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Personal Problems

Examining the barriers to widespread adoption of personalized medicine

Earlier this year, The Pathologist reported on the Estonian Biobank's ambitious vision of personalized health care for an entire nation (1). But, with so many other services competing for precious health care funding, is genetic testing ever likely to enter mainstream medicine?

On page 15, Jeremy Nicholson recognizes that high-tech solutions can be a barrier to progress, warning, "Science should benefit all of humanity, not just those in wealthy areas. Unfortunately, current omics technologies are costly and require extensive data analysis, which delays results."

Meanwhile, AMP has been facilitating important work in standardizing pharmacogenomics methodology (page 17), which will surely aid its acceptance in the few institutions in the world that can afford to offer it. But while the cost remains so high, it seems likely that pharmacogenomic testing will only be available to a small percentage of patients worldwide.

Even in precision oncology, patient access to testing remains suboptimal. In the United States, for example, an estimated 60 percent of eligible patients are missing out on targeted therapies for advanced non-small-cell lung cancer (2).

In response to such barriers, The Royal College of Pathologists of Australasia has issued a set of recommendations to improve accessibility to pharmacogenomic testing (page 19). These include wider inclusion on health insurance, improved education on the benefits, and greater investment in research.

I'm sure that the many thousands of patients who have benefited from personalized medicine would attest to it representing the future of healthcare. But for those who are missing out, it may feel more like a steady march toward inequity and unfilled potential.

Helen Bristow,
Editor

See references online

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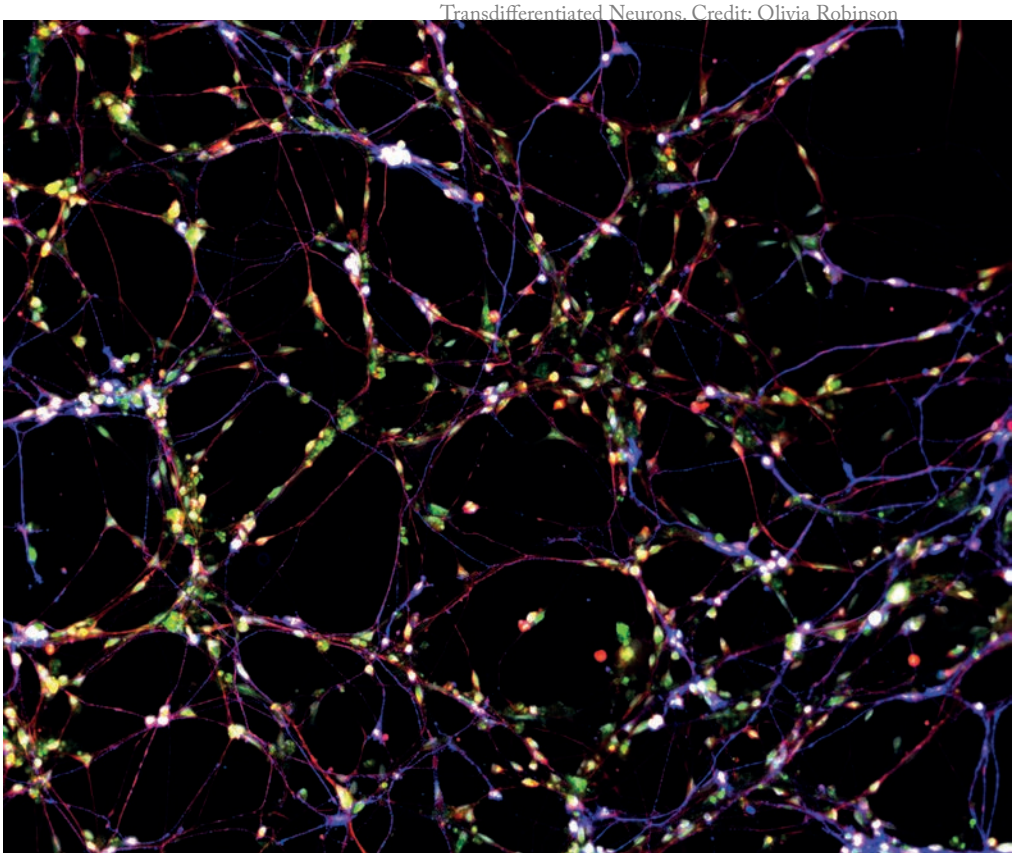
Skin Sample Success Story

How an RNA test using small skin samples could provide non-invasive diagnostics for rare diseases



Transdifferentiated Neurons. Credit: Olivia Robinson

More than 70 percent of rare diseases are of genetic origin, yet only half of such individuals receive a diagnosis following a genetic test. To tackle the imbalance, researchers at the University of Adelaide developed a method that leans on Nobel-prize-winning discoveries to make "silent" genes accessible through more accessible samples. (1).

We connected with corresponding author Lachlan Jolly to learn more about this initiative.

How does your new method help find genetic variants?

About one-third of disease-related genes aren't active in blood or skin samples, making their RNA unavailable without invasive biopsies. We call these "silent" Mendelian genes. We developed two methods based on Nobel Prize-winning discoveries: gene transactivation and cellular transdifferentiation. Both start by growing a small skin sample from the patient in the lab. In gene transactivation, we modify the skin cells to activate the silent gene. In cellular transdifferentiation, we transform the skin cell into another type, like a brain cell, where the silent gene is naturally active. Both methods allow us to study RNA from these silent genes and assess genetic variants.

Specifically, we can see how gene variants affect mRNA processing, leading to two key outcomes. First, it can enable a diagnosis. If a variant disrupts mRNA processing, it suggests that the variant harms gene function and supports its role in causing disease. Second, it opens the door to personalized treatments. Understanding how the variant mRNA is processed can help in designing therapies, such as antisense oligonucleotide treatments like nusinersen (Spinraza), which is approved for spinal muscular atrophy in countries like the US and Australia.

How might your findings change the way we diagnose genetic disorders?

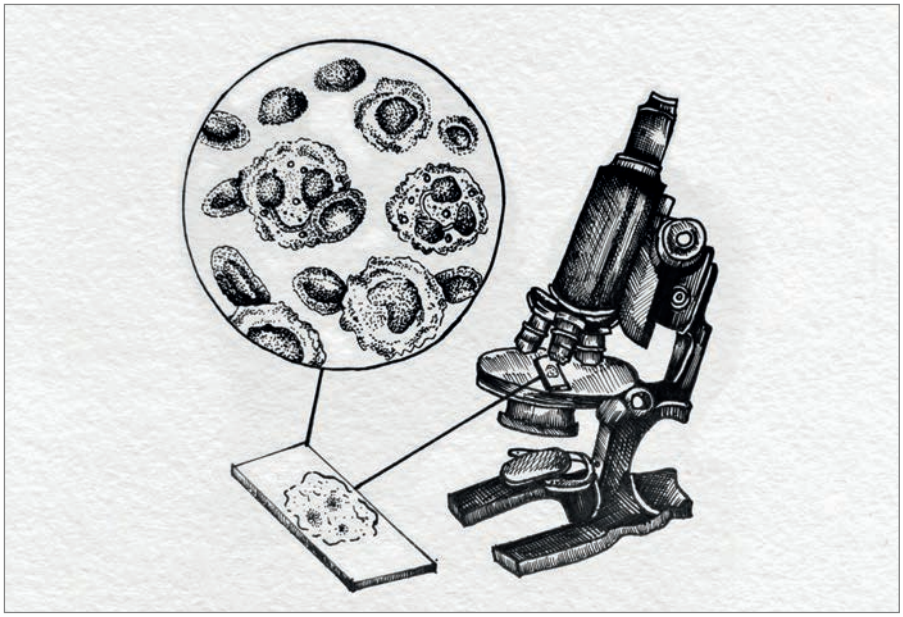
Variants of uncertain significance in silent disease genes make up 22.2 percent of all such variants in ClinVar, a database of human genetic variations and their clinical significance hosted by the National Center for Biotechnology Information. This leaves hundreds of thousands of people worldwide without a genetic diagnosis for their disorder, and this is likely just the tip of the iceberg. Though RNA-based tests can help in around 30 percent of cases, obtaining variant RNA has been difficult because it usually requires invasive biopsies – for example, of the brain. Our new method to obtain variant RNA from silent genes using skin samples offers a less invasive way to conduct RNA-based tests, improving the chances of diagnosis for many patients.

And though more than 90 percent of rare diseases currently have no precision therapies, there are over 14,000 clinical trials underway for such treatments. Access to these trials depends on having a genetic diagnosis.

Beyond diagnosis, our research highlights the potential to develop new therapies to reverse the harmful effects of gene variants on mRNA. These could include antisense oligonucleotide therapies to change RNA splicing or drugs that modify mRNA decay and translation.

Reference

1. *EC Nicolas-Martinez et al., Am J Hum Genet, 111, 8 (2024). PMID: 39084224.*



Through the Lens

Taking a closer look at microscopy in our image of the month

Our image of the month comes from Misha Dalal. She says, "This artwork celebrates the essential role of the microscope in the field of pathology, highlighting the intricacies that remain hidden from the naked eye."

Credit: Misha Dalal, Graduate from Government Medical College Surat, Gujarat, India

From Grossing to Diagnosis

Why pre-analytics deserves a digital revolution

By Soufiane Z. Azdad, Pathologist, CEO and Cofounder of Algoscope

In the fast-paced world of pathology and laboratory medicine, where cutting-edge molecular techniques and digital innovations dominate headlines, it is easy to overlook the foundation of our diagnostic process: pre-analytics. And yet this crucial phase – encompassing specimen handling, labeling, and grossing – remains largely unchanged since the dawn of our specialty. As a pathologist who has witnessed both the marvels of modern diagnostics and the persistent challenges in our workflow, I have a question: Are we neglecting the very cornerstone of our practice?

The stakes in pathology are undeniably high. A single lapse in attention during specimen handling or labeling can lead to sample mix-ups, potentially resulting in misdiagnosis and severe consequences for patient care. Despite this, the medical literature on error rates in pathology remains surprisingly sparse. A systematic review by Raab et al. (2005) found that error rates in anatomic pathology range from 1–43 percent depending on the type of error and detection method (1).

Parts of our workflow – particularly grossing – have remained virtually unchanged for over a century. Our forebears in pathology worked with formalin, alcohol, cutting boards, knives, and rulers. These same tools are still staples in many grossing rooms today. This striking contrast between the advanced end of our process and the relatively outdated beginning is a testament to the need for innovation across the entire pathology workflow.

A personal experience during the development of a prototype clearly highlighted this disparity. When a mechanical engineer asked for a measurement of a component, I instinctively reached for a tape measure. Horrified, he exclaimed, "Are you crazy? That's not precise enough. Use a caliper!" As shame washed over me, I had a sobering thought: "If only he knew what we use to measure tumors – critical measurements that can change TNM staging..." This moment underscored the urgent need for bringing our measurement techniques in line with the precision demanded by modern medicine.

The training process for grossing further illustrates this point. As residents, many of us learned through a time-honored but potentially flawed method: observe, practice under supervision, then dive in solo. This apprenticeship model has its merits, but it may not be sufficient in an era where precision and traceability are paramount.

Moreover, gross examination learning typically occurs in the grossing room itself. Although resources exist in textbooks and videos, accessing this information mid-procedure is challenging. Picture a resident, aproned and gloved, hands deep in a specimen. Their workspace is often limited to a cutting board on a ventilated bench. In this setting, digital resources and AI assistance are conspicuously absent. This harsh reality highlights a critical gap in the specimen's diagnostic journey, where modern technology could potentially offer significant support and guidance.

Compared with the transformations in other areas of healthcare – and in our daily lives, our pre-analytical processes seem stuck in time. This disparity hit home for me in 2016 when I first used a food delivery app. That same day, a biopsy was misplaced in the lab, causing panic and a work stoppage until it was found. Later that evening, as I received real-time notifications about my pizza's journey across town, the irony struck me: we appear to have better traceability for fast food than for biosamples that can determine a patient's diagnosis and treatment…

It is time we bridge this gap. The technology exists to revolutionize our pre-analytical processes, enhancing traceability, reducing errors, and ultimately improving patient care. As Bussolati and colleagues pointed out back a decade ago, addressing pre-analytical issues in anatomic pathology is crucial for ensuring the quality and reliability of diagnostic results (2). And back in 2011, Nakleh and colleagues emphasized the need for quality indicators and solutions in the pre-analytical phase of surgical pathology (3).

As a pathologist deeply concerned with these issues, I've made it my personal mission to address the challenges in pre-analytics. I'm dedicating my time and expertise to developing innovative solutions that aim to bring the precision and traceability of modern technology to the grossing room. Though the journey is ongoing, I'm committed to bridging the gap between our advanced diagnostic tools and the relatively outdated methods in specimen handling and grossing.

Let's not forget that every diagnostic journey begins with pre-analytics; improving this foundational step will shape the future of pathology.

See references online

Bridging the Workforce Gap

The expanding role of pathologists' assistants

By Emily Nangano, Research Pathologists' Assistant, Virginia Commonwealth University, USA

Credit: Jane Day Loter

Pathology is at a pivotal moment as it faces both tremendous opportunity for growth and a growing workforce crisis. With advances in diagnostic tools, the complexity of cases is rising, while the number of pathologists globally is insufficient to meet the demand. This imbalance is felt acutely across healthcare systems, with delays in diagnoses, increased workloads, and a growing pressure to maintain quality patient care. But there is a solution that could be more robustly embraced: expanding the role of pathologists' assistants (PAs).

PAs have long been vital contributors to anatomic pathology labs, handling specimen grossing, autopsy procedures, frozen sections, and other technical tasks. However, the potential for PAs to do much more – especially in the face of the ongoing pathologist shortage – remains largely untapped. Though this idea might stir controversy in some circles, it is an approach that several progressive institutions are already successfully exploring. I believe it is not just practical but essential for the future of our field.

A shifting landscape

Over the last decade, the scope of responsibilities for PAs has gradually evolved. Initially, PAs were primarily responsible for technical duties, such as grossing specimens and assisting with autopsies. However, several institutions have moved toward a more comprehensive use of PAs that might be described as "pathologist extenders" – incorporating responsibilities once considered the exclusive domain of senior residents and fellows. These include reviewing slides, ordering initial immunohistochemical stains, and even writing preliminary diagnoses.

This shift has led to improved efficiency in many labs, allowing pathologists to focus on the most complex cases that demand their full expertise. By extending the PA role, the pathology team can work more efficiently, ensuring that cases move through the pipeline more quickly, without sacrificing quality. Pathologists still maintain final review and sign-out authority, ensuring diagnostic integrity, but PAs can augment their efficiency by handling some of the preliminary work.

We are already seeing this change take hold across many disciplines in pathology. In forensic settings, responsibilities of PAs can now include reviewing social histories and conducting examinations, collecting forensic evidence critical to criminal investigations, and drafting preliminary reports. In academic institutions with research and innovation centers, partnerships with anatomic pathology laboratories are becoming more common. These collaborations often fund research PA positions aimed at increasing the procurement of fresh specimens destined for both diagnostic purposes and research. This growing trend highlights how PAs are instrumental in ensuring that research needs are met without compromising the diagnostic integrity of patient specimens.

Addressing the controversy

Despite the many benefits, there are understandable concerns about expanding the role of PAs. Pathologists may worry about the potential erosion of their authority or the risk of diagnostic errors without their direct involvement at every step. However, these concerns can be addressed through structured supervision and clear delineation of roles.

It is worth noting that this model already exists in the support of allied professionals, such as cytotechnologists, who screen slides and render diagnoses on routine cytology tests like Pap smears. Similarly, in clinical settings, physician associates work very similarly to physicians – they see patients, order diagnostic tests, and prescribe therapeutic interventions, truly extending the capabilities of their supervising doctors.

I would argue that we are doing a disservice to pathologists by not allowing them the same structure that could maximize their time and efforts on tasks requiring their full focus and expertise. Expanding the role of PAs in the pathology lab offers an opportunity to build a similar support framework, ensuring that pathologists can dedicate their attention to the most challenging and critical aspects of their work.

Some argue that expanding the role of PAs may lead to an over-reliance on non-physicians in diagnostic decision-making. But with adequate training, mentorship, and supervision, PAs can act as an extension of the pathologist's knowledge and expertise, ensuring that the highest standards of patient care are maintained. The current shortage of pathologists is not going away any time soon; if we do not adopt innovative solutions, the strain on labs will only intensify.

PAs are a highly educated, yet underutilized resource in anatomic pathology labs. With the right training, support, and oversight, PAs can take on more responsibilities, improve lab efficiency, and help bridge the gap left by the shortage of pathologists. This model is not about diminishing the role of the pathologist; it is about using the full capabilities of every team member to provide the highest level of care.

Leading in an Era of Personalized Medicine

Pathology labs are ideally positioned to drive patient-centric care

By E. Blair Holladay

Personalized medicine is playing an increasingly important role in healthcare, presenting a great opportunity for pathologists and medical laboratory scientists to solidify their role as foundational leaders.

Our collective responsibility is to provide high-quality patient care for all – and to ensure that each test and each diagnosis fulfills our mission of providing patient-centered care. We play a crucial role of delivering precise, patient-specific data that personalized medicine would be nothing without. As the era of personalized medicine expands, pathologists and medical laboratory scientists are ideally positioned to lead the way – and to usher in a new standard of patient care.

The data we provide is what drives individualized treatment decisions. We are the ones delivering the results and information from genetic testing, molecular diagnostics, or biomarker identification. These data directly inform courses of action and treatment. We all know that no two patients – or their genetic signatures – are alike, and that's why, by better understanding each person's unique biological characteristics, we can point them towards the most effective therapies, which ultimately helps improve their outcomes.

In short, data is everything in personalized medicine – and the medical laboratory is the collector and the keeper of that data. Our ability to test and discover can profoundly affect clinical decisions. Our ability and expertise to collect and interpret this data is what makes the laboratory indispensable.

"Data is everything in personalized medicine – and the medical laboratory is the collector and the keeper of that data."

Leading with AI

As precision medicine continues to evolve, the avalanche of data generated grows. To efficiently use this data to provide personalized care for our patients, we must embrace artificial intelligence (AI).

We know AI is not a catch-all solution; it cannot replace the complex and critical thinking needed in pathology and laboratory medicine. But what it can do is analyze data more quickly, providing the laboratory with information in a timelier fashion than we might otherwise achieve. What does that mean in practice? We can accelerate discovery, optimize tests, and do so much more to improve patient care and outcomes.

To embrace AI is to embrace actionable insights for our patients and to solidify our leadership in personalized medicine.

A challenging road ahead

Navigating this burgeoning era of medicine is not without its challenges. Technology can be difficult to access due to budgetary constraints or lack of reimbursement. AI brings regulatory issues to contend with, and comes with a massive educational need and a great deal of training to organize. Yet the opportunities opening up for laboratories far outweigh the challenges. When we embrace innovation and when we challenge ourselves to expand upon our expertise, we create space to showcase our role as essential partners in healthcare and elevate our tenet of patient-centric care for all.

As healthcare rapidly shifts toward precision medicine, we are uniquely positioned to provide the insights and expertise needed to provide high-quality care. We are not just contributors; we are the drivers of this change and will help shape what care looks like for each and every patient.

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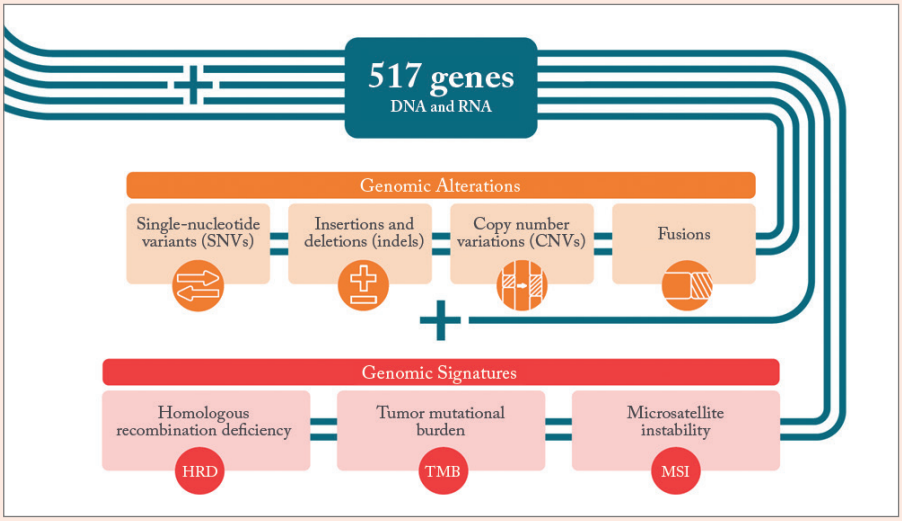


Comprehensive genomic profiling with the Oncomine Comprehensive Assay Plus

Advancements in precision medicine are driving the need for comprehensive genomic profiling (CGP). In short, CGP facilitates the simultaneous analysis of a broad range of biomarkers in one test to maximize insights into the underlying oncogenic drivers of cancer. Both common and rare alterations can be assessed in a timely manner, while minimizing the risk of tissue exhaustion associated with sequential testing. Additionally, complex genomic signatures or characteristic patterns of somatic mutations in cancer genomes can be assessed, reflecting the underlying mutational processes of the cancer.

As we gain a deeper understanding of the molecular mechanisms of tumor biology, CGP is critical to help drive insights into advancing the future of personalized medicine.

Research needs assessment

Several questions arise when evaluating CGP assays. What are the advantages of amplicon- versus hybrid-capture-based next-generation sequencing (NGS) methods? Should we choose in-house CGP or send-out services? When making these decisions, it is useful to consider the lab's individual situation and priorities.

If your lab handles many cytological research samples where tissue is limited, amplicon-based CGP assays may be more appropriate – these have a high success rate of ~94 percent, as opposed to hybrid-capture based methods where quantity not sufficient (QNS) rates up to 30 percent have been reported (1).

If timely results are critical for important insights and decisions, bringing CGP in-house not only greatly reduces the turnaround time – to days instead of weeks – but also allows more control over the sample and preanalytical parameters.

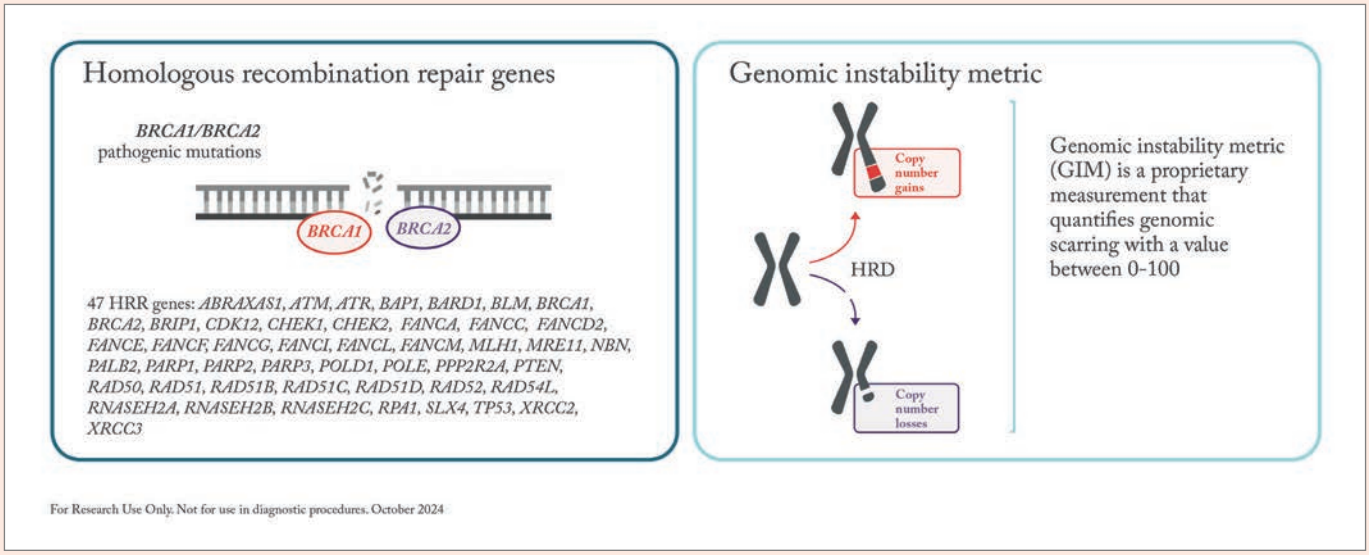
New-to-NGS users may value a high level of automation to reduce labor-intensive steps, as well as integrated bioinformatics to simplify data interpretation without the need for specialized bioinformaticians.

The Ion Torrent™ Oncomine™ Comprehensive Assay Plus, available on the Ion GeneStudio™ S5 System, is an amplicon-based CGP assay that brings the power of in-house CGP with a highly automated approach to meet the needs of labs at varying levels of NGS expertise. With highly automated library prep and sequencing systems that only require around one hour of hands-on time, the assay detects a broad range of genomic alterations – including single-nucleotide variants (SNVs), insertions and deletions (indels), copy number variations (CNVs), and fusions across 517 genes. Additionally, the assay detects complex biomarkers or genomic signatures such as homologous recombination deficiency (HRD), tumor mutational burden (TMB), and microsatellite instability (MSI).

"With turnaround times of as little as 3 days, results are delivered in a timely manner to support critical decisions."

Finding HRD causes and consequences

HRD is a phenotype that is characterized by the inability of a cell to effectively repair DNA double-stranded breaks using the homologous recombination repair (HRR) pathway (2). Of the genomic signatures, HRD is becoming increasingly relevant – especially in ovarian, breast, prostate, and pancreatic cancer – because of its association with poly (adenosine



Oncomine Comprehensive Assay Plus measures both causes and consequences of HRD.

diphosphate [ADP]-ribose) polymerase (PARP) inhibitors.

The Oncomine Comprehensive Assay Plus measures both the causes and consequences of HRD. Causes are assessed by detecting mutations in 47 genes associated with HRR, including large genomic rearrangements in *BRCA1* and *BRCA2*. Consequences of HRD or genomic scarring are measured using a genomic instability metric (GIM) – a numeric value between 0 and 100 that summarizes the unbalanced copy number changes across the autosomes resulting from HRD with higher GIM values correlating with more genomic instability. Turmor research samples that have *BRCA1/BRCA2* pathogenic mutations or markers of genomic instability are categorized as being HRD positive in ovarian cancer.

Case study: detecting HRD in ovarian cancer research samples

In a retrospective multicenter study of stage III–IV ovarian cancer research samples treated with chemotherapy from the MITO16/MaNGO-OV2 clinical study (n=100), HRD status was determined based on the presence of pathogenic mutations in *BRCA1* and *BRCA2* in combination with GIM using a predefined threshold of ≥16 to define high GIM (3). The Oncomine Comprehensive Assay Plus had good overall concordance with the reference method. Further studies will be needed to determine the appropriate thresholds for other cancer types, such as breast and prostate cancer.

Streamlining the workflow

When evaluating CGP assays, ease of use, turnaround times, and robustness with commonly encountered sample input requirements should all be considered. The Oncomine Comprehensive Assay Plus is a complete CGP solution that detects genomic alterations in 517 genes – plus genomic signatures such as HRD, TMB, and MSI – without the need for any additional add-on kits. One comprehensive assay for genomic profiling across tumor types greatly streamlines a lab's workflow when it comes to operations, and logistics. In addition, as a single vendor of sample-to-report solutions, including instruments, consumables, analysis, and support, Thermo Fisher Scientific helps simplify the introduction of in-house CGP to your lab at varying levels of NGS expertise.

References

1. *E Jantus-Lewintre et al., "Multicentric evaluation of amplicon-based next-generation sequencing solution for local comprehensive molecular tumor profiling." Poster presented at ESMO 2023; October 20-24; Madrid; Spain. Poster 219P.*
2. *MD Stewart et al., "Homologous recombination deficiency: concepts, definitions, and assays," Oncologist 27, 3 (2022). PMID: 35274707.*
3. *N Normanno, "Future Clinical Perspective of HRD Testing in Ovarian Cancer Samples Using NGS CGP," European Medical Journal Webinar (2023). Available at: https://www.emjreviews.com/type/webinars/*

Learn more about the Oncomine Comprehensive Assay Plus at thermofisher.com/oncomine-ocaplus

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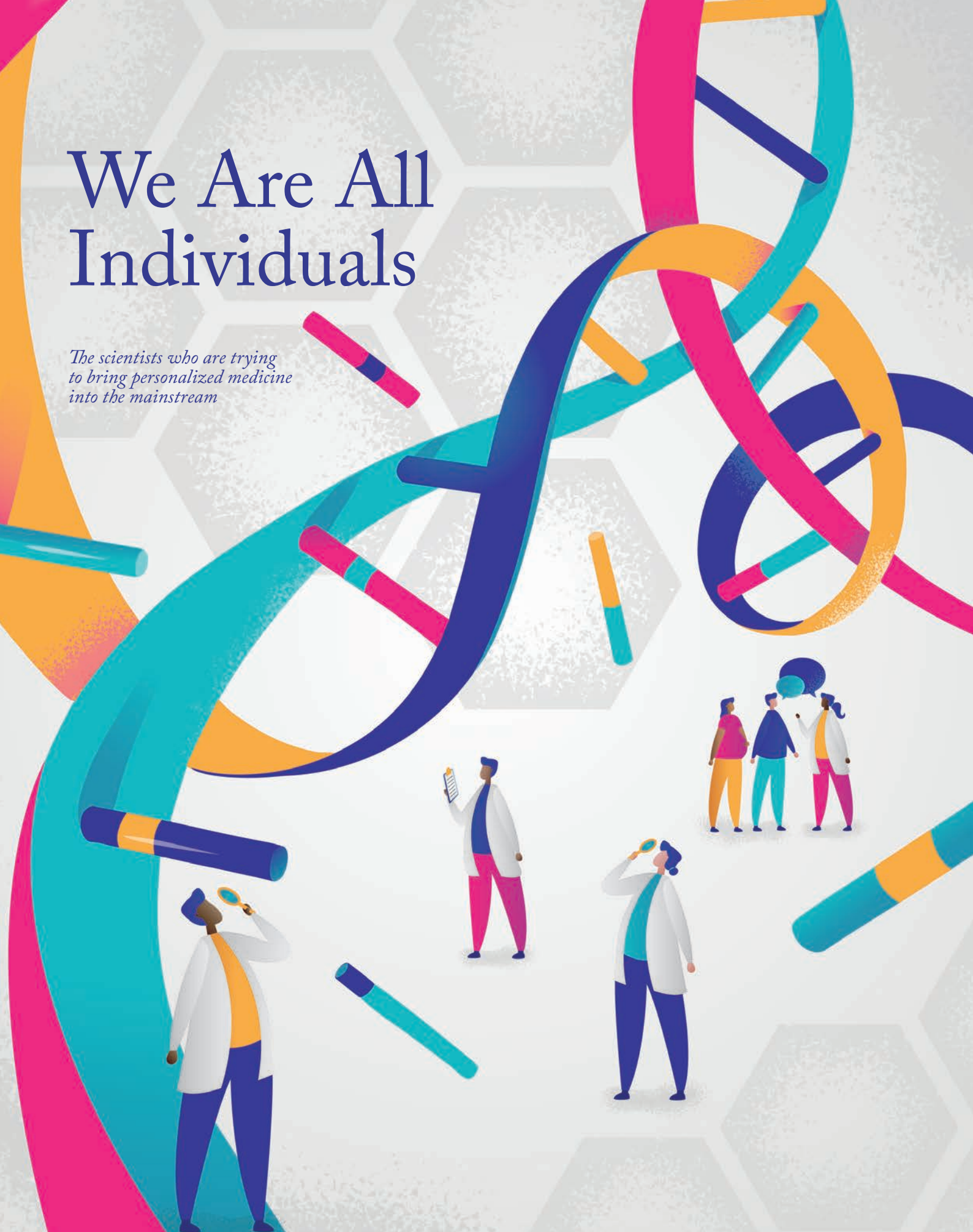
The scientists who are trying to bring personalized medicine into the mainstream



GENETIC COUNSELING

Why both patients and clinicians need guidance from genetics experts

Genetic testing has opened the floodgates to a wealth of disease understanding. But genetic testing can be difficult for patients to access – and the results can be challenging for clinicians to interpret.

Here, we speak with Ellen Matloff, Founder of My Gene Counsel, about the past, present, and future of genetic counseling – and how pathology is involved.

What is your background and how did you get into genetic counseling?

After graduating in biology, I went on to gain a master's degree in genetic counseling, and started my career in rare adult and pediatric disease. After two years, I moved to the Yale School of Medicine in Connecticut to establish their first program in cancer genetic counseling, running it for the next 18 years. During that time, I witnessed an explosion in the field of genomics – it grew from an occasional test for a handful of patients with rare disease to a commonplace technique with wide-ranging applications in oncology. Not only was it used to guide surgical and radiology decision making, but also to inform risk management for patients' families.

Following that revelation, I left academia to start My Gene Counsel.

How would you describe genetic counseling to the uninitiated?

Genetic counseling has been around for 50 years or more. In the early days, most counselors worked directly with clinicians and patients in hospitals or clinics. They would advise clinicians on which genetic tests might be of most benefit to each patient and how to best incorporate the test results into the patient's treatment plan. And they would counsel patients to help them understand the testing and the results.

At the start of my career, I worked with children and adults with genetic conditions, such as Down syndrome, cystic fibrosis, or Fragile X syndrome. I would help diagnose their condition and help them access appropriate support services and resources. Then I could use test results to advise the family members on the chances of having future children with the same condition.

After I moved into cancer genetics at Yale, I would see patients who either had a personal history or a family history of cancer and determine if they carried a germline genetic mutation and what that meant for their family members.

More recently, genetic counseling has greatly expanded its scope. Not only do we find genetic counselors in many different specialties within the healthcare system, but also in specialist genetic testing companies, pharmaceutical companies, health insurance, regulatory teams, venture capital, private equity, and genomic technology companies. Some work in patient foundations or other types of research foundations, in direct research, or in digital health companies.

How does genetic counseling contribute to the field of personalized medicine?

Many precision medicines now have FDA authorizations across oncology, rare diseases, and other indications. And we've seen an exponential growth in the cell and gene therapy space for potentially curative treatments. As a Forbes contributor, I interviewed the first patient to receive gene therapy for sickle cell disease; she no longer has symptoms of the condition. It's mind blowing!

Many new technologies are now being driven by genomics. In the oncology space, these are reliant on techniques like cell-free DNA testing and minimal residual disease testing, which are complex and evolving. And the skill sets of genetic counselors – a deep understanding of genomics and the related technologies combined with the communication skills to discuss these issues with patients and clinicians – can really help the field move forward.

How can pathology contribute to this effort?

In the United States, every single patient with ovarian, pancreatic, or metastatic prostate cancer, and many patients with breast and colon cancer, are candidates for genetic testing. They qualify for germline testing to help guide their surgical and radiation treatment pathways. And the results could also be helpful – or even life-saving – to their family members. What's more, it could identify the patient as a candidate for precision medicine. But what if they don't receive that genetic testing?

I believe that the pathologists are actually the linchpins of the entire process. They know who has been diagnosed with these cancers and, as part of a system-wide effort, they can feed them into a workflow such that every single patient diagnosed with pancreatic cancer, for example, is offered access to genetic counseling information on their phone or device. The patients

would then be aware of their option for genetic testing and receive up-to-date, easy to understand genetic counseling information.

What is the current situation with access to genetic testing?

What we find is that many of these eligible patients in the United States – particularly those who are not white and not wealthy – never learn of their option for genetic testing. And for those with a new diagnosis of advanced cancer – as we see all too often with pancreatic and ovarian disease – the option of genetic testing may be regarded as very low priority by the clinician. Those patients may not ever be offered this option.

If we can get pathologists on board with automatically feeding eligible patients into a loop to make sure that they learn, along with their clinicians, of the genetic testing option, that is how we get entire health systems on board.

What needs to change to improve access to genetic testing?

Amazingly, here in the United States genetic counselors are not recognized as providers of genetic counseling by CMS, Medicare, or Medicaid. This presents a huge barrier. If these people – who have graduate degrees in genetic counseling and continue ongoing education in the field to maintain certification – are not recognized as the providers of genetic counseling, they cannot be reimbursed adequately. And that means that a healthcare system may not employ as many genetic counselors as it should because payers will not reimburse them. Or, in some instances, a system might replace genetic counselors with other health care providers, who can bill CMS, even if those providers are not experts in genetics.

That's the first thing that needs to change here in the United States – we desperately need qualified genetic counselors to be recognized as providers of service by the funding bodies. This change would result in cost savings because other providers of genetic counseling, like physicians, charge more for their services than a graduate-trained genetic counselor. There would also be cost savings as a result of the reduction in errors.

Though there will be a new CPT code that goes live January 1, 2025, that will allow genetic counselors more reimbursement, Medicare and Medicaid still won't recognize genetic counselors as providers. Consequently, many other payers won't recognize them either. That needs to change – and it needs to change now.

What errors can occur in genetic testing?

I've been the senior author on a series of papers showing what happens when genetic testing is mis-ordered or when the results are misinterpreted. The results are breathtaking! For instance, we reported cases of healthy patients having parts of their body removed preventatively, and then learning that they didn't carry a pathogenic mutation.

These mistakes hurt patients, they are expensive for payers, and bad for clinicians, hospitals, and healthcare systems. And in many of these cases, we found that no genetics professional was involved in the testing process.

What is the future direction of genetic counseling?

As noted, I would like to see genetic counselors recognized as the providers of genetic counseling services and I would like to see more health systems hire and set up teams of genetic counselors. But because of the widening guidelines for candidates for genetic testing, those genetics professionals will also need embedded digital tools in their electronic medical records systems to help them identify all the eligible patients. Alongside this, the patients will need digital tools to make sure that they can access the information they need in a safe, equitable way.

Ideally, the genetic counseling process will not end when the patient gets their test result, which is what happens now. Digital tools will allow genetic counselors to keep in touch with those patients and providers over time. In that way, if the guidelines change, a new precision medicine becomes available, or we need to collect outcome data, we can maintain that relationship with the patient and the provider. I dream of a future where precision medicine can be a lifetime game instead of a "one and done."

Do you anticipate a future in which genetic testing will move into mainstream medicine?

I do think that day will come. There are already some genetic counselors working in primary care, which is very exciting. But I would like to see genetic testing and counseling used more widely for all patients in different subsets of disease who need these services. I would eventually like it to be a routine part of primary care medicine.

THE FUTURE LIES IN PHENOMIC MEDICINE

Jeremy Nicholson explores the potential of metabolic phenotyping in personalized medicine

Almost 10 years ago, we heard from three pioneers of precision medicine about the drive for faster diagnostics and better-informed treatment decisions. Now, Jeremy Nicholson rejoins us to discuss where phenomic medicine stands a decade later – and where this evolving field is heading next.

How has the field of metabolic phenotyping evolved over the past decade?

The field of metabolic phenotyping has grown rapidly, with thousands of labs worldwide performing studies to inform and enhance diagnostics and prognostics for the future. This growth is encouraging but has also introduced variability in scientific quality. Our work primarily uses NMR spectroscopy and chromatography coupled with mass spectrometry on accessible samples like urine and plasma to find molecular signatures linked to disease risks or patient subgroups. This area shows promise, though large-scale applications are still emerging.

The basic principle we work with involves identifying key metabolites that can predict disease, including those influenced by the microbiome, which adds complexity due to interactions with our genetics and diet. Each person's metabolism is unique and changes over time, making statistical analysis challenging yet crucial for understanding longevity and quality of life. The world has become a more complex place over the last decade, but the value proposition for large scale metabolic phenotyping is now greater than ever.

The iKnife was a groundbreaking tool in metabolic diagnostics when it was first developed. How has its role in real-time diagnostics for surgery advanced in clinical practice over the years? And are there any updates on its integration into more routine surgical procedures?

Imperial College remains the hub for developing iKnife real-time mass spectrometry technology, which has seen several advancements to improve its efficiency for surgical use. Although my recent focus has shifted towards preventive medicine, we've made significant progress in optimizing care for burns patients, particularly in minimizing healthy tissue removal, through collaboration with Fiona Wood at the University of Western Australia. Wood now has the first public iKnife system in an Australian operating theater. We also have an iKnife in our research lab to develop surgical models. This technology, along with the iEndoscope, holds great promise for the future.

What is Jeremy Nicholson doing now?

As well as being Emeritus Professor at Imperial College London, I've served as Professor of Medicine and Director of the Australian National Phenome Centre (ANPC) in Perth, Australia, since 2019. The ANPC is part of a network of laboratories, called the International Phenome Centre Network, which I helped establish. This network uses standardized equipment, protocols, and informatics to harmonize clinical research globally – a key step for translating new technologies into medical practice. At the ANPC, we focus on population studies, disease prevention, and personalized treatments.

In your 2015 article, you mentioned the importance of collaboration between physical scientists and clinicians. Have you seen this interdisciplinary approach gain broader adoption in clinical research?

This largely depends on the institution, researchers, and the research philosophy of each group. Unfortunately, it's still quite rare and less common than it should be. The UK offers unique advantages, especially through the NHS and NIHR, which support the translation of scientific innovation into clinical practice. Imperial College London exemplifies this approach, with world-class research and medical capabilities, but other institutions also need the resources, funding, and vision to make it work. I believe clinical science will eventually adopt life-saving innovations; however, the spread of new practices can take time due to practical limitations.

"The world has become a more complex place over the last decade, but the value proposition for large scale metabolic phenotyping is now greater than ever."

Reflecting on your early goals for stratified and personalized medicine, where do you think the field has succeeded? And what challenges remain for integrating precision medicine into everyday clinical workflows?

Though new high-performance AI approaches make things technically easier over time, personalized healthcare for entire populations is still a distant goal, likely achievable only for rare diseases. For common diseases, which involve complex interactions of genes, environment, and behaviors, the focus should be on prevention – a key objective at the Australian National Phenome Centre (ANPC).

Science should benefit all of humanity – not just those in wealthy areas. Unfortunately, current omics technologies are costly and require extensive data analysis, which delays results. ANPC's approach is to rigorously discover and validate new disease markers, then simplify analytics so they are understandable, fast, affordable, and clinically useful for physicians – essential for real-world impact.

What role do you foresee for newer technologies, such as AI and machine learning, in enhancing the capabilities of personalized medicine?

The scope of AI is vast, but the concept isn't new. We published papers on using pattern recognition in NMR spectroscopic diagnostics back in the 1980s, which would now be called AI. Computers have simply become faster and cheaper, making it easier to handle large clinical datasets.

The challenge with AI is that it requires massive data to yield insights, which then need to be applied on an individual level for decision-making. Success depends heavily on the quality and relevance of the data. If the question or dataset is off, it's not artificial intelligence but "artificial stupidity" – and there's already plenty of that around!

As personalized medicine continues to evolve, what advice would you offer to pathologists and clinical laboratory staff looking to incorporate advanced phenotyping and precision diagnostics into their practices?

Get involved! Translational advances require pathologists to engage with scientific experts, whether local or remote, like us at ANPC. We currently have over 100 worldwide collaborations and are always open to new challenges. Molecular phenotyping can tackle almost any biomedical issue, given appropriate and well-designed sampling. We believe the future is in phenomic medicine, which integrates the full complexity of human biology from genes to environment. One of the quickest, most cost-effective, and informative ways to understand this complexity is through an individual's metabolic phenotype.

TRUSTED BODIES FOR PGX

With new pharmacogenomics programs appearing with increasing regularity, AMP is on a mission to standardize the methodology

Pharmacogenomics (PGx) is a rapidly growing field of medicine that explores how a person's DNA, or their genetic makeup, affects how their body processes or metabolizes medication.

As with any technique in its growth phase, it will only become trusted once the methods and results are comparable between different centers. And that's why guidelines, agreed by the most trusted bodies in the field, are so valuable in informing lab processes.

The Association for Molecular Pathology (AMP) has been instrumental in facilitating the standardization of PGx methodology. Here, Vicky Pratt, Co-Chair of the AMP Clinical Practice Committee's PGx Working Group, tells us about the group's progress in this area.

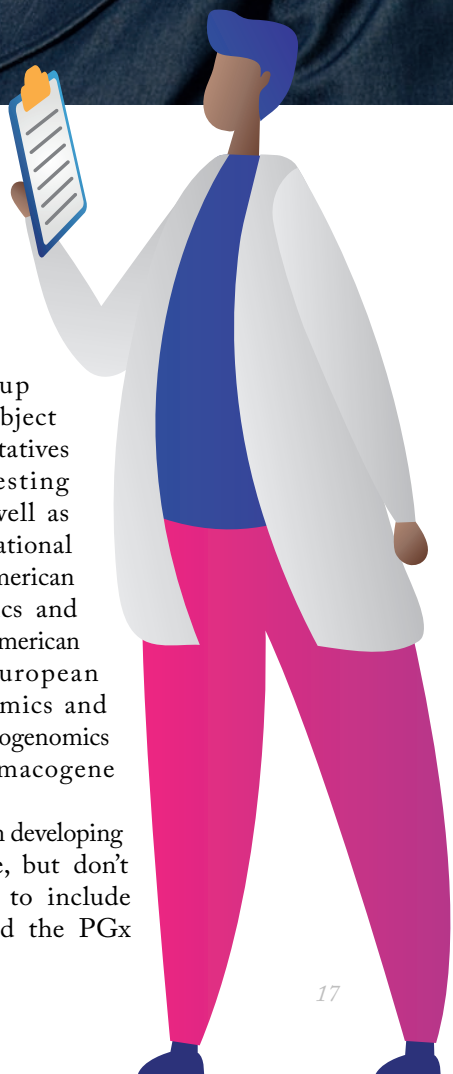
What is the history of PGx?

PGx has been around for quite a while. One of the earliest described versions of it came about from research into Fauvism – an hereditary disorder that causes an allergic reaction to fava beans. Scientists wanted to establish why the allergy was selective. The cause was eventually linked to a deficiency of the enzyme glucose-6-phosphate dehydrogenase (G6PD). People with that G6PD deficiency are at risk of developing acute hemolytic anemia when they eat fava beans. And the deficiency was found to result from a genetic disorder.

This opened up a whole field of genetic research to explain why human bodies react to chemicals in different ways.

What work still needs to be done to bring pharmacogenomics into mainstream pathology practice?

Until recently, there's been little effort to standardize the content or specific variants or alleles that should be included in clinical PGx testing. One of the issues is that PGx spans a number of medical specialties, each of which prefers to use its own recognized guidelines. Outside of pathology, there is little recognition of all the work done by the Clinical Pharmacogenomics Implementation Consortium (CPIC) or the Dutch Pharmacogenetics Working Group (DPWG), for example. For PGx to enter mainstream practice, standardization of testing will need to be adopted across those different specialties.



How will the work of the AMP PGx Working Group help with that standardization?

The PGx Working Group brings together leading subject matter experts and representatives from the clinical PGx testing community in the US as well as Europe. It includes organizational representation from AMP, American College of Medical Genetics and Genomics, CPIC, College of American Pathologists, DPWG, European Society for Pharmacogenomics and Personalized Therapy, Pharmacogenomics Knowledgebase, and Pharmacogene Variation Consortium.

CPIC and DPWG have been developing PGx guidelines for a while, but don't recommend specific alleles to include in testing. AMP established the PGx

Working Group to help standardize clinical testing across laboratories such that assays investigate the most clinically relevant variants or alleles, and enable health care professionals to provide high quality patient care. The aim of the group is to define a minimum set of variants – what I call a must test list – that should be included in common clinical genotyping assays.

The working group has invested a lot of time and effort in this work, resulting in seven PGx guidelines being published so far – most recently the DPYD Genotyping Recommendations. Testing for variants in the DPYD gene can help identify cancer patients who may be at increased risk of toxicity from fluoropyrimidine-based chemotherapy.

This new report is intended to improve clinical practice and facilitate standardization across clinical laboratories and ensure that the appropriate variants are included in clinical PGx DPYD assays. It builds on our earlier clinical genotyping recommendations for CYP3A4/CYP3A5, TPMT/NUDT15, CYP2D6, genes important for warfarin testing, CYP2C9, and CYP2C19. We will continue to update the recommendations as new data and reference materials become available.

It is important that the recommendations are implemented along with other relevant clinical guidelines, such as those issued by CPIC and DPWG, which focus on interpreting PGx test results, and give therapeutic recommendations for specific drug–gene pairs.

With all those learned bodies involved, how difficult is it to reach consensus on the guidelines?

So far, we've all managed to agree. What's interesting is the degree of health equity that's introduced by having an international panel. The DPWG's original label for the drug 5FU recommended PGx testing for four genetic variants. However, those variants are very specific to people with white European ancestry. Collectively, the AMP PGx Working Group's recommendation for 5FU takes a more pan-ethnic approach, including variants that are common throughout the world.

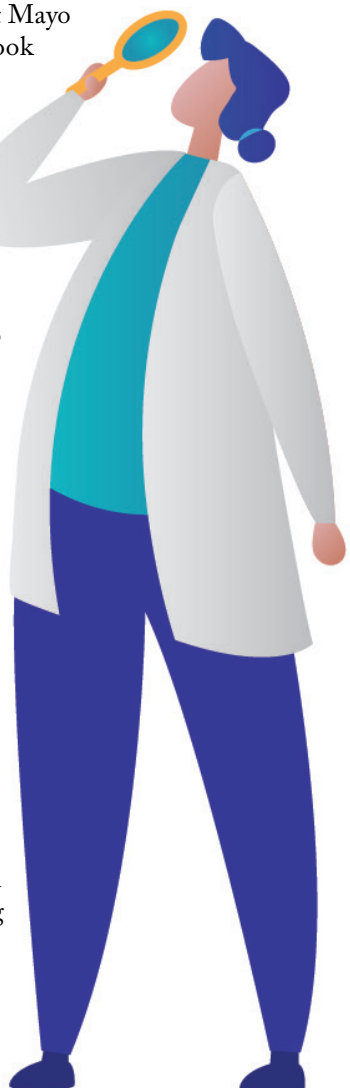
How have the guidelines been received by the laboratories delivering these services?

We have received some favorable feedback, particularly on the DPYD guidelines. That gene has been regularly mentioned in the news as there have been some lawsuits related to the tragic deaths of patients with DPYD variants from adverse drug reactions. So the DPYD Genotyping Recommendations have been regarded as very timely.

Are you able to share any case studies of pharmacogenomics success stories?

One famous case involved Miss America 2020, Camille Schrier. She was struggling with depression and anxiety that were not responding to medication. PGx testing was able to match Shrier with medication that would be metabolized more efficiently, according to her genetic profile. After switching medications, her symptoms improved and she was able to move on with her life.

There was also a patient treated at Mayo Clinic – Karen Daggett – who took ill due to adverse reactions to her regular medications. PGx testing revealed a hereditary variant in her CYP2D6 gene, which controlled metabolization of her medications. Daggett urged her family members to undergo testing, of whom 19 tested positive for the same CYP2D6 variant. Some of her close relatives also went on to receive life-changing medication switches due to the PGx test results.



Stanford Medicine also has a PGx program, called the Humanwide Project. One of their patients, Debbie Spaizman, experienced dizziness and disorientation when she used pain medication. Her Humanwide PGx evaluation found this was due to a CYP2D6 variant, and she then received advice on more suitable medication to use after an important operation.

We hope that our PGx guidelines will result in many more patients receiving improved treatment outcomes.

IMPROVING ACCESS TO PHARMACOGENOMICS

The Royal College of Pathologists of Australasia issues recommendations

In Australia, it is estimated that around 250,000 hospital admissions a year result from medication toxicities – at a cost of over a billion dollars to the healthcare service. The Royal College of Pathologists of Australasia (RCPA) maintains that many of these could be prevented with pharmacogenomic testing, but recognizes that many barriers still exist to its wider implementation nationally.

In response to the growing demand for pharmacogenomic testing, the RCPA issued recommendations to improve its accessibility. These include expanded public funding through the Medicare Benefits Schedule (MBS), better education for patients and clinicians, and research to understand genetic variation in Australia, including First Nations people.

Here, Luke Hesson, co-chair of the RCPA's Pharmacogenomics Advisory Group explains the reasoning behind the recommendations and what it is hoped they will achieve.

Why is pharmacogenomic testing important in terms of patient outcomes in Australia?

Pharmacogenomic testing plays a critical role in optimizing patient outcomes by allowing treatments to be personalized based on an individual's genetic profile. This approach can significantly improve patient outcomes by enhancing medication efficacy and reducing the risk of adverse drug reactions. Currently, accessibility to this testing in Australia is limited, placing the nation several years behind other countries in implementing widespread pharmacogenomics.

What is the current status of accessibility to pharmacogenomic testing in Australia?

Access to pharmacogenomic testing remains limited in Australia. Most tests are not covered under the MBS, which restricts availability, particularly for patients in rural and remote areas. To bridge this gap, the RCPA has submitted two applications to the Medical Services Advisory Committee (MSAC) for public funding for two pharmacogenomics tests, with decisions expected in 2025.

One is for DPYD testing, which identifies patients with genetic variants that increase the risk of severe, potentially life-threatening reactions to fluoropyrimidine chemotherapy. The other is for human leukocyte antigen genotyping, which assesses sensitivity to carbamazepine in epilepsy patients.

"Ideally, all patients should have access to pharmacogenomic testing before receiving certain medications."

What would the ideal situation be, according to the RCPA?

Ideally, all patients should have access to pharmacogenomic testing before receiving certain medications. This would allow for personalized medication plans that reduce adverse drug reactions, prevent hospitalizations, and ultimately improve patient safety and treatment outcomes.

What needs to change in order to get there?

Achieving broader access to pharmacogenomic testing requires expanded public funding through the MBS, greater education and awareness of the benefits of pharmacogenomics for both clinicians and patients, and targeted research to understand genetic variations across Australia's diverse population.

What recommendations has the RCPA made towards improving accessibility?

On International Pathology Day, the RCPA calls for wider inclusion of pharmacogenomic testing on the MBS and highlights the need for improved education of pharmacogenomic testing benefits for clinicians and patients. The RCPA also stresses the importance of funding research to better understand genetic variation across the diverse Australian population.

Additionally, the RCPA has issued national guidelines on pharmacogenomic testing for 35 commonly used medications, providing clinicians with a resource to determine when testing may be beneficial.

What research is underway to assess the benefits of pharmacogenomic testing in Australia?

Several national trials are underway to assess the impact of pharmacogenomic-guided prescribing. This includes randomized controlled trials for the prescribing of antidepressants for mental health disorders, and several interventional trials.

From NGS Naive to Fully Accredited

Cork University Hospital's transformation in precision oncology services

In the rapidly evolving field of precision oncology, the implementation of next-generation sequencing (NGS) has become a game-changer for diagnostic laboratories worldwide. Recently, we had the opportunity to interview Professor Louise Burke, Professor of Pathology, University College Cork and lead Thoracic Pathologist, Cork University Hospital, which serves a population of approximately 1.4 million people. The hospital's tertiary cancer facility, part of Ireland's National Cancer Control Program, has successfully transitioned from single-gene oncology biomarker testing to the sophisticated realms of NGS. Here, we explore their journey, challenges, and significant improvements in their biomarker testing capabilities following NGS accreditation.

What prompted your laboratory to transition to NGS technology?
We were doing single gene tests, but we really needed to expand our expertise to be able to meet the clinical demands. Over the past five years, we've seen a five-fold increase in requests driven by advancements in precision oncology. It was essential for us to integrate NGS seamlessly into our workflow while ensuring compliance with ISO 15189 requirements.

What were some of the initial challenges you faced in implementing NGS?
Transitioning to NGS was certainly not without its hurdles. We were NGS naive without in-house bioinformatics expertise, which is crucial for the successful implementation of NGS. However, we were determined to advance our diagnostic capabilities despite these obstacles.

What were the key factors you considered when choosing the NGS technology?
We needed a system that would fit within our existing infrastructure and staffing resources. We wanted something that had minimal hands-on time. Ease of integration and simplicity were also critical, ensuring a smooth and efficient transition.

What improvements have you noticed since implementing NGS?
One of the most notable advancements is the dramatic reduction in turnaround time. With NGS in-house, we've achieved greater than fifty percent reduction in turnaround time within the first year, achieving turnaround times of seven days, and we've further improved on that. This efficiency has been maintained despite an increase in workload, enabling us to provide exceptional service to oncologists and patients alike.

NGS has empowered us to better manage tissue samples, particularly in cases of non-small cell lung cancer (NSCLC) where sample size and quality are critical. Additionally, the implementation of NGS has fostered an educational program within our laboratory and opened numerous multidisciplinary collaborations with clinical colleagues and academic institutions – enriching the professional development of all staff members involved.

"The implementation of NGS has fostered an educational program within our laboratory and opened numerous multidisciplinary collaborations with clinical colleagues and academic institutions."

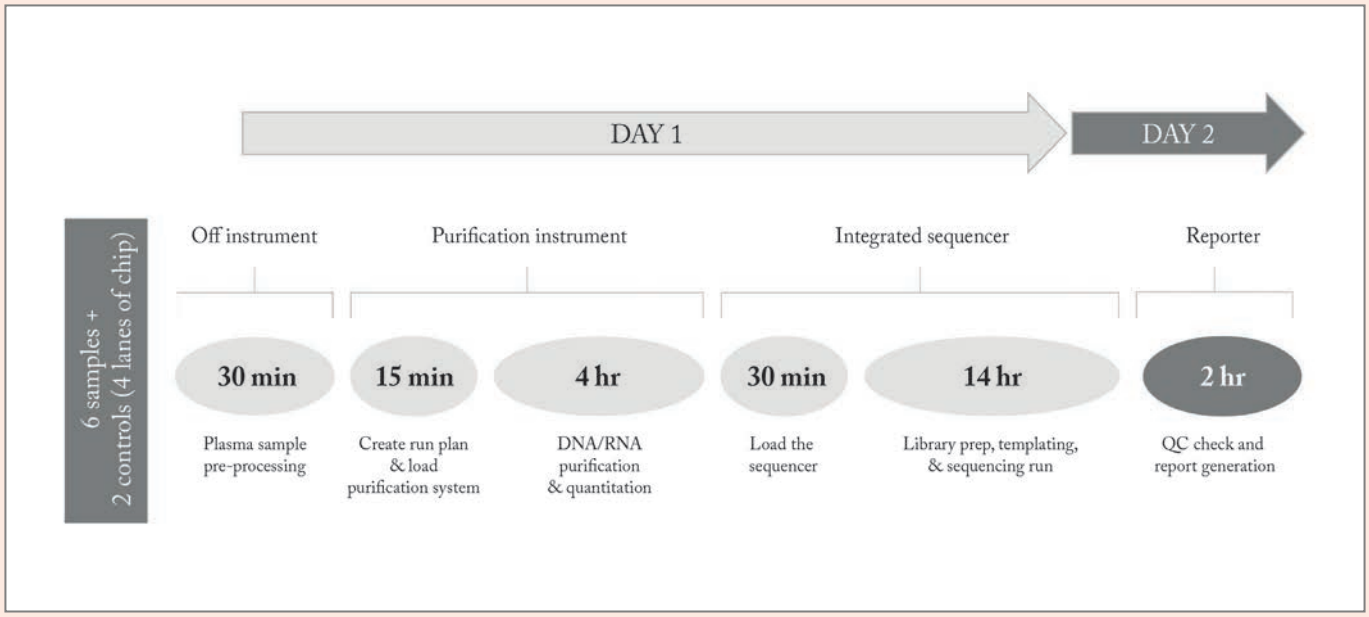


Figure: Schematic of the NGS cfTNA processing workflow established in-house with a 2-day TAT and minimal hands-on time. cfTNA, cell-free total nucleic acid; NGS, next-generation sequencing; TAT, turnaround time. Credit: BMJ, doi: 10.1136/jcp-2024-209514. Re-use permitted under license CC BY.

Can you summarize your experience with NGS accreditation?

The pursuit of ISO 15189 accreditation was driven by our commitment to delivering the highest standards of quality and reliability in genomic testing. This accreditation ensures that our testing processes meet stringent international criteria, providing confidence to healthcare providers and patients.

Achieving accreditation was a rigorous yet rewarding process. We, of course, had experience from accrediting other methods in past, and the template is generally the same. One of the key elements is ensuring that we can demonstrate our performance metrics reliably and reproducibly. It requires meticulous documentation and validation of all our processes.

In 2022 we accredited in-house NGS testing of cancer tissue samples to provide rapid and accurate genomic analysis – ultimately enhancing personalized medicine and targeted therapy. And in 2023, we followed this by accrediting NGS testing for cell-free total nucleic acid (cfTNA) analysis from liquid biopsy samples. This minimally invasive technology offers a promising alternative to traditional tissue biopsies, enabling real-time monitoring of cancer mutations and treatment responses.

We achieved accreditation of this service with high sensitivity (>83 percent) and specificity between plasma and tissue and a sequencing LOD of 1.2 percent (at depth of coverage >22 000x). We achieved a 5-day turnaround time for in-house samples, from sample receipt to final report, and developed a service for supplementary testing to tissue samples. This is made possible by our rapid NGS solution, which provides a workflow of just 2 days from plasma sample to report.

Any advice you might have for other laboratories looking to undergo this process?

My advice would be to keep the end goal (ISO 15189 accreditation) in mind as you are implementing and clinically validating the method, and ensure that every step in the development of your service meets the required standards across pre-analytics, analytics, and post-analytics. You need comprehensive understanding of these standards and being prepared to demonstrate compliance in every aspect of your testing will be fundamental to your success.

The journey from NGS naive to a fully accredited NGS facility has been transformative for the service provided by the Department of Pathology at Cork University Hospital. The significant reduction in turnaround times, enhanced sample management, and collaborative opportunities underscore the profound impact of NGS on their diagnostic capabilities. As the field of precision oncology continues to evolve, this hospital stands as a testament to the benefits of embracing advanced technologies, and the importance of continuous learning and adaptation in the pursuit of excellence in patient care.

To find out more about rapid NGS go to https://www.oncomine.com/rapid-lung-ngs-tumor-profiling

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MOLECULAR PATHOLOGY

Forens-omics

How a multi-omics approach can reveal the mysteries of the postmortem interval

By Noemi Procopio

When a body is discovered, scientists play a crucial role in helping investigators piece together the story. They work to uncover the identity of the victim, determine the cause of death, and, most importantly, estimate the time since death. This estimation, known as the postmortem interval (PMI), can be crucial when solving a case.

Traditional methods for estimating PMI – such as analyzing body temperature or insect activity – have limitations, especially as time passes. These methods can be subjective, often lack reproducibility, and become unusable when only skeletal remains are left.

That's where the "Forens-OMICS" approach comes into play. This emerging field, led by my team at the University of Central Lancashire, employs proteomics, metabolomics, and metabarcoding (analyzing microbial populations) to identify and measure various biological molecules in human remains. By examining how proteins, metabolites, and microbes change over time, the team is working toward more accurate PMI estimates.

In the bones

This work began with proteomics analysis on animal bones left to decompose in different environments (1). The goal was to identify proteins whose abundance decreased with increasing PMI and proteins with chemical modifications (post-translational modifications) that grew over time. The same method was later applied to human bones from taphonomy facilities in Texas and cemeteries in Italy, where similar patterns emerged, confirming that bone proteomics is a reliable tool for estimating PMI, especially for intervals greater than six months (2,3).

Proteomics analyses first require the extraction of proteins from the bone mineral matrix (4), which are then analyzed via high-accuracy liquid chromatograph–tandem mass spectrometry (LC-MS/MS) instruments. The mass spectrometry analysis returns a list of identified proteins in addition to their relative abundance in the sample. It also identifies the presence of post-translational chemical modifications. This information is used to identify protein markers correlating with PMI.

Similarly, metabolites and lipids found in bones can offer valuable information about PMI (5). As decomposition progresses, internal metabolites, microbial metabolites, and decaying lipids create a unique signature over time. Proteins and lipids, due to their larger, more stable structures, are better suited for estimating longer PMIs, while smaller, more dynamic metabolites provide precise estimates for shorter intervals, typically up to six months.

The team is currently combining proteomics, metabolomics, and lipidomics analyses on skeletal remains from individuals who died up to six years ago. These samples, exposed to environmental elements during decomposition, come from two human taphonomy facilities in Texas: the Southeast Texas Applied Forensic Science Facility (STAFS) and the Forensic Anthropology Center at Texas State (FACTS). Preliminary results show an estimation error of 230 days (6). Although this margin may seem wide, it represents a major advancement, given that PMI estimation from bones is often labeled "N/D" – not determined. The team is actively refining this approach by focusing on specific biomarkers, aiming to improve accuracy.

Tissue dating

Microbial successions in soft tissues after death can also help estimate PMI with precision. The team also uses metabarcoding to analyze the 16S rRNA bacterial gene, which identifies bacterial species by tracking how microbial communities change over time. By applying this technique to soft tissues and swab samples from both animals and humans, the team has achieved highly accurate PMI estimates, with an average error of nine days for samples up to six and a half months old in extreme cold environments (7) and just eight hours for samples with a 10-day decomposition period in a temperate climate (8).

Similarly, metabolomics conducted by the same team and applied to soft tissues has shown comparable accuracy, with a 12-hour error over a 10-day decomposition period (9). Combining metabolomics and metabarcoding for PMI estimation on shorter timescales could represent the future of forensic science, while protein and lipid biomarkers remain key for skeletal remains with longer PMIs.

The team is now working on targeted approaches to reliably quantify the key molecular markers already identified. The ultimate goal is to develop easy-to-use assays that forensic laboratories can implement with their existing equipment, eliminating the need for specialized expertise in -omics disciplines.

In court

Though proteomics is being applied to specific forensic questions such as bodily fluid identification, omics and metabarcoding strategies have not yet been employed for PMI estimation in court. For these methods to be accepted in legal contexts, it's not only necessary to have a validated technique, but also for practitioners to be aware of the new possibilities and open to integrating them into their practice.

As Principal Investigator of the Forens-OMICS team, I will be more than keen to provide training to colleagues interested in these advancements, so we can collectively position ourselves to apply this technology effectively when it is validated, ultimately bringing cutting-edge tools into the courtroom to solve real cases.

Noemi Procopio is UKRI Future Leaders Fellow and Principal Investigator at the University of Central Lancashire, UK

See references online

DIGITAL PATHOLOGY

Digital Networks in the United States

A case study from a full-service medical laboratory

Labs in the United States have been relatively slow to adopt digital pathology compared with Europe and Asia (1) – but the pace of change appears to be accelerating.

As the digital pathology conference offerings grow across the States, more laboratory medicine professionals are coming together to share their experiences, inspiring new waves of regional digital networks.

One early adopter is HNL Lab Medicine in Pennsylvania. Sajjad Malik – surgical pathologist and Medical Director of Digital Pathology – was tasked with setting up HNL's digital system from scratch. Here, we share the story of how the plan came together.

Drivers

Introducing such a major change to the pathology workflow requires a strong motivation and vision. In HNL's case, the vision started in the anatomical pathology department: to empower its professionals to be the best surgical pathologists possible.

There was also, perhaps, an element of FOMO (fear of missing out) involved, as Malik explains: "It is my belief that with the inception of AI and its incorporation into our daily practice, there will be a gap between pathologists who utilize this technology and those that do not. Ultimately, those working with AI assistance will be more efficient and provide the best care for their patients."

As a committed AI convert, Malik believes that, once labs catch onto its innate advantages, AI will become part of routine pathology practice. But he also acknowledges another good reason to get ahead of the digital game: "We were also motivated by the possibility of working remotely and recruiting pathologists to join our practice in the future."

Research

With the motivators for change well established, next came information gathering. Malik started reaching out to experts in both the private lab and academic communities.

"For starters, Sam Terese, the President of Alverno Labs – one of the first private labs in the US to digitize its practice – was instrumental in our understanding of digital pathology and providing us a framework for how we could implement it at HNL," continues Malik. "He invited us to his lab and we were able to see firsthand how the digital system was being used. Terese and his team shared with us some of the struggles they went through so we could avoid making the same mistakes."

Planning

The information gathered by Malik and his team fed directly into the creation of a business plan and a project team, which included management, pathologists, histologists, and the IT department.

Next came the procurement decisions. "After demoing a multitude of scanners and viewing systems, we had weekly meetings planning out our next steps," recalls Malik. "This process took about one year before we felt comfortable committing to our vision and starting to implement it."

Barriers

In the US, private labs are sometimes slower to adopt new technologies than institutional labs due to the large initial investment for which no reimbursement is available. In HNL's case, this barrier was overcome by having, in Malik's words, "a visionary CEO."

"Put simply, Martin Till believes that implementation of the latest technologies will improve the laboratory," says Malik.

Another major barrier to implementing digital pathology is having sufficient IT resources to build and maintain the necessary data management structure. "We are fortunate to have experienced IT managers who were able to take on this responsibility," explains Malik.

Rollout

Three years after conception, HNL's digital pathology system has been installed, validated, and rolled out across anatomical pathology.

"So far in our early adoption of digital pathology we have benefitted from being able to share cases seamlessly within our department," reflects Malik. "And although it is too early to measure any efficiency gains, I can see the potential that it has to ultimately reduce our turnaround times."

Next steps

Malik and team now plan to ensure all members of the anatomical pathology department are comfortable using the digital platform. They will then begin to phase out the use of glass slides, with a few specific exemptions.

After that, Malik says the team will work on incorporating hematopathology and cytology into the digital platform – a process he anticipates will take 6–12 months.

The final part of the process will be incorporating AI tools into the digital system. Malik is already on the case – researching and trialing algorithms on the market to find those most likely to benefit HNL's practice.

Inspiring

So has this enormous project been worth the investment of time?

Malik believes so: "This is the most exciting project I have ever taken on in my professional career. It has been very rewarding to start something that didn't exist in our lab and make it the new standard."

Reference

1. *The Pathologist, "Digital Pathology Adoption Trends: Europe and Asia," (2024). Available at: https://bit.ly/4fDpkGm*

INFECTIOUS DISEASE

Significant Steps for Sepsis

How an ultra-rapid antimicrobial susceptibility test could dramatically reduce diagnostic times for sepsis

Sepsis affects over 40 million people around the world each year, and it has an extremely high mortality rate – 20–50 percent – meaning that more than 10 million people can die from sepsis annually. To reduce this mortality, it is crucial to quickly diagnose and administer optimal antibiotics to the patients. Enter a team of researchers from Seoul, Korea, working on a rapid-diagnosis sepsis test.

We spoke with Tae Hyun Kim, one of the lead researchers on the "Blood culture-free ultra-rapid antimicrobial susceptibility testing" study, to learn more.

What inspired your study?

The current hospital protocol for determining the appropriate antibiotic, known as antibiotic susceptibility testing (AST), typically takes 3-4 days. This waiting period could make the difference between a successful or fatal case and, as engineers and life scientists, we needed to do something about it. To understand why AST takes so long, we had to examine the workflow and procedures carried out in the hospital.

AST is composed of a series of complex microbiological procedures:

- Blood culturing to detect and grow the pathogens present in the blood.
- Purifying the pathogens from other blood components.
- Identifying the type of pathogen.
- Testing which drugs the pathogen is susceptible to.
- Additional steps like cell counting and gram staining.

To expedite the lengthy traditional AST process, many research groups have developed a rapid AST (RAST) method, which eliminates the purification procedure, and shortens the entire process by 20-40 hours. Despite these advancements, the requirement for blood cultures, which takes at least a day, remains a significant hurdle.

We sought to overcome this limitation by developing an integrated technology capable of completing all necessary AST testing steps in a single day without the need for blood cultures.

What challenges did you overcome during this research?

We faced numerous challenges in our research, as we aimed to develop cutting-edge technology that could make a significant clinical impact in hospitals. Unlike other studies that focus on improving just one step of the diagnostic process, our goal was to create a comprehensive solution that could transform how doctors prescribe antimicrobial treatments, especially for sepsis patients.

We wanted to combine all the key steps of AST – pathogen isolation, fast cultivation, identification, and drug susceptibility testing – directly from blood samples. To achieve this, we had to carefully design and optimize each step to function seamlessly together. This involved a lot of trial and error, especially when testing with different bacteria, to make sure the system performed consistently and met hospital standards.

We also worked closely with physicians to understand the practical requirements for real-world use. By observing hospital diagnostic procedures, we continuously improved our platform's design. Though this project took a lot of time and effort, we believe our commitment to integrating new technologies at every step made this breakthrough possible.

How does your method work?

Our ultra-rapid AST (uRAST) assay operates through the following steps:

1) **Isolating pathogens:** We use nanoparticles coated with beta-2-glycoprotein 1 peptides (β2GPI-nanoparticles) that attach to a wide range of pathogens without binding to blood cells. A magnetic field is then applied to separate the blood components, leaving behind pure pathogen samples. These samples are then used for both (2A) species identification and (2B) drug susceptibility testing at the same time.

2a) **Species identification (QmapID):** Part of the isolated pathogen sample is used to identify the type of bacteria. Our test uses microdiscs with unique patterns and DNA probes that detect specific bacteria. When a pathogen's DNA binds to the correct microdisc, a fluorescent marker is added, which helps identify the bacteria by reading the microdisc's pattern.

2b) **Drug susceptibility testing:** Meanwhile, the pathogen is cultured in a special liquid that speeds up bacterial growth. After a few hours, the bacteria are placed into wells on a microfluidic chip, each containing different antibiotics. We monitor the bacterial growth using time-lapse imaging to determine which antibiotics are effective.

By integrating and streamlining these steps, we have developed the fastest method for this testing process.

Credit: Cube3D Graphic

What types of infections could benefit most from this method approach?

In this study, we focused on bloodstream infections caused by bacteria because they can benefit the most from our technology. However, our approach could also transform AST for fungal infections. Patients with fungal sepsis face higher death rates because fungal cultures take even longer than bacterial ones. By adjusting our platform to meet the needs of fungi, we aim to continue our research and provide an effective solution for these challenging cases.

Do you think this method could be easily adopted in hospitals and clinics? What challenges might there be in wider implementation?

Unfortunately, despite significant technical advancements, even RAST methods developed over a decade ago have yet to see widespread adoption in hospitals. One of the main barriers is the stringent yet somewhat outdated regulatory standards, which are still based on traditional AST methods and don't fully understand the benefits of newer technologies like ours. Additionally, new technologies must undergo strict clinical evaluations to get approval and insurance coverage, which is a slow and difficult process for companies. Introducing new technology could also create uncertainty as they require hospitals to reorganize roles, train staff, and change workflows, which many are hesitant to do.

Despite these hurdles, we believe that the uRAST system has the potential for widespread implementation in the near future. To facilitate this, we're developing an automated device that can perform all the tests, simplifying the process and reducing the need for staff training. By automating procedures, we aim to reduce delays and increase the system's clinical impact.

Our team has dedicated over a decade to AST research with the goal of saving lives in hospitals. During our clinical pilot study, we saw many sepsis patients lose their lives, which strengthened our commitment to this cause. Our goal extends beyond academic achievements; we aim for the successful implementation of our technology in hospitals, where it can truly make a life-saving impact.

How do you see this method influencing future diagnostic practices, especially in the fight against antibiotic resistance?

Antimicrobial resistance is a significant global threat, largely fueled by the unnecessary use of broad-spectrum antibiotics. Because current AST methods take too long, healthcare providers often give broad-spectrum antibiotics as a precaution. It is estimated that 14–78 percent of antibiotics prescribed are unnecessary or ineffective, exposing pathogens to treatments that don't work and speeding up the development of resistance.

This delay in diagnosis directly contributes to the rise of antibiotic-resistant bacteria. As resistance increases, standard treatments become less effective. The World Health Organization predicts that by 2050, antibiotic-resistant infections could cause 10 million deaths each year.

Developing new antibiotics is difficult, with few new drugs in recent years. Therefore, we need to treat existing antibiotics as a valuable global resource and minimize unnecessary use to slow down resistance.

Our uRAST method offers a solution by helping healthcare providers quickly identify the right antibiotic, reducing the need for broad-spectrum drugs. This approach can help prevent antibiotic resistance, preserve current antibiotics, and support better antibiotic use.

"Our goal extends beyond academic achievements; we aim for the successful implementation of our technology in hospitals, where it can truly make a life-saving impact."


"Working with many different components of army hospital systems taught me a lot about regulations, collaboration skills, and problem solving."

Serving Patients and Country

Sitting Down With…
Barbara Crothers, Associate Professor of Pathology, James H. Quillen Veterans Affairs Medical Center, Tennessee, USA

What drew you to pathology as a career?
In medical school, I rotated in cellular pathology at the Armed Forces Institute of Pathology, learned about cytology diagnostics, and had an early introduction to digital pathology. Further rotations in pathology introduced me to the diversity and complexity of the practice.

Pathology is detective work – and it suited my curious nature. I was drawn to the opportunities to work independently, but still have the full support of a team, to balance technical work with laboratory management, and to interact with patients both directly, via procedures, and indirectly through advising clinical tumor boards.

How did your time as an army pathologist shape your personal and professional development?
Working with many different components of army hospital systems taught me a lot about regulations, collaboration skills, and problem solving. I've been intimately involved in the remodeling, consolidation or moving of every hospital in which I was stationed. Because we often lack the resources necessary to complete a job, especially during deployment, the military teaches you to be inventive and creative by default.

A military career requires one to be flexible and to embrace change. Frequent moves mean that you have to learn to build teams quickly and garner consensus from diverse personalities. The military provides excellent training courses in management, leadership, and quality assurance, as well as in other skill areas. I took advantage of any training that was offered, but it was the positions to which I was assigned that potentiated my growth by exposing me to so many different areas of medicine and management.

What did receiving the ASC's 2024 Papanicolaou award mean to you?
Quite simply, it means that others in my field recognize the love and hard work that I have dedicated to cytopathology during my career. The ASC is replete with high-caliber individuals dedicated to the cause of human health – "one cell at a time" – and it has been such a delight to work with them all on many different committees and working groups. I hope they understand that they share this award.

This is the highest honor that a cytopathologist can receive and, frankly, I didn't expect it. I prefer to work on a team, behind the scenes, and, at times, even let others take credit for my work or ideas. I am not the traditional academic pathologist with a lengthy list of publications and significant breakthroughs in medical practice, which personifies most of the other recipients upon whose shoulders I stand. But I think that I do share some common traits with the great Papanicolaou: a curious mind, a thirst for knowledge and truth, a desire to help heal others, and a love of the basic unit of life – the cell.

What is your involvement with cytology AI software development, and how did that come about?
I work part-time with a company that has a software solution that identifies abnormal cells in liquid-based samples and analyzes diseased cell characteristics for interpretation by a pathologist. A former colleague recommended me for the position of Chief Scientist, and the role has given me incredible insight into the industry side of cytopathology and a better understanding of regulatory hurdles facing start-ups.

The role involves advising on software development from the end user perspective – designing research projects, creating training materials, advising on regulatory compliance, and participating in software evaluation. I work with a remarkable, dedicated team of creative individuals who seek to bridge the gap in personnel loss in our field through technology, and I find it very enjoyable.

What do you think the lab of the future will look like?
For pathologists, specimens will become increasingly digital, and AI assistance will be the norm. These advances will free pathologists to take on other responsibilities, both as consultants and direct providers of medical care. The laboratory will become more fragmented as medicine continues to specialize; anatomic pathology and clinical pathology may become divided.

As more people take responsibility for their own healthcare, there is more demand for and access to laboratory results – but patients cannot always interpret them. Laboratories and pathologists can play a part in that by providing guidance on follow up or treatment of laboratory results, although this may also be through the design of algorithms.

Who inspires you?
People (humanity), every day, by their goodwill, courage, and persistence. I've been motivated by so many role models during my career – both well-known icons, such as other Papanicolaou awardees, and by colleagues and students who probably don't even realize the effect that they have had on my aspirations and direction. Role models are all around us. Everyone has some lesson to teach us, some wisdom or inspiration to offer. We just have to pay attention.

Renewing your ASCP membership is about so much more than maintaining the status quo; it is about affirming your commitment to excellence and growth as a pathologist. It is about saying YES to a career that is the cornerstone of patient care. It is about saying YES to a future where innovation and collaboration drive our field forward. It is about saying YES not only to affecting change in my career, but also to the lives of my patients.

Renew your membership today at www.ascp.org/renew.