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POWER List

This year's finalists have their say on the key challenges and emerging trends in pathology today

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Hidden Heroes

From rising stars to champions of change, we celebrate pathologists, laboratory medicine professionals, and researchers who represent the success of the entire field

Once again, it is time for The Pathologist Power List to throw the spotlight on the few to reflect the success of the many. Yes, the Power List is a celebration of this wonderful field – but it is also a beacon that calls attention to an area of medicine that urgently needs to attract a new generation of pathologists and laboratory medicine professionals that are just as passionate as the last.

We acknowledge that no such list can ever be definitive – but, to at least give us the best chance of reaching all corners, we split the 2024 Power List into five categories: Champions for Change, Destined for Excellence, Heroes of Pathology, Idols of Innovation, and In the Wings.

Certainly, you will find several familiar names on the Power List, but – thanks to an overwhelming reaction to the open nomination process and the time and consideration of our open-minded international judging panel – you'll also find new names that are arguably no less deserving of recognition. You can find the full Power List online here: *https://bit.ly/4ewrSp6*

While we held the collective attention of this year's Power Listers, we took the opportunity to ask them to share their views on the current state of the field – and also to ponder on its future. Turn to page 10 to find out what they told us…

What controversial opinions do they harbor? What are the biggest challenges in pathology today? You'll find answers to these questions and more. And as The Pathologist gears up to celebrate its 10th anniversary, we're particularly interested in exploring what the next 10 years will look like. Watch this space!

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A Heightened Zoonotic Threat?

Researchers confirm spillover of H5N1 avian influenza virus to dairy cattle

Credit: Images for collage sourced from Adobe Stock and Pixabay.com

A Nature study reports the spillover of a new highly pathogenic avian influenza (HPAI) H5N1 virus clade 2.3.4.4b into dairy cattle, as well as evidence of sustained mammal-to-mammal transmission, for the first time (1).

The virus is known for causing widespread death in domestic and wild birds and the findings – in particular, transmission at a non-traditional interface – raise concerns about the pandemic risk for humans.

The study documents a morbidity event affecting dairy cattle in nine farms across Texas, New Mexico, Kansas, and Ohio, beginning in January 2024. Affected cows exhibited several symptoms, including reduced feed intake, breathing difficulties, and a drop in milk production – with the milk turning yellowish and resembling colostrum. Viral RNA was consistently found in milk samples, linking these symptoms to HPAI H5N1 infection and the observed clinical symptoms.

Diagnostic investigations using real-time reverse-transcriptase PCR (rRT-PCR) revealed the presence of HPAI H5N1 in various tissues, particularly in the mammary gland. High viral loads were also found in milk and other tissues, such as the lung and supramammary lymph nodes. These findings suggest that milk could be a key route for transmission to other species – such as farm cats, which may drink raw milk.

Indeed, the researchers documented viral sequences recovered from birds, domestic cats, and a raccoon. The spread of the virus between farms was also noted, suggesting both local and interstate transmission – likely due to cattle movement, wild birds, shared equipment, and personnel.

There is concern that HPAI H5N1 clade 2.3.4.4b will adapt to its new mammalian host and increase the risk of increased infectivity and transmissibility to humans; however, no human cases have been reported from the affected farms in this study.

References

1. *LC Caserta et al., Nature (2024). PMID: 39053575.*

Palaeopathology at the Double

Forensic analysis reveals ancient history of cancer research

This incredible image of skull 236 and skull E270 was taken by Tatiana Tondini and colleagues at the Institute for Archaeological Sciences, Eberhard Karls University of Tübingen. The skulls were pivotal to the team's research on ancient cancer, which used micro-CT scanning and microscopy to reveal hidden information about ancient Egyptian medical care and research.

Credit: Tatiana Tondini

The Value of Neuropathology

It's time to address reimbursement challenges in the field

Credit: University of Texas Health Center

By Maggie Flanagan, Associate Professor of Pathology, Nun Study Director, South Texas Alzheimer's Disease Research Center Neuropathology Core Leader, Bigg's Institute Brain Bank Director, Baptist Health Foundation of San Antonio's Endowed Chair, University of Texas Health Science Center San Antonio, USA

Neuropathologists play a vital role in diagnosing complex diseases and neurodegenerative conditions that require a high degree of technical skill and specialized knowledge. Despite this, their contributions – and those of pathologists in general – are often undervalued within the broader healthcare system, particularly when it comes to reimbursement models. This undervaluation of pathology services not only affects the financial sustainability of labs but also directly impacts the quality of patient care.

This issue is especially pressing in neuropathology, where diagnostic procedures, such as brain tumor biopsies, brain autopsies, amyloid and tau protein analyses, and cerebrospinal fluid testing, require significant expertise and advanced technology. Yet, these highly specialized services are frequently reimbursed at rates that fail to reflect the complexity and time required to perform them accurately. For example, both a complex brain tumor biopsy and a relatively simpler tubular adenoma are reimbursed under the same billing code, CPT 88305, which is designated for "Level IV Surgical pathology, gross, and microscopic examination." Brain tumor biopsies understandably require far more time, technical expertise, and advanced diagnostic tools compared with a routine tubular adenoma gastrointestinal biopsy. Equal compensation for unequal work undermines the financial sustainability of neuropathology services, which depend on highly skilled labor and cutting-edge technology for accurate diagnoses.

Under the traditional fee-for-service model, pathologists are reimbursed based on the number of tests or procedures they perform. However, many essential diagnostic services in neuropathology, such as immunohistochemical staining for tumor classification or advanced molecular testing for brain tumor evaluations, are reimbursed at relatively low rates. This can be especially challenging for neuropathology laboratories that depend on high-cost, cutting-edge equipment to deliver precise diagnostic results. Moreover, fee-for-service models can incentivize higher testing volumes rather than prioritizing the accuracy and necessity of those tests – something particularly critical in neuropathology, where false positives or negatives can have serious clinical consequences.

The shift toward value-based care, while intended to improve outcomes and lower costs, presents additional challenges. Bundled payments – where services related to a particular treatment or condition are grouped together – further undervalue pathology services, including those provided by neuropathologists. This system puts undue pressure on lab leaders to reduce costs, which can limit their ability to invest in essential technology and training that keeps neuropathology at the forefront of patient care. One of the reasons for this undervaluation is the "invisibility" of much of the work performed by neuropathologists and pathologists overall. Unlike clinical specialties, where patient interaction is direct and visible, much of our work happens behind the scenes. This, combined with a lack of understanding of the complexity of neuropathological diagnoses, contributes to the misalignment between the value of our services and the compensation provided for them.

Addressing these reimbursement challenges requires a targeted, multifaceted approach. Advocacy efforts by professional organizations, such as the College of American Pathologists and the American Association of Neuropathologists, are essential to raise awareness among healthcare providers, insurers, and policymakers about the critical role of neuropathology in patient care. These organizations must also continue lobbying for reimbursement models that accurately reflect the value and expertise required in our field. Moreover, alternative payment models that better align incentives with the quality and outcomes of neuropathology services are urgently needed. Neuropathology-specific bundles that account for the complexity of individual diagnostic services could ensure fairer reimbursement, while quality-based models would better reflect the outcome-driven focus of our work, particularly in the context of neurodegenerative diseases.

However, advocating for these changes will require data. Demonstrating the cost-effectiveness of timely, accurate diagnoses provided by neuropathologists will provide the evidence needed to support more equitable reimbursement models.

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Attention and Support

Advocating for your profession is a need, not a want

By E. Blair Holladay

Professional advocacy should be regarded not as something nice to do, if you have some spare time. It is a crucial endeavor that helps not only our profession and our careers, but also our patients. Advocacy raises awareness of our profession and influences public policies, ensuring pathology and laboratory medicine remain the cornerstone of healthcare.

ASCP is deeply dedicated to advocating for our members, our profession, and our patients, and the primary outcome of these efforts is raising awareness about the significant impact of the laboratory on patient care. It is with a patient-centric mindset that we pursue our advocacy efforts – and because of this approach, we see incredible success.

We recently secured a win in this space when, along with the ASCP Board of Certification (BOC), we successfully advocated for the Centers for Medicare & Medicaid Services (CMS) to abandon their plans to allow individuals with Bachelor of Nursing degrees to perform high complexity testing. Not only did this combined effort succeed in preventing Bachelor of Nursing degrees from qualifying individuals to perform high complexity testing, but also in reversing CMS' policy of considering nursing degrees as equivalent to biology degrees.

That is one win among many, but our efforts to ensure that all patients are receiving the highest-quality care don't stop there. Several ongoing measures in the US have our attention and support, including:

- The Public Health Infrastructure Saves Lives Act, which is intended to address chronic underfunding of the state, local, tribal, and territorial public health infrastructure. The legislation seeks to ensure a dedicated investment in foundational public health capabilities and workforce. The program would award grants to state and territorial health departments, and to local health departments serving more than 500,000 people, based on a formula determined by several factors, including population size, burden of preventable disease and disability, and poverty rate. ASCP has endorsed this act and will continue to monitor its progress.
- The Sickle Cell Disease Comprehensive Care Act (SCDCCA), which is legislation that would enable state Medicaid programs to provide comprehensive, coordinated care through a health home model for individuals with sickle cell disease. The bill sponsors have indicated that it could be considered by the Energy and Commerce Committee in an upcoming committee hearing. ASCP, together with ASH, has urged that this measure is included on the committee's agenda for consideration as soon as possible.
- Calling on members of Congress to fix the Medicare Physician and Clinical Laboratory Fee Schedules. ASCP encourages its members and those in the pathology and laboratory medicine community to contact their representatives on this matter, as these two fee schedules are critical players in determining whether laboratories get adequately reimbursed for the services they provide their patients. As these fee schedules aren't keeping pace with the cost of medical inflation, the financial challenges are making it increasingly difficult for laboratories to ensure they can continue to meet the needs of their patients.

This is only a small sample of the efforts we are advocating, knowing that we are "StrongerTogether" when our voices are as one. We are shining a light on the essential care the laboratory community provides daily, and we don't do this work alone. When you engage in advocacy work, you help the public, policymakers, and other stakeholders better understand the breadth and importance of the contributions you make to healthcare. And that can ultimately lead to better support and resources for you, for our community, and, importantly, for our patients.

Moving Forward with Multiplexing

Improved scanning and processing of stained multiplexed tissue samples with the Invitrogen™ EVOS™ S1000 Spatial Imaging System

The EVOS lineup from Thermo Fisher Scientific emphasizes sophisticated simplicity, offering usability for scientists – even those with less experience, while still producing high-resolution microscopy images. The new EVOS S1000 Spatial Imaging System uses spectral technology – allowing users to capture images of tissue samples with multiple markers in a single step. Here, The Pathologist speaks with Chris Langsdorf and Adyary Fallarero at Thermo Fisher Scientific to learn more about the EVOS S1000 Spatial Imaging System – and the future of multiplexed tissue samples.

How does spectral technology overcome some of the barriers to multiplexing multiple biomarkers in a single sample?

The workflow for spatial biologists performing multiplexing and spatial imaging is roughly divided into three phases. The first is fluorescence labeling – finding the right combination of targets – antibodies and fluorophores to label the tissue. We're working on simplifying this process to help users prepare samples more effectively. Secondly, the imaging process itself can be slow, difficult, and sometimes lacks sufficient resolution. The goal is to make it simpler for users and speed up this process while maintaining high resolution. And thirdly, analyzing the data of a single tissue sample remains complicated. Extracting quantitative data from images (what we call "feature extraction") is an area we're continuously investigating so that we can improve the process for users.

Traditional fluorescence microscopy methods typically allow imaging of up to four targets. However, for spatial biology, four targets is insufficient to truly understand cellular diversity. To overcome that barrier, researchers now use fluorophore-conjugated primary antibodies or amplification strategies to study a larger number of targets. The shift from traditional methods to these new approaches is significant, and researchers need support to adapt to these changes effectively.

What are the benefits of the multiplexing approach?

A multiplexed approach in spatial biology provides a much deeper understanding of heterogeneous cell populations while keeping the spatial context of molecular data intact. For example, when comparing healthy and cancerous tissues, we can detect distinct patterns and cell types that may be likely missed with fewer markers. This is particularly important for improving our understanding and developing more accurate biomarkers for tracking disease progression, developing more effective therapies, and achieving improved clinical trial outcomes.

This approach also makes use of many of the same tools as in standard fluorescence microscopy, such as fluorophore-conjugated antibodies for detecting antigens and identifying different cell types in a tissue sample. We also use standard reagents, such as streptavidin conjugates for biotinylated antibody detection and DAPI to stain cell nuclei.

How does the EVOS S1000 Spatial Imaging System aid in the visualization of multiplex biomarkers in single tissue samples?

Using the EVOS S1000 can be truly advantageous because it enables both traditional color imaging and advanced fluorescent microscopy with high resolution. It has an intuitive, streamlined acquisition software that enables easy protocol set-up and fast scanning capabilities – acquiring 8 protein targets and DAPI in one single round, due to its spectral technology.

In addition, the system is designed to handle a wide range of dyes and spectral acquisitions, allowing it to work with over 30 different dyes, including Alexa Fluor, Alexa Fluor Plus, and Aluora Spatial Amplification Reagents, among others. It offers great flexibility and removes the limitations of using only certain specific fluorophores, which gives more options for labeling and imaging.

What impact will the new system have on lab workflows?

The EVOS S1000 improves lab workflows by offering fast scanning with the highest level of imaging with a beginner friendly acquisition software, similarly to all other EVOS systems. Pathologists familiar with traditional staining methods can confidently transition to multiplex fluorescence imaging without needing to become experts, thanks to the system's ease of use.

We're focused on making the entire process – from sample labeling to image acquisition – simple and user-friendly, addressing common challenges at every step. And we aren't stopping there.

Adyary Fallarero Ph.D. is Senior Product Manager at Thermo Fisher Scientific.

Chris Langsdorf is Product Manager at Thermo Fisher Scientific.

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the Pathologist

POWER *List*

What are the challenges, trends, and aspirations driving pathology forward? This year's Power Listers have (some of) the answers.

The Pathologist Power List recognizes pathologists and laboratory medicine professionals who are going the extra mile or breaking boundaries. Inspiring mentors, change managers, diversity champions, and selfless volunteers represent just some of the superstars who were nominated by their colleagues and scored by an international judging panel of their peers.

We asked this year's Power Listers to share their thoughts, opinions, hopes, dreams – and the issues that keep them awake at night or get them pumped for action each morning.

One question – "What is the biggest challenge facing the pathology field right now?" – unleashed a torrent of frustrations and potential fixes that you might relate to or apply in your daily practice.

Meanwhile, "What is the most exciting development or emerging trend in pathology today?" gave our finalists the chance to speak passionately about the great motivators in their chosen profession. Finally, "What would your dream laboratory look like?" opened doors to some answers we really weren't expecting.

Here we share a hand-picked selection of the most representative – and, in some cases, most surprising – answers we received. We wonder whether you will recognize or reject the views expressed… Enjoy!

See the complete Power List online:

Important note: The Pathologist Power List is not intended to denote powerful pathologists or laboratory professionals. Rather, to formulate the Power List, The Pathologist solicited nominations of pathologists and laboratory professionals in any stage of their careers, who have made accomplishments in the past year in one of the following categories: (i) Heroes of Pathology; (ii) Champions for Change; (iii) Idols of Innovation; (iv) In the Wings; and (v) Destined for Excellence. All decisions were made by The Pathologist. As the American Society for Clinical Pathology (ASCP) did not participate in the nomination or selection process, it does not formally endorse the list.

What is the biggest challenge facing the pathology field right now?

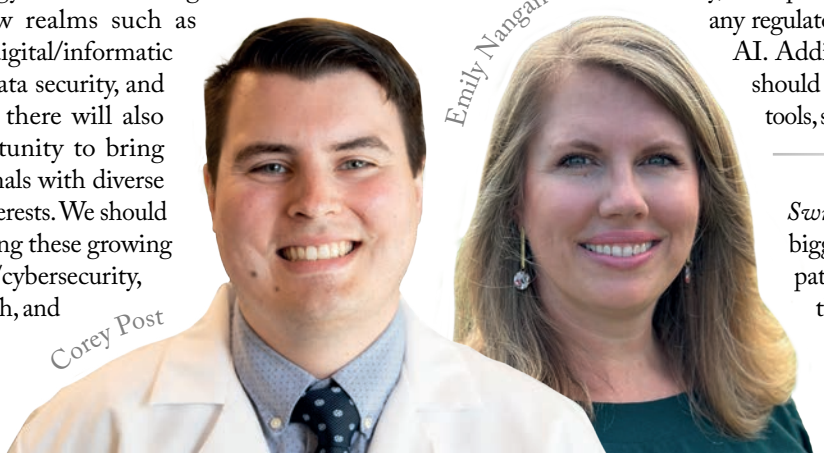
Casey P. Schukow: Recruitment and visibility. I am still very young in my career, but I've seen many pathologists shy away from "the spotlight." This is completely understandable – we typically work behind the scenes in the grand scheme of patient care. But, for many patients and other clinicians alike, this hides the genuine work we do and allows misconceptions of our roles in the "continuum of patient care" (as a mentor of mine would put it).

Additionally, we're facing a critical shortage of pathologists worldwide, and if we do not do our part as an academic pathology community to meet the next generation where they are (i.e., through social media and in the classroom), they will never set foot in a pathology lab and our labor shortages will worsen. Of course, this negatively impacts patient care, which is a risk we cannot take. We need to step outside our comfort zones (as much as our schedules allow) and give the next generation of physicians reasons to consider pursuing a career in pathology – whether it be practice logistics, lifework balance, compensation, etc – through presentations, rotations, and consistent professional online engagement.

Corey Post: The changing regulatory environment in which laboratories must operate. The FDA's "final rule on LDTs" is a prominent example, but the recent overturning of the Chevron deference also helps to highlight the major shifts occurring within the federal regulation landscape. While proper regulation of laboratory testing is essential to ensure quality patient care, proper balances must be maintained to allow for innovation and equitable access to testing.

Changes to enforcement that aren't well understood, rolled out too quickly, or are incongruent with healthcare practice trends can cause further burdens on healthcare systems and pathology practitioners. As we move forward, I expect it will be important for pathologists to remain ahead of these changes and maintain compliance, while also serving as advocates to influence future regulations.

Cullen Lilley: As pathology continues to grow in breadth taking on new realms such as molecular genetics/omics, digital/informatic pathology, bioinformatics/data security, and even cellular therapeutics, there will also be a corresponding opportunity to bring pathology to new professionals with diverse training backgrounds and interests. We should capitalize on this by marketing these growing areas to professionals in IT/cybersecurity, bioinformatics, omics research, and beyond. Pathology and laboratory medicine sits at such a unique juncture, and I think many people in the biomedical sciences would thrive in this field, but they just don't know about it.



Becky Stankowski: A real challenge in pathology is staffing. Our lab is usually fully staffed with Pathologists' Assistants (PAs), histotechs, and lab assistants, but we don't have nearly enough pathologists for our workload. PAs are often involved in the training of pathology residents, and do most of the grossing (and sometimes autopsies and frozen sections) in many places across America. The pathologist shortage is an opportunity to expand the scope of pathologists' assistants in additional ways. PAs that are involved with previewing cases microscopically, attending signout and tumor boards, and communicating with surgeons and clinicians can lighten the load for surgical pathologists. PAs performing forensic autopsies in medical examiner offices would help alleviate the often critical shortages of forensic pathologists. This is definitely starting to happen in some areas, but there's more to be done. An overhaul of current workflows and an examination of resident education standards may be needed to address this ongoing problem.

Emily Nangano: Another key challenge is the responsible integration of AI into anatomic pathology labs. While AI has the potential to significantly augment the work of laboratorians by improving accuracy and efficiency, it must be integrated in a way that enhances rather than replaces human expertise. Ensuring AI tools are implemented thoughtfully and ethically will be essential to complement the skilled work of pathologists and pathologists' assistants, maintaining the exacting standards of care and precision required in this field.

Swati Bhardwaj: Pathology is currently leading the wave of AI applications in medicine. The specialty has generally embraced new technologies, including AI, though with some caution. How AI is integrated as a diagnostic tool will greatly impact the future of pathology. Since pathology generates vast amounts of data used by other medical fields, it's crucial to maintain control of this data and ensure it's used ethically for patient care, research, and education. To do this, clear regulations must be established by a governing body, with pathologists represented in any regulatory authority overseeing AI. Additionally, AI algorithms should have specific validation tools, similar to laboratory tests.

Swikrity U. Baskota: The biggest challenge facing the pathology field right now is the workforce shortage.

Following the COVID-19 pandemic, many have considered early retirement from practice – leading to a vacuum that we are constantly struggling to fill. We must focus on creating more awareness about our field of practice, develop training programs, introduce high school seniors to our specialty, and build resources like www.MatchToPath.com, which can come in handy while learning to get into pathology training programs.

Aaron Odegard: One of the biggest challenges in medical laboratory medicine is demonstrating our value as a crucial member of the healthcare team. Diagnostic testing continues to play an even greater role in positive patient outcomes. The laboratory has the potential to provide value beyond the walls of the hospital, extending health equity to our patients and the surrounding communities. In order to answer this call, we have to demonstrate our value to not only the rest of the healthcare team but also to the executive c-suite as a potential revenue stream for our institutions. One strategy to achieve these goals is to expand our outreach laboratory services and try innovative approaches to reach more patients (e.g., mobile phlebotomy or further extend POCT in new venues).

Christina Narakorn: There is a scarcity of eligible applicants for careers in pathology fields at laboratory and consultant level due to the limited number of educational programs and the specialized nature of the professions. Retention becomes an integral component of workforce planning with factors such as job satisfaction, working conditions, and technological adaptation being of paramount importance. Some strategies I use to tackle this challenge include personality workshops, laboratory awareness and outreach sessions, and offering hospital lab tours with individual observations.

Have you ever wondered if your work personality is the same as your at home personality? My career mentor encouraged me to invest in a weeklong personality facilitator course. After completion of the course, I now schedule virtual and in-person workshops to leverage personality preferences to enhance job satisfaction, productivity, and work culture. Understanding laboratorians' personalities allows tailored recruitment and retention efforts.

Tiffany Telemaque: Laboratory science and pathology remain relatively unfamiliar as career options in society. Like many others, my discovery of the field was largely by chance, a common experience among professionals in the field. This pattern must change. Laboratory science and pathology should be promoted as viable career paths starting from elementary education. This initiative requires contributions from all laboratory professionals. Inclusivity across all aspects is essential for meaningful impact. By addressing this concern appropriately, vacancies can be reduced and burnout can be tackled to an extent.

Tiffany Telemaque

Barnali Das

Eric Q. Konnick: The FDA's final rule regulating laboratory developed tests poses a huge challenge to the field of pathology. The ability of pathologists to adapt new scientific and medical knowledge to patient care could be dramatically hindered, and the financial costs to practice are likely to be greatly increased. Pathologists will be expected to comply with new regulations that are very different from CLIA requirements and have much more severe consequences if we are not in compliance. It is going to be an interesting few years while the final rule is implemented and lawsuits make their way through the courts.

Fatma Alzahraa A. Elkhamisy: In many medical schools in the developing world, the use of digital pathology for teaching is still not appreciated for its actual value. Until now, many pathologists, and policymakers of medical programs outside pathology, saw digital pathology as similar to data-show images, with the only hands-on experience being with glass slides and light microscope lenses. They push against the use of digital pathology slides in the practical labs. Advocates like myself work to increase the awareness of digital pathology's true capabilities and how the recent advances in AI work on analyzing digital slides and improving the accuracy of the diagnoses. We, as pathologists, need to align our efforts and utilize all resources to push the transformation to digital pathology, as it is the building block for advancing the field.

Ahmed Kalebi: The most significant challenge facing the pathology field right now is ensuring that everyone who


Casey P. Schukow

Fatma Alzahraa
A. Elkhamisy


Cullen Lilley


Christina Narakorn


Becky Stankowski

Eric Q. Konnick


Aaron Odegard


Swati Bhardwaj


Swikrity U. Baskota


Ahmed Kalebi


Kalisha Hill

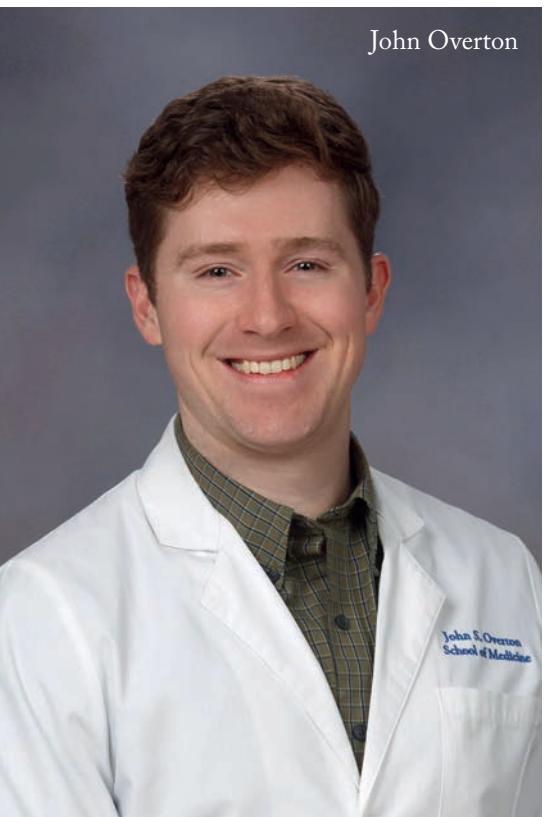

Nicole Aqui


Stephanie Whitehead


Caddie Laberiano


Courtney Lawrence


Woo Cheal Cho


John Overton


Danny A. Milner

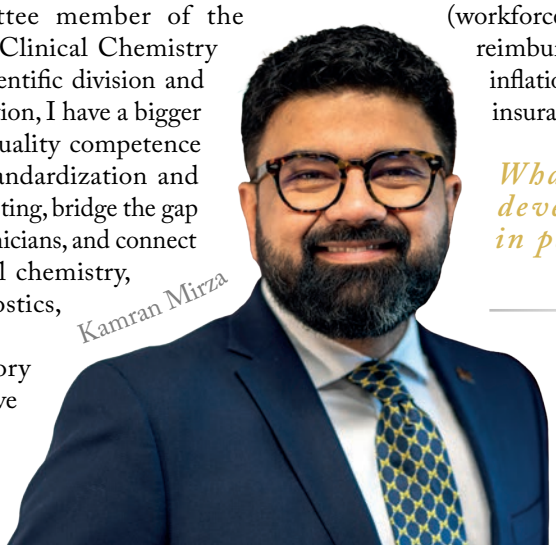

Leonie Wheeldon

needs our essential services can access them. Pathology laboratory testing is critical to public health, yet billions of patients and their healthcare providers lack access to these services when they need them – from preventive and promotive screening laboratory services to advanced diagnostic testing services. Unfortunately, inequity in pathology services exist across the globe, whether between high and low income countries, and within individual communities. These disparities stem from lack of accessibility, availability, acceptance, and the quality of pathology laboratory services.

Barnali Das: Harmonization and standardization of laboratory testing is the need of the hour. Clinical chemistry and immunoassay tests form a very important set of tests in a pathology laboratory, a tool that clinicians and patients alike depend on to pin down the symptoms for treatment and relief. However, this very set of tests has come into question as the acceptable ranges for biomarkers can change in relation to other biochemicals, biomolecules, and hormones, which themselves vary considerably with race, gender, age, different physiological conditions (like pregnancy, newborn), and other illnesses and interfering substances. Individual variations in thyroid-stimulating hormone (TSH), for example, can be so pronounced that each person may seem to have their own set-point. In addition, clinicians and diagnosticians have to grapple with the variability of test results. Even a broadly similar set of instruments and methods can provide different results, to as much as 40 percent, for example, in case of TSH values.

As an executive committee member of the International Federation of Clinical Chemistry and Laboratory Medicine scientific division and chair of the ADLM India section, I have a bigger role to play to incorporate quality competence in healthcare, implement standardization and harmonization of laboratory testing, bridge the gap between diagnosticians and clinicians, and connect with professionals in clinical chemistry, pathology, molecular diagnostics, and the IVD industry.

The roadmap for laboratory medicine therefore will involve strategies for harmonizing, communicating, and integrating with all stakeholders to formulate guidelines for assisting in correct measurement, diagnosis, and management of diseases.


Kamran Mirza

Danny A. Milner: Everyone knows about the threats associated with the advent of digital pathology and artificial intelligence. But they aren't the real challenge. The major threat to the field of pathology today is multi-cancer early detection. This has the power to screen entire populations potentially before a cancer is detectable by routine methods. Once this is in place, functioning, and following appropriate clinical trials and studies, patients with positive signals but no obvious cancer can undergo a pan-cancer therapy for a limited period and re-test. This paradigm will remove surgeons, pathologists, and oncologists (and all of their staff) from the process and create a primary care role for the elimination of cancer. Of course that situation is *best* for patients because everyone survives, no one suffers, and cancer loses its psychological hold on society. But such disruptive innovation has a creative destruction in its wake. The challenge for the field of pathology is to embrace this eventuality and determine where quality, safety, and outcomes monitoring are ideally suited for laboratory professionals to oversee in such a new paradigm.

Kamran Mirza: The biggest challenge facing the pathology field today is the shortage of trained pathologists and laboratory professionals. This shortage strains our healthcare systems and impacts patient care, particularly in underserved areas. Additionally, the rapid advancements in technology require continuous education and adaptation, which can be daunting. Addressing these challenges requires a multifaceted approach, including increased investment in pathology education, better support systems for professionals, and leveraging technology to streamline workflows and improve diagnostic accuracy.

Kalisha Hill: The greatest challenge facing pathology now is reimbursement for services. The cost of practicing pathology (workforce, diagnostic tools, facility costs) is rising as reimbursement rates are declining. Advocating for inflationary adjustment for physicians and Medicare/insurance reforms is warranted.

What is the most exciting development or emerging trend in pathology today?

Caddie Laberiano: I find everything related to cytology very exciting, especially when

it involves new modern techniques like molecular testing. The goal of cytology has always been to improve diagnosis with less material, and I believe this should be explored by current residents, fellows, and pathologists in general.

Casey P. Schukow: Digital pathology and the flexibility to work from home. When I entered medical school, I wasn't sure which direction to take my career in. As I completed more courses and clinical rotations, I realized that the day-to-day routine of many medical and surgical fields was not my forte – mainly due to schedule rigidity. I noticed that I valued the flexibility when I practice, particularly in my daily schedule.

Another major element that drew me into pathology was that my patients are on glass, whether through a microscope lens or digitalized via a computer screen. In the next few years I hope to become a father, which will make it crucial for me to be able to step away from my work at a moment's notice for family emergencies. As a healthcare employee, my family's well being is my priority and, in most other fields, you aren't given the flexibility many parents and carers require – you must be with physical patients from dusk till dawn. As a pathologist, I'm able to see my "glass" patients and provide superior patient care at any hour of the day, while still being prompt in diagnostic turnaround times.

As digital pathology becomes more tried, tested, and true, it's only a matter of time until I can complete part of my clinical duties from home without compromising personal or professional obligations. As with any team-based organization, we must balance our onsite and at-home duties to maintain a sense of team camaraderie, trust, and high morale, especially as the digital age expands. But, anecdotally at least, a lot of medical students are looking for opportunities to work from home – so why isn't our academic pathology community sharing more about the developments of digital pathology that allow for flexibility and remote working? We should also be training future pathologists from day one to be comfortable in using digital and computational pathology, which is undoubtedly where the field is heading.

These trends are exciting, but we need to make more of an effort to embrace, highlight, and refine them to direct our field in the right direction. The next generation needs to see pathology as an attractive and competitive speciality for 21st century medical students to consider pursuing it further down the road.

Cullen Lilley: In surgical and medical pathology, I think we've seen exciting developments in the areas of spatial transcriptomics and proteomics. There are certainly still challenges in this area to work through, however, even if spatial omics does not get integrated into the pathology workflow, I think the knowledge gained form this field will ultimately impact how we understand diseases and histopathologic findings.

Of course, we can't discuss exciting developments without mentioning digital pathology and informatics, which is likely to completely alter how pathology is practiced and taught in the upcoming years. The ability to digest large amounts of data and more accurately quantify certain histopathological findings is sure to strengthen our field and support the delivery of higher quality patient care.

Stephanie Whitehead: The field of laboratory medicine is experiencing exciting advancements in molecular pathology and personalized medicine. With an enhanced understanding of the genetic underpinnings of diseases, we can offer more targeted and personalized treatment recommendations based on an individual's genetic profile. This approach is revolutionizing the management of conditions such as cancer, where therapies are tailored to the specific genetic mutations present in tumors.

Additionally, there is a growing focus on the role of pathology in preventative medicine and public health. By identifying biomarkers and early signs of disease, laboratories are at the forefront of early detection and prevention strategies, ultimately improving patient outcomes and reducing healthcare costs.

Woo Cheal Cho: One of the most thrilling advancements, particularly in dermatopathology, is the integration of advanced molecular testing into routine practice. This evolution enables the identification of potentially targetable genetic abnormalities, accurate diagnosis of complex lesions, and even the discovery of novel tumor types based on specific molecular alterations such as gene fusions. This transformation not only enhances diagnostic precision but also opens up new avenues for personalized treatment strategies – ultimately improving patient outcomes.

Emily Nangano: The rapid advancement and expanding roles of PAs, particularly in fields such as forensics and research. PAs are taking on more responsibilities in the preparation and examination of surgical specimens and autopsy cases, contributing to more efficient workflows and allowing pathologists to focus on complex diagnostic tasks. In forensic pathology, PAs are increasingly involved in autopsy procedures and the analysis of forensic evidence, playing a crucial role in criminal investigations and legal proceedings. In the research domain, PAs contribute to the collection and analysis of data, supporting the development of new diagnostic techniques and treatments.

The combination of advanced digital tools and the growing expertise of pathologists' assistants is transforming the field of pathology, leading to more accurate diagnoses, improved patient outcomes, and exciting new possibilities in research and forensic pathology.

John Overton: Learning about pathology clinics, where patients come and discuss their diagnoses and review slides with pathologists, has been super exciting. I would love the chance to see one of these in action!


Laura Severs


Niki Boisso


Anna Marie White


Debbie Gonzalez

What would your dream laboratory look like?

Anna Marie White: Fully staffed with current instrumentation and a Quality Assurance Technologist for competency assessments, CAP compliance, and updates. Supervisors can focus on supervisory duties instead of bench work, and have time for meetings to discuss changes, address problems, and hold learning sessions.

Debbie Gonzalez: Wow, maybe like the Jetsons! Automation, hidden electrical (no cords anywhere!), state-of-the-art equipment, robotics, and an open, modular floor plan that allows for growth and changes. Each testing section would have big screens monitoring test turnaround time and other KPIs. I'd love cushioned flooring so techs have the best working condition for standing, complete with ergonomic chairs. In a private section, a mommy room for nursing moms, a medication room with vibrating massage chairs for all employees to take a break, listen to some music, or read a book. I'd also like to have a student/intern section with a full simulation lab for teaching.

Niki Boisso: My dream gross room would prioritize safety and space, which should always be a top priority. Grossing can strain the body, especially the neck, as we often work with our heads forward for much of the day. In an ideal gross room, all workstations would be height-adjustable to improve ergonomics and accommodate grossers of different sizes and preferences, whether they prefer to sit or stand. Each station should also have its own cassette printer to reduce the risk of submitting tissue in the wrong cassettes and to improve efficiency by eliminating the need to wait for other cases to print or walk to a shared printer.

Space is another important consideration. The gross room should be a large, open area, which is especially important for teaching first-year residents. A workstation that is accessible from all sides would allow for better demonstrations, without everyone crowding or speaking with their backs to the learners. It would also be helpful to have a designated area for frozen sections, with specific stations available for frozen grossing and a well-ventilated area for cryostats and stain lines.

Lastly, but certainly not least, windows. There should always be windows.

Laura Severs: When I think about a dream laboratory my first thoughts aren't space, location, or equipment – they're people. My dream laboratory is a group of people from diverse backgrounds with a passion for patients and high quality laboratory services. I want this laboratory to be a safe space for people to envision the world through a new lens and to be courageous in their innovative ideas. I envision this laboratory to be a space where everyone feels valued by people inside and outside of the laboratory.

Courtney Lawrence: In the Medical College of Georgia Forensic Pathology Fellowship Program at the Georgia Bureau of Investigation, an exciting trend is emerging: sharing information about our field with younger people or anyone interested in learning more. This is essential, especially given the current shortage of medical examiners in the country. It takes about 13 years of education to become a forensic pathologist, so we're starting early to build interest in the field.

We're actively engaging with younger people by allowing them to attend court appearances, participate in shadow days, discuss their educational plans, and more. By building relationships with them now, we're laying the foundation for them to possibly join us in the future and help address the shortage of forensic pathologists.

Program Director Rachel Geller, past fellows, and I take every opportunity to promote forensic pathology. Some of our efforts include:

- Speaking at high schools across the state about the importance of forensic pathology.
- Providing virtual lectures to high school students on the dangers of drug use, distracted driving, and speeding.
- Offering virtual lectures on forensic topics for residents.
- Setting up electives at nearby medical schools, allowing students to observe our work firsthand.
- Hosting shadow days for pre-med and medical students.
- Giving high school tour groups a look at human skeletal remains and histology slides while explaining our work.
- Hosting rotations for residents who may apply for our fellowship program.
- Attending specialty fairs at local medical schools.
- Discussing the current shortage with prosecutors, investigators, interns, and coroners to improve collaboration and ensure timely case completion and report releases.

These efforts aim to spark interest in forensic pathology and create a future workforce to address the shortage in this crucial field.

Nicole Aqui: I may be biased because it's my field, but the expanding role of pathologists into therapeutics is incredibly exciting. Chimeric antigen receptor T cells (CAR-T) and gene-modified stem cells are revolutionizing the treatment of hematopoietic cancers and hemoglobinopathies. With several FDA-approved cellular products, pathologists play a major part in these innovative, personalized therapies by providing the starting material for manufacture of the product. Our expertise in cell collection, processing, and quality control uniquely positions us to shepherd these research breakthroughs into clinical use. At the University of Pennsylvania (UPenn), for example, cells are collected in our apheresis unit and, in some cases, the gene-modified product is also infused here. On a personal note, it is gratifying to participate in the entire process, vein to vein.

Leonie Wheeldon: Technological advancements with regards to digital telepathology and AI. At MDT, I've observed how effective the lung cancer screening programme is in radiology, with early detection leading to curative surgical treatment. There are many parallels between radiology and pathology and the implementation of AI and digital telepathology would be key for enhancing workflows, automating routine tasks, and automating image analysis.

Implementing telecytology ROSE in our trust has really demonstrated the benefits for multi-site centers where procedures are performed at peripheral sites. This equipment improves accessibility to patients without heavy resource burdens on cytology laboratories. Telecytology also provides opportunities for training, learning, and development with no geographical boundaries or limitations (provided the IT infrastructure is available so opportunities for network-based care can be facilitated).

Niki Boisso: This isn't a product placement (I doubt our lab will ever purchase one!), but I'm really excited about the technology behind the Cision Vision's InVision unit for helping with lymph node searches.

It's well known that finding more lymph nodes leads to better prognosis for patients. Whether it's because removing cancerous lymph nodes lowers the risk of recurrence or because it helps with more accurate staging, every grosser knows they can't stop searching after finding a set minimum number of lymph nodes for a specific cancer type. This can lead to long, frustrating searches, often requiring multiple attempts or extra tissue samples to meet the necessary count. The InVision unit uses shortwave infrared technology to highlight the difference between the water content in lymph nodes and the surrounding fat, providing a real-time image that helps the grosser spot more lymph nodes without relying solely on touch.

This tool would be great for teaching residents and new grossers what to look for during a lymph node search. Explaining what lymph nodes feel like can be tough because touch is subjective, and there's nothing in everyday life that feels like lymph nodes in fat. Even when I guide a resident's fingers to a lymph node and say, "Here! This is a lymph node! This is what you are palpating for!" they often still seem unsure. The real-time image from the InVision unit would make it easier for them to recognize and associate what they're feeling.

New learners spend a lot of time in the gross room and often find cancer resections intimidating because of the required lymph node searches. The InVision makes these cases a bit less daunting. While it doesn't replace the need for a manual search, it helps find tiny nodes and those in previously treated cases, saving time on large cases and allowing grossers to move on to other tasks. Anything that makes teaching easier and reduces stress is definitely something to get excited about.

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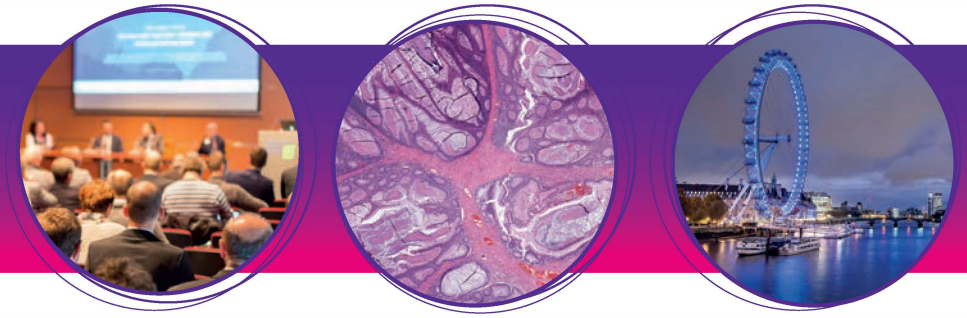

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ANDREW JANOWCZYK
Assistant Professor, Department of Biomedical Engineering, Emory University and Georgia Institute of Technology and Department of Oncology, Division of Precision Oncology, Department of Diagnostics, Division of Clinical Pathology, Geneva University Hospitals, Switzerland

MARILYN M. BUI
Senior Member and Professor of Pathology and Machine Learning Departments, Scientific Director of Analytic Microscopy Core, Moffitt Cancer Center & Research Institute, Tampa, FL, USA; Chair of Digital and Computation Pathology Committee of CAP

PETER SCHIRMACHER
Director, Institute of Pathology, Heidelberg University Hospital; President, European Society of Pathology

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MOLECULAR PATHOLOGY

Biobank Boost

Estonian Biobank paves the way for the future of personalized health care at a national level

Founded in 2000, the Estonian Biobank has expanded in both size and importance over the last two decades. Approximately 20 percent of the adult population of Estonia – around 212,000 adult individuals – have now joined the biobank and had their DNA genotyped.

In addition to its genetic research, the biobank is also used as a testing site for the development of personalized health care. Several recall studies have been carried out based on the biobank's monogenic findings, polygenic risk score results, and findings in pharmacogenetics. Biobank participants were then invited into disease-specific studies and investigated by clinicians. The project has demonstrated a genetics-first approach to health care that leaders now want to implement on a national scale.

Recently, the Biobank received a funding boost from the European Commission, with an equal investment from the Estonian government. These additional funds have enabled set-up of a new center for personalized medicine in Estonia, as well as investment in long-read sequencing technology that will be used to expand the genomic database.

To find out more about this project – and what the cash injection could mean – we spoke with Lili Milani, Head of Estonian Biobank and Professor of Pharmacogenomics, at the University of Tartu, Estonia, and genomics expert Neil Ward, Vice President and General Manager EMEA at PacBio.

Now the Biobank has received more funding, what will the next steps be?

Lili Milani (LM): This investment will enable us to set up a center for personalized medicine in Estonia, in collaboration with partners from the Netherlands and Finland. It will also allow genomic sequencing of a further 10,000 biobank participants. The purpose is both to maximize clinical findings in the genomes themselves and to build an improved genotype imputation reference panel.

The funding has also enabled us to upgrade to long-read sequencing technology. We will use the data to create a population-specific reference for rare variants, structural variants, and any other relevant genetic variation that we can then impute into the genotype data.

How has the biobank impacted healthcare in Estonia?

LM: So far we have used the findings mostly for research. But what's unique about the Estonian Biobank is that we share individuals' results directly with them. For comparison, the UK Biobank is number one for research, but they do not run genetics-based recall studies and they don't return results to the participants.

Our first two studies focused on breast cancer mutation carriers and people with familial hypercholesterolemia – common monogenic disorders, where carrying a mutation in one gene results in a considerably higher risk for breast cancer or cardiovascular disease. We identified those individuals in the biobank with mutations in these genes and invited them to participate in a study.

Overall we found that, although most of them had family history of early onset breast cancer or cardiovascular disease, very few of them had actually been referred to a medical geneticist for further review, and were unaware of the risk. These findings really brought oncologists and cardiologists on board – they demonstrated that the biobank is a great resource for identifying people at high risk for disease.

The next step we took was to find polygenic risk scores – both for breast cancer and cardiovascular disease. A thousand individuals with high risk for breast cancer or cardiovascular disease participated in the studies. They were referred to an oncologist for mammography screening or to a cardiologist for a cardiovascular health review, prescribed preventive medications, and offered new treatment plans.

The success of this trial has led to the roll out of a national polygenic screening program for breast cancer. It has also led to a reduction in the age threshold for regular calls for mammographic screening for people with high polygenic risk for breast cancer.

What are the advantages of long-read genomic sequencing technology?

Neil Ward (NW): The Estonian Biobank, and many biobanks around the world, have typically carried out genetic analysis with microarray data. That technique uses small glass slides with spots of DNA on them that allow researchers to look at around a million locations in the genome prone to variation. That can be very informative across many diseases, but there are a lot of other parts of the human genome that are difficult to assess accurately within the microarray technology or short-read sequencing technology.

Long-read sequencing technology allows us to look at very long stretches of DNA – typically 15,000 to 20,000 base pairs of fragments – very accurately at any one point in time. That is often sufficient to understand different genetic variations inherited from parents, for example. It is much easier to understand those differences with our technology than with short-read sequencing.

Having long-reads, with accurate sequencing, allows us to understand the subtle genetic variations between genes that are very closely related to one another. Sometimes you can have genes that are 99 percent similar but have different functions in the human genome. Long-read sequencing allows us to disambiguate what would otherwise be a sort of mixed signal on those similar genes. The pharmacogenomics genes typically fall into that category, and there are a number of other conditions and genes where the information generated from long reads is particularly useful.

How do long-read and short-read sequencing technologies compare in terms of time and cost?

NW: Typically, the short-read methodologies "parallelize" better. They yield billions of measurements from a single glass slide on a single surface that can be imaged by the specialist equipment. Currently, the long-read platforms achieve an order of magnitude less numbers of reads, but longer read lengths. So, overall, similar amounts of data could be produced, but with a slightly different form factor.

"The success of this trial has led to the roll out of a national polygenic screening program for breast cancer. It has also led to a reduction in the age threshold for regular calls for mammographic screening."

Historically, there has been quite a differential in price between generating short-read versus long-read sequencing genomes. And it is really only in the last year or so, with the latest technologies, that those price points have started to converge. This price trend means that initiatives like the Estonian Biobank can start projects that would previously have been unaffordable with long-read technology. In short, we can now achieve a superior accuracy and read length – and at a price that's becoming closer to that of the older technologies.

How can the environmental impacts of data storage be mitigated?

NW: As technology providers, we have been working hard to minimize the data footprint from our DNA sequencing machines, while retaining the useful information. Actually, the amount of data for one individual's genome record these days is relatively modest – around 50 gigabytes of sequencing data. That is relatively small in comparison to the image files from a PET scan or some other imaging modalities in the healthcare space. To achieve the biological insights required by the Estonian biobank, software is required to analyze big data, but we will continue to work on keeping the data footprints as small as possible. We also want to make the computer algorithms as efficient as possible to minimize the computing cost.

LM: We did take environmental impact into account when deciding which sequencing technology to use. We also had to consider that the costs of data storage and analysis can be close to the cost of the sequencing itself. On the system we selected, the amount of data generated is approximately ten times smaller than others we evaluated, whilst retaining excellent data quality.

What are the implications of the Estonian Biobank findings for health policy and strategy across Europe and beyond?

LM: Firstly, I hope the findings will lead to more centers – like the one that is now funded by this European Commission and Estonian government grant – that can see personalized medicine through all the necessary steps.

One of the other goals of our new funding is to run clinical studies – randomized clinical trials implementing new polygenic risk scores or a randomized study of pharmacogenetics implementing genetic testing prior to prescribing drugs, for example.

Ultimately, we are trying to take all the necessary steps for building and implementing personalized medicine in Europe and internationally.

DIGITAL PATHOLOGY

Connected Pathology in the UK: Part 1

An interview with digital visionary and NPIC leader, Darren Treanor

The elegant city of Leeds in the north of England plays home to a digital pathology revolution. The pathology department at the Leeds Teaching Hospitals (Leeds TH) National Health Service (NHS) Trust was the first in the UK to own digital slide scanners, back in the early 2000s. Since then, the team, along with the University of Leeds, has built up expertise and renown in delivering world-leading digital pathology innovation and research.

In 2018, the UK Government injected money into the NHS to stimulate digitalization as a platform for artificial intelligence. Pathologist Darren Treanor and his team saw this as the ideal opportunity to fully digitize the histopathology service at Leeds TH and connect it to other pathology departments in the region. The National Pathology Imaging Cooperative (NPIC) was born.

The initial grant was for a network of six connected hospitals in the West Yorkshire region of England. Around two years later, thanks to additional government funding from NHS England and the UK Office for Life Sciences, the program expanded to build a system for a wider region. But, piggybacking on the general improvements in information technology, computing power, screen resolution, and data storage technologies, Treanor and his team had a much larger vision – a digital pathology network for the whole of the UK's NHS.

Fast-forward to today, and NPIC has rolled out its program to six hospitals with 100 percent digitization. A further 30 have signed up to join – creating the world's largest digital pathology network – and enquiries are rolling in from all corners of the UK.

Keen to understand what goes into executing such an ambitious and groundbreaking project, we sat down with five of NPIC's leaders to learn what was involved and what a difference it is making. What unfolded was a story of extraordinary vision, drive, collaboration, and teamwork – all on a huge scale.

What is your background and what is your role on the NPIC team?

I went to medical school in Dublin, Ireland, and also started my pathology training there. But I was keen to study abroad, to broaden my training, so I came to Leeds. That was mainly because it was a world famous center for academic pathology, but also because it allowed me to do a computing degree in the evenings at Leeds Metropolitan University. That training led quite naturally to a PhD in digital pathology, which was just kicking off at Leeds.

I actually have a number of jobs today. My NHS job, which is my clinical commitment, is diagnosing liver disease. In addition, I'm Professor of Pathology at Linköping University in Sweden. They were one of the first pathology departments to go fully digital

in around 2010. The other job I have is as professional lead for digital pathology and AI for the Royal College of Pathologists (RCPath) – our professional body in the UK.

On the NPIC program, which is probably my biggest job by far, I'm Director. I develop the program – with the help of Dal Bansal and Bash Hussain – and oversee its day-to-day running.

It sounds like I wear a lot of hats, but there's a lot of synergy between the roles: things I learned here, I've shared with Sweden; my observations in Sweden feed into NPIC; and the RCPath work is informed by NPIC's practical deployments.

What goals and values drive the team?

The official aims of the program are to deploy digital pathology in the NHS, and then use the infrastructure firstly for diagnosis, but also to assist the development, evaluation, and use of AI, and to be a platform for further research and innovation.

Perhaps the core value that we place on this amazing technology is the many benefits to patients. Just today, we will scan samples from between 300 and 500 patients across the NPIC network; and those patients will benefit from it.

At a micro level, we make sure we manage that service well so that, day to day, everything is running smoothly. But, at the macro level, we recognize that the system will only be optimized if we are highly strategic. We need to think big – about centralizing the data and the artificial intelligence on a national level. So it's a combination of doing things well day to day, but also thinking forwards.

How do patients respond to the NPIC project?

We have a patient advisory group of about 20 patients and members of the public, led by Graham Prestwich, our patient lead. We've learned from the group that patients actually expect their NHS hospital to be using digital technology to improve care. They think it's nonsensical and inefficient for the NHS not to be digital.

In reality, the NHS often struggles to invest in digital technology because of the upfront cost. But patients expect digital – they don't go into a GP surgery and think it's okay for them to write notes on a piece of paper any more…

From our group, we hear that patients want to know whether they're getting the right diagnosis from the right person quickly enough. For example, if a patient's cancer biopsy needs a second opinion, it's important to them that digital technology is used to get that second opinion quickly, which improves the quality of the diagnosis. There's a personal benefit to them.

The other thing that our patients care about is that NHS staff are able to provide the best care together, working in networks. They tell us they don't just want this fancy technology in the big teaching hospitals, they want it in their small, local district general hospitals or community hospitals as well. They like our centralized approach, because all the centers have the same digital system installed. Those smaller hospitals that sometimes suffer in terms of recruitment of staff and ability to maintain services – they get the same standard of kit as the larger centers. And that's the sort of thing patients tell us that they want from digital pathology.

What would be your "elevator pitch" to reassure skeptical pathologists about digital pathology?

Well, one of the things we've achieved as a team is to publish the "Leeds Guide to Digital Pathology," which really serves as our elevator pitch.

When we first started running our workshops, a few years ago, pathologists would ask us, "Why should I go digital?" We'd answer by explaining the benefits, the use cases, the business case, and so on. So, if you'd asked me that question three or four years ago, I'd be telling you about significant pushback and skepticism from a vocal minority. I heard and agreed with some of their concerns and we improved the systems accordingly.

"We need to think big – about centralizing the data and the artificial intelligence on a national level."

Now people say to us, "We have decided to go digital; how are we going to do it?" There has been a massive step change, and now the more cautious people are in a really small minority. And I'm proud to say that some of the people who were anti-digital are now avidly using it. Because it's useful, and it works.

What has been your highlight so far?

The thing that really gives me great satisfaction is when I'm using the digital pathology system, and I can see that a lab that's just gone live is also using it. About a year ago, I was preparing a talk and I wanted to show an image from another hospital that was new to the network. I logged on to the system, opened a test image and zoomed in and, spontaneously, a little box and an annotation appeared – a simple box drawn around a piece of tissue, with the word "Wow!" beside it. Someone at that other hospital must have been testing the system and practicing with the annotation tools on the same test image, and left a spontaneous message of their impressions of the NPIC system. That little moment was really gratifying and makes all the effort worthwhile, especially when we know, at the larger scale, that is just one of hundreds of users in over 30 hospitals that will benefit from our work.

INFECTIOUS DISEASE

The Zombie Virus

Thawing Siberian permafrost suggests that ancient viruses could re-emerge in the near future

By Jean-Michel Claverie

Over the past decade or so, media outlets have periodically reported on a new global threat linked to global warming: a pandemic initiated by the release of prehistoric viruses by thawing ancient permafrost layers. But is the return of "the zombie virus" as plausible as tabloids have been insinuating?

The frozen ground

Permafrost is permanently frozen ground (with temperatures hovering around -10 °C) in which all metabolic activity is suspended due to a lack of water. These cold environments with neutral pH and sheltered from light and oxygen are perfect for housing microorganisms buried deep within the permafrost. With a hardness comparable to concrete, some water-rich permafrosts, such as Yedoma, exhibit high stratigraphical stability for easy and reliable dating.

Studying microbes in permafrost has been a long research tradition in Russia, with the first viable microorganism finding dating back to 1911 (1). Between the 1950s and present day, a veritable discipline has developed from realization of global warming consequences on microbial flora. After several controversial studies with possible contamination by modern microbes, there's now a consensus that bacteria can survive permafrost samples up to half a million years in age (2).

From plants to viruses

My team's interest in permafrost was sparked by a study to resuscitate a small flowering plant whose tissues had been frozen for more than 30,000 years (3). This research suggested that alongside bacteria, multicellular organisms could also remain alive once trapped in ancient permafrost. This finding has since extended to animals with a nematode species revival after 46,000 years of cryptobiosis in Siberian permafrost (4).

I was sure that, if a plant could be revived, then a virus would surely survive in permafrost. I contacted the team behind the research and they were happy to provide me with a few grams of their permafrost sample, and our project took off rapidly.

Our first attempts at reviving the Amoeba-infecting virus were quickly successful. Within 12 months, we could identify and describe two different viruses from the 30,000 year old sample. Moreover, these first zombie viruses (called Pithovirus and Mollivirus (5,6)) were representatives of two new viral families never seen before – supporting us in dispelling a putative laboratory contamination.

Introducing metagenomics

But what about the presence of other viruses in ancient permafrost? Thanks to advances in sequencing technology, it's now possible to analyze all living organism DNA present in a sample. The result is a mixture of several billion fragments of genomic sequences (including viruses, bacteria, plants, and animals) that modern bioinformatic techniques sort and identify through comparison with gigantic databases. This metagenomic approach (7) allows for identification of viruses in permafrost without the risk of reactivation.

Preventing a zombie virus pandemic

The probability of a pandemic triggered by a completely new virus is extremely low. However, if a virus of this nature spreads through the human population, it would have drastic consequences on a far greater scale than the COVID-19 pandemic. So is it possible to prevent a zombie virus pandemic? Our team proposes focusing surveillance on sick patients who are frequently exposed to environmental hazards (miners) or zoonotic risks (animal handlers). This way, we only need to study new viruses that have already infected humans or jumped from animals to humans. It would also reduce the data size and help detect emerging viruses early, before they can spread from person to person.

Jean-Michel Claverie is Emeritus Professor of Medicine at Aix-Marseille University, Marseille, France

See references online

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"Genomics has become a fundamental tool for pathologists and other healthcare professionals, arriving faster on the scene than any of us anticipated."

The Genome Pioneer

Sitting Down With…
Eric Green, Director of the National Human Genome Research Institute (NHGRI), Bethesda, Maryland, USA

Reflecting on the 20th anniversary of the completion of the Human Genome Project (HGP) in 2023, what do you see as the most significant advancements that have followed?
The most impactful advance we have seen in genomics since the HGP's completion has been the technical strides in genome sequencing. Back then, sequencing that first human genome cost about $1 billion. Now, less than two decades later, we can sequence a patient's genome for diagnostic purposes for less than $1,000. Having inexpensive genome sequencing available also means you can do all sorts of research studies to gain a deeper understanding of how the human genome works and how variants in patients' genome sequence influence their health.

What role has the NHGRI played in driving these advancements?
Since the HGP's completion, the NHGRI has morphed quite significantly and is now responsible for leading basic and clinical human genome research in the United States. Twenty years ago we were the only institute at NIH doing genomics; now, all institutes at NIH fund and conduct genomics research. At NHGRI, we aim to be at the forefront, driving advancements in the field and enabling others to use genomics in their studies.

How has the landscape of genomics research and its applications in pathology evolved since the completion of the HGP?
I became involved in genomics when I was a resident in clinical pathology. At that time, genomics was not very relevant in pathology. At most, we would do Southern blots to look at gene rearrangements for a handful of cancers – but no genomes were being sequenced back then, certainly not human genomes! Today, genomics is pervasive in pathology – especially in cancer diagnostics, but also in other areas, such as microbiology. It has become a fundamental tool for pathologists and other healthcare professionals, arriving faster on the scene than any of us anticipated.

Looking ahead, what emerging technologies or methodologies in genomics do you anticipate will have the greatest impact on the practice of pathology and laboratory medicine?
The next big frontier is not acquiring but rather analyzing the data – and we should expect to see significant progress in this space. Meanwhile, the area of multiomics – integrating genomics with other technologies such as metabolomics and glycomics – will continue to evolve and give clues about people's health and disease state. Such advances may become mainstream in pathology and laboratory medicine in the coming years.

As genomics becomes increasingly integrated into routine clinical care, what challenges do you foresee – and how might they be addressed?
Genomics is encountering the exact same challenges that technical advances often experience in medicine. There are complex issues related to literacy, regulation, payment, and so on. And the additional problem is that genomics is moving fast. If genomics were a bit "sleepier," then maybe the medical field could keep up.

Meanwhile, genomics has permeated into many different medical specialties, without any grand plan as to which discipline would be the major provider of genomics expertise. In that way, there is a real opportunity for pathologists to play a crucial role.

Separately, there has been considerable private sector involvement in genomics because of the opportunities that it brings. For example, noninvasive prenatal genetic testing is now the most common genomic test worldwide, and it is performed almost exclusively in the private sector.

Your institute recently published the 2020 NHGRI Strategic Vision. Could you give us a little insight?
This latest edition acknowledges that we can no longer strategically plan for everything going on in genomics – the field has become too expansive. And NHGRI is now just one of many funding organizations investing heavily in genomics research. However, as I said earlier, we are the leaders even though the institute is relatively small. We now consider ourselves "at the forefront of genomics" – our organizational mantra.

What advice would you offer to pathologists and laboratory medicine professionals who are navigating the evolving landscape of genomics?
First, I'd remind them that they should not rely on what they have learned to date to guide their future area of expertise. If I had done that, I would have never been in genomics because I did not have any formal training in the field. In that sense, I'm a good example of a life-long learner. By doing so, it is allowing me to be part of a transformation in medicine that is changing the medical landscape, whereby all boats are being raised – including those associated with the field of pathology.

Second, if I was going to go into pathology now I would commit to becoming agile, literate, and competent in genomics and data science so that I could help teach others. That would allow me to establish great partnerships with oncologists, ophthalmologists, and others across many different domains. Such multidisciplinary teams will come together and, the more comfortable you are in genomics and data science, the more you will be able to contribute to advancing medicine as part of the team.

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