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Advances in Molecular Pathology



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Gene Test May Refine Chemo Choices

Real-world study suggests genomic testing could help laboratories support more personalized chemotherapy decisions in early breast cancer

A genomic test may help identify which patients with hormone receptor-positive, HER2-negative early breast cancer are most likely to benefit from anthracycline-containing chemotherapy, potentially allowing others to avoid unnecessary treatment-related toxicity.

Researchers analyzed prospectively collected real-world data from 1,259 patients enrolled in the FLEX registry who had stage I–III disease. Eligibility required a high-risk result on the MammaPrint 70-gene assay, and a Luminal B tumor profile on the BluePrint 80-gene molecular subtyping test. Patients received either an anthracycline- and taxane-based regimen or a taxane/cyclophosphamide regimen after surgery.

The key finding was that the high-risk category was not uniform. Patients classified as High Risk 2 experienced better invasive disease-free survival with anthracycline-containing treatment, while those classified as High Risk 1 achieved similar outcomes regardless of whether anthracyclines were included. Standard clinical features, including tumor size, lymph node involvement and tumor grade, did not distinguish patients who benefited from anthracyclines.
The study, published in JCO Precision Oncology, highlights an emerging role for genomic assays beyond estimating recurrence risk. Corresponding author William Audeh, Chief Medical Officer of Agendia, said, "This study answers a question that randomized clinical trials have been unable to resolve, illustrating the value of genomic profiling to predict benefit from a specific cancer therapy. The FLEX Study highlights the power of a multi-modal, real-world evidence database to produce robust, clinically relevant data which not only inform treatment decisions, but also change clinical practice guidelines."

The findings also reinforce the growing importance of integrated molecular diagnostics. In this study, patient selection combined results from both the MammaPrint genomic risk assay and the BluePrint molecular subtype classification, illustrating how multiple genomic tests can contribute to increasingly personalized treatment decisions.

The results suggest that genomic classification may help clinicians balance the potential benefits of anthracyclines against their recognized risks, including cardiac toxicity and treatment-related blood disorders. If validated in further studies, testing could support more confident decisions both to recommend anthracyclines for patients most likely to benefit and to avoid exposing others to additional toxicity without improving outcomes.

The authors note that the analysis was based on an observational registry with a median follow-up of just over three years, although statistical methods were used to reduce treatment-selection bias. They conclude that additional validation, including analyses of data from randomized clinical trials, will be needed before the approach is adopted more widely in clinical practice.



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ctDNA Tracks Relapse Risk in Breast Cancer

Personalized liquid biopsy testing identified molecular residual disease months before clinical recurrence

Circulating tumor DNA (ctDNA) monitoring before and after surgery predicted relapse and survival outcomes in patients with early breast cancer more accurately than standard measures of treatment response, according to a prospective study published in EMBO Molecular Medicine.

Researchers followed 136 patients undergoing neoadjuvant treatment for early breast cancer and monitored ctDNA levels across nearly 1,500 plasma samples collected over a median follow-up of 6.5 years. The study evaluated a personalized assay that tracks structural variants, large-scale genomic alterations unique to each patient's tumor, using multiplex digital PCR.

The investigators found that persistence of ctDNA after neoadjuvant therapy was strongly associated with recurrence and death. Patients whose ctDNA cleared during treatment had substantially better outcomes, while those with ongoing ctDNA detection faced markedly higher relapse risk. Importantly, ctDNA dynamics appeared more prognostic than pathologic complete response, which is currently widely used to assess treatment effectiveness after neoadjuvant therapy.

The assay also identified molecular residual disease after surgery, often long before recurrence became clinically apparent. Among patients who later developed distant metastases, ctDNA detection preceded clinical relapse by a median of 13.8 months and, in some cases, by almost four years.

The study highlights the growing clinical relevance of ultrasensitive liquid biopsy testing in routine cancer management. Unlike many existing ctDNA approaches that focus on single nucleotide mutations, the assay targets tumor-specific structural variants identified through low-coverage whole-genome sequencing. The authors argue that these structural changes may provide greater specificity and stability for longitudinal monitoring because they are less likely to arise from technical artifacts or age-related clonal hematopoiesis.

The workflow was designed with scalability in mind. After tumor sequencing establishes a personalized "fingerprint," follow-up testing can be performed using digital PCR, a platform that offers relatively rapid turnaround times and lower analytical complexity than next-generation sequencing-based monitoring.

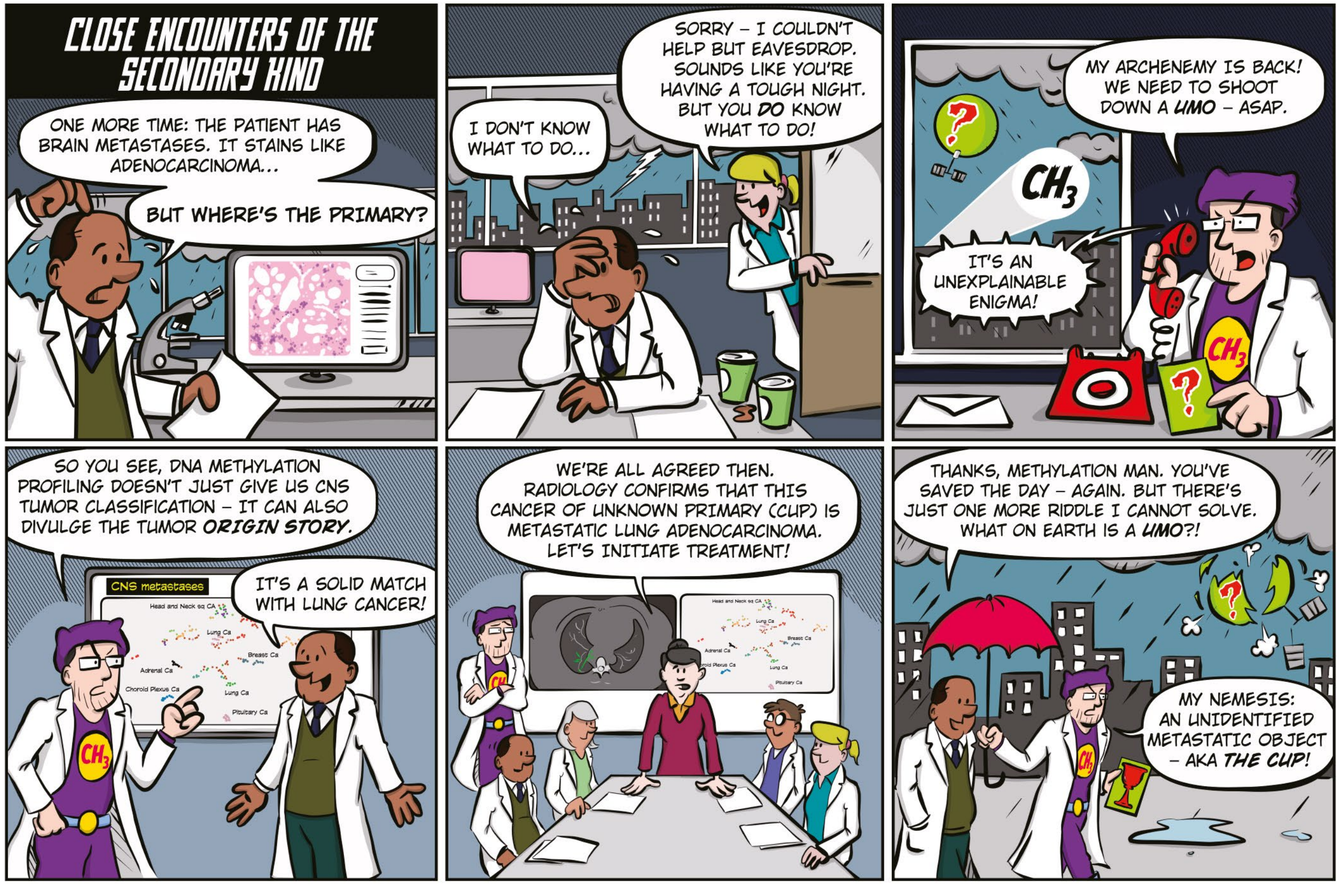
The findings support broader integration of ctDNA testing into breast cancer surveillance and treatment stratification, particularly for identifying patients at high risk of relapse despite apparently successful therapy.

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Methylation Man – Origin Story

Methylation Man targets a cancer of unknown primary with some serious firepower – and a nemesis emerges



Bringing it Home: Why We Switched to In-House WGS

Annette Kim shares her experience of a real-world clinical laboratory transition to whole-genome sequencing

When Annette Kim first considered implementing in-house whole-genome sequencing (WGS) workflows at Michigan Medicine, she soon found that the project reached far beyond simply expanding testing capabilities. Conversations about informatics, scalability, future-proofing, and finances quickly became routine. But, with effective teamwork and valuable partnerships, the plan came together…

Here, Kim shares her experience of creating a molecular pathology workflow that benefits patients, the hospital, research, and the entire university – while expanding in-house testing with a scalable foundation for diverse genomics initiatives.

What was the basis of the molecular pathology workflows at Michigan Medicine before the switch to WGS?
We used a commercial clinical exome panel. It had capacity for eight patient samples per run, each of which required almost two full days of wet bench work. That would be followed by 30 hours on the sequencer and then an additional full day of manually pushing data through the individual pipeline components.

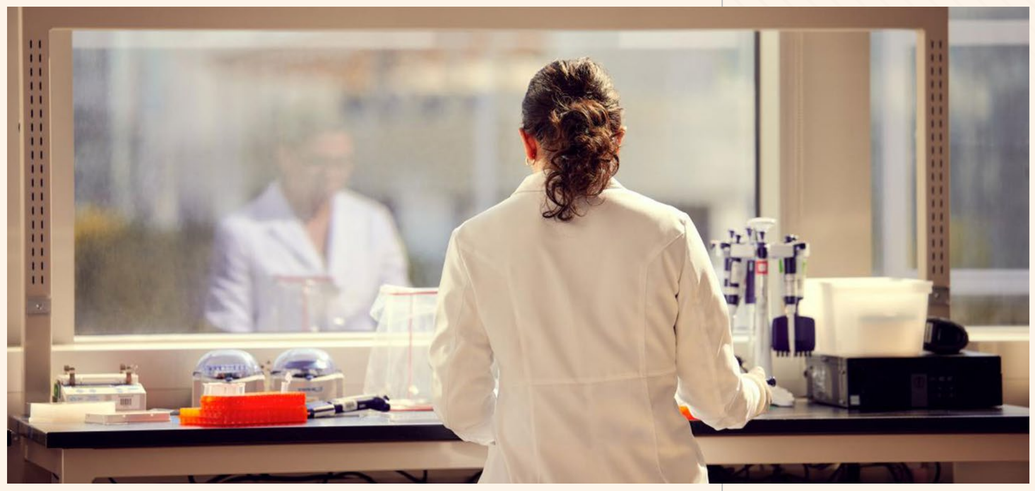
What aspects of that workflow were not working well??
Frustratingly, the panel we used didn't cover all the regions of genes in our exome slice panels sufficiently well. Those gaps resulted in 43 percent of our runs requiring fill-in Sanger sequencing. Other genes were very poorly covered or not covered all together. We had to design spike-in probes to help provide adequate depth for those targets.

All that extra work added a lot of time to each assay run and made it very onerous to perform.

What were the main drivers for the migration to WGS workflows?
Turnaround was the key driver. The workflow was so long and complex that we were barely meeting our published 4-week turnaround times for samples. That timescale was no longer meeting the clinical needs of our patients – particularly some of our sickest infants in the neonatal and pediatric intensive care units.

Another pinch point was the growing demand from our clinicians for send-out testing for whole exome or genome sequencing. With all our in-house technical expertise, it felt counterintuitive to be sending testing to reference laboratories. If we had WGS capability in-house, we could provide germline testing alongside targeted panels from a single, consolidated platform. What's more, it would future-proof our genomic analysis against any new disease markers that are discovered, even in dark regions of the genome where currently little is known about disease associations.

What were the key operational considerations for the WGS implementation?
We launched WGS for clinical and research applications asynchronously. We first kicked off a pilot project with the



Michigan Genomics Initiative (MGI) to sequence DNA for 10,000 patients in the University of Michigan's biobank. Once we were smoothly in production for MGI, we launched clinical WGS, co-sequencing the clinical samples with the research samples. This process allowed us to leverage the MGI volume of cases to use larger flow cells – with lower cost per genome – and decreased turnaround times, since we did not need to wait to accumulate sufficient clinical samples for a fixed batch size.

For the MGI cohort, we had to set up bulk accessioning for its DNA cases. By contrast, the clinical blood samples were individually accessioned and extracted. It required merging tasks into a single run list and automating both liquid handling and data processing.

Informatics streamlining was essential to build the cloud procedures. We had to send research data into one bucket while the clinical data needed further processing. We started using bioinformatics software platforms to support clinical reporting. In addition, we needed to format and upload our pre-existing variant knowledge databases into the new software.

What were the key personnel utilization considerations in transitioning to WGS workflows?
The WGS workflow requires around 8 to 10 hours of hands-on time, which is a big reduction on the 16 to 20 hours required for our previous assay. Analysis and reporting time was also reduced with the introduction of the analysis software.

With such substantial efficiency gains, some staff had concerns about what they would be doing when we transitioned to WGS. We were able to reassure the team that their increased bandwidth would be refocused on additional validations and new technology implementation. That generated real excitement for the whole team.

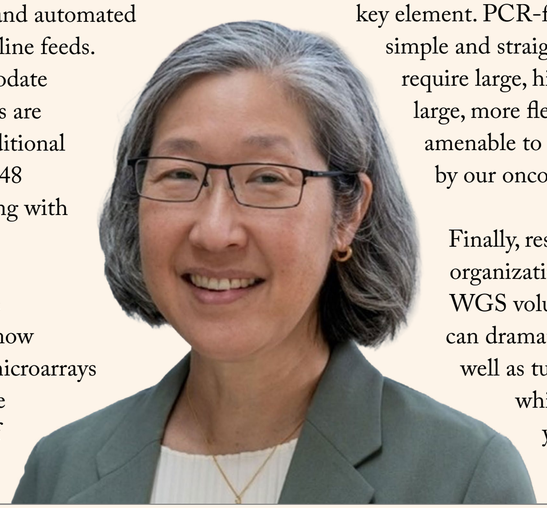
Informatics was a key consideration in establishing the WGS workflow, and part of my responsibility was growing that capacity in-house. We now have a dedicated informatics team, as well as clinical informatics faculty experts who liaise between the faculty and informatics experts.

What are the financial implications of the transition?
When we factored in the reductions in technologists' time and consumables compared with our prior clinical exome panel, the cost per genome was considerably less. I'm also hoping that the WGS workflow will lead to greater job satisfaction and less turnover of technologists – an intangible but important cost benefit.

What are the main clinical benefits of the transition?
We're finding that the WGS as a platform is very robust, delivering good quality sequencing every time. Without the amplification bias of PCR, WGS provides more uniform coverage, allowing us to detect variants that we couldn't see before. We can look for pathogenic variants in non-coding regions of the genome, or upstream or downstream variants that aren't part of the coding sequence. None of that was possible with our exome-directed panel.

Another important benefit of WGS platforms is scalability – an important factor in our workflow design. We incorporated bulk accessioning protocols and data analysis, and automated elements such as liquid handlers and pipeline feeds. Where our previous panel could accommodate only eight patients per run, the WGS runs are able to expand easily to accommodate additional volume as required – anywhere from 4 to 48 clinical samples per run, variably backfilling with research samples.

We also have much more flexibility in the testing we can provide. Because WGS is now recommended in place of chromosomal microarrays for the workup of developmental delay, we can offer testing to a whole new cohort of patients in-house. We're also able to reflex or reanalyze samples on different or broader panels, or even whole genome reporting, which is hugely beneficial for patients and clinicians.



All those capabilities are of huge benefit to our patients and our relationship with the clinicians.

What is your advice for other labs looking to transition to a WGS workflow?
One of the first considerations is building the IT infrastructure and cloud networks, and configuring software required to run the technology. Labs should start with creating a first-rate informatics team who will work closely with your vendor to achieve that.

If you're building for scale, a simple, robust liquid handler is a key element. PCR-free library preparation is relatively simple and straightforward, and doesn't necessarily require large, high-end liquid handlers. We chose a large, more flexible instrument that would also be amenable to the complex library preparations used by our oncology assays.

Finally, research partnerships within your organization can be invaluable in increasing your WGS volume. Leveraging that additional volume can dramatically decrease the cost per genome as well as turnaround times to meet clinical needs while enhancing the academic mission of your institution.

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From Variants to Voices: Rethinking Success in Genomic Medicine

"We found the variant, but now what?" asks Dina Abdelhakam

By Dina Abdelhakam

For much of the past two decades, progress in genomic medicine has been measured by technical achievement. Sequencing technologies became faster, databases grew larger, bioinformatics pipelines more sophisticated, and diagnostic yields steadily improved.

These advances transformed the ability of clinicians and laboratories to identify the genetic causes of rare and complex conditions. Yet, despite these achievements, an important question remains largely unanswered: what happens after a genomic answer is found?

A genetic diagnosis is often treated as the endpoint of a successful clinical journey. In reality, it is usually the beginning of a much longer one. Families leave clinics carrying new information, new uncertainties, and new decisions. They are expected to understand unfamiliar scientific concepts, communicate results to relatives, and navigate healthcare systems. They must make choices about treatment, surveillance, reproduction, and future planning.

The technical report may be complete. The patient's journey is not.

Unanswered questions

I encountered this gap directly in my work in clinical genomics and molecular diagnostics. A family who had waited nearly three years for a diagnosis received their result on a Sunday afternoon. The variant was classified. The report was accurate.

By Tuesday, they had sent eleven messages to the clinic – not about the science, but about what to tell the school, whether to test the siblings, and whether the diagnosis would affect their insurance. The report had answered the genetic question. It had not prepared them for what came next.

This is not an isolated experience. Laboratories routinely monitor quality indicators such as turnaround time, sequencing coverage, and diagnostic yield. These measures are essential. But they tell us very little about whether patients understood their results, whether expectations were aligned with reality, or whether recommended follow-up actually happened.

There is a real distance between the moment a result is issued and the moment it becomes meaningful to the person receiving it. For laboratories, the challenge is no longer simply generating accurate results, but ensuring those results can be translated into informed decisions and meaningful care.

The challenge extends beyond patients and families. Many healthcare professionals now encounter genomic information in routine practice but have received limited formal training in how to interpret, communicate, and apply these findings.

Dina Abdelhakam



Understanding as standard

That distance grows more significant as genomics moves into an increasingly interventional era. Advances in gene therapy, RNA-based therapeutics, and precision medicine are changing what a genetic diagnosis means. For some conditions, identifying a pathogenic variant is no longer the end of the process. It is the beginning of a therapeutic pathway, and that shift carries new responsibilities for everyone involved.

Families are now exposed to information about emerging treatments, clinical trials, and future possibilities before those possibilities are ready for them. Hope becomes part of the clinical conversation. That is not a bad thing. But hope without context can lead to confusion, misaligned expectations, and real emotional burden.

The challenge is not simply explaining what is scientifically possible. It is helping patients and families understand what is available, accessible, and relevant to their situation right now.

This experience has led me to view communication, education, and storytelling as integral components of genomic care rather than optional additions to it. Quality in this field cannot be measured by technical performance alone. It also lives in whether people understood what they were told, whether they felt supported in making decisions, and whether the care they received reflected some awareness of the life they were returning to after the appointment.

The wider conversation

Scientific knowledge and lived experience have too often been treated as separate concerns. Patients, families, clinicians, laboratory professionals, counselors, educators, and advocates all carry different parts of the same story. When those perspectives come together, they reveal things that data alone does not show: where communication breaks down, where expectations diverge, and where people fall through the gaps between what the system offers and what they actually need.

The field is moving quickly. As genomic testing becomes more accessible, and therapeutic options continue to grow, the work of connecting scientific progress to human experience becomes more urgent, not less. What is measured, communicated, and prioritized in the clinic and the laboratory will shape whether that progress reaches people in ways that are genuinely useful to them.

Policy plays an equally important role. Decisions about coverage, reimbursement, genetic privacy, and research funding matter. They determine not only who can access genomic medicine but how much space exists within it for education, counseling, and follow-up care.

These conversations should not be held separate from the science. They are part of what makes the science matter.

The variants are just the beginning

In many Middle Eastern settings, these challenges are further shaped by limited access to genetic counseling, variable insurance coverage, cultural stigma surrounding inherited conditions, and uneven availability of advanced therapies or clinical trials. In such contexts, genomic care cannot rely on testing alone. It requires culturally sensitive education, stronger clinician support, and policies that make follow-up care, counseling, and family communication more accessible.

Genomic medicine has always been about more than identifying variants. It is about helping people make sense of information that can change how they understand themselves, their families, and their futures. As the field enters a new era of therapeutic possibility, success will depend not only on what we discover in the genome, but on how effectively we translate those discoveries into understanding, action, and care.

The future of genomics will be shaped not only by the variants we identify, but by the voices we learn to hear.



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Precision Diagnostics and the ADC Revolution

Antibody-drug conjugates are transforming cancer care, but their success depends on more precise, sensitive, and data-driven diagnostics

As antibody-drug conjugates (ADCs) expand across tumor types – and begin to work even at low levels of biomarker expression – the demands on diagnostics are rapidly evolving. Traditional approaches to biomarker assessment are being pushed to their limits, opening the door to computational pathology, multiplex assays, and more quantitative imaging strategies.

We spoke with Rob Monroe, Chief Medical Officer at Leica Biosystems, about the analytical advances driving this transition and what the next generation of precision diagnostics might look like.

How would you describe the current state of the ADC field, and what factors do you see as most influential in shaping its direction right now?
The ADC field is among the fastest-growing areas of oncology therapeutic development, with hundreds of clinical trials underway targeting dozens of different tumor antigens with antibody-drug conjugate technology (1) This growth trajectory is reflected in broader market projections: the oncology companion diagnostics market is forecast to expand at a compound annual rate of 8.7 percent, reaching $8.4 billion by 2030 (2).

Recent regulatory successes have been a major catalyst, including approvals of several new ADCs – HER2-targeting agents, as well as those directed against Claudin 18.2, folate receptor, and NECTIN4 – spanning multiple tumor types including lung, breast, and bladder cancers (3).

A second major driver has been the dramatic improvement in linker technology, which connects the cytotoxic payload to the monoclonal antibody and enables more precise, site-specific release of the toxin within the tumor (4). These advances have significantly enhanced targeting precision and local drug delivery. While ADCs have existed for more than two decades, these recent technological refinements have produced dramatic gains in efficacy and propelled the field's rapid growth. We are also beginning to see growing interest in combining ADCs with immune checkpoint inhibitors, which is in turn driving the need for diagnostics capable of simultaneously detecting ADC target antigens such as HER2 and TROP2 alongside immune checkpoint biomarkers like PD-L1 and PD-1.

In your view, what features of ADC mechanism or clinical use make accurate biomarker assessment especially important?
The key mechanistic feature of ADCs is their ability to target protein biomarkers – typically surface proteins on tumor cells. Because ADCs target proteins rather than genomic alterations such as mutations or gene amplifications, they can remain effective even when that protein is expressed at relatively low levels (5). This fundamentally changes the standard for biomarker assessment.

Rob Monroe



Unlike traditional HER2-targeted therapies such as Herceptin, which require high protein expression, ADCs deliver a cytotoxic payload directly into the cell upon internalization. They do not depend on high target expression to be effective. Once internalized, the chemotherapeutic payload kills the tumor cell and can also be released into the surrounding tumor microenvironment, extending its effect to neighboring cells that may not themselves express the ADC target. This "bystander effect" is a major driver of ADC efficacy (6).

Because even low biomarker levels can determine whether an ADC is clinically effective for a given patient, the ability to detect small amounts of target protein with precision becomes critical. Accurate biomarker assessment is therefore not merely a technical requirement – it is a gatekeeper for patient access to potentially life-saving therapies. Improving upon semi-quantitative and qualitative approaches that may overlook patients with low expression is an urgent priority for the field.

How do you view the role of traditional IHC in assessing biomarkers relevant to ADCs, and in what situations might its limitations become more apparent?
IHC has evolved to become the preferred method for assessing ADC biomarkers and guiding patient selection. Many early ADCs were approved without formal companion diagnostics because their target biomarkers were broadly expressed across the relevant tumor type. However, as multiple ADCs are now being developed for the same cancers, it is increasingly important to identify which ADC is most appropriate based on differential protein target expression. IHC is widely available, well-validated, and amenable to automation – Leica Biosystems has invested in automating IHC workflows to make it the most direct and reproducible approach for protein expression assessment in clinical laboratories.

That said, IHC has real limitations, particularly with respect to dynamic range and sensitivity at low expression levels. This has become especially apparent with HER2, where the concept of "HER2-low" and now "HER2-ultralow" expression is pushing the boundaries of assays that were originally designed and optimized for high protein expression. Traditional IHC scoring systems were not built with this sensitivity in mind, and as ADCs continue to expand the therapeutically relevant range of target expression, these limitations become more consequential.

What does computational pathology contribute to the evaluation of ADC targets that may be difficult to achieve through conventional microscopy alone?
Computational pathology, built on digital imaging and AI-powered analysis, provides capabilities that are simply beyond what conventional microscopy can deliver. One important contribution is helping pathologists navigate borderline cases more confidently – for example, applying AI algorithms to assess PD-L1 expression at clinically significant thresholds such as 1 percent or 50 percent tumor cell positivity, where a wrong call can directly affect treatment access (7).

Another key benefit is the ability to distinguish true biomarker staining from background or nonspecific signal – a persistent challenge in IHC, and one that becomes especially problematic at low expression levels where the human eye struggles to make reliable calls. Computational pathology improves sensitivity and specificity in these borderline scenarios and enhances reproducibility across institutions, so that different pathologists reviewing the same slide consistently arrive at the same – and more accurate – conclusion.

Perhaps most significantly, computational pathology enables biomarker assessments that cannot be performed by the human eye at all. A compelling example is AstraZeneca's Quantitative Continuous Scoring (QCS) system for the ADC target TROP2, which received FDA Breakthrough Device Designation and uses a computational approach to measure a normalized membrane-to-cytoplasm staining ratio as a surrogate for target internalization (8). This ratio cannot be determined through visual microscopy. If an ADC is approved using a QCS-based cutoff, the companion diagnostic would rely entirely on computational output – a paradigm shift illustrating how digital pathology is moving from support tool to essential infrastructure.

How are newer staining and imaging approaches influencing the way researchers assess biomarkers related to ADC development?
Beyond quantitative computational scoring systems, fluorescence-based imaging is emerging as an important alternative to conventional chromogenic staining for ADC biomarker research. Fluorescence imaging offers a substantially greater dynamic range, enabling finer discrimination of protein expression levels

"Computational approaches open up biomarker development possibilities that were inaccessible through conventional microscopy and traditional IHC scoring."

and supporting patient stratification at much lower expression thresholds than traditional chromogenic IHC.

Fluorescent approaches can also be used to correlate signal intensity with defined protein quantities, enabling estimation of actual protein concentrations within tumor cells – not just relative staining patterns. This is particularly valuable for ADC development, where understanding the absolute level of target expression in a tumor may help predict whether payload delivery will be sufficient for a therapeutic effect.

In parallel, there is growing interest in chromogenic dyes that offer some of the same advantages as fluorescent stains – including more linear relationships between staining intensity and actual protein levels – while remaining more compatible with existing brightfield imaging infrastructure in clinical laboratories. Both approaches are active areas of translational ADC research aimed at resolving low-level expression with greater precision than is achievable with conventional methods.

What developments in analytical technologies – whether in imaging, assay chemistry, or spatial methods – are having the greatest impact on how ADC targets are measured and interpreted?
Across imaging, assay chemistry, and spatial biology, several converging developments are reshaping how ADC biomarkers are measured and interpreted.

In imaging and computational analysis, AI algorithms applied to digitized IHC images can now identify subtle differences in the pattern, spatial distribution, and overall quantity of protein expression between patient populations that respond to an ADC and those that do not. These computational approaches open up biomarker development possibilities that were inaccessible through conventional microscopy and traditional IHC scoring. The TROP2 QCS method is the leading clinical example of this paradigm, and its regulatory success is likely to catalyze similar computational approaches for other ADC targets.

In assay chemistry, fluorescent staining and advanced chromogenic dyes both offer improvements in quantitative precision that are driving translational research. The ability to generate more linear correlations between staining intensity and actual protein levels is critical for developing robust, analytically sensitive companion diagnostics.

In spatial biology, multiplex assays capable of assessing several biomarkers simultaneously – and capturing information about the tumor microenvironment – are among the most impactful emerging tools. Evaluating the spatial arrangement of immune cells relative to tumor cells can inform predictions of ADC efficacy: for instance, understanding whether ADC target-expressing cells are spatially clustered or intermixed with non-expressing cells helps predict whether the bystander effect will meaningfully extend cytotoxic activity. Parallel assessment of H&E images alongside IHC can also provide inferred genomic and transcriptomic information that complements biomarker interpretation. Together, spatial approaches represent an important frontier for refining patient selection beyond what protein expression alone can provide.

How is artificial intelligence being used to analyze biomarker expression in the context of ADCs, and what kinds of insights can it help uncover? Are there considerations around validation or interpretability?
AI is being applied to ADC biomarker analysis in two primary and complementary ways. First, it delivers more accurate and reproducible assessment of known biomarkers – improving tumor cell scoring, quantifying percentages of positive cells, and reducing inter-pathologist and inter-laboratory variability that can otherwise lead to inconsistent patient selection. Studies have shown that

pathologists' interpretations can vary substantially from one reader to another and from one lab to the next, with real consequences for patients who may or may not qualify for a given therapy.

Second, AI enables entirely novel forms of biomarker analysis that go beyond what human reviewers can extract from a slide. AstraZeneca's QCS system for TROP2 is the defining example: AI measures the relative distribution of biomarker expression across the membrane and cytoplasm, generating a normalized membrane ratio that predicts patient response – a biological insight that simply cannot be captured through manual scoring. The FDA's granting of Breakthrough Device Designation for the TROP2 QCS assay validates this approach and signals the opening of a new chapter for computational pathology companion diagnostics.

With regard to validation, any AI-generated biomarker result used for clinical decision-making requires rigorous analytical and clinical validation. Interpretability is also an active consideration – as AI-derived scores become increasingly abstract (ratios, spatial interaction metrics, and multimodal features), it is critical that they are mechanistically linked to the underlying biology and clinically validated against treatment outcomes. Regulatory agencies including the FDA are increasingly engaged as partners in defining these validation frameworks, a development that is accelerating the field's progress.

What potential do you see for approaches that assess multiple ADC targets within the same assay, and what would be necessary to make this practical in research or clinical settings?

The potential for multiplex ADC biomarker assays is substantial – and increasingly urgent. We are rapidly approaching a situation where multiple ADCs, potentially five or more, may be approved for a single tumor type such as lung, breast, bladder, or colorectal cancer. Testing each target individually with a separate IHC assay is neither tissue-efficient nor cost-effective, and it will simply be impractical at scale. Multiplex methods that can evaluate several ADC targets simultaneously on the same tissue section represent an essential future solution.

In research settings, multiplexing is already well established. Fluorescent technologies, validated antibodies, and imaging platforms capable of multi-target assessment are widely used in translational and discovery contexts. The challenge lies in clinical translation. For broad clinical deployment, assays must be simplified: panels should ideally contain no more than three to five biomarkers, staining reagents must be compatible with standard automated IHC platforms available in most labs, and the full workflow from staining through imaging to computational analysis must be seamlessly integrated.

Both chromogenic and fluorescent multiplexing formats have roles to play, with chromogenic approaches likely more accessible to clinical laboratories in the near term given their compatibility with existing brightfield infrastructure. In either format, computational pathology is an absolute prerequisite for interpretation – once assays move beyond a single chromogen or fluorescent channel, the complexity exceeds what conventional microscopy can handle reliably. Close collaboration within diagnostics companies between antibody development, staining platform development, digital pathology, and AI software teams will be essential to bring these integrated solutions to the clinic.

How might digital pathology fit alongside other analytical approaches – such as genomic profiling, flow-based methods, or spatial omics – to build a more comprehensive understanding of ADC response?
For ADC therapeutics, the effector molecule is the surface protein itself – which means protein-level assessment is the most direct and biologically relevant way to evaluate patient suitability for a given ADC. This gives IHC paired with digital computational analysis a fundamental advantage over genomic profiling, which uses DNA copy number or gene amplification as surrogates for protein expression, and over RNA profiling, which measures transcript levels that may not faithfully predict final protein abundance or membrane localization. When the goal is to determine whether an ADC target is present at a therapeutically meaningful level on the tumor cell surface, protein-based measurement is the preferred approach.

That said, digital pathology is most powerful when integrated with complementary modalities. For example, combining IHC with AI-powered H&E analysis can reveal genomic and transcriptomic profiles from standard histology slides – a potentially democratizing development, given that H&E images are universally available while genomic sequencing is not always accessible. AI applied to H&E can, for instance, infer EGFR mutation status, helping prioritize which patients require formal molecular testing.

Flow cytometry offers another complementary approach for assessing protein expression in liquid tumors or dissociated cell preparations, particularly relevant for hematologic malignancies. And as discussed, spatial omics approaches add the important dimension of microenvironmental context – immune cell composition, spatial architecture, and biomarker co-localization – that can refine response prediction beyond protein expression levels alone. Together, these modalities form an increasingly multimodal diagnostic ecosystem, with IHC and digital pathology as the central pillar for solid tumor ADC assessment.

If you look five to ten years ahead, what might ADC biomarker assessment look like, and what developments do you expect will have the most influence?

Looking five to ten years ahead, I expect the most transformative development will be the clinical standardization of multiplex assays that simultaneously evaluate multiple ADC targets in the same tumor specimen. As more ADCs are approved for individual tumor types – a near-certainty given the current pipeline – single-target IHC will become insufficient and inefficient. Multiplex panels assessing three to five ADC targets at once will become standard of care in lung, breast, colorectal, and other high-prevalence cancers, enabled by automated staining platforms paired with AI-powered computational analysis.

Computational pathology will be indispensable in this future. The broader adoption of digital pathology across clinical laboratories – currently still below 20 percent globally – will accelerate, driven by the regulatory approval of AI-enabled companion diagnostics and by demonstrated clinical utility that overcomes current adoption barriers. AI will not only enable pathologists to interpret complex multiplex data but will also introduce fundamentally new biomarker paradigms: quantitative continuous scoring, normalized membrane expression ratios, spatial interaction metrics, and multimodal biomarkers derived from combined IHC, H&E, and potentially radiology data.

The TROP2 QCS and normalized membrane ratio represent early prototypes of this next generation of computational companion diagnostics. Their regulatory success will encourage other pharmaceutical companies to develop analogous approaches for their own ADC programs. Beyond ADCs, this same infrastructure – multiplex protein assays combined with AI-driven analysis – will support the growing field of multispecific antibodies and will deepen the integration of ADC therapy with immune checkpoint inhibition. The vision is a future in which a single, AI-interpreted multiplex assay provides oncologists with a comprehensive molecular portrait of a tumor, enabling them to select the optimal therapy – or combination of therapies – for each individual patient at the right point in their cancer journey.

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Smoothing the Path to In-House NGS

Experts share how IVD testing can simplify verification, reporting, and reimbursement for clinical NGS

Bringing next-generation sequencing (NGS) into routine oncology care can require laboratories to solve several challenges at once: selecting an assay, verifying performance, managing workflows, reporting results, and securing reimbursement. In a recent webinar, four speakers described how an FDA-approved in vitro diagnostic (IVD) workflow can help laboratories address these needs, from initial verification through payment*.

**Reimbursement information applies only in the United States.*

Verification, not validation

Xia Li, Medical Director of the Molecular Pathology Laboratory at Clin-Path Associates, and Associate Professor of Pathology at the University of Arizona, explained that laboratories implementing an unmodified FDA-cleared or approved non-waived test system in the United States verify its performance under local conditions. This is a narrower process than validating a laboratory-developed test (LDT).


Xia Li

Under Clinical Laboratory Improvement Amendments (CLIA) requirements, verification confirms that the manufacturer's established performance specifications can be reproduced before results are reported. It is faster and less expensive, helping the lab implement the test more efficiently. Laboratories can keep verification data within their quality management systems rather than submitting it for review, which further reduces the complexity and duration of the process.


Gary Pestano

Using the Oncomine DX Express Test as an example, Li recommended testing representative clinical specimens across relevant tumor types and variant classes, and assessing accuracy, precision, reportable range, and specificity.


Theresa Wheeler

Li summarized that laboratories using an IVD test can introduce genomic profiling into routine practice in weeks rather than months.

Evidence from routine practice


Rob Dumanois

Gary Pestano, Chief Development Officer at Biodesix, described his laboratory's experience verifying the test. The study included 48 tumor specimens from 13 tumor types and 84 genomic variants. The team compared results with independent reference findings and investigated initial discrepancies using orthogonal methods. Final concordance was 98 percent at the variant level and 96 percent at the sample level.



Additional reference materials covered major variant classes. The team detected expected copy number alterations and fusions; one expected single nucleotide variant was initially missed, likely because of an artifact in the synthetic material. Pestano said the automated workflow, turnaround of less than two days, and low input requirements support time-sensitive oncology testing. He also noted that the predefined panel is intended for targeted

"The speakers' examples show how an IVD solution can reduce practical barriers to clinical NGS through a narrower verification scope, integrated software, and improved access to reimbursement."

profiling and companion diagnostics, rather than exploratory sequencing or ultra-low-frequency variant detection.

A guided informatics workflow from sample to report

Teresa Wheeler, Product Manager at Thermo Fisher Scientific, showed how Genexus DX software guides users through sample management, run planning, quality control, analysis, and reporting in one interface. Staff enter sample information and create a run plan before sequencing. The system then automates extraction, quantification, library preparation, sequencing, and predefined quality checks.

After the run starts, the software monitors progress and performs primary analysis, including base calling and quality assessment, followed by secondary analysis to align reads, identify variants, and generate reports. Staff review quality metrics and variant calls before authorizing the clinical report.

Application programming interfaces can connect the software with laboratory information management systems for sample registration and report transfer.

Wheeler said this integrated, automated approach can reduce manual work and reliance on bioinformatics expertise, helping more laboratories offer clinical NGS.

A clearer path to reimbursement

Rob Dumanois, Director, Reimbursement Strategy, at Thermo Fisher Scientific, described the coding and coverage strategy for the assay. Laboratories can use dedicated coding pathways, including a PLA code and an assigned MolDX Z-code, to support billing. He said the assay is covered nationally by Medicare following FDA approval, while commercial insurers are beginning to announce policies. A national CMS payment rate of $1,822.06 was announced on September 24, 2026, and will take effect on January 1, 2027. Interim reimbursement is already available. This update came after the webinar.

Together, the speakers' examples show how an IVD solution can reduce practical barriers to clinical NGS through a narrower verification scope, integrated software, and improved access to reimbursement.

For In vitro diagnostics. "The Oncomine DX Express Test is indicated in US as a companion diagnostic (CDx) to identify non-small cell lung cancer (NSCLC) patients with EGFR exon 20 insertion mutations for treatment with ZEGFROVY™ (sunvozertinib) in accordance with the approved therapeutic product labeling. The Oncomine Dx Express Test detects biomarkers recommended by professional guidelines for multiple solid tumors, including substitutions, insertions, and deletions in 42 genes, copy number variants in 10 genes, and fusions or splice variants in 18 genes.

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The AACR 2026 Roundup: Why Quantitative Precision Matters

From detection to decision support, here are the key precision diagnostic updates from this year's conference

By Marwan A. Alsarraj

The American Association for Cancer Research (AACR) Annual Meeting 2026 in San Diego reflected how precision oncology goals are shifting. The questions have evolved from whether we can detect cancer signals to whether we can measure them well enough to act on them.

Across plenary sessions, oral presentations, and poster discussions, a consistent theme emerged: the capacity to detect circulating tumor DNA (ctDNA) and other blood-based biomarkers has advanced considerably, yet the constraints on clinical translation are increasingly analytical rather than biological. Reproducibility and precise quantification are now recognized as central challenges, particularly as liquid biopsy applications move from research settings into clinical trials.

Here, I report on the most compelling new liquid biopsy studies presented at the meeting.

Liquid biopsy as a longitudinal tool

Liquid biopsy has been an active area of discussion at major oncology meetings for several years as it is increasingly used for assessing molecular residual disease (MRD), relapse risk, and treatment response. At AACR 2026, presentations largely focused on the parameters that determine whether ctDNA measurements are reliable enough to support clinical decisions. This includes sensitivity at very low variant allele fractions (VAF), run-to-run reproducibility, and the establishment of analytically validated thresholds for positivity and data interpretation.

A dedicated session on liquid biopsy performance standards, led by The Blood Profiling Atlas in Cancer (BLOODPAC), explored the criteria required for regulatory validation, including defining intended-use populations and target conditions, and evaluating data accuracy. These considerations are particularly relevant as ctDNA assays transition from exploratory biomarker work to clinical trial endpoints in the context of single and multi-cancer detection.

Demonstrating what longitudinal ctDNA monitoring can enable in practice, the TOMBOLA trial, a Danish multicenter study, evaluated ctDNA-guided immunotherapy following cystectomy in muscle-invasive bladder cancer. Patient-specific droplet digital PCR (ddPCR) assays targeting tumor-derived single nucleotide variants were used to monitor plasma ctDNA status in the postoperative period. Patients who tested ctDNA-positive received atezolizumab regardless of imaging findings, with the intent of intervening at a stage of minimal metastatic burden.

Preliminary data showed that ctDNA clearance following immunotherapy was observed in a substantial proportion of treated

Credit: Adobe Stock



patients, and that ctDNA levels correlated with recurrence risk and treatment response. This positions ctDNA as a quantitative response biomarker with potential implications for treatment stratification.

At AACR, the researchers shared further insights from the TOMBOLA trial, outlining the results from a comparative study between ddPCR and whole-genome sequencing (WGS). They found that, even though there was a high concordance in ctDNA detection in plasma between the two methods, 12 percent of the samples (particularly those with low tumor fractions) were only positive with ddPCR. This further demonstrates the power of this tool in the quantification of rare analytes.

Epigenetics and methylation move into the spotlight

Epigenetic markers, and DNA methylation in particular, also received substantial attention at AACR 2026. The topic reflects the growing recognition that mutation-based ctDNA analysis alone is insufficient for certain clinical contexts. Methylation patterns carry tissue-of-origin information that genetic alterations do not, and methylated cell-free (cf)DNA fragments can be detected in plasma even when tumor mutational burden is low. This is an important consideration in early-stage disease, where ctDNA fractions are often at the limit of detection for mutation-based assays.

Data presented at the meeting included work on integrated genomic and epigenomic ctDNA detection in colorectal cancer using multiplex ddPCR technology. The study showed that simultaneous profiling of somatic mutations and methylation markers improved sensitivity relative to either analyte type alone.

This approach showcases a broader trend in the field whereby multi-marker strategies that combine mutation and methylation data are used to increase the probability of detection, particularly at low tumor fractions. The analytical properties of ddPCR technology – which enables absolute quantification through Poisson statistics without reliance on a standard curve – make it well suited to the detection of methylated cfDNA at the low concentrations encountered in plasma.

MRD as a clinical and translational endpoint

The Discovery Science Plenary session, titled "The Next Frontier in Minimal Residual Disease: Solid Tumors," aimed to showcase the technological advances behind MRD detection and its impact on therapeutic and disease outcomes, as well as biological mechanisms driving disease progression and drug resistance.

MRD detection has already influenced treatment strategies in hematologic malignancies, where assay sensitivity, reproducibility, and regulatory acceptance are more established. The abstract landscape at AACR 2026 suggested that solid tumor MRD is reaching a comparable level of research, with data spanning colorectal, lung, breast, and urothelial cancers. Several of those abstracts demonstrate how ddPCR technology can support MRD monitoring and targeted therapeutic strategies, including work on MRD detection and monitoring in solid tumors and hematologic malignancies presented in an exhibitor spotlight session.

Resistance tracking: earlier signals, clearer decisions

Another thread running through the meeting includes early resistance tracking during therapy. For well-defined molecular mechanisms of resistance – such as EGFR-driven non-small cell lung cancer or KRAS-mutant colorectal cancer – longitudinal ctDNA analysis enables the detection of emergent resistant clones prior to any changes detectable by imaging. However, as highlighted in multiple sessions during the meeting, the frequency of monitoring and the sensitivity threshold of the assay used have direct implications for the clinical utility of this approach.

The evolution of quantitative precision diagnostics

The scientific program at AACR 2026 reinforced that the translation of liquid biopsy from research to clinical practice is closer than ever, with longitudinal monitoring using ultra-sensitive tools proving to be a major driver behind these advancements. Next-generation sequencing continues to expand the scope of genomic discovery and plays an established role in novel target identification. Meanwhile, precise technologies that deliver rapid, reproducible, and interpretable quantitative results offer a complementary and, in certain monitoring contexts, more practical approach in oncology research.

Scaling Science: My Precision Medicine Accessibility Mission

Sitting Down With… Luca Quagliata, Vice President and Global Head of Medical Affairs at Thermo Fisher Scientific

Was leadership part of your career plan, or did it happen organically?
I've had a curious nature for as long as I can remember. Even from a young age, I had a passion for understanding what's happening behind the scenes – how things really work. For me, choosing science as a career path felt completely natural. But as time went on, I realized that curiosity alone wasn't enough. I wanted to translate problem-solving into something actionable that could make a real difference.

That's when I understood I needed to combine scientific expertise with business capability to solve real-world problems and the goal of science leadership began to take shape.

What prompted your transition from academia to industry?
I was incredibly fulfilled by my work at University Hospital Basel, but I felt this growing need to scale up the impact of what we were doing. That's where a company like Thermo Fisher becomes so compelling. They are at the cutting edge of technological innovation, and have the capacity to create tangible impact at a scale that's simply not possible in an academic setting.

When I joined Thermo Fisher, I went from serving a community within my region of Basel to serving the entire global oncology community. The decisions we make and the solutions we develop every day reach laboratories and clinicians around the world. Being part of such a large, influential organization is a privilege I've experienced every day since joining.

How would you describe your leadership philosophy?
My leadership style is really the product of the incredible mentors I've had throughout my career. They taught me so much, and one principle I've truly embraced in my daily work as a manager is this: when projects are delivered successfully – the team needs to be recognized for its achievements while the manager steps back into the shadows. But whenever there's a problem or a failure, the responsibility falls squarely on the manager.

What else shapes your approach to leadership?
I would describe my philosophy as people-first, but I'm also deeply purpose-oriented. In my experience, I couldn't do what I do without strongly believing in our mission and vision. But it's also about how we execute that mission – that's what truly makes the difference, and that's a core part of my leadership style.

I'm not there to make decisions for other people, but to create the environment that enables my team members to make the best possible decisions – and execute on them. It's about enablement, not direction.


Luca Quagliata

As a global leader, how do you maintain your own development and stay current in such a rapidly evolving field?
I'm privileged in this regard because, in my position as global leader of medical and scientific affairs, I'm essentially paid to stay on top of science. Part of my job is to continuously learn what's happening out in the field. Even with the busy agenda we all have, I always make sure to carve out what I call a safe space – dedicated time to study what's happening in our discipline. I continue to read scientific articles the same way I did at the beginning of my career. Without that, I honestly couldn't do my job.

Is there anything else that informs your development?
There's one more thing I believe I've learned throughout my career that's crucial: always try to look outside your own box. I worked in academia for many years and published numerous peer-reviewed articles, and I've observed that scientists tend to stay within their own field. But I think it's equally important to learn things outside your day job. It will make you a better professional if you sometimes change your angle or shift your perspective. That broader view enriches everything you do.

Can you give us an example of how looking at problems from a different perspective has shaped your work?
Industry has really enabled me to do this. I was always accustomed to looking at things from a purely scientific point of view. But when you work in a large organization like Thermo Fisher, you start building business cases, and you realize that things aren't necessarily and exclusively driven by numbers and data as we see them in science. There are other factors at play – for example, social responsibility. That's something we as scientists should all have, but sometimes we don't actively think about it.

How does that play out differently between academia and industry?
As a scientist working in academia, you're usually given public funding, and have an obligation to use those resources for the benefit of not just your own career, but the grant providers. In industry, there is a misconception that everything is driven exclusively by a business case. That's not true. There's a component that's sometimes intangible, which is social responsibility.

Oftentimes we do things not because they're the most remunerative, but because they're the right thing to do. That perspective has been transformative for how I approach problems and make decisions.

What gets you out of bed in the morning?
It's the idea of fulfilling my mission, which is completely aligned with that of Thermo Fisher. I won't rest until we ensure that the solutions we've built are truly accessible for everyone. We already have incredible solutions that are changing and impacting the lives of hundreds of thousands of patients all over the globe. But that's still just a tiny fraction of who could benefit. That's what keeps me going every single day.

What do you think would help us achieve globally accessible precision medicine?
I truly hope the future will be full of new technological advances that will unleash the full power of precision medicine. But to make it happen, we all need to do one thing – collaborate. It doesn't matter how large your company is or how high your h-index is, nobody is going to be able to make this happen alone. The only way forward is to come together.

I hope that in the future, the partnerships between academia and industry, medical societies, and the media – disseminating science and knowledge through journals like The Pathologist – will work together more effectively. First and foremost, patients need to go back to the center of what we do. If we can all adopt a genuinely patient-centric view, I think we can achieve that next quantum leap in pathology much faster.

That's what it will take – all of us, working together, with the patient at the heart of everything we do.