a diagnosis that cannot be contested; and lab administrators who manage people and logistics while delivering outcomes to patients and lab owners.

Most digital pathology leaders have made it clear that labs must become more vigilant about specimen handling, data management, and cost optimization. This trend – combined with the burden on technicians to create the perfect glass slide or to learn how many sampling points to choose for a tissue – has put enormous pressure on training and compliance. However, intelligent scanning systems with embedded AI are set to usher in a new era of the lab – reducing many of these laborious steps and eliminating some steps altogether.

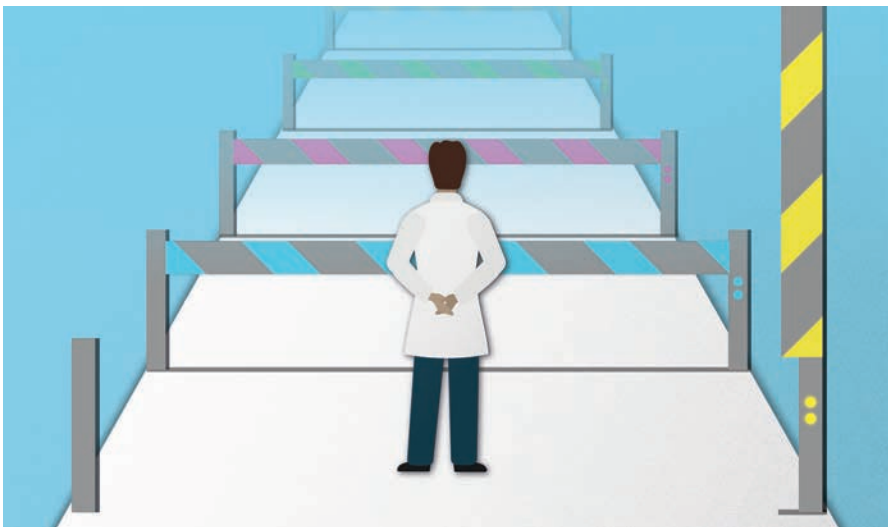
The interpretation of images, metadata, and their interactions is a major source of disagreement among pathologists, but software capable of advanced visualization techniques can smooth them out. Relevant data can be presented in a contextual manner to pathologists as they review a case with several digital slides – everything from physician notes to radiology reports. By using appropriate viewing software, tissue specimens can be aligned, rotated, and manipulated to gain better insights and avoid potential pitfalls. This advanced software can empower pathologists to achieve greater efficiency and accuracy, providing a degree of control previously unheard of.

In speaking with various lab managers, a common theme has emerged: the need to increase capacity while improving turn-around times, all without incurring additional costs or hiring more staff. A well-designed digital pathology solution can provide seamless scalability, and progressive business models offering digital pathology as a service can achieve commercial objectives.

But it is only through a close and trusted partnership between providers and users – that is, between people – that the digital transformation can come to pass.

Prasanth Perugupalli is Chief Product Officer at Pramana, Cambridge, Massachusetts, USA.

"Two key factors that determine mass adoption of any new technology are trust and ease-of-use."



An Imaging Revolution: from CERN to the Clinic

Could recent developments in secondary ion mass spectrometry imaging revolutionize digital molecular pathology?

By Ron M. A. Heeren

The evolution of physical-chemical analytical instruments has traditionally focused on the improvement of resolution, separation, sensitivity, and throughput. Here, resolution refers to different parameters such as spectral resolution, molecular resolution, structural resolution, spatial resolution, and several more. In pathology based clinical diagnosis, the speed of analysis is key. Optical scanning of immunostained slides can be performed in minutes, but limited possibilities for multiplexing exist. For example, imaging lanthanide-labeled antibodies with SIMS offers the multiplexing capabilities but lacks the speed. In imaging technologies in particular, the detail that can be observed is crucial and the "resolution revolution" is strongly based on advances in detector technology and image processing. But it usually comes at the expense of throughput. Make the pixel size 10 times smaller and the same analytical area requires 100 times longer data acquisition time.

But a new development in secondary ion mass spectrometry imaging changes that paradigm – based on an innovation in mass spectrometry that takes advantage of massively parallel detection of arrival time and position capabilities, combined with an innovative detector coming from CERN: the Timepix3 system. The detector offers nanosecond timing resolution and continuous time resolved image detection. M4i researchers have coupled it to a microscope-mode mass spectrometry imaging system that allows for the detection of more than a million pixels per second – that's orders of magnitude faster than what is possible with conventional imaging experiments. It uniquely combines throughput and spatial resolution with single ion detection capabilities for large m/z ions.

We've applied this new system for ultrafast SIMS based molecular imaging of large areas at submicron spatial resolution. When applied to biomedical tissue analysis, a variety of molecules can be visualized at cellular detail in a matter of minutes. I believe this approach could revolutionize digital molecular pathology, as well as peri-operative diagnostics in a true clinical translational setting. In other words, bridging the translational gap between fundamental mass spec research and pathology – by making tissue diagnoses more precise and rapidly improving precision medicine through more individually tailored therapies.

Ron M. A. Heeren is Director, M4I, and Distinguished Professor, University of Maastricht, Netherlands.

Profession

Your career
Your business
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Work Hard, Play Hard

The lab can be intense, but Sophia Chandrasekar makes sure any drudgery comes with its fair share of recreation

By Georgia Hulme

The world of pathology and laboratory medicine can be characterized by long hours and overwhelming workloads. And that's why Sophia Chandrasekar – artist, podcaster, and fashionista – is committed to lightening the laboratory mood. Whether it's through her business (Warbler Works Studio) or her *Off the Bench* podcast, Chandrasekar knows that all lab and no play is a recipe for running out of steam. After finding a space for fun in her profession, Chandrasekar shares her illustrations to offer a breather from the stresses of laboratory life.

I caught up with Chandrasekar to learn more.

Tell us about your double life…

I am a medical laboratory scientist in the US. But I am also the founder of Warbler Works Studio – a laboratory themed comic strip that publishes every Monday and Thursday. Warbler Works Studio is also an online store that is filled with all sorts of laboratory-based illustrations and merchandise. In my senior year, just before I was about to graduate with a biology and anthropology double at UNC Chapel Hill, I saw an ad on the way to campus for the Clinical Laboratory Science bachelor's degree. It drew me in with the question: "Do you want to solve the patient puzzle?" I guess I did, because two weeks after I graduated I started the program, and have been in the lab field ever since!

What do you love most about your job?

I love being a part of patient care! Although, I'll admit we often don't get the credit we deserve. A good analogy can be found in theater – you don't

realize how important the crew, pit, costume, and set designers are until they're missing. I would love it if we were more front-facing so that people knew exactly what we did.

How do you think recognition can be improved?

I am a part of the American Society for Clinical Laboratory Science (ASCLS), and one of our biggest goals is advocacy. Although self promotion is important, there's only so much we can do. We need more recognition from hospitals and other sectors of the care team. Some hospitals have huge celebrations for lab week, but some hardly have any. You constantly hear about nurses, doctors, pharmacists, and radiologists, but people generally neglect jobs in the lab. It's a whole practice of medicine that people don't even know about. If hospitals recognize their laboratory staff on the same level as nurses and doctors, we will get somewhere – because, at the end of the day, hospitals have the largest voice in the medical community.

Where does your artistic inspiration come from?

I got into scientific art as a way to study in college because I am very visual. I took a lot of invertebrate anatomy and anthropology classes – and some of the concepts were extremely lofty. If I didn't understand the concept, I would sit and draw out the process. But it was COVID-19 that really pushed me into pursuing scientific art more seriously. Art was my way of journaling what I was going through as a laboratory professional. I went from working day shifts to night shifts with hot instruments and a mask on my face; a corner of hell, as I liked to call it. Writing little comics for myself was my way of dealing with everything; my art became a medium to convey how I was feeling.

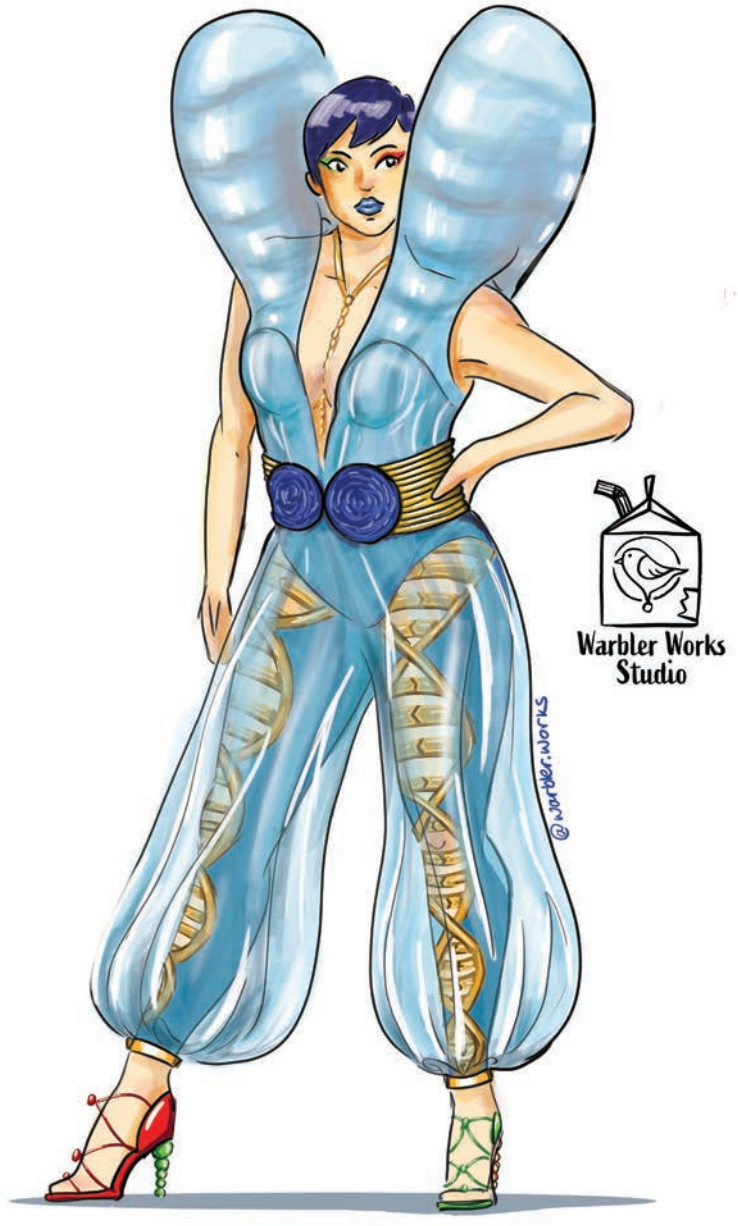


Figure 1. (top right): A chromosome jumpsuit with sheer pant fabric to show the DNA leggings underneath, and reinforced vinyl shoulder pads. The belt is clasped behind the two large centromere discs, with gold ribbing all the way around. The shoes have red and green FISH beading for the heels, with matching eye makeup.

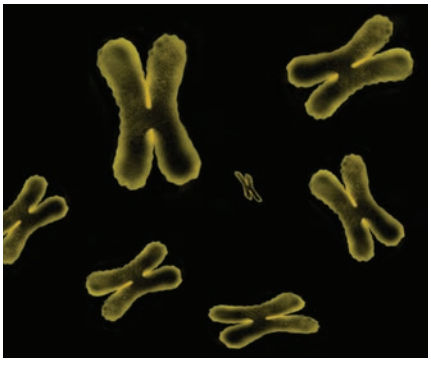


Figure 1. Inspiration (bottom right)
Credit: Zappys Technology Solutions / flikr.com

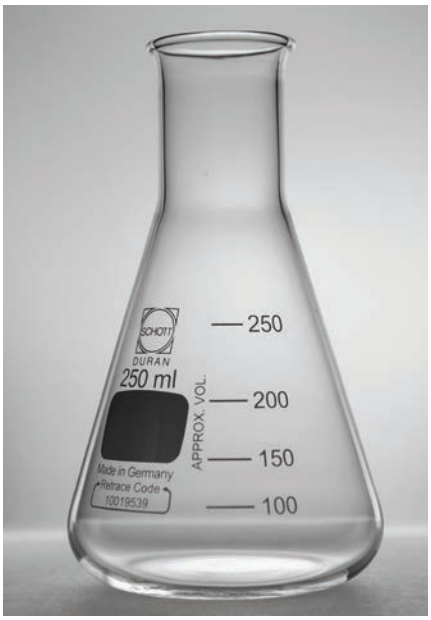
Why did you start Warbler Works Studio?
The store started because I really liked what I was creating. I wanted to make lab-based ephemera that people could relate to. I would often go online, and just see clipart microscopes plastered on everything. I think I had the laboratory mindset of, "If no one else will do it, then I will." I like to think my comics bring awareness to the profession, and help to showcase the ups and downs of laboratory life. The lab can be stressful – it's tiring and long hours are often inevitable, so I hope that people get enjoyment out of my art. There are so many cool and funny memes for nurses and doctors, but the laboratory field was missing that. It's nice to have created a space to joke about the highs and lows of our niche.

Could you walk us through the process of creating one of your designs?
I'm a very slow illustrator! For my "Lab, but make it fashion," series, I start off by picking an object or a subject in the laboratory. For my chromosome fashion piece (Figure 1), I sat and thought, what makes a chromosome a chromosome? You've got the X shape. You've got the DNA. You've got the centromeres. I then put the shape on a paper doll, grabbed my sketchbook, and did some general form and silhouette sketches while I figured out the color combination. Once I'd got that, I drew it out on my computer before painting and coloring. For the entire process, it usually takes four to seven hours. I think my Erlenmeyer flask fashion piece took the longest (Figure 2).

And where did the idea for the "Lab, but make it fashion" series come from?
I started the series after a bad day in the lab! My fashion inspiration is definitely the 2000s, and some of my favorite designers include Alexander McQueen, Elie Saab, Paolo Sebastian, and Ruth Carter. My more outlandish designs – like the chromosome and the Erlenmeyer flask fashion pieces – are a huge nod to

Figure 2. (bottom right): An iridescent structured vinyl overdress in the shape of an Erlenmeyer flask, paired with a stir bar shaped pill purse, and stir plate boots. Boots include RPM display and adjustment knob. The hair is designed to be 'bubbles', even though that never really happens in the lab.

Figure 2. Inspiration (bottom left)
Credit: Wikimedia Commons



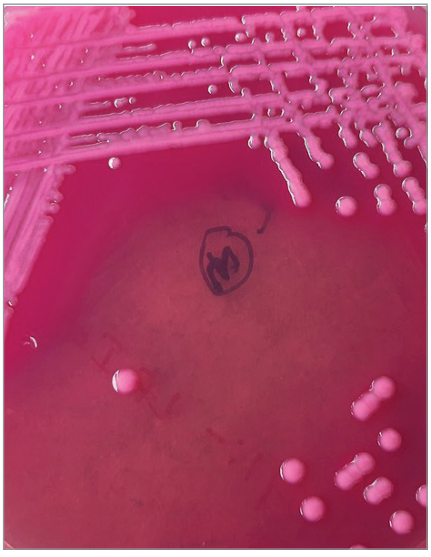


Figure 3. Inspiration (top left)
Credit: Wikimedia Commons

Figure 3. (top right): An evening gown that has a base of a single shoulder, mauve evening gown with a mermaid skirt. Overlaying the dress form is a pink goo-like, viscous material, resembling *Klebsiella pneumoniae*. The choker also had several droplets of viscous *K. pneumoniae*, with a faux-hawk formed by four gram-negative rod shaped buns.

Cirque du Soleil. I love the dramatic sculptural looks and the huge shapes.

What's your favorite lab-based design so far?
The *Klebsiella pneumoniae* fashion piece (Figure 3). It looks horrifying and disgusting – but also beautiful. I love the juxtaposition.

Illustrations aside, you're also a co-host for the laboratory-based podcast *Off the Bench*. What's that like?
Off the Bench is a podcast run by ASCLS. We discuss a wide range of topics, from addressing gaps in healthcare quality for transgender patients to an interview with Alan H. B. Wu – a laboratory storyteller that has published a selection of short stories, books, and has a laboratory TV show currently in the works. There are so many educational podcasts for laboratories, so we thought it would be fun to have an educational and laboratory-adjacent podcast that covers more light-hearted topics. In one of our episodes, we sat down and watched medical TV shows and just talked about how inaccurate the laboratory scenes were! I think that some professional organizations forget that lab professionals are more than just the laboratory. We're people who like to have a laugh! It's nice to have built a community where we can connect without having to be so professional all the time.

"I like to think my comics bring awareness to the profession, and help to showcase the ups and downs of laboratory life."

NextGen

Research advances
New technologies
Future practice

A Giant, Genomic Discovery

Helen Firth tells all about the Deciphering Developmental Disorders study – a project committed to finding diagnoses for children with rare developmental disorders and advancing clinical genetic practice

By Georgia Hulme

Finding molecular diagnoses for rare pediatric disorders is challenging – and something that the Deciphering Developmental Disorders (DDD) study has been dedicated to for over a decade. In partnership with the Wellcome Sanger Institute, the project provides world-class expertise in genomic sequencing and computational analysis for the NHS genetic services. Their latest publication revealed that – using their advanced genome-sequencing methods – 5,500 children were successfully diagnosed with rare genetic diseases. And this is only the beginning. Though recruitment ended in 2015, the study continues to 2030.

We spoke with Helen Firth, senior co-author and clinical lead of the DDD study, about ethical concerns, challenges, and future hopes.

What are the project's main aims?

The project has two main aims – discovery and diagnosis. We wanted to discover the genomic architecture of severe developmental disorders. We also planned to transform the way that diagnosis of such disorders is made in the NHS by pioneering the use of genome-wide sequencing with a trio-exome approach.

The study was inspired by the poor diagnostic rate in clinical practice for children with severe developmental disorders, which – prior to the DDD study – was only around 25 percent. With the novel genome-wide approaches used in the study, this figure has risen to around 40 percent. There is still a lot to learn and discover to find diagnoses for the remaining children.

How was recruitment conducted?

We decided to focus our study on babies and young children with severe disorders that affect their development. In terms of neurodevelopmental disorders and congenital anomalies, we chose this demographic because it has a high clinical

impact. We recruited patients through the NHS genetic services and focused on patients that had high suspicion of a monogenic cause – despite negative genetic testing on the routine tests available in the NHS at that time.

Each individual genome contains four to five million variants where the sequence differs from the reference sequence. Finding the causative variant (or variants) for a rare disorder among this wealth of benign variation was a huge challenge. We therefore chose disorders of infancy and early childhood – since they were likely to be caused by variants that, at least for monoallelic disorders, were unlikely to be found in a healthy adult population.

What types of genetic testing are used in the study, and how are results analyzed and interpreted?

We used a trio-exome approach supplemented by a high-resolution array with five probes per exon of every gene and a SNP array. Combining these three types of data has been helpful in developing algorithms to detect copy number variants (CNVs) in exome data.

What are some of the most important insights that have emerged from the DDD study so far?

The most important discovery is that around 75 percent of the diagnoses of severe developmental disorders in monoallelic genes are due to de novo variants. We've found diagnoses for around 5,500 children across the UK whose variants fall in one of 800 genes. For many of the diagnoses we have made, there is just a single child in the study – indicating the enormous heterogeneity of developmental disorders. The study has shown how combining data and expertise across the NHS genetic services is crucially important. And it has taught us that a large dataset is needed for discovery and to evaluate rare variants.

We've discovered 60 new genes for developmental disorders, and the project has been a key contributor to ~300 papers in the peer-reviewed literature. The DDD study has laid the foundations for the 100,000 genomes project and the NHS Genome Medicine Service.

Were there any ethical challenges for such a large study?

The DDD study raised several ethical issues; however, we included an ethicist in our management committee from the start and employed a genetic counselor/social scientist to complete studies of public attitudes to genomic testing. In our latest publication, we have included a table of the ethical challenges we faced and how we addressed them (1).

What other hurdles did you have to overcome?

The main challenge was coordinating such a large study across 24 participating centers in the UK and Ireland. Setting up the systems to recruit 13,500 families, sequence 33,500 exomes, and report candidate diagnostic variants back to the recruiting centers for evaluation was far from easy! We used the Human Phenotype Ontology (HPO) for phenotyping and worked with their team to develop and optimize the HPO so that it had the scope (>10,000 terms) to enable accurate capture of the diverse clinical features encountered in the study. We also systematically collected detailed morphometric and developmental milestone data and information about family history, pregnancy, and perinatal events. This rich phenotypic data has been invaluable in interpreting the genomic data.

What lies on the horizon?

DDD is facilitated by the DECIPHER informatics platform, which is based at the European Bioinformatics Center. DECIPHER correlates phenotype with rare variants to map the clinically relevant variants in the human genome. The informatics infrastructure used in the DDD study and the knowledge gained are shared via DECIPHER to facilitate future diagnosis for patients globally.

Also looking to the future, DDD continues to search for diagnoses for the undiagnosed participants and, when diagnoses are found, we immediately report back to the patient's clinical geneticist. We hope to continue making new discoveries and have been amazed at how successful this collaboration between patients, clinicians, scientists, bioinformaticians, ethicists, and patient support groups – such as Unique – has been in finding answers for patients and their families.

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Turn Up the AMP!

Sitting Down With… Laura Tafe, President of the Association for Molecular Pathology

What's your current role?

I work as an anatomic and molecular pathologist at Dartmouth-Hitchcock Medical Center in New Hampshire, where I am an associate professor of pathology and laboratory medicine. My interests are in GYN and lung pathology and solid tumor molecular diagnostics. I am part of our Laboratory for Clinical Genomics and Advanced Technologies (CGAT) and I direct the institutional Molecular Tumor Board. Beyond my day job, I am a mother, a partner, and an artist.

How did you get involved in AMP?

I attended my first AMP annual meeting as a resident to present a poster on a project. The molecular director at my residency program, who is now a colleague of mine, has always been very encouraging of resident projects. It was actually a conversation at that meeting with an AMP member that solidified my decision to pursue fellowship training in molecular genetic pathology. After fellowship training, as junior faculty, I became a member of AMP's Training and Education Committee and ended up being Chair of that committee. The rest is history. I consider AMP my primary professional society, and I have benefited greatly by being involved with AMP – both personally and professionally. It's a real honor to serve in this role as AMP President.

What does the president of AMP do day to day?

Given that AMP is a relatively young society that represents a very fast-moving field, the role of president keeps me busy. The day-to-day work of the AMP president is never boring. This past week I reviewed and weighed in on a couple of position statements in support of AMP's public policies, had a call to discuss a speaking opportunity as part of a panel discussion, and reviewed CVs for candidates seeking appointment to volunteer positions. I am fortunate that my institution and my family are supportive of my role with AMP. I am continually impressed by the fact AMP's Board, committees, and working groups are made up entirely of volunteers. We are all working together on top of our daily professional commitments to advance AMP's mission.

Have there been any standout moments of your tenure so far?

A former AMP president once told me: "You never know what will come along during your Presidency year." So, I'm open to the unexpected. AMP was very pleased to see the VALID Act was not included in the omnibus spending package at the end of 2022. This decision helped protect access to the more than 160,000 laboratory developed testing procedures (LDPs), which benefit patients each and every day.

What is your goal as president of AMP?

It is very important to me to help continue AMP's work in raising the visibility of pathology, especially the work being done by molecular professionals. AMP is working hard to ensure that molecular professionals are recognized for the integral part they play. We saw a temporary increase in public recognition during the COVID-19 pandemic, but that is subsiding. I am also pleased to be working with AMP on the continuation of our efforts to incorporate diversity, equity, and inclusion into everything we do as an organization. One example is the creation of standardized evaluation rubrics for the assessment of applicants for volunteer positions and awards. Equity in accessibility to molecular diagnostic testing is also a high priority.

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Where is molecular pathology heading? Do you feel any topics go under-represented?

We have seen an explosion of growth in the oncology space with the introduction and adoption of molecular biomarker-targeted therapies. Increasingly, solid tumor and lymphoid malignancy diagnosis and characterization is based upon molecular attributes, which also can provide prognostic and predictive information.

I think that some of the topics that go under-represented are those that often come with the incredible growth of our field. How does evidence-based genomic medicine keep pace with discovery while providing accessible and equitable care for all patients? How do we best leverage the existing oversight mechanisms to address a field that is changing so quickly? How do we provide coverage and reimbursement for the professional work required to interpret and report the result of a complex molecular diagnostic test? What will happen if gene patenting – which AMP, of course, feels is an issue that was already adjudicated and decided years ago – resurfaces for discussion?

How did you get started as an artist? And what connections do you see between art and pathology?

I'm an analog collage artist. Pathology (especially anatomic pathology) is very aesthetic and visual, which I think was part of the appeal for me. It involves putting pieces together to make the diagnosis, making sure nothing's missing. You need to be comprehensive and pay attention to the details to get the overall picture. Pathology is an art in itself.

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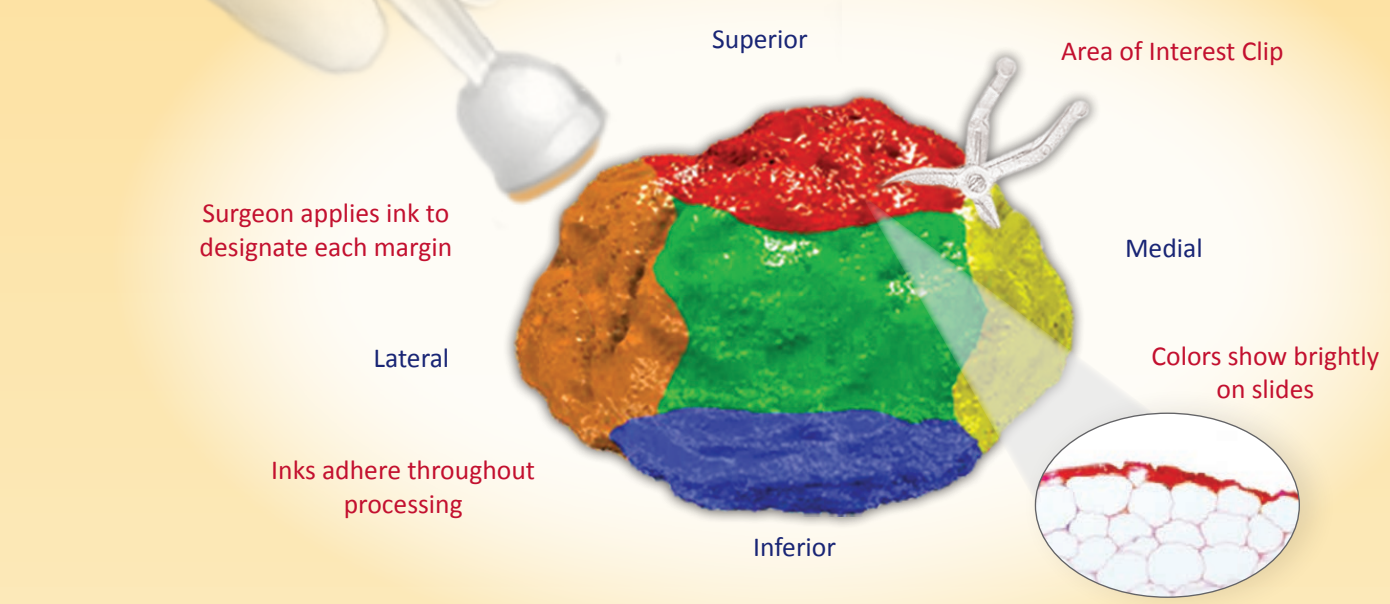

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