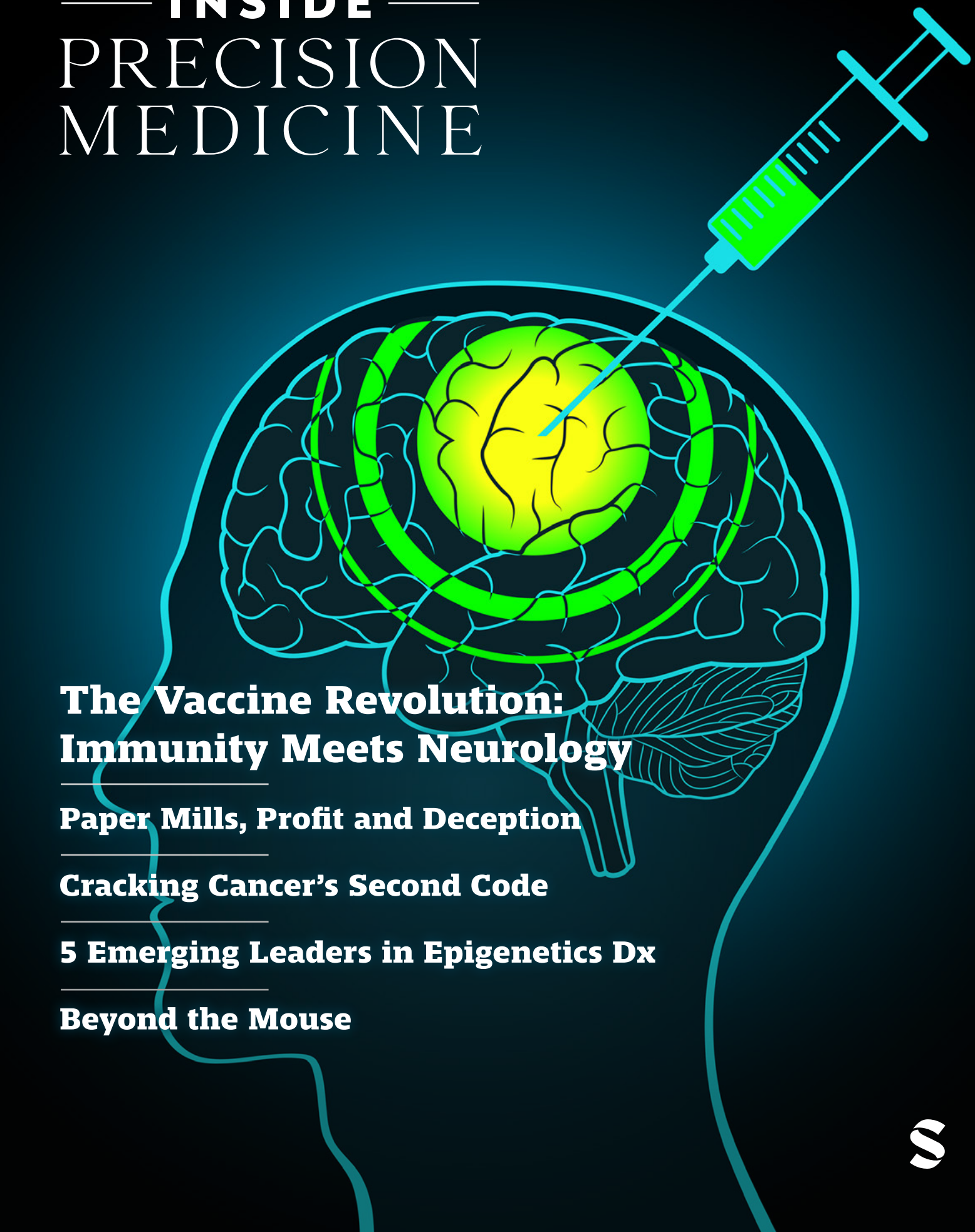
INSIDE PRECISION MEDICINE

JUNE 2026



The Vaccine Revolution: Immunity Meets Neurology

Paper Mills, Profit and Deception

Cracking Cancer's Second Code

5 Emerging Leaders in Epigenetics Dx

Beyond the Mouse

The State of Multiomics & NGS VIRTUAL SUMMIT

WATCH ON DEMAND NOW

Next-generation sequencing (NGS) has never been cheaper or more accessible. In turn, spatial biology, single-cell, and proteomics are fueling exciting advances in biology.

In *The State of Multiomics and NGS* virtual summit, sponsored by Illumina, *GEN* invites you to watch a superb line-up of presenters covering key topics in the world of multiomics and NGS, including spatial biology, multiomics data handling, and an appraisal of the latest NGS platforms.

REGISTER NOW FOR FREE

HOSTED BY GEN

SPONSORED BY illumina®

INSIDE PRECISION MEDICINE

Editor in Chief **Damian Doherty**
North American Editor **Jonathan D. Grinstein, PhD**
Managing Editor **Corinna Singleman, PhD**

Founder **Mary Ann Liebert**
Director, Professional Media Content Development **Kevin Davies, PhD**
Director, Advertising Sales–Professional Media **Bill Levine**

Creative Manager **Byron Duque**
Content Manager **Robert M. Reis**
Online Editorial Manager **Katherine Vuksanaj**
Senior Editor **Helen Albert**
Associate Editor **Savannah Wiegel**
Contributing Editors **Mike May, PhD, Clara Rodríguez Fernández, Laura Cowen, Jonathan Smith, PhD, Lindsey Leake**

Advertising
Account Executive **Jessica Shook**
jessica.shook@sagepub.com
Sales Development Specialist **Scott Perillo**
scott.perillo@sagepub.com / 914-740-2178
Senior Account Specialist II **Fallon Murphy**
Advertising Material **Robert M. Reis**
advertising@sagepub.com

Inside Precision Medicine (ISSN-2334-1351) is published bimonthly by GEN Publishing, 140 Huguenot St., 3rd Floor, New Rochelle, NY 10801-5215. For subscription information go to: www.insideprecisionmedicine.com

In Partnership with

National Society of Genetic Counselors

Cover image: ValeryBrozhinsky / iStock / Getty Images Plus

Editor's Note

"The trouble with the world is not that people know too little; it's that they know so many things that just aren't so."
—Mark Twain

Vaccines are irrefutably among the most effective public health interventions ever developed, yet we are living through a paradox: at the very moment scientific progress is unlocking transformative new applications—from neurodegenerative disease to cancer immunotherapy—we have sizeable issues around public trust. Recent studies have illuminated that the CDC's capricious approach to its communication strategies, which underscore scientific ambiguity, have undeniably led to increased perceived risk around vaccine uptake.

These decisions are contributing directly to declining childhood immunization rates and the current measles resurgence. The machinery of distribution, already at capacity, is now entangled with political interference and institutional decay. We are not merely facing a vaccine hesitancy problem; we are witnessing the erosion of the very framework that makes mass immunization possible.

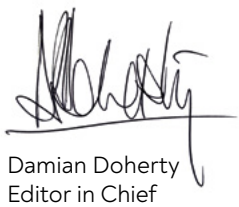
Despite this, the science has never been more promising. In neurodegeneration, active immunotherapies targeting Alzheimer's and Parkinson's disease are showing disease-stabilizing potential with fewer side effects than monoclonal antibodies. In oncology, personalized cancer vaccines are demonstrating zero recurrence in early kidney cancer trials and unexpected successes in pancreatic cancer and glioblastoma. These are not incremental advances; they represent a fundamental reimagining of how we treat—and potentially prevent—some of humanity's most devastating diseases.

The departure of FDA Commissioner Marty Makary, MD offers a cautionary moment. His tenure was marked by the circumvention of advisory committees, age-stratified restrictions on COVID-19 vaccination that contradicted broader scientific consensus, and an elevation of political preference over evidence-based process. For those campaigning for tighter controls and scientific rigor around trials, his exit is indeed a relief. But relief is not recovery. The FDA remains hollowed out by mass layoffs and the departure of senior leaders like Peter Marks, MD, PhD, leaving the agency with depleted expertise at precisely the moment novel vaccines require sophisticated, consistent regulatory oversight.

We must also reframe the narrative. Vaccines are not merely tools of infectious disease control; they are platforms for precision medicine. The same mRNA and immunotherapy technologies revolutionizing oncology and neurology emerged from decades of foundational vaccine science. To abandon or delegitimize this enterprise now is to forfeit the next frontier of medicine.

The framework must change. Access to vaccines—whether for measles, HPV, cancer, or Alzheimer's—must be understood as a public good requiring sustained investment, transparent governance, and political insulation. Scientific advisory committees must be restored, not bypassed. Regulatory agencies must be staffed, not stripped. And public communication must be relentless, honest, and community-rooted.

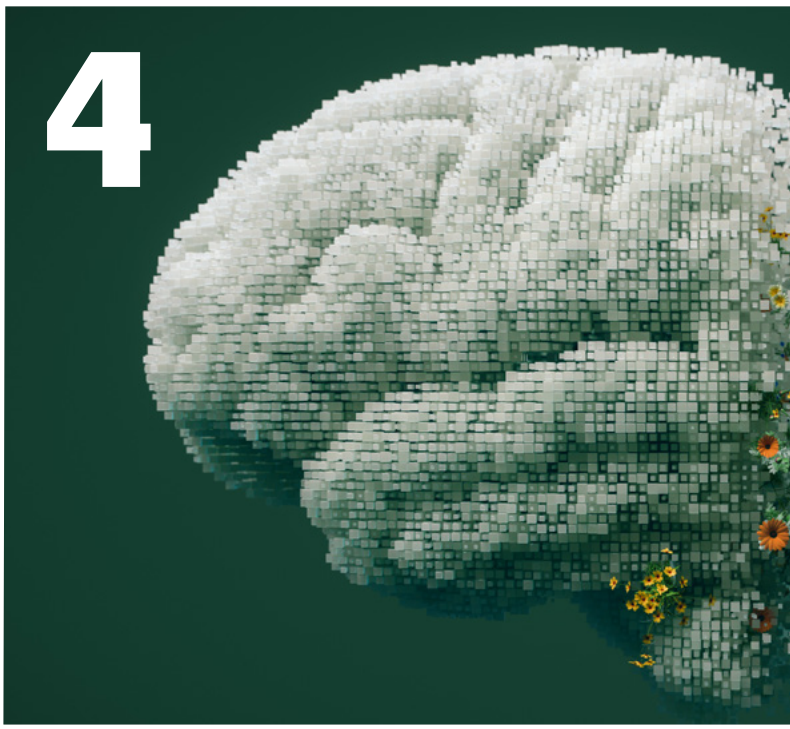
The alternative is a retreat into an era where preventable diseases return, and potential cures remain trapped in laboratories. We have the science. What we need is the will to protect the systems that deliver it.

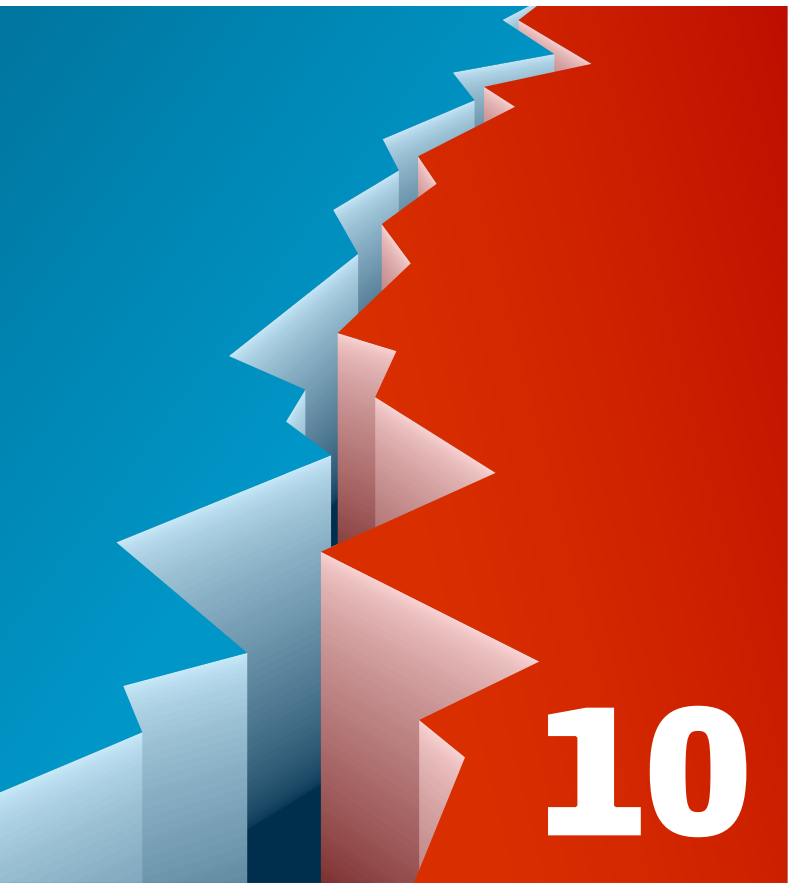


Damian Doherty
Editor in Chief

INSIDE PRECISION MEDICINE

Contents



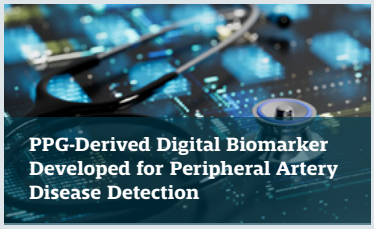


Features

View The Latest Online

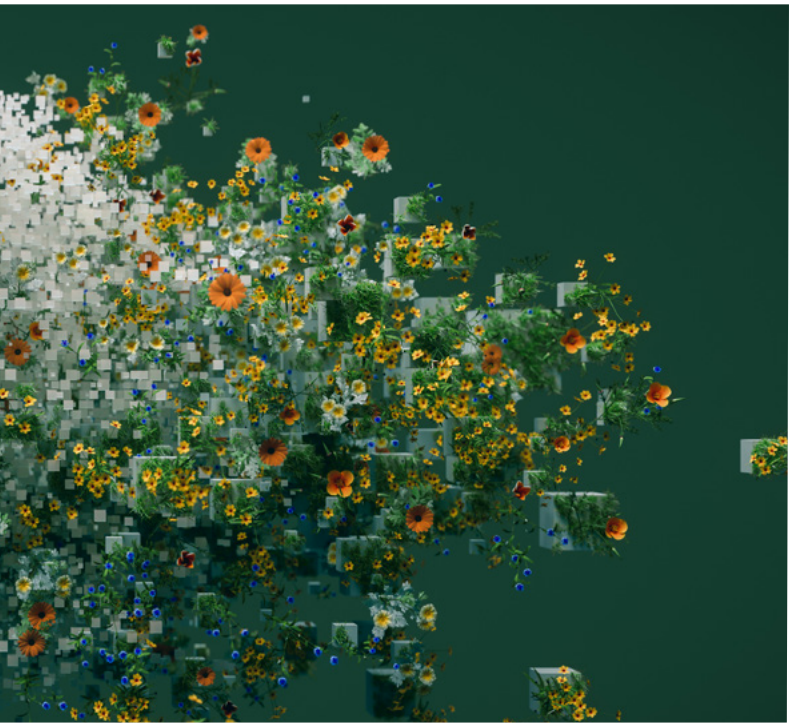
www.insideprecisionmedicine.com

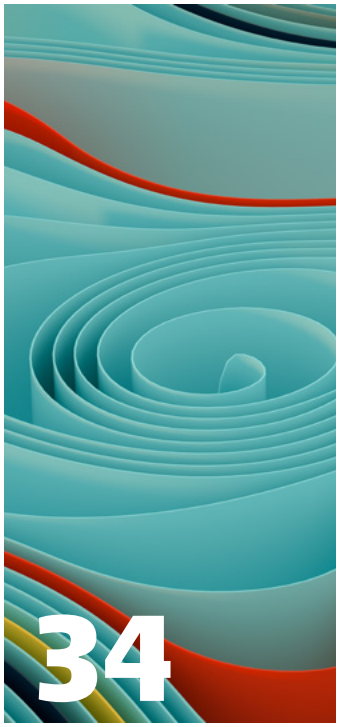
Antibody-Drug Conjugate Shows Activity in Hard-to-Treat Uterine Cancer



PPG-Derived Digital Biomarker Developed for Peripheral Artery Disease Detection

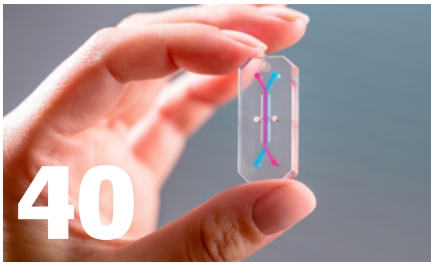
Exchange Marketplace Launched to Help Stalled Cell and Gene Therapies





34

20

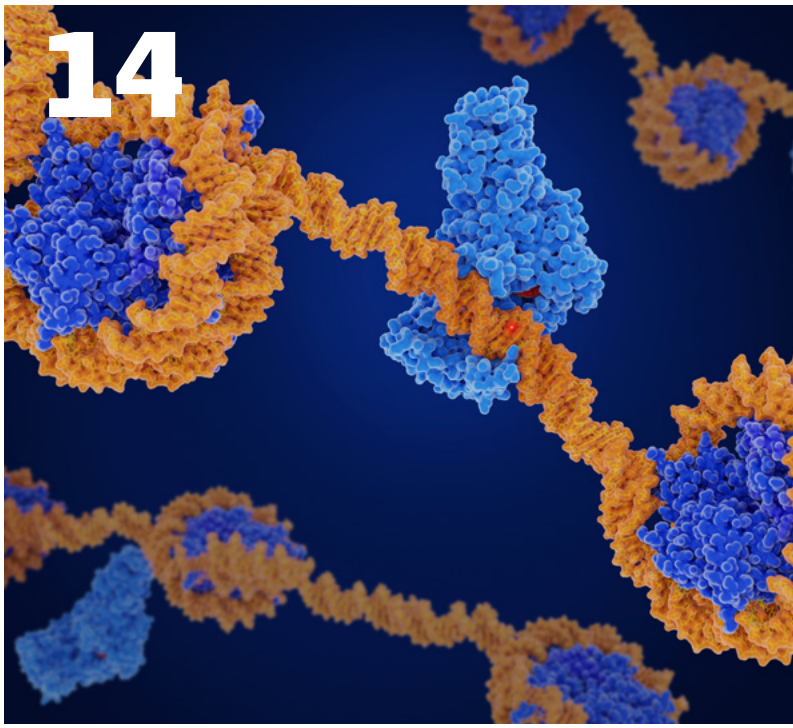


40

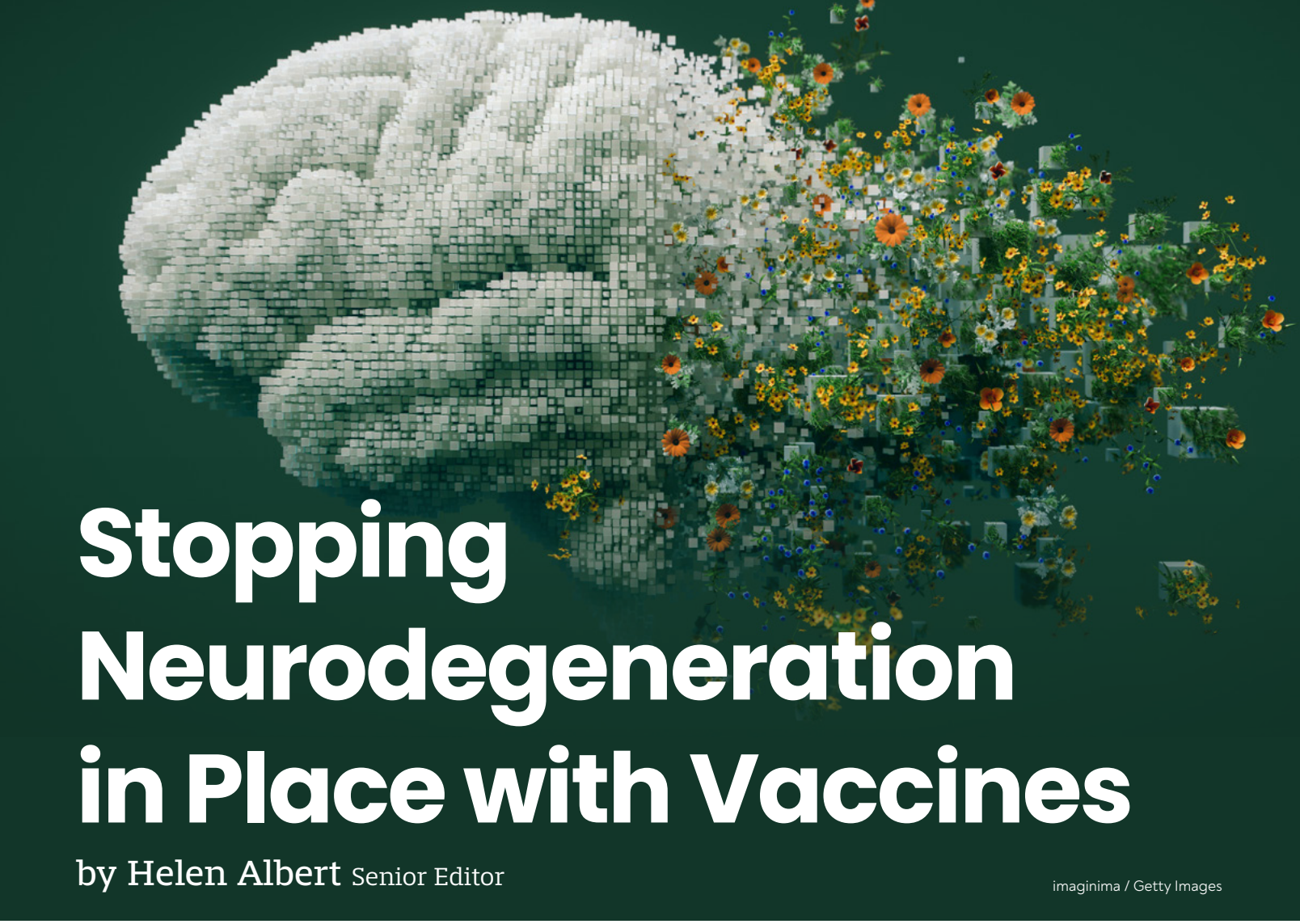
Interview

44

Columns



14



Stopping Neurodegeneration in Place with Vaccines

by Helen Albert Senior Editor

imaginima / Getty Images

Developing truly disease-changing treatments for Alzheimer's disease and other neurodegenerative conditions has proved challenging, with many failed trials over the last few decades. The approval of Eisai/Biogen's monoclonal antibody lecanemab in 2023, the first such treatment to have a positive, albeit modest, impact on symptoms of Alzheimer's disease, was therefore received with enthusiasm by many.

Critics of lecanemab and Eli Lilly's donanemab, approved a year later for the same indication, argue that the small benefit gained from the drugs does not outweigh the economic costs, possible side effects, and burden of regular intravenous infusions.

Using a vaccine-style approach, where the treatment prompts the body to generate its own antibodies, has the potential to solve these problems. Several companies are developing active immunotherapies to target Alzheimer's and Parkinson's disease, as well as other neurological conditions.

"What we're trying to do is link the antigen to a carrier and bring it into a form which mimics the pathology," explained Andrea Pfeifer, PhD, CEO and co-founder of Swiss company AC Immune, a leading biotech taking the active immunotherapy route to target Alzheimer's and Parkinson's disease.

Andrea Pfiefer, PhD
CEO and Co-founder
AC Immune

"We inject it into the immune system, and what it recognizes is the misfolded protein. So, because of that, the immune system only makes antibodies against this pathological protein."

Although none have yet reached the market, the active vaccine-style approach potentially has a number of advantages over passive treatment with monoclonal antibodies. Importantly, fewer rounds of treatment are required. The exact dosing is yet to be determined, but it would certainly be less frequent than the regular infusions of lecanemab or donanemab that are currently prescribed. This would help reduce costs and treatment burdens for patients and their families. There is also likely to be less risk of amyloid-related imaging abnormalities (ARIA) due to the relatively slower onset of antibody generation by the body.

"If you have to take the patient every two to four weeks to get a

two-hour infusion in a hospital, and then you have to wait and do imaging, it's really burdensome," said Pfeifer.

"After a certain while, they just don't want to go. … They say, 'Sorry, we believe your science, we believe everything, but we don't want this."

Tord Labuda, PhD
CEO, Alzinova

To date, most vaccine trials have enrolled people with at least some degree of Alzheimer's or Parkinson's disease, as preventive vaccine trials need to be large and long in duration. Theoretically, developing a preventive vaccine is a feasible approach, as many neurodegenerative diseases typically have a slow onset before noticeable symptoms appear. However, reliable biomarkers that can accurately predict disease onset have been in short supply.

This is changing, though. Last year, two blood tests that measure phosphorylated tau and amyloid ratios were approved by the U.S. Food and Drug Administration (FDA) for Alzheimer's diagnosis. The biomarker field is less developed for Parkinson's and other neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS), but things are slowly improving.

Promising mid-stage results from front-runners like AC Immune and Alzinova suggest that this pathway has merit, but whether they can succeed in larger registrational trials going forward is unclear.

"It remains to be seen how our immune system reacts. I think that when we look at the titers we see from the vaccine, they're similar to what we get with passive immunizations. So I think there are a lot of things that point in the right direction," said Tord Labuda, PhD, CEO of Swedish biotech Alzinova, which has an amyloid beta vaccine in development.

"Personally, I don't think that the vaccine or passive immunization is the real challenge. The real challenge is to have the right target."

Taking a more active approach to immunotherapy

While passive immunotherapies like lecanemab and donanemab are groundbreaking in that they are the first disease-modifying treatments for Alzheimer's to be approved by the FDA and they slow cognitive decline by around 25%–35% over two years, these drugs can cause significant side effects such as ARIA.

This can cause brain swelling and bleeding in some people. Individuals at highest risk for some neurodegenerative conditions, such as carriers of the *APOE4* gene variant, are prevented from accessing these therapies at all, as they have a higher-than-average risk of experiencing ARIA-like side effects.

Treating neurodegenerative diseases like Alzheimer's and Parkinson's disease when symptoms commence is problematic, as currently, there is no known method of regaining neuronal function once it has been lost.

Classic pathology studies suggest that, by the time the typical motor symptoms of Parkinson's appear, around 50%–70% of dopaminergic neurons are already lost from the brain. Similarly, in early clinical Alzheimer's disease, where those affected have mild dementia, hippocampal volume in the brain seen on imaging is already up to 25% lower than that of age-matched controls. This means, however good the treatment is, the patients will never regain complete function.

"There's no way we can restore these neurons," said Roman Kniazev, CEO of U.S.-biotech Nuravax, which is developing several different Alzheimer's vaccines. "They are gone forever. So that is why the best strategy, and this is our motto in our company, is to not let the pathology kill the neurons."

Researchers trying to develop new therapies for Alzheimer's and Parkinson's are increasingly moving towards an early or even preventive approach. The idea of a vaccine-like approach to targeting Alzheimer's is not new. Animal work in the late 1990s showed that vaccinating against amyloid-beta could clear plaques and improve cognition in transgenic mouse models.

Alzinova

ALZ-101 – Alzinova's disease-modifying vaccine candidate for Alzheimer's disease

This led to the development of Elan/Wyeth's amyloid-beta vaccine, AN1792.

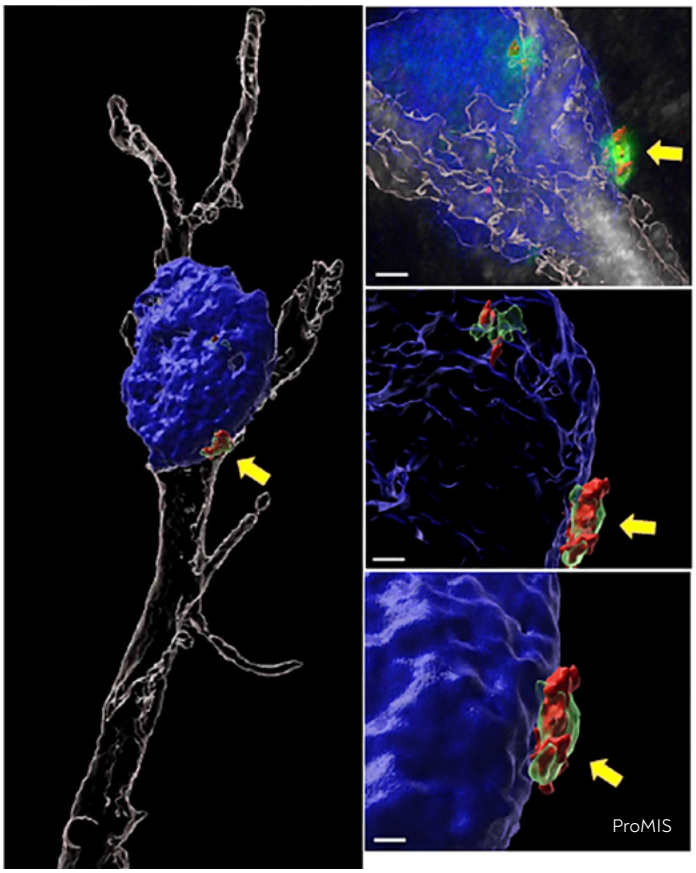
It entered Phase I/II trials for mild-to-moderate Alzheimer's and successfully induced anti-amyloid beta antibodies in some patients. But the study had to be stopped in 2002 because around six percent of the participants developed meningoencephalitis, linked to T cell–mediated inflammation in the brain. Despite strong amyloid plaque clearance, there was little impact on symptoms in the clinical trial participants.

Several other candidates, designed to avoid the T-cell activation seen with AN1792, have been unsuccessfully trialed over the last two decades. Although largely safe and antibody-producing, most of these programs were discontinued due to a lack of efficacy.

(continued on next page)

(continued from previous page)

The field has persevered despite this, with improvements in technology, safety, biomarkers, and clinical trial design having led to a new generation of vaccine candidates that, while not yet approved, are showing good results in Phase I and II trials.



Staining of neurons in the brain from Neil Cashman's lab-1.

"I think what we've learned over the past five or 10 years from other vaccine approaches is that the next generation are those that come with a very precise approach to generating antibodies against the toxic species of a given protein for that specific neurodegenerative disease," said Neil Warma, CEO of ProMIS Neurosciences, a U.S.-based company taking an antibody and a vaccine-based approach to treating Alzheimer's and other neurodegenerative diseases.

"Those are really the things that make the vaccine approach much more interesting now. The sophistication of the biomarkers, the data we've learned from past and current products in the market, and then this ability to design and create antibodies that are highly specific to a targeted pathogenic form of the protein."

AC Immune has three active immunotherapy candidates in Phase II: an anti-amyloid beta therapy, ACI-24, that is being developed with Takeda; an anti-tau therapy, ACF 35, being developed with Johnson & Johnson; and an anti-alpha synuclein candidate targeting Parkinson's disease.

The company reported good results for its Parkinson's Phase II study at the end of last year. The interim study results showed a 100% response rate and a good safety profile in people with early Parkinson's disease. Alpha-synuclein and neurofilament light levels in the blood, as well as scores from standard movement tests, suggested that disease stabilization had occurred.

If confirmed by results from the second part of the study, this would be the first time that disease modification, rather than symptom management, has shown promise for Parkinson's disease. It would also confirm alpha synuclein as a pathogenic contributor to the condition.

"The statistical variability was very, very small, which was a surprise to us. Every single marker, preclinical biomarker, clinical imaging, went into the same direction," said Pfeifer. "For me, what was particularly rewarding was that there was a connection between the titers, so the antibody response in the people versus the reduction of this pathology … the alpha-synuclein versus the imaging, which showed that the neurons can be protected."

Better targeting to improve safety and efficacy

A common theme among vaccine developers in the neurodegeneration space is precision targeting. There is a strong consensus that a lack of specificity when picking targets is likely why many trials failed to show efficacy and had significant side effect issues in the past.

Different companies or research groups back slightly different protein targets, but the experts all emphasize the importance of avoiding binding to inert plaque in the brain in Alzheimer's disease, and of targeting toxic, misfolded proteins that are disease-specific.

Neil Warma
CEO, ProMIS Neurosciences

"We provide the body with active immunotherapy, and then the body induces the antibodies. But what is important is that these antibodies are really specific for the pathological form," said Pfeifer.

AC Immune is not the only company with a keen focus on tightening up targeting in this area. Alzinova is specifically targeting toxic amyloid beta oligomers with its lead candidate ALZ-101, a therapeutic Alzheimer's vaccine.

It received a recent FDA Fast Track designation for ALZ-101 after good safety and efficacy data were reported last year from its completed Phase Ib clinical trial.

"They have shown in many *in vitro* and *in vivo* models that … when you remove these toxic oligomers using antibodies towards them, you can basically neutralize the toxicity in these extracts towards the neurons," explained Labuda.

Kiran Bhaskar, PhD
Professor
University of New Mexico

He added that many of the "vaccines, as well as the monoclonal antibodies, are going for the N-terminal part of the protein. … By doing that, you will target the monomers, all the fibrils, but most importantly, also the plaques. Very little will be left to bind to something else that might be more important for the disease. I think this is what we see with the current treatments on the market. There's a lot of off-target effects … and that's why we have these huge challenges."

ProMIS is also targeting amyloid beta oligomers in Alzheimer's using both a monoclonal antibody and vaccine approach. It has developed a special method with the help of artificial intelligence to develop antibodies, taking both conformational shape and protein sequence into account.

"These three-dimensional shapes don't exist on monomers, and they're buried in plaque. We've tried and tried and tried to get these antibodies to bind monomers, to bind plaque, and they really don't, which is good," said Warma.

"We've done side-by-side testing with other antibodies to see if ours is truly differentiated. … In many different studies before we got to the clinic, PMN-310, our therapeutic antibody, was the only one that bound oligomers and avoided monomers and plaque. All the others cross-reacted with everything."

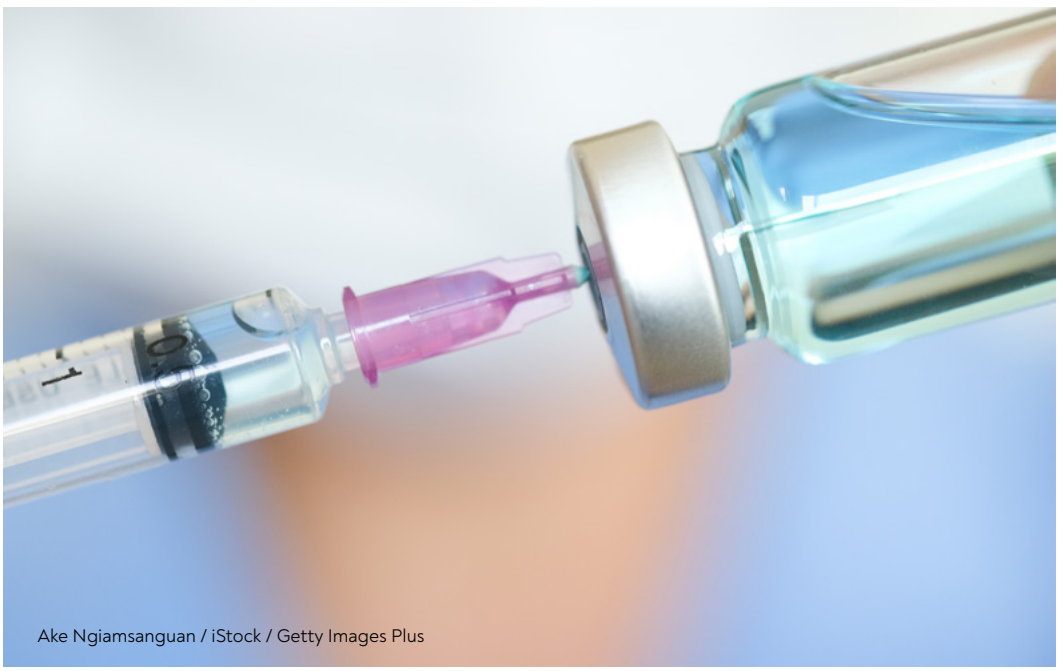
ProMIS is testing its PMN-310 antibody before moving on to the vaccine approach. "If we can come with that one-two punch to say we've got a drug now that can treat patients with Alzheimer's, we've got the ability to detect the onset of disease pathology in Alzheimer's, and we have a vaccine that prevents you from developing that disease, I mean, that would be a pretty powerful combination," noted Warma.

Nuravax is aiming to address two key shortcomings of first-generation Alzheimer's vaccines, such as AN1792: the risk of problematic T cell-driven inflammation and uneven immune responses in older adults. Its MultiTEP-based candidates (AV-1959R, AV-1980R, and Duvax) are engineered to elicit a strong, antibody-dominant response against amyloid-beta and tau while minimizing activation of potentially autoreactive T cells and maintaining effectiveness.

> "The platform which we developed makes the vaccine highly immunogenic, and this high immunogenic feature is essential for diseases in the brain."

"The platform which we developed makes the vaccine highly immunogenic, and this high immunogenic feature is essential for diseases in the brain," said Kniazev.

Kiran Bhaskar, PhD, is a professor and group leader at the University of New Mexico. He has worked on Alzheimer's disease for many years and is also a scientific co-founder of TheraVac Biologics. He and his colleagues are developing an anti-tau Alzheimer's vaccine that is about to start human trials.



Ake Ngiamsanguan / iStock / Getty Images Plus

They are also aiming to reduce risks associated with immune reactions to vaccine adjuvants, which can contribute to ARIA, and have created a vaccine that does not need an adjuvant.

"We use a strategy called a virus-like particle," he explained. "You don't need to expect any side effects because of adjuvants. In this way, we trick the immune system into thinking that there is a viral attack on the body. It immediately starts an immune response against the virus-like particle

(continued on next page)

(continued from previous page)

and also anything sticking to the surface of those virus-like particles, which in this case is pathological or phosphorylated tau proteins."

Overall, in the trials carried out so far in the active immune therapy space in Alzheimer's disease, rates of ARIA have been very low, which is another selling point for the vaccine approach. "We don't expect to see ARIA in active immunotherapy because we are using the host's own immune response system to generate antibodies. … So that way there'll be less unanticipated immune response," explained Bhaskar.

> "We need better and safer treatments, but it's also linked to having the right biomarkers, because if you have a risk factor it doesn't mean necessarily that you have the disease."

Overcoming challenges on the road to the clinic

There is no doubt that active immunotherapies or vaccines to target Alzheimer's and Parkinson's disease are more advanced than they have ever been before, but they are still a long way from a mainstream rollout.

One reason the conversation has shifted is that the approval and broader use of the first anti-amyloid antibodies, for all their modest effect sizes and ARIA issues, shows that lowering the right protein species can slow deterioration. Using a more vaccine-like approach, where people make their own antibodies, does have the potential to make targeting these conditions safer, cheaper, and more accessible for patients.

But basic clinical questions remain unanswered. For example, how long vaccine-induced protection will last, how often boosters will be needed, and whether early stabilization of biomarkers and motor or cognitive scores—such as AC Immune's interim Parkinson's data or Alzinova's Phase Ib Alzheimer's study results—will translate into true preserved function a decade later.

Biomarkers are a big potential stumbling block for the development of preventive vaccines. The position is better for Alzheimer's disease; the FDA's approval of two blood-based Alzheimer's biomarkers now gives developers a way to find people with silent pathologies without relying solely on positron emission tomography imaging. But there is still a lot more to do on this front, particularly in diseases like Parkinson's, ALS, or other neurological or neurodegenerative diseases where less is known.

"We need better and safer treatments, but it's also linked to having the right biomarkers, because if you have a risk factor, it doesn't mean necessarily that you have the disease," said Pfeifer. "These biomarkers are still not very well established. … The goal is absolutely to go to preclinical, and preclinical will require these biomarkers. If you ask me what is needed most in Parkinson's right now, [it] is definitely to have better biomarkers."

A second stumbling block for companies that want to develop vaccines that can effectively immunize people against neurodegenerative disease is that clinical trials of vaccines in populations of people with no symptoms have historically been large, expensive, and time-consuming—something out of reach of most biotechs without significant outside investment.

ProMIS and others are hoping that the efficacy of their therapeutic antibodies will boost their vaccine pipeline in the future. "If we show that it works in Alzheimer's, then a similar approach should work in these other diseases," said Warma. "Since it's an almost identical process for vaccines, it also shows proof of concept for this whole wave of vaccines coming behind it."

For now, active immunotherapies promise something that is more modest than true disease prevention but still crucially important. Namely, cheaper, less burdensome, and potentially safer ways to target the same disease biology as today's monoclonal antibodies, ideally years earlier in the process. ■

Martin Philip / iStock / Getty Images Plus

Helen Albert is senior editor at *Inside Precision Medicine* and a freelance science journalist. Prior to going freelance, she was editor-in-chief at *Labiotech*, an English-language, digital publication based in Berlin focusing on the European biotech industry. Before moving to Germany, she worked at a range of different science and health-focused publications in London. She was editor of *The Biochemist* magazine and blog, but also worked as a senior reporter at Springer Nature's *medwireNews* for a number of years, as well as freelancing for various international publications. She has written for *New Scientist, Chemistry World, Biodesigned, The BMJ, Forbes, Science Business, Cosmos* magazine, and *GEN*. Helen has academic degrees in genetics and anthropology, and also spent some time early in her career working at the Sanger Institute in Cambridge before deciding to move into journalism.

ProPure™ Endotoxin-Free Proteins for Reliable Cancer Research

Minimize immune interference in sensitive oncology applications

In cancer research and therapy development, even trace levels of endotoxins (LPS) in recombinant proteins can severely distort results. In discovery and preclinical studies, endotoxins are silent disruptors of animal immunization, sensitive biological assays, and toxicity assessments, compromising results and safety evaluations. Endotoxin-free recombinant proteins are therefore essential for generating reliable research data and successful development of next-generation cancer therapeutics.

Invisible interference in cancer therapy and vaccine development

Endotoxin contamination can severely compromise antibody generation in animal models. Even small amounts of endotoxins can alter the host's immune response, reducing antibody specificity, consistency, and overall quality. Endotoxin-contaminated recombinant proteins can subtly—but significantly—alter cellular behavior through immunostimulatory and cytotoxic effects. Endotoxin-induced systemic inflammation in animals can further disrupt experiments, potentially leading to study suspension or even termination.

In cell-based studies, endotoxin contamination can be a hidden disruptor. Immune cells such as dendritic cells, macrophages, monocytes, and T cells can respond strongly even to trace amounts of endotoxins, leading to cytokine release, altered proliferation, or unexpected activation. These effects can easily produce misleading or non-reproducible results.

The demand for endotoxin-free reagents is even more critical in the development of cancer vaccines. Since these therapies rely on precise modulation of the immune system, endotoxin contamination can trigger unintended immune activation, masking the true efficacy of the vaccine candidate and introducing safety risks. Using endotoxin-free proteins is therefore vital to accurately evaluate immunogenicity and support safe clinical translation.

Sino Biological's ProPure™ solution to minimize endotoxin risk

While pharmacopeial guidelines such as USP <85> provide general limits for endotoxin, cutting-edge immunology and translational oncology studies often require far stricter control. Sino Biological's ProPure endotoxin-free recombinant proteins are designed to eliminate this variable at the source, supporting reliable results from early discovery through IND-enabling studies. Produced at the state-of-the-art Center for Bioprocessing (C4B) in Houston, Texas, ProPure reagents are rigorously controlled to achieve levels as low as 0.05 EU/mg, with select products reaching an exceptional 0.01 EU/mg—over ten times lower than typical industry standards.

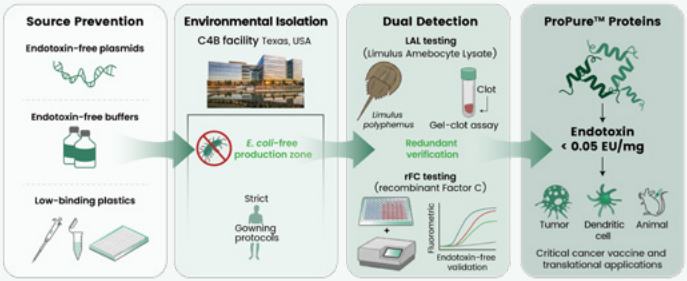
By incorporating endotoxin-free proteins, researchers in cancer therapy and vaccine development can confidently achieve consistent and accurate results in critical applications, including:

- Animal immunization for antibody generation—ensuring high-quality antibodies and predictable host immune responses.
- Preclinical toxicology and pharmacokinetics (PK)—minimizing confounding immune activation in animal models.
- *In vitro* cell proliferation and differentiation assays—reducing false positives caused by endotoxin-sensitive cells such as dendritic cells, macrophages, and T cells.
- Precise detection and quantification of cytokines—supporting reliable immunological readouts and biomarker analyses.

How ProPure achieves ultra-low endotoxin levels

ProPure quality is not achieved by end-stage cleanup alone. C4B employs an integrated Prevention–Isolation–Detection strategy across the entire production lifecycle.

- Prevention at the source: Endotoxin-free plasmids and buffers, low endotoxin-binding plastics, and stringent clean-in-place (CIP) procedures minimize endotoxin introduction from cloning through purification.
- Environmental isolation: The facility follows an *E. coli*-free principle, eliminating a major source of endotoxin introduction in recombinant protein production.
- Dual detection: Each batch is tested using Limulus Amebocyte Lysate (LAL) and/or recombinant Factor C (rFC) assays for sensitive, redundant detection, and fully traceable batch data.



ProPure triple-control strategy for ultra-low endotoxin.

This end-to-end design ensures that ProPure proteins arrive ready for use in the most demanding oncology and immunology applications, without extra purification steps that can damage protein quality or delay timelines.

With advanced technologies and rigorous quality control, Sino Biological delivers endotoxin-free proteins that meet the needs of highly sensitive research and translational applications. ProPure proteins help researchers reduce variability, improve reproducibility, and accelerate the development of next-generation cancer therapies.

Learn more about ProPure™ endotoxin-free proteins at
sinobiological.com/category/endotoxin-free-proteins

Sino Biological

Two Women, One Mission: Closing the Gap Between Cancer Science and Survival

A journalist-turned-advocate and a physician-scientist unite at the Parker Institute for Cancer Immunotherapy to accelerate cancer vaccines from lab discovery to lifesaving treatment

Jonathan D. Grinstein, PhD North American Editor

Kristen Dahlgren never expected to leave her successful 25-year career as a correspondent for NBC News, let alone become part of the fabric advancing cancer medicines. The transition was not driven by professional restlessness but by something far more personal: Dahlgren was diagnosed with stage II breast cancer in 2019.

"I thought I was a lifer at NBC," Dahlgren told *Inside Precision Medicine* on leaving NBC News in 2024 to advocate for accelerating the development of cancer vaccines. "I loved my job. But a cancer diagnosis changes you." That diagnosis would eventually lead her to found the Cancer Vaccine Coalition (CVC).

Her story, however, is only half of a larger narrative. The other half belongs to Parker Institute for Cancer Immunotherapy (PICI) chief executive officer Karen Knudsen, PhD, an oncology leader and healthcare executive whose career has been defined by a single, persistent challenge: how to turn scientific discovery into real-world patient impact.

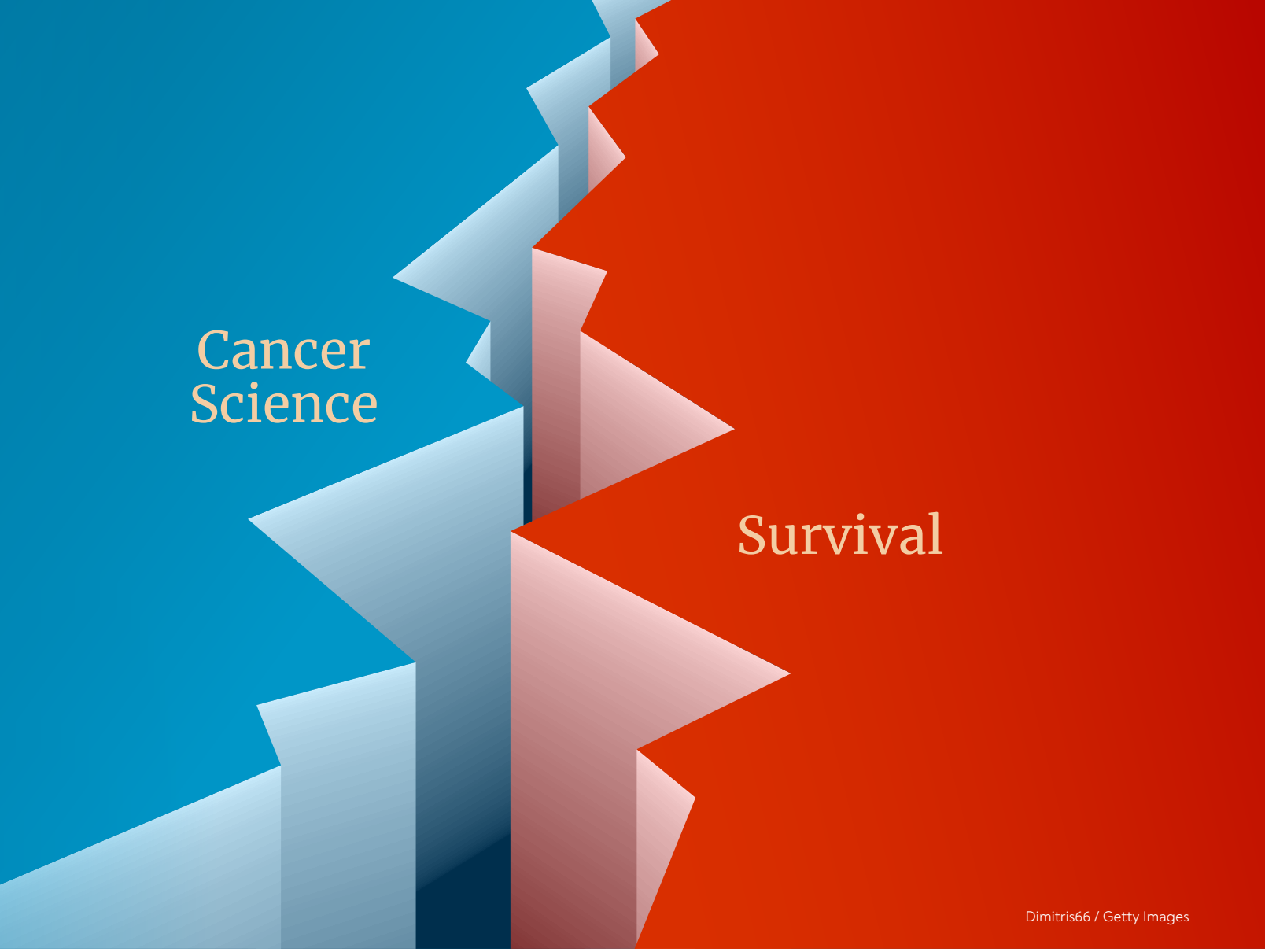
With the advent of new scientific discoveries, more investment, and increasing public and private support, cancer vaccines are entering a new phase of development, which includes this integration. The goal of these vaccines is to teach the immune system to identify and attack tumors.

Kristen Dahlgren
Chief External Affairs Officer
Parker Institute for Cancer Immunotherapy (PICI)

Together, Dahlgren and Knudsen aim to accelerate the development and delivery of cancer vaccines, one of the most promising frontiers in cancer research. Their partnership reflects a broader shift in oncology, one that is less about isolated breakthroughs and more about building systems that can deliver those breakthroughs to patients faster.

Two paths, one problem

Before joining PICI, Knudsen had navigated the upper echelons of academic medicine and healthcare leadership. As an oncology healthcare executive for Jefferson Health, Knudsen ran one of the largest health systems in the country. She also led one of the major cancer centers in the United



Dimitris66 / Getty Images

States, a National Cancer Institute (NCI)-designated cancer center, in a role that placed her at the intersection of science and care delivery.

The experience exposed Knudsen to a stark reality: the greatest challenge in cancer care is not always discovery—it can be cancer care delivery. "I love science, and we are funding more of it," Knudsen told *Inside Precision Medicine*. "However, I don't think that we have a science problem in the U.S. There's a ton of science. What we have is a translation problem." Dahlgren arrived at the same conclusion by asking researchers what was preventing them from moving forward and finding that they often felt like they were operating in silos.

Karen Knudsen, PhD
CEO, Parker Institute for Cancer Immunotherapy (PICI)

What neither woman accepted was the idea that this gap was inevitable. A systemic gap exists between research and patient care, and it is not subtle. Knudsen saw it daily in the clinic. "If you've ever run an oncology unit, the first thing you do … is walk the infusion center. The sense of urgency gets much higher."

Even without new scientific breakthroughs, the system has room for improvement. "Current data indicate that we could reduce cancer mortality by 20% if everyone in the U.S. with a cancer diagnosis received guideline-concordant care," Knudsen said. "Forget even new discoveries."

As a patient, Dahlgren encountered a different version of the same problem: she wasn't informed of cancer vaccines or any related clinical trials. "I did a lot of medical reporting at NBC and had just been treated at one of the top hospitals, but nobody ever mentioned [cancer vaccines] as a possibility," said Dahlgren. "There just weren't the clinical trials available to me. I think there is a lack of awareness."

Dahlgren continued, "The CVC started with a conversation with some doctors who were working on cancer vaccines because, frankly, I didn't really believe that they were real or that far along because I hadn't heard anything about it. I think that was

(continued on next page)

(continued from previous page)

part of the problem. There just isn't a large public awareness of some of the research that's going on. Even some oncologists are unable to keep up with all the cutting-edge developments."

Between those two perspectives lies a critical insight: innovation alone is not enough. It must be accessible, scalable, and visible. That insight is at the core of PICI's model, originally conceived by entrepreneur Sean Parker, co-founder of Napster and the first president of Facebook. With a $250-million grant from The Parker Foundation, PICI is an attempt to redesign the entire cancer immunotherapy pipeline, from discovery to commercialization.

Unlike traditional funding bodies, PICI does not simply award grants but rather establishes research sites across the country, of which there are currently seven. "The agreements allow our investigators, irrespective of geography, to freely share data and materials, so they truly are functioning [as] one institute, multiple geographies," said Knudsen. "The whole concept here is to advance those studies from preclinical to clinical, obtaining a clinical signal so that other investors and biopharma follow suit toward the goal of near-term patient benefit."

Cancer vaccines, now!

When Knudsen met Dahlgren at a Milken Institute event, the alignment was immediate. Dahlgren, for her part, had already recognized that PICI was building something she could not replicate alone. "They were already doing everything I wanted to do: building a system where the ecosystem could thrive and where these discoveries could reach patients."

That meeting led PICI to strategically integrate the CVC to accelerate the development of next-generation cancer vaccines, including personalized neoantigen therapies. "Cancer vaccines have been around, but we really are at this tipping point," Dahlgren said, who is now at a new role within the PICI as chief external affairs officer, placing vaccines at the top of PICI's strategic priorities. Knudsen said, "As part of the scientific priorities, vaccines rise right to the top. Cancer vaccines offer a genuine opportunity to revolutionize cancer therapies."

Several forces have converged to create this moment: advances in genomics, improved understanding of immune biology, and new platforms for vaccine delivery. "We understand the immune system better," Dahlgren said. "This is the time to fully support this technology and get it through trials, approved, and to patients." Dahlgren points to emerging data from clinical studies on vaccines across multiple cancer types, she said, "You hear about the work in pancreatic cancer or glioblastoma … patients who have achieved unexpected success."

For Knudsen, the cancer vaccines won't just be abundant and accessible; they'll be personalized. Early clinical results, while small, are compelling, especially for hard-to-treat solid cancers (BOX 1). Knudsen highlighted a 2025 *Nature* study on kidney cancer led by Catherine Wu, MD, and Toni K. Choueiri, MD. "There were zero recurrences," said Knudsen, "and everybody in that study got the vaccine. It's a small study with single-digit patients; I believe there were nine patients. The science is getting there."

The implications are profound, but so are the challenges. "But then who's going to take it to the next step in a larger clinical trial?" Knudsen asked. "Biopharma wants the clinical signal."

That gap between early success and large-scale validation is precisely where PICI aims to operate.

Patients are ready

Part of the problem is financial. The traditional venture ecosystem is not always aligned with early-stage scientific risk. "The venture world is currently locked up due to a lack of IPOs. … They do not have dry powder available to invest capital in opportunities," Knudsen said.

PICI's model attempts to bypass that constraint. "We ourselves are a major investor," Knudsen said. "We've put

BOX 1. The Rise of Personalized Cancer Vaccines

Personalized cancer vaccines are rapidly emerging as one of the most promising frontiers in oncology. Unlike traditional therapies, these vaccines are designed for each individual patient, using the unique mutations in their tumor to train the immune system to recognize and destroy cancer cells. Powered by advances in mRNA technology and genomic sequencing, this approach has shifted from theory to real clinical momentum in just a few years.

Early trial results are beginning to validate the strategy. In pancreatic cancer, one of the most difficult diseases to treat, a personalized mRNA vaccine developed by teams led by Vinod P. Balachandran, MD, and Benjamin D. Greenbaum, PhD, at Memorial Sloan Kettering Cancer Center triggered strong, lasting immune responses and extended survival in early-stage studies. In melanoma, combining a personalized vaccine with Keytruda reduced the risk of recurrence or death by 44% to 50%, advancing the approach into large Phase III trials.

Trials in lung, breast, and other tumors show that these vaccines are safe, feasible, and capable of generating strong T-cell responses. Increasingly, they are used in combination with checkpoint inhibitors, acting as a primer that enhances broader immune attack.

The pipeline is growing quickly. Dozens of personalized mRNA and DNA vaccines are now in development, with many expected to reach late-stage trials before 2030. Preventive versions, aimed at stopping cancer before it develops, are also beginning to enter human testing.

Investment is accelerating alongside the science. Pharmaceutical companies, biotech firms, and governments are committing billions to personalized vaccine platforms. In the United Kingdom, a partnership between the National Health Service and BioNTech aims to treat up to 10,000 patients with individualized vaccines by 2030.

Challenges remain, including small trial sizes, complex manufacturing, and the need for large-scale validation. Still, the trajectory is clear. Personalized cancer vaccines are moving steadily toward mainstream clinical use.

about $400 million into 17 portfolio companies. … Or we just start new companies." Revenue generated from successful commercialization is reinvested into new research, creating a self-sustaining cycle. "That's how the nonprofit model works."

If there is uncertainty in the system, it does not come from patients. "We're getting reach-outs from patients … 'What do I need to start to think about so that I can get enrolled in a trial to prevent recurrence?'" Knudsen said. "Who wouldn't want that?" Dahlgren echoed the urgency from personal experience. "My current course of treatment is to 'call us when you get a headache,' and that's a horrible way to live."

Cancer vaccines offer a different paradigm, one that emphasizes long-term immune protection. "Imagine if you could get a vaccine … that boosts your T-cell response. … It's just a matter of taking care of it for the rest of your life."

Despite growing momentum, cancer vaccines remain misunderstood. "There's definitely a misunderstanding with the term 'vaccine,'" Dahlgren said. Knudsen is less concerned about semantics, asserting, "I don't know if we have a name problem. I don't think there's anyone who is going to say, 'I don't want to take a vaccine' when facing cancer."

Where education does matter, however, is prevention. Knudsen points to the Gardasil vaccine as a case study. "When you reframe that appropriately, as a cancer vaccine … you say actually, we have cancer vaccines that will prevent cancer." In places like Puerto Rico, Knudsen notes that high uptake of HPV vaccination has already demonstrated what is possible. "They'll be the first place in the U.S. where cervical cancer will no longer be a thing."

A shared urgency

While vaccines are a major focus, they are part of a broader transformation in cancer therapy. "Immunotherapy *is* the same as cancer therapy," Knudsen said. "Name a cancer modality that does not have a root in the immune system." This shift indicates a deeper understanding of cancer as an immune-mediated disease, paving the way for more personalized treatments.

What ultimately unites Dahlgren and Knudsen is not just a belief in science but a shared sense of urgency. Dahlgren frames it in deeply personal terms. "There's no evidence of disease—I'm in remission, and I still think about it every day," said Dahlgren.

With CVC working lockstep with PICI, Dahlgren and Knudsen are working together to remove those barriers by building a system that does not just generate knowledge but delivers it. For Dahlgren, joining PICI is not a departure from her mission but an amplification of it. "I've always looked for the quickest path to these better treatments, and there's just no doubt that under this new structure that we'll be able to have a lot more impact." For Knudsen, it is the continuation of a career spent bridging science and care. "It's the businessperson in me always looking for how we go faster and farther and make it so that patients benefit more quickly."

Dahlgren and Knudsen are betting on a future where cancer vaccines and the systems that support them transform not just how cancer is treated but how innovation itself happens. If they're right, the question will be how quickly these breakthroughs can reach those who need them most. ■

Timeline: Cancer Vaccine Milestones

1890s — **First immune therapy:** William B. Coley uses bacteria to stimulate anti-tumor immunity.

1990s — **Early vaccine trials:** First modern cancer vaccines enter trials; limited success but proof of concept.

2006 — **HPV vaccine:** The HPV vaccine Gardasil was first approved by the U.S. FDA in 2006 for females ages 9–26.

2010 — **First approval:** Provenge becomes the first FDA-approved cancer vaccine.

2010s — **Immunotherapy era:** Checkpoint inhibitors like Keytruda reshape cancer care and enable combos.

LATE 2010s — **Personalization begins:** Genomics enables neoantigen targeting and patient-specific vaccine design.

2020 — **mRNA breakthrough:** COVID-19 vaccines validate speed and scalability of mRNA platforms.

2023 — **Pancreatic milestone:** Vinod P. Balachandran and Benjamin D. Greenbaum show strong immune responses in early trials.

2024 — **Melanoma progress:** Combination of personalized vaccines and Keytruda cut recurrence risk by ~50%.

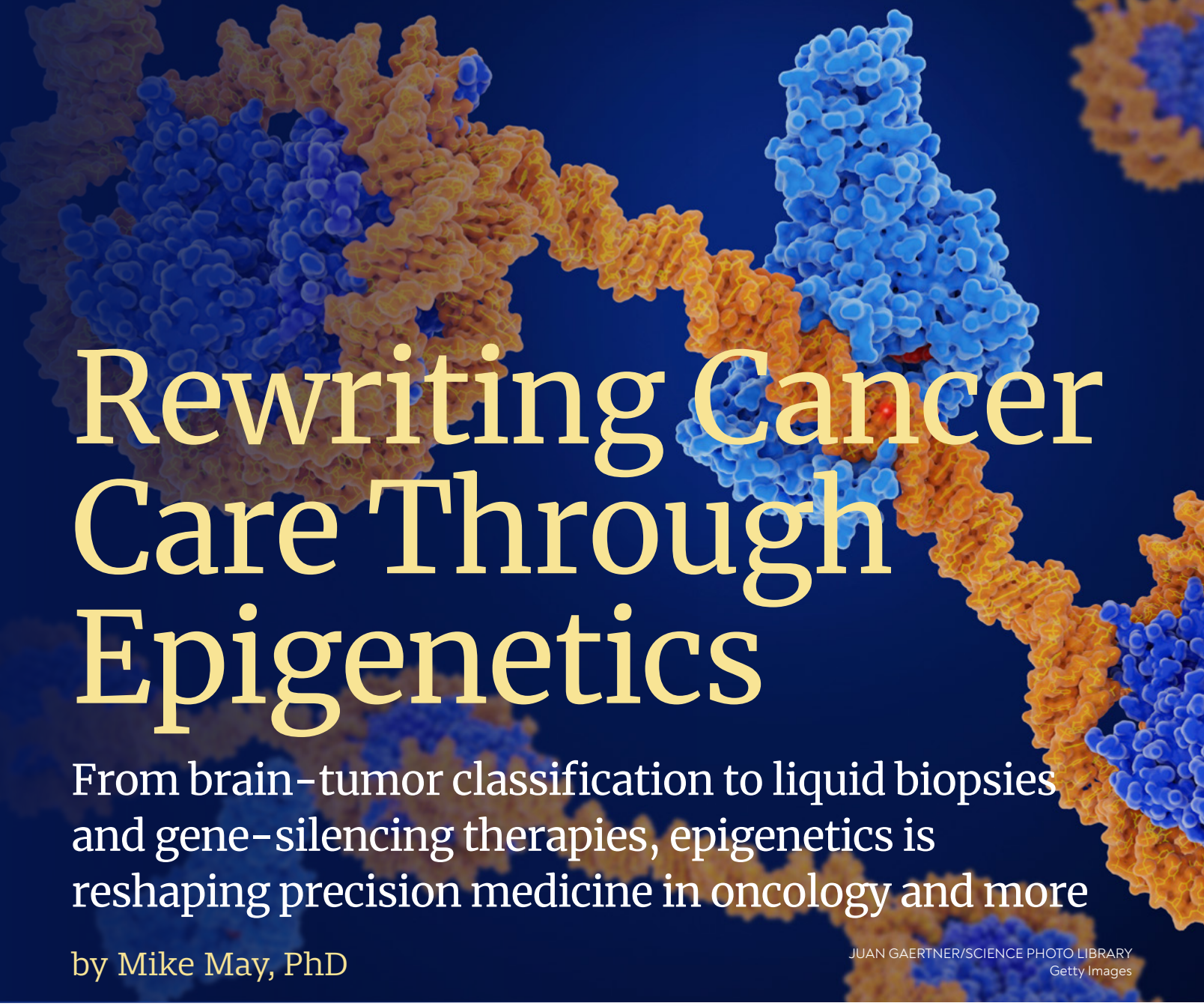
2025 — **Expansion phase:** Catherine Wu and Toni K. Choueiri report zero recurrences in small kidney cancer cohort.

2025–2030 — **Scaling up:** BioNTech and NHS aim to treat 10,000 patients; preventive vaccines emerge.

Where We Are Now

Cancer vaccines have moved from experimental to credible. The field is now focused on scaling manufacturing, proving survival benefit in large trials, and integrating personalized vaccines into routine care.

Jonathan D. Grinstein, PhD, North American editor for *Inside Precision Medicine*, investigates the most recent research and developments in a wide range of human healthcare topics and emerging trends, such as next-generation diagnostics, cell and gene therapy, and AI/ML for drug discovery. He is also the host of the *Behind the Breakthroughs* podcast, featuring people shaping the future of medicine. Jonathan earned his PhD in biomedical science from the University of California, San Diego, and a BA in neural science from New York University.



Rewriting Cancer Care Through Epigenetics

From brain-tumor classification to liquid biopsies and gene-silencing therapies, epigenetics is reshaping precision medicine in oncology and more

by Mike May, PhD

JUAN GAERTNER/SCIENCE PHOTO LIBRARY
Getty Images

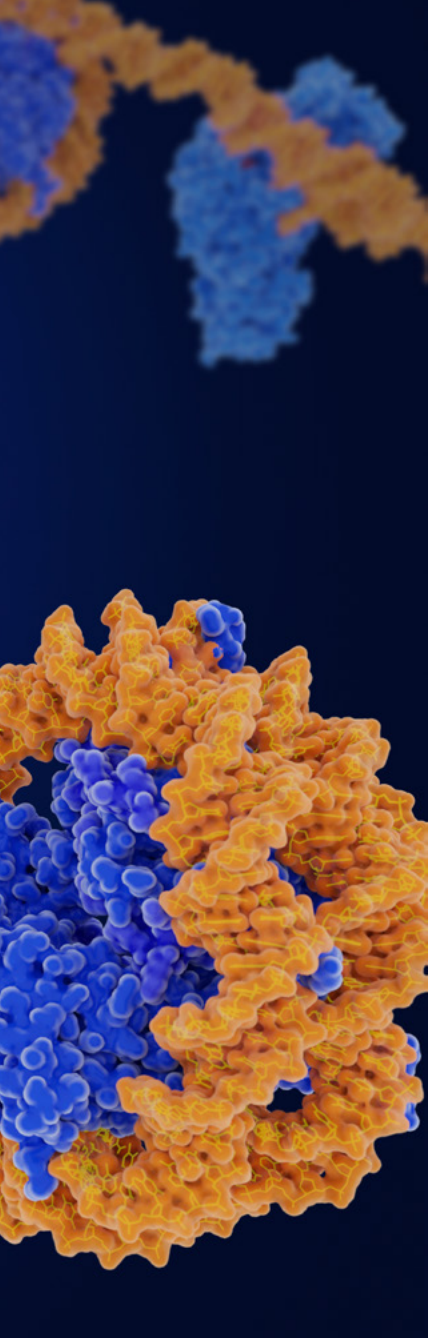
For decades, cancer medicine has been driven primarily by genetics—the search for mutations, deletions, amplifications, and other DNA changes that directly alter how cells behave. Precision oncology has largely focused on identifying these genomic drivers and matching them with targeted therapies. But another biological layer has steadily moved from the margins of research into the center of clinical care: epigenetics.

Epigenetics refers to chemical modifications that regulate how genes are turned on or off without changing the underlying DNA sequence itself. One of the best-known examples is DNA methylation, in which small chemical tags called methyl groups attach to DNA and influence whether genes are active or silenced. These marks help explain one of biology's most fundamental questions: how a brain cell and a heart cell can contain the exact same genetic code yet function in completely different ways.

Matija Snuderl, MD
Neuropathologist
NYU Langone

Rather than rewriting DNA, epigenetics controls how a stretch of DNA is read. It shapes normal development, tissue specialization, immune responses, aging, and disease progression. In cancer, epigenetic disruption can silence tumor-suppressor genes, activate harmful pathways, and create stable molecular fingerprints that reveal where a tumor came from and how it behaves. Increasingly, those fingerprints are becoming clinically actionable.

Today, epigenetics is helping physicians classify brain tumors more accurately, detect pancreatic cancer from a simple blood



draw, improve molecular sequencing workflows, and even therapeutically silence disease-causing genes. Across diagnostics and therapeutics, the field is rapidly becoming one of the most practical and powerful tools in precision medicine.

Few people have watched that transformation more closely than Matija Snuderl, MD, a neuropathologist at NYU Langone. He remembers a time when epigenetics barely registered in medical education.

"When I was in medical school," he said, "there were literally like two pages on epigenetics in the genetics book, and it had no implications for cancer whatsoever."

That changed quickly.

Brain tumors become a clinical test case

Snuderl became deeply interested in epigenetics around 2013, when researchers began realizing that epigenetic patterns could do far more than explain developmental biology. They could also reveal a tumor's cell of origin and, in some cancers, directly illuminate the mechanisms driving carcinogenesis.

Brain tumors proved to be one of the most compelling settings for that work. "Brain tumors are only about two percent of all cancers," Snuderl explained, "but they are disproportionately heterogeneous."

That heterogeneity is extraordinary. There are now roughly 180 recognized molecular subtypes of central nervous system tumors. Yet for decades, many of those diseases were classified almost entirely by histology—how the tumor looked under a microscope. Tumors with similar visual features were grouped together, even when they were biologically distinct.

The result was predictable. "We ended up putting a lot of tumors that are completely different into the same basket, treating them the same way, and then we were surprised that we didn't see results," Snuderl said.

Epigenetics offered a way out of that problem. Because DNA methylation reflects both developmental lineage and disease biology, it provides a stable molecular fingerprint of tumor identity. Unlike RNA, which fluctuates significantly and degrades quickly after tissue collection, methylation patterns are remarkably durable. "The beauty of methylation," Snuderl said, "is that it's an incredibly robust biomarker."

A molecular fingerprint for diagnosis

Snuderl began a collaboration with the German Cancer Research Center (DKFZ) in Heidelberg and proposed a simple but powerful hypothesis: every tumor type has a distinct methylation signature—a recognizable pattern of hypermethylated and hypomethylated regions that functions like a fingerprint.

Using thousands of tumor samples, the team built a machine learning classifier based on a random forest model. The algorithm was trained to recognize these methylation signatures and assign new tumor samples to the most likely disease subtype. "At every decision point," Snuderl explained, the classifier essentially asks, "Are you methylated or are you unmethylated?"

The system evaluates more than 10,000 decision trees before generating a calibrated confidence score that indicates how certain the classifier is about a diagnosis.

The visual output is particularly striking. On uniform manifold approximation and projections (UMAPs), which is a method of viewing high-dimensional data in a low-dimensional manner, each tumor appears as a colored dot that clusters with biologically similar tumors. Some groups are extremely tight, reflecting genetically simple and highly consistent diseases. Others are more diffuse, showing greater heterogeneity and multiple biological drivers.

These patterns helped reveal that some long-standing diagnostic categories were fundamentally wrong. One major example involved primitive neuroectodermal tumors (PNETs), once considered a distinct diagnosis. Methylation profiling showed that PNET was largely a "waste basket" category: about 80% of those tumors were misclassified, while the remaining cases represented multiple separate molecular diseases, said Snuderl.

Another example came from low-grade epilepsy-associated tumors in young adults, known as polymorphous low-grade neuroepithelial tumor of the young. It emerged as a clearly distinct clinical and pathological entity through methylation analysis.

These discoveries were not simply academic refinements. They changed how patients were diagnosed and treated.

Taking research to the clinic

Snuderl is quick to point out that many important scientific discoveries never reach patients because researchers stop at publication. A high-impact paper may generate excitement, but translating a method into a clinical diagnostic requires an entirely different level of work—regulatory validation, reproducibility testing, and operational rigor.

"There is very little glory in going through the regulatory framework," he said. Still, his team decided that it was an essential step.

(continued on next page)

(continued from previous page)

In 2019, NYU became the first CLIA-certified laboratory in the United States to clinically implement DNA methylation–based brain tumor classification. It was also the first to use machine learning as a primary diagnostic tool for cancer classification.

That achievement was especially significant because New York State has some of the strictest molecular diagnostic regulations in the country. "The benefit of that," Snuderl said, "is the tests approved in New York State are really rigorous."

Jeffrey Venstrom, MD
CMO
ClearNote Health

The clinical validation study made clear just how necessary the assay was. Rather than testing only difficult or ambiguous cases, the team prospectively profiled nearly 2,000 consecutive brain tumors to determine real-world utility across all diagnoses.

The results were striking. Approximately 15% of tumors experienced a complete change in diagnosis. Another seven percent were further sub-stratified into clinically meaningful categories. In cases where pathologists could not make a diagnosis at all, methylation profiling resolved the case in more than 85% of patients.

This meant that patients who might have received unnecessary radiation and chemotherapy could avoid overtreatment, while those with aggressive disease who might otherwise have been undertreated were correctly escalated to more appropriate care.

Liquid biopsies and the rise of 5hmC

While brain tumors demonstrate the power of methylation in tissue diagnostics, other companies are applying epigenetics to blood-based cancer detection.

At ClearNote Health, Jeffrey Venstrom, MD, CMO, focuses not on traditional 5-methylcytosine (5mC), but on 5-hydroxymethylcytosine (5hmC), a related epigenetic mark that provides a different kind of biological signal.

"While much of the scientific focus on methylation has centered around the 5mC mark," he said, "we have found the 5hmC mark to be more relevant to the detection of cancer."

The distinction is important. While 5mC often reflects silenced genes, 5hmC marks genes that are actively being expressed. That makes it particularly useful for identifying active cancer biology, including the upregulated genetic programs associated with tumor growth.

There are also major technical advantages. Because much more of the genome is silenced than active, there is less 5hmC signal to analyze, requiring less sequencing depth to achieve reliable results. Unlike 5mC analysis, 5hmC detection avoids bisulfite conversion, a harsh chemical step that can damage DNA and complicate sequence mapping. Scientific studies have shown that 5hmC is a reliable signal even in early-stage cancers and carries tissue-specific signatures that help identify where a tumor originated.

ClearNote's platform analyzes cell-free DNA (cfDNA) from a standard blood draw, integrating 5hmC signals with other genomic features and applying machine learning to detect cancer. "Our machine learning model has now been trained on thousands of patient samples and independently validated," Venstrom said. That platform powers the company's Avantect® tests for one of the most clinically important targets in oncology: pancreatic cancer.

Pancreatic cancer remains a highly lethal malignancy, largely because it is rarely detected early enough for effective intervention. Standard imaging often misses disease during the narrow window when curative treatment is still possible.

ClearNote designed the Avantect Pancreatic Cancer Test specifically for individuals at elevated risk, including people over age 50 with newly diagnosed type 2 diabetes, those with *BRCA* mutations, and patients with a strong family history of pancreatic cancer.

Paolo Piatti, PhD
Director
Zymo Research

The test is a simple blood draw, but its performance is substantial. It now achieves 82.6% sensitivity and 97.5% specificity—metrics that Venstrom says will supplement standard imaging technologies for early detection.

The assay is supported by a robust body of evidence, including multiple conference presentations and peer-reviewed scientific publications, representing more than 20,000 test runs across more than 7,000 patients. It is also being deployed in major global studies, including the U.K.'s National Health Service-led SAFE-D study and the international Pancreatic Cancer Early Detection PRECEDE Consortium.

ClearNote is expanding into ovarian cancer and multi-cancer early detection. Its Avantect Multi-Cancer Detection Test is designed to simultaneously identify eight cancers while predicting tissue of origin. That capability is crucial because, as Snuderl notes of metastatic brain tumors, knowing that cancer is present is only the beginning—knowing where it came from determines how it should be treated. This assay was one of only two selected for the National Cancer Institute's Vanguard Study, which is evaluating real-world implementation across up to 24,000 participants. For cancers that currently lack practical screening tools, multi-cancer detection might represent the next major leap forward.

Reliable epigenetics in clinics

From Zymo Research, Xiaojing Yang, PhD, epigenetics group

leader, and Paolo Piatti, PhD, director of applied epigenetics, pointed out that one of the biggest barriers to using epigenetics in clinics is ensuring that DNA methylation testing is "reliable, reproducible, and cost-effective," especially when working with poor-quality samples like cfDNA from plasma, stool, or urine. These samples are often scarce, degraded, and contain only trace amounts of DNA, making it difficult to accurately detect rare epigenetic signals.

Cora Vacher, PhD
Director
Oxford Nanopore Technologies

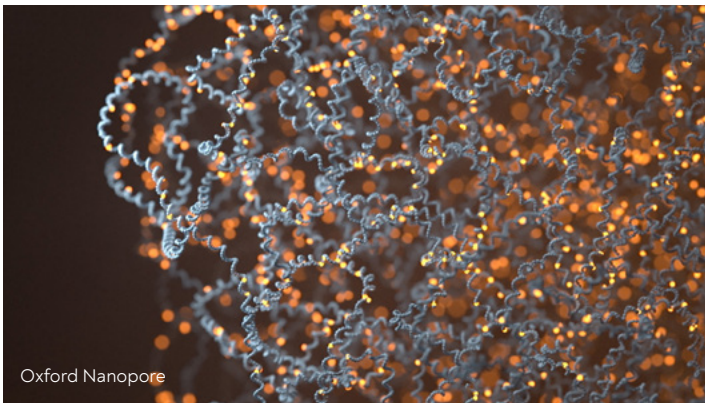
The researchers note that bisulfite-based methods continue to outperform newer approaches in difficult clinical settings. Comparative studies, they say, show these methods provide "higher reproducibility and more stable performance" and align better with reference methods such as EPIC arrays. Although newer enzymatic approaches are promising, they might create systematic biases like methylation overestimation. Because of this, they argue that "bisulfite conversion chemistry continues to be reinforced as the clinical gold standard for DNA methylation analysis."

To address these issues, Zymo developed CE IVD-marked bisulfite conversion kits such as the EZ-96 DNA Methylation Lightning MagPrep. Designed for high-throughput clinical workflows, the kit works with automation platforms like Hamilton, KingFisher Flex, and Tecan Fluent. Its magnetic bead-based system improves DNA recovery and supports downstream PCR, microarrays, and next-generation sequencing.

> "Oxford Nanopore sequencing can read native DNA and RNA directly, without PCR amplification or chemical conversion."

Beyond products, Zymo offers full-service epigenetic workflows like assay optimization, sequencing, and bioinformatics. Their whole-genome bisulfite sequencing service is optimized for low-input and degraded samples like cfDNA and formalin-fixed, paraffin-embedded tissue. These services are supported by "rigorous quality control," Yang and Piatti noted, and can extend into CLIA/CAP-compliant environments through partner laboratories.

Looking ahead, the company is developing NGS-based workflows that preserve fragmentomic information from cfDNA. This could enable more sensitive tests for "early disease detection and longitudinal monitoring," Yang and Piatti said, combining both epigenetic and fragmentomic insights for stronger clinical decision-making.



Methylation, represented here by bright areas, appears across the genome and regulates gene expression. Oxford Nanopore sequencers, like the PromethION 2 Integrated, can read these methylated bases directly, alongside typical base information including single point mutations and structural variants.

Measuring epigenetics more directly

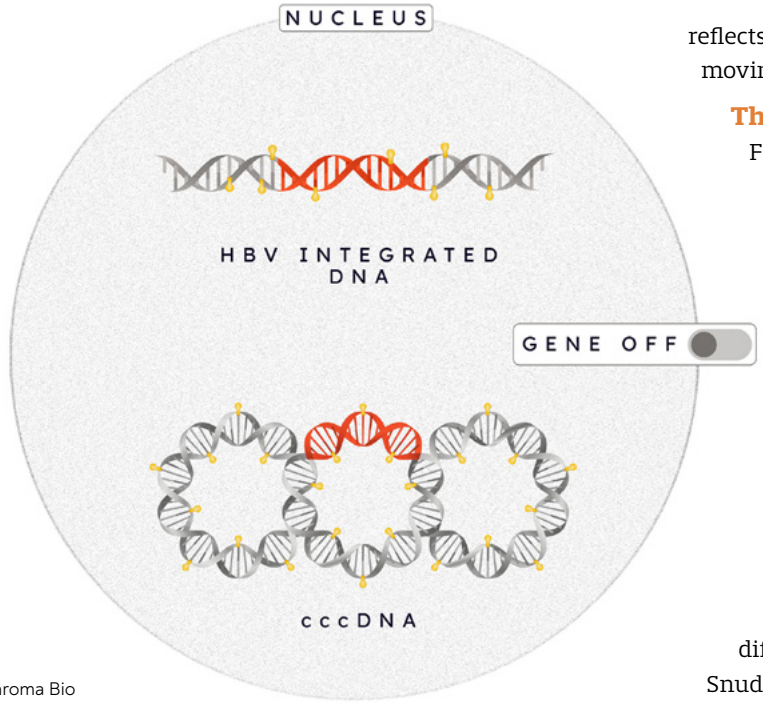
As epigenetic diagnostics expand, another challenge becomes increasingly important: how to measure these signals accurately and efficiently. Cora Vacher, PhD, director of segment marketing for human genetics at Oxford Nanopore Technologies, argues that traditional workflows often make epigenetics unnecessarily complex. "Oxford Nanopore sequencing can read native DNA and RNA directly, without PCR amplification or chemical conversion," she said. That means methylation and other epigenetic modifications can be detected alongside the sequence from the same molecule, in the same experiment.

Instead of stitching together multiple assays for sequencing, structural variation, and methylation analysis, researchers can capture all this information simultaneously. "Our technology reads individual DNA or RNA molecules directly as they pass through a nanopore," Vacher explained, using changes in electrical current to identify both nucleotide sequence and chemical modifications in real time.

Because amplification and chemical conversion are not required, the method preserves long reads and native biological context. It also enables the detection of multiple epigenetic modifications beyond traditional forms of methylation.

In cancer and rare-disease research, this creates a much richer picture of disease biology by linking sequence variation, haplotype phasing, structural variants, and epigenetic regulation on the same molecule. "Because epigenetic information is captured directly," she said, "the technology is well-suited to developing simpler, more integrated assays that could support future clinical workflows."

(continued on next page)



nChroma Bio

Preclinical data suggests CRMA-1001 durably silences hepatitis B virus (HBV) covalently closed circular DNA (cccDNA) and integrated viral DNA at the level of transcription.

Therapeutics move beyond diagnosis

Epigenetics is not only improving diagnostics, it is also increasingly becoming the therapy itself. At nChroma Bio, CSO Melissa Bonner, PhD, and CSO Jenny Marlowe, PhD, are developing treatments based on epigenetic silencing rather than gene editing. "Epigenetic silencing enables potent, durable gene silencing without cutting or permanently altering the DNA sequence," they explained. Instead of editing DNA directly, the approach uses the cell's own epigenetic machinery—particularly DNA methylation—to turn genes off in a controlled and durable way.

Melissa Bonner, PhD
CSO, nChroma Bio

Their lead program, CRMA-1001, an investigational, clinical-stage therapy, targets chronic hepatitis B, where viral persistence depends on both episomal covalently closed circular DNA (cccDNA) and integrated viral DNA. By permanently methylating both forms, the therapy aims to durably silence viral gene expression and potentially deliver a functional cure.

In preclinical studies, CRMA-1001 produced durable suppression of hepatitis B virus (HBV) biomarkers, with up to 90% of animals achieving complete loss of HBV surface antigen and DNA.

The company is also expanding into cardiometabolic disease, central nervous system, and oncology programs. The shift reflects a larger truth across precision medicine: epigenetics is moving from classification to direct intervention.

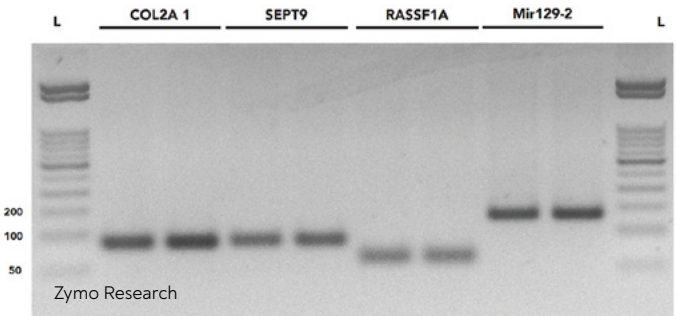
The next phase of precision medicine

For Snuderl, the next frontier is clear. After spending more than a decade improving diagnosis, today's goal is to use that molecular knowledge to improve therapy. "Now we know what we are dealing with and, hopefully, we can find better therapies," he said.

Future applications of epigenetics might resolve other challenges in today's healthcare. For example, epigenetics might help identify the origins of metastatic brain tumors when physicians are unable to determine where the cancer began. Epigenetics could also improve clinical-trial enrollment by ensuring that the right patients are matched with the most appropriate studies. "If 15% of patients on your clinical trial have a different type of cancer," Snuderl said, "there's a statistically very good chance your trial will fail."

Jenny Marlowe, PhD
CDO, nChroma Bio

Precision medicine depends on precision diagnosis. Without accurate classification, targeted therapies and biomarker-driven trials cannot succeed. That is where epigenetics has become indispensable. It provides not just more molecular data, but biological context—revealing lineage, vulnerability, treatment response, and increasingly, therapeutic opportunity. What was once a forgotten footnote in a medical school textbook has become one of the most clinically transformative tools in modern oncology. ■



DNA isolated from a non-small-cell lung cancer was bisulfite-converted using the EZ DNA Methylation-Lightning Kit, then PCR amplified with methylation-specific primers for cancer biomarkers *SEPT9*, *RASSF1A*, and *Mir129-2*, and control primer COL2A1. (L = 50 base-pair marker.)

Mike May, PhD, is a freelance writer and editor with more than 30 years of experience. He earned an MS in biological engineering from the University of Connecticut and a PhD in neurobiology and behavior from Cornell University. He worked as an associate editor at *American Scientist*, and he is the author of more than 1,000 articles for clients that include *GEN, Nature, Science, Scientific American,* and many others. In addition, he served as the editorial director of many publications, including several *Nature Outlooks* and *Scientific American Worldview.*

TARGA Imager Enables High-Resolution Imaging of Neurodevelopmental Models

Neurodevelopment in schizophrenia poses major challenges for experimental study due at least in part to the brain's genetic complexity, cellular diversity, and limitations in accessing living human tissue. To overcome such barriers, researchers often use complementary human stem cell–derived models: adherent cortical organoids and Neurogenin-2 (NGN2) induced neurons. Adherent cortical organoids form three-dimensional cultures containing diverse cortical neuron types, enabling analysis of network development and long-term maturation over months.[1] In contrast, NGN2 neurons generate rapid, two-dimensional, homogeneous populations of excitatory neurons that display robust activity within weeks, making them well suited for scalable, functional assays, and high-throughput screening.[2]

With the added insight that stem cell models offer into the neural development of the schizophrenic brain, the quantification of patient-derived neurons' collective function is a priority.[3] At Columbia University's Mortimer B. Zuckerman Mind Brain and Behavior Institute, researchers use NGN2 neurons, yielding reproducible populations of excitatory cortical neurons that scale reliably across experiments.

Calcium imaging provides a powerful functional readout in these NGN2 neuron networks. When a neuron fires an action potential, voltage-gated calcium channels open and intracellular calcium rises sharply.[4] Fluorescence calcium indicators convert transient, ionic changes into fluorescence emission that can be quantitatively detected via light microscopy across thousands of cells simultaneously. Coupling calcium-sensitive reporters with high-speed optical microscopy enables noninvasive, population-level measurement of neural activity, synchrony, and network dynamics. Interpreting these rich image sequences requires sophisticated theoretical and numerical approaches.[5]

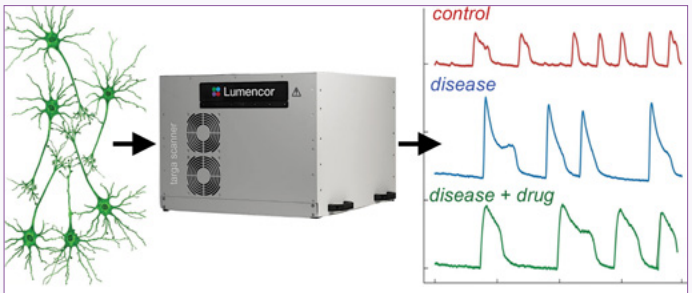


Figure 1. TARGA implementation for NGN2-neurons calcium imaging workflow

Building on the ability to measure neural activity with calcium imaging at scale, Lumencor's TARGA Imager represents a transformative step in the development of optical imaging hardware for the study of neurodevelopmental conditions such as schizophrenia. It is well suited to workflows where NGN2-neuron cultures are studied across multiple conditions in parallel (*Figure 1*). In these contexts, TARGA delivers calcium fluorescence images over millimeter-scale fields of view within standard 96-well plates, entire well areas, while maintaining high-speed, faster-than video rate imaging with precision resolution.

These capabilities allow researchers to observe chemical communications across large neuronal networks rather than isolated cells in real time. Images can be acquired at frequencies up to 100 Hz, enabling capture of fast calcium transients of collective neuronal dynamics. Rapid switching of multicolor excitation light supports multiplexed fluorescence dyes, linking functional activity with cellular structure and organization.

Overall, TARGA achieves high spatial, temporal, and spectral resolution simultaneously with precise, automated opto-mechanical architecture. These data are well matched to modern image analysis and AI algorithms, generating robust fluorescence traces from complex neuronal populations (*Figure 2*). In combination, these features make the TARGA Imager a revelatory neuroscience tool, uniquely enabling visualization of emergent collective behavior at millimeter scale with exceptional resolution. Such integrated performance accelerates discovery by bridging cellular mechanisms and systems-level phenotypes relevant to schizophrenia pathophysiology and therapeutic screening. By uniting scale, speed, and precision in a single optical platform, TARGA empowers researchers to probe experimental neuroscience and strengthens translational studies of complex psychiatric disease at population scale.

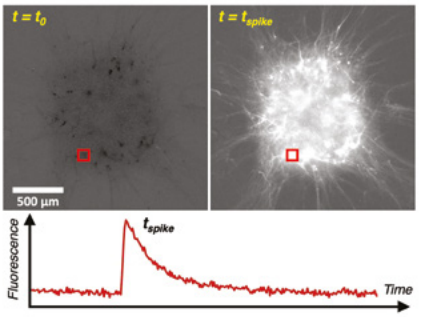


Figure 2. Calcium fluorescence trace detection from millimeter scale neuronal tissue

References

1. Van der Kroeg et al. Human adherent cortical organoids in a multiwell format. *eLife*. 2024. 13:e98340.
2. Shan et al. Fully defined NGN2 neuron protocol reveals diverse signatures of neuronal maturation. *Cell Reports Methods*. 2024. 4:100858.
3. Rao et al. Aberrant pace of cortical neuron development in brain organoids from patients with 22q11.2 deletion syndrome-associated schizophrenia. *Nature Communications*. 2025. 16:6986.
4. Zhang et al. Fast and sensitive GCaMP calcium indicators for imaging neural populations. *Nature*. 2023. 615:884–891.
5. Pasarkar et al. maskNMF: A denoise-sparsen-detect approach for extracting neural signals from dense imaging data. *bioRxiv*. 2023. 2023.09.14.557777.

Pioneering innovation in transplant diagnostics

Sara Barrington is CEO of Verici Dx, a precision diagnostics company redefining how transplant clinicians understand and predict graft health. By combining multi-omic analysis with proprietary artificial intelligence (AI) models, Verici Dx delivers predictive, actionable intelligence that helps clinicians optimize therapy, inform biopsy decisions, and stratify risk for complex transplant patients.

In this edition of Asked & Answered, Barrington speaks with *Inside Precision Medicine* Editor in Chief Damian Doherty about pioneering innovation in transplant diagnostics to better reflect biological and patient complexity, and ultimately, improve health outcomes.

Q: Tell me about Verici Dx, its founding, mission, and products.

Sara Barrington: Verici Dx was founded with a very clear purpose: to fundamentally improve how transplant clinicians are informed and manage graft health. Transplant medicine requires high-stakes, time-sensitive decision-making to promote longevity of the graft, minimize the risk of complications, and improve the patient's quality of life.

Kidney transplantation has long struggled with one fundamental challenge: accurately identifying rejection early and distinguishing it from other causes of injury and graft dysfunction. Clinicians often rely on conventional blood markers such as serum creatinine or, more recently, donor-derived cell-free DNA. While these tools are useful for signaling that "something is wrong," they are injury markers and lack a level of precision important in rejection biology.

Sara Barrington

Creatinine levels, for example, increase only after functional damage has already occurred and cannot differentiate rejection from non-immune causes of injury such as ischemic reperfusion injury, drug toxicity, or viral infections like BK

hyframestudio / iStock / Getty Images Plus

virus–associated nephropathy. Biomarkers can generate false positives, triggering biopsies or treatment escalation that may not be necessary and can expose patients to avoidable risk.

This lack of specificity has made rejection difficult to manage proactively. By the time rejection is clearly identified, tissue injury may already be established. At the same time, clinicians are understandably cautious about intensifying immunosuppression without clear evidence, given the associated risks of infection, malignancy, and toxicity.

Our mission is to close this information gap by delivering precision diagnostics that reflect the true complexity of transplant biology and translate that complexity into insights clinicians can proactively and confidently apply to patient care.

We operate at the intersection of multi-omic science, advanced analytics, and clinical reality. We know that transplant rejection and graft injury are not single-signal events, but are multifactorial, dynamic biological processes. We design our diagnostics to capture that complex biology in a way that mirrors how clinicians think about their patients, rather than forcing clinical decision-making to fit the limitations of older technologies.

Our lead product, Tutivia™, is a blood-based test that assesses the immune and broader, relevant biological status of kidney transplant patients to identify the risk of all forms of acute rejection, including T cell (TCMR) and antibody-mediated rejection (ABMR). Tutivia combines transcriptomics with proprietary AI models to address this precise unmet need: biologically accurate insight into what is actually happening within the graft.

The test delivers a risk score that enables more precise immunosuppression management by distinguishing rejection from other causes of graft injury, such as BK virus–associated nephropathy and ischemia-reperfusion injury, which can confound conventional blood tests like serum creatinine and donor-derived cell-free DNA.

By focusing on the immune and other pathways associated with rejection, Tutivia moves beyond damage markers and toward a direct assessment of rejection biology itself. That shift, from injury detection to biological interpretation, is what makes the test such a valuable tool for transplant clinicians.

Thermo Fisher Scientific recently launched its One Lambda™ Pre-Transplant Risk Assessment (PTRA) assay, using pre-transplant prognostic technology licensed from Verici Dx. The assay provides a risk score for early acute rejection based on a patient's unique gene profile, helping clinicians better balance the risk of rejection against the potential side effects of over-immunosuppression. Using a 29-gene mRNA signature, the PTRA assay stratifies patients into high- and low-risk categories, with clinical validation showing high-risk patients are seven times more likely to experience early acute rejection.

Q: Tutivia is built on RNA sequencing. Why is precision transcriptomic analysis well-suited for identifying rejection biology?

Barrington: The need for reliable biomarkers is crucial for individualizing therapy that offers the potential to extend allograft survival.

Early research underpinning the science leading to the development of Tutivia was led by principal investigators at The Mount Sinai Hospital in New York, one of the world's leading transplant research centers, combining decades of clinical expertise with rigorous science. The underlying

(continued on next page)

(continued from previous page)

science reflects the fact that rejection in kidney transplant patients is not driven by a single molecule or pathway, it results from coordinated immune and other biologic pathways across multiple cell types, signaling cascades, and regulatory mechanisms. Injury-driven biomarkers capture only a narrow slice of this biology and can be influenced by non-rejection factors, limiting their specificity and reliability.

> "In short, RNA sequencing lets us ask better biological questions: not just whether the kidney is injured, but whether immune-mediated rejection is driving that injury."

Precision transcriptomic analysis, on the other hand, measures gene expression patterns across thousands of genes simultaneously. In developing specific tests, this analysis is the basis for gene selection using unsupervised deep learning mathematical modeling, allowing the most impactful and reproducible gene expression signals and interactions to be included in the final signature.

Tutivia uses a peripheral blood next-generation sequencing assay to evaluate a 17-gene mRNA signature in combination with a proprietary artificial intelligence algorithm to categorize kidney transplant patients as at low risk or high risk of acute rejection.

This provides a comprehensive view of immune activation, regulation, and injury responses within the transplanted organ, allowing the identification of signature changes that are truly characteristic of rejection biology.

In short, RNA sequencing lets us ask better biological questions: not just whether the kidney is injured, but whether immune-mediated rejection is driving that injury. That distinction is critical for precision medicine in transplantation.

Q: What does earlier and more precise identification of rejection biology mean for patient management and outcomes?

Barrington: Earlier identification of rejection biology can create an opportunity to intervene before irreversible damage occurs. When clinicians have confidence in what the biology is telling them, they can make timely, targeted decisions that may preserve graft function.

This precision also supports more individualized care. Rather than applying broad treatment strategies, clinicians can tailor immunosuppression based on biological risk, potentially reducing over-treatment and its associated complications.

For patients, this can translate into fewer unnecessary biopsies, fewer adverse events related to immunosuppression, and a greater likelihood of long-term graft survival. Ultimately, better information leads to better decisions, and better decisions lead to better outcomes.

Our vision is that precision diagnostics like Tutivia become a standard component of transplant management, providing earlier insight into rejection biology, supporting more informed clinical decisions, and helping clinicians intervene at the right time for the right patient.

Q: AI is central to your platform. How does Verici Dx apply AI differently from others in diagnostics?

Barrington: We apply AI with rigor and restraint. We use advanced machine learning and mathematical modeling to analyze highly complex biological data, but always within a disciplined scientific framework. Our models are developed using unsupervised approaches and validated extensively on inclusive patient populations. Once validated, they are locked and reproducible; they are not evolving over time. That distinction matters because clinicians are making life-altering decisions based on these results, and trust, consistency, and validation are essential.

Q: Validation and standards are recurring themes for Verici Dx. How was Tutivia validated?

Barrington: Tutivia was validated through a rigorous clinical study that included a broad and diverse transplant patient population, rather than narrowly curated cohorts. We deliberately chose a more difficult validation path because clinical reality is complex, and diagnostics must perform under those conditions. While this approach requires more time and effort, it ensures the test is reliable, reproducible, and clinically relevant across the full spectrum of patients that clinicians see every day.

Q: What's in the future for the company?

Barrington: Verici Dx is focused on deepening the clinical adoption of Tutivia as well as expanding the studies demonstrating the utility of an earlier and more precise biomarker in improving patient outcomes. Long-term outcomes for transplant patients involve more biological pathways, and significant complexity is involved in managing care. We are focused on developing and validating tests using both transcriptomic and proteomic precision tools to assist clinicians and their patients in this journey. ■

Damian Doherty has been in media and publishing for over 30 years, beginning at News Corporation. Damian has managed, edited, and launched life science titles in drug discovery and precision medicine. He was features editor of *Drug Discovery World* and founded the *Precision Medicine Leaders Summit* and the *Journal of Precision Medicine*. He edited *AIMed* magazine before launching Photo51Media, a platform for illuminating untold, compelling stories in precision healthcare. Damian joined Mary Ann Liebert in 2021 to help steer the new rebrand and relaunch of *Clinical OMICS* to *Inside Precision Medicine*.

Navigate the Evolving Landscape with *Inside Precision Medicine* eNewsletters

FREE SUBSCRIPTION

Inside Precision Medicine delivers curated content written by the most trusted editorial experts in the field

Join the ranks of industry and academic leaders who trust *Inside Precision Medicine* for cutting-edge insights and updates. Our exclusive eNewsletters delivers the latest breakthroughs, trends, and innovations in the world of precision medicine – all tailored to your interests.

Subscribe Today and Gain Access to:

INSIDE PRECISION MEDICINE TODAY

Your daily dose of vital updates, expert opinions, and in-depth analysis. Stay informed every day with the most relevant news in precision medicine.

INSIDE PRECISION ONCOLOGY

Dive deep into the specialized world of cancer research and treatment. Discover the latest advancements in precision oncology and stay ahead of the curve.

SPECIAL EDITIONS

Get comprehensive coverage of key conferences in precision medicine. Receive exclusive reports, highlights, and expert takeaways from the industry's most important events.

PRODUCT INSIDER

Be the first to know about new precision medicine products and solutions. Stay updated on the latest innovations shaping the future of healthcare.

Be the owner of your inbox.

Subscribe now for free and empower your precision medicine journey with the knowledge and insights you need to succeed.

SUBSCRIBE NOW

INSIDE PRECISION MEDICINE

From Multi-Omics to Digital Twins: A Data-Driven Future for Precision Medicine

by Clara Rodríguez Fernández

First coined over a decade ago in the aerospace industry to describe a digital replica of a physical object, the concept of a "digital twin" has since found its way into medicine, where it refers to the simulation of a patient's unique biology. Drawing on multiple layers of patient health data, these computer models promise to predict how a person's health will evolve over time and how they will respond to any given intervention.

Digital twins represent a transformative shift in medicine, moving from reactive health interventions toward preventive strategies. While this technology is still in early stages, it is already being used to guide personalized cancer treatment, simulate the outcomes of cardiology interventions, and manage complex metabolic diseases like diabetes. However, most applications today are closer to small-scale digital models of a specific tissue or condition rather than a complete digital twin that dynamically adapts to real-world data from each simulated patient.

A convergence of rapid technological advances across multi-omics and artificial intelligence (AI) is priming the development of powerful computational models that can capture intricate biological processes beyond the capabilities of any of their predecessors. As large-scale multi-omics datasets are increasingly combined with clinical and real-time physiological data, digital twins are laying the foundation for a more precise and individualized understanding of human health.

Ellen M. McDonagh, PhD
Group Team Lead
European Bioinformatics Institute

Exploring uncharted territory

Digital twins could have a particularly meaningful impact in areas of medicine where knowledge is limited and currently available technologies have fallen short. One such area is rare diseases. Although rare diseases collectively affect more than

Donald Iain Smith / Getty Images

300 million people worldwide, each of the over 7,000 conditions covered under this definition only affects a small number of patients—sometimes even just a single person. This scarcity makes it difficult to study the underlying biology and hinders the development of much-needed treatments and diagnostics.

"We can use digital twins to address the fact that, with a rare disease, you might only have a handful of patients with that diagnosis," said Ellen M. McDonagh, PhD, group team lead at the European Bioinformatics Institute (EMBL-EBI) in the U.K. and translational informatics director at Open Targets.

Through a project funded by the Chan Zuckerberg Initiative, McDonagh's team is developing digital twins of human tissues that combine multi-omics data with a patient's clinical history and additional phenotype data. Their approach begins by modeling biological processes in healthy tissue, and then bringing in data from common diseases affecting the same tissue to train AI models to predict patterns of dysfunction. This would allow researchers to feed the algorithm data from patients with rare diseases to better understand the underlying biological mechanisms driving each condition.

Integrating diverse layers of multi-omics data will be critical to achieving a more comprehensive understanding of the molecular basis of these rare conditions. In some countries, including the U.K., patients with rare diseases routinely undergo whole-genome or whole-exome sequencing as part of diagnostic testing. However, many of the identified genetic variants remain difficult to interpret with limited current knowledge. By combining genomics with other modalities such as transcriptomics, proteomics, and metabolomics, researchers can develop a more complete picture of the underlying molecular interactions and better determine the relevance of these previously uncharacterized variants.

On this front, a major challenge lies in collecting and integrating data across a wide range of modalities, cohorts, and institutions. To address this, McDonagh's team is actively developing workflows to standardize data collected from the scientific literature, public datasets, and research environments, enabling more reliable comparisons across datasets and facilitating their integration into digital twin models.

This work also involves efforts to fill gaps in the data, as not all data modalities will be available for every patient. For instance, a computer model could predict what the transcriptomic profile will look like based on genomics data, and vice versa.

"We are benchmarking different methods that can help with predicting missing data, but also evaluating how confident we are in those predictions," said McDonagh. Knowing which biological processes can be predicted with high confidence, and which cannot, can help researchers draw more robust conclusions and guide future data collection efforts.

"We are benchmarking different methods that can help with predicting missing data, but also evaluating how confident we are in those predictions."

As digital twin models keep growing and becoming more refined, they will enable the identification of new therapeutic targets and diagnostic markers, while also forecasting the precise effects an intervention will have on a given person. McDonagh highlights their potential to develop more personalized treatment plans for each patient, adding that, "Monitoring patients over time, one could also predict whether a patient might develop resistance to a given drug and switch them to an alternative treatment."

(continued on next page)

(continued from previous page)

Integrating real-time data

Integrating multi-omics data with physiological measurements, obtained from continuous sensors and wearable devices, could help digital twins take a significant step forward in accurately simulating complex and dynamic biological processes. In turn, this could help advance healthcare from a reactive model to a more proactive approach.

Tadao Ooka, MD, PhD
Associate Professor
University of Yamanashi

"Today, much of medicine begins after a disease has become clinically apparent," said Tadao Ooka, MD, PhD, associate professor at the University of Yamanashi in Japan. "In contrast, preemptive medicine aims to detect subtle biological changes before symptoms or irreversible damage occur, and to intervene earlier through lifestyle, environmental, pharmacological, or behavioral approaches."

Achieving such a transformative shift could significantly reduce the burden of chronic diseases such as diabetes, cardiovascular disease, and neurodegenerative disorders. This is becoming an increasingly urgent goal in aging societies, including Japan, where preventing health decline and extending healthy life expectancy are currently major public health priorities.

Ooka's lab is developing digital twins that integrate patient data from longitudinal multi-omics, wearables, and lifestyle questionnaires. Through Taomics, a company he co-founded, Ooka is also building a platform to collect longitudinal data from patients and healthy individuals. This data is used to create digital twins that can provide users with personalized health recommendations while informing drug discovery and identifying target populations for a more precise approach to clinical development.

"One major objective is to identify biological pathways related to insulin resistance and metabolic dysfunction," he added. "The goal is not only to predict risk, but also to understand which behaviors or interventions may improve a person's molecular and metabolic state."

While multi-omics data can tell researchers what is happening within the body at the molecular level, continuous data obtained from sensors and wearables can provide a deeper insight into what a person is experiencing in daily life, including physical activity, sleep, heart rate, and stress levels.

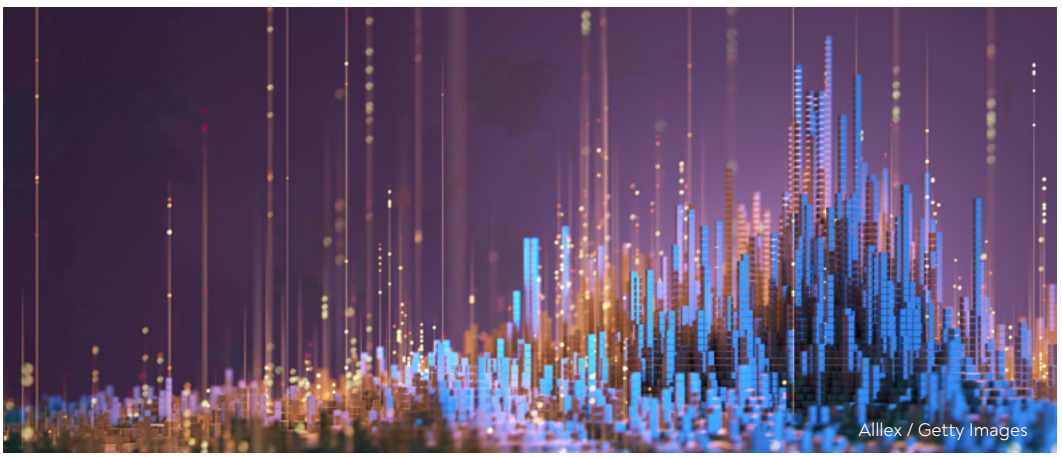
"The key is to connect these two layers," said Ooka. "Together, they allow us to move from general advice to personalized, testable, and adaptive recommendations. For example, if a person's sleep, physical activity, or dietary pattern changes, we can examine how their inflammatory, metabolic, or insulin resistance-related protein signatures change afterward. Conversely, if a molecular pathway appears to be deteriorating, [sensor] data may help identify the behavioral or environmental context behind that change."

Kyung-In Jang, PhD
Associate Professor
Daegu Gyeongbuk Institute of Science and Technology (DGIST)

Across all medical specialties, Ooka expects digital twins to make the greatest early impact in diseases where progression is continuous, multifactorial, and strongly influenced by the patient's lifestyle and environment. These include metabolic diseases, which develop over many years and are shaped by interactions between genetics, environment, and behavioral patterns. Oncology will also be particularly relevant given the complexity of treatment response and resistance processes at the molecular level.

To reach these ambitious goals, however, a number of challenges must be addressed. In addition to ensuring the data used to train digital twin models is robust and reliable, implementation needs to be carefully planned so that digital twins can adapt to and integrate into real-world clinical workflows, reimbursement systems, regulatory frameworks, and ethical governance structures.

"The goal should be to create systems that benefit the broader population," explained Ooka. "We need to ensure that prediction does not become discrimination, that data is handled securely, and that people receive understandable and actionable recommendations."



Alllex / Getty Images

Oscar Wong / Getty Images

Towards dynamic predictions

In the future, experts expect to see digital twins that integrate multi-omics data with wearable, imaging, clinical, and environmental data to capture the full complexity of human biology, becoming intelligent decision-support platforms. This progress will be underpinned by continued improvements in multi-omics technology, with the coming decade being primed for advances in longitudinal data collection and spatial multi-omics. Coupled with increasingly lower prices, this technology is expected to become much more accessible to researchers and clinicians alike.

> "While omics data were once confined to laboratory analysis, emerging wearable technologies now allow real-time detection of certain metabolites and protein markers."

"While omics data were once confined to laboratory analysis, emerging wearable technologies now allow real-time detection of certain metabolites and protein markers," wrote Kyung-In Jang, PhD, associate professor at the Daegu Gyeongbuk Institute of Science and Technology (DGIST) in South Korea. "These innovations support integrating omics into everyday health monitoring, contributing to the accessibility and responsiveness of precision healthcare."

Within the next decade, McDonagh expects to see the first translational applications of digital twins in the clinic, whether to support diagnosis, patient stratification in clinical trials, or predicting how a patient will respond to a given treatment. "It really does open the door to being able to identify new targets that are causing disease in rare disease patients, but also in more complex, common diseases," she said. "Ultimately, digital twins will help in the development of new, safer, more effective treatments and more personalized medicine."

Going forward, Ooka expects medical applications of digital twins to evolve in stages, starting with smaller, disease-specific models, and later becoming large-scale tools that can predict future outcomes and enable patients to alter their disease trajectories through personalized interventions. This evolution will go beyond purely technical improvements, potentially shaking the foundations of healthcare systems as we know them today.

"The field will require new ecosystem models, not only new analytical technologies," said Ooka. "Medical digital twins cannot be built by academia, industry, hospitals, or technology companies alone. They require long-term participant engagement, trusted data governance, scientific rigor, clinical relevance, and business sustainability."

Ooka has been actively working on setting up such an ecosystem in Japan through the COI-NEXT initiative, bringing together universities, regional companies, and global partners to return insights derived from their data to local communities.

"Ultimately, I would like to create a system in which individuals can receive personalized health recommendations based on their own longitudinal biological data," he concluded. "This means moving beyond one-time testing toward a continuous feedback loop: measure, interpret, intervene, and re-measure. At the same time, such a platform could contribute to pharmaceutical research by connecting real-world human biology, lifestyle, and molecular data in a way that supports more precise and efficient drug development.

"My hope is that digital twins will help create a future where healthcare is no longer centered only on diagnosing and treating disease, but on continuously supporting each person's optimal health throughout life." ■

Clara Rodríguez Fernández is a science journalist specializing in biotechnology, medicine, deeptech, and startup innovation. She previously worked as a reporter at *Sifted* and editor at *Labiotech*, and she holds an MRes degree in bioengineering from Imperial College London.

Signatera™ as a Pan-Cancer Decision-Making Tool to Illuminate the Care Pathway

To date, precision oncology has largely focused on selecting therapies based on tumor genomics. One of the most persistent challenges in clinical practice remains knowing what to do next. After surgery, during systemic therapy or in surveillance, clinicians are often navigating uncertainty, balancing overtreatment against the risk of recurrence.

Reshaping patient management

Circulating tumor DNA (ctDNA)–based minimal residual disease (MRD) assessment with tumor-informed Signatera™ is reshaping this paradigm by providing a dynamic, patient-specific signal that can illuminate next steps across the continuum of care. Unlike conventional imaging or clinicopathologic risk factors, ctDNA offers a real-time measure of tumor burden at the molecular level. Signatera is designed using the patient's tumor, enabling highly sensitive and specific detection of residual disease at levels far below radiographic visibility. This creates a new layer of clinical intelligence that is actionable across neoadjuvant, adjuvant, surveillance, metastatic, and treatment response settings.

Neoadjuvant setting: early readouts to adapt therapy

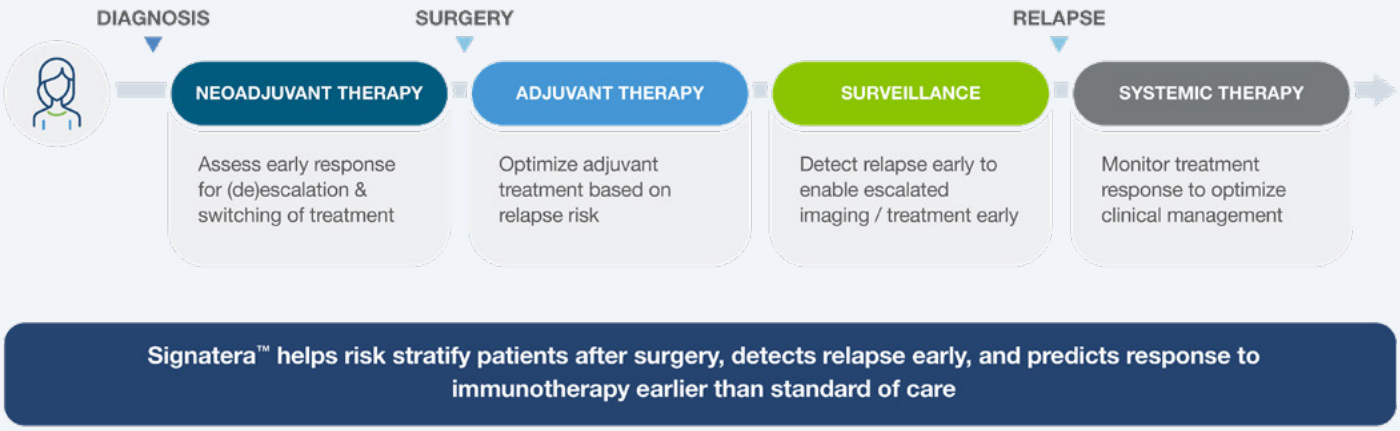
In the neoadjuvant setting, clinicians often need to wait until the time of surgery to determine whether therapy was effective. Assessing ctDNA dynamics during neoadjuvant therapy can provide an early indication of treatment response; ctDNA clearance has been associated with improved outcomes while conversely, persistent ctDNA may signal resistance, prompting consideration of treatment escalation, clinical trial enrollment, or alternative regimens.[1] This creates an opportunity to move beyond static endpoints toward adaptive treatment strategies. Clinicians can watch ctDNA trends to refine therapy in real time. This is especially relevant in aggressive tumor types where early response assessment is critical.

Adjuvant setting: refining who may benefit from additional therapy

MRD testing may provide immediate clinical impact in the adjuvant setting. Current decision-making relies heavily on population-level risk factors, often leading to overtreatment in some patients and undertreatment in others. Postoperative ctDNA positivity is a strong, independent predictor of recurrence across multiple tumor types. Signatera data demonstrates that ctDNA-positive patients after surgery can have dramatically higher recurrence risk compared with ctDNA-negative patients.[2] More importantly, Signatera ctDNA status can help predict who benefits from adjuvant therapy. Evidence suggests that ctDNA-positive patients derive meaningful benefit from additional systemic treatment, while ctDNA-negative patients may not.[3]

Surveillance: detecting recurrence earlier

Surveillance after curative-intent therapy remains a gray zone as imaging can often be intermittent and insensitive to early recurrence. While many biomarkers like CEA, CA-19-9, CA-125 generally have limitations in both sensitivity and specificity, Signatera ctDNA testing offers a more sensitive approach to detect molecular relapse earlier than imaging and other blood biomarkers. Studies have shown that Signatera can identify recurrence months before it becomes radiographically apparent with high sensitivity and specificity and substantial lead times.[4] Earlier detection opens the door to intervention at a lower disease burden, when therapies may be more effective. It also enables more tailored surveillance strategies to intensify monitoring or imaging when ctDNA becomes positive, provides reassurance, and potentially reduces imaging frequency in persistently negative patients. Rather than a fixed surveillance schedule, ctDNA enables a response-guided follow-up strategy.



Treatment on MRD (TOMR)

TOMR is a new paradigm in precision oncology that is used to guide earlier, more proactive therapy decisions to escalate treatment in MRD-positive patients at high risk of relapse and de-escalate or avoid unnecessary toxicity in MRD-negative patients. For clinicians, this moves decision-making from prognostic to personalized, anchored by the presence of residual disease at an earlier and potentially curable stage.

Metastatic setting: real-time disease monitoring

In metastatic disease, treatment decisions are often based on imaging intervals that may lag behind molecular changes in disease burden. A newer technology like ctDNA introduces a more immediate and dynamic tool. Because ctDNA reflects tumor burden and molecular activity, it can be used to monitor treatment response earlier than imaging and identify emerging resistance to inform timely switches in therapy. In practice, this allows clinicians to avoid prolonged exposure to ineffective therapies and pivot more quickly. Additionally, Signatera is being used to monitor response to immunotherapy across tumor types, providing a pan-cancer application in advanced disease.

Treatment response monitoring: a continuous feedback Loop

Across all stages, one of the most powerful aspects of ctDNA is its ability to create a longitudinal feedback loop. Serial testing enables clinicians to track ctDNA trends over time:

- Clearance means favorable response and improved prognosis
- ctDNA dynamics have been shown to correlate strongly with outcomes. Patients who remain ctDNA negative demonstrate significantly better survival than those who become or remain ctDNA positive which could mean there is a higher risk of disease progression

This transforms monitoring from episodic snapshots into a continuous signal, providing actionable insight at each decision point.

A pan-cancer framework for clinical decision-making

What makes Signatera particularly compelling is its pan-cancer applicability. Its tumor-informed design allows it to be used across multiple solid tumors, including colorectal, breast, lung, bladder, ovarian, and melanoma. This consistency enables a unified framework for integrating MRD into clinical workflows:

1. **At diagnosis or pre-treatment**—establish baseline and design assay
2. **During neoadjuvant therapy—**assess early response
3. **Post-surgery—**evaluate MRD and guide adjuvant decisions
4. **During surveillance—**detect molecular relapse early
5. **In advanced disease—**monitor response and resistance

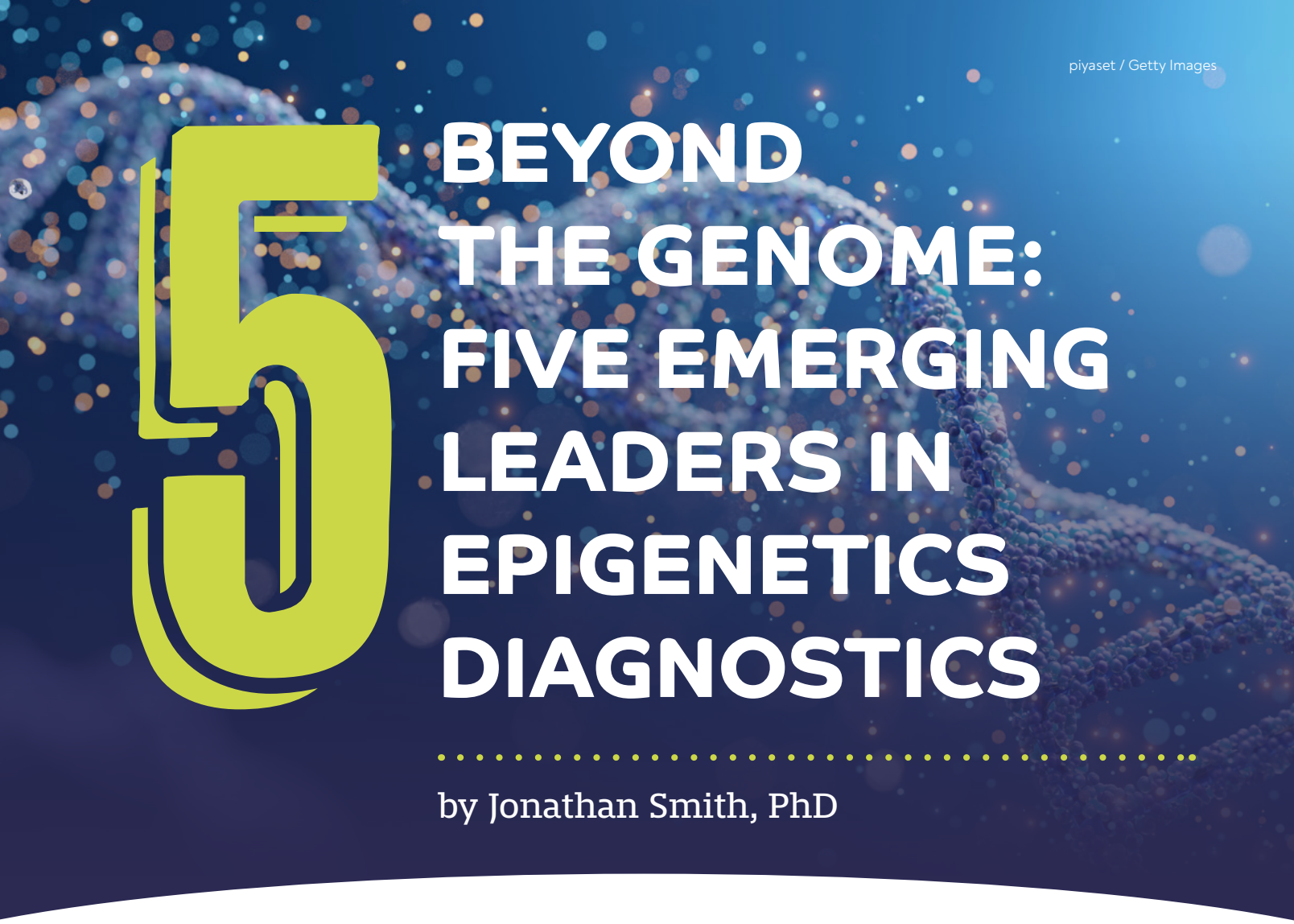
Rather than being confined to a single decision point, ctDNA becomes a longitudinal biomarker embedded throughout the care pathway.

From uncertainty to actionability

Signatera ctDNA testing bridges the gap from uncertainty to actionability by answering clinically meaningful questions at each stage of the patient's journey: Is there still disease present, and is it changing? By doing so, ctDNA doesn't just add another biomarker. It redefines how clinicians navigate the care pathway, moving from reactive to proactive care.

References

1. Chakrabarti S, Cohen S, Tin A, et al. Utility of Circulating Tumor DNA to Assess Tumor Response in Patients with Locally Advanced Rectal Cancer Undergoing Neoadjuvant Therapy. Cancers. 2026; 18(4):589.
2. Reinert T, Henriksen TV, Christensen E, et al. Analysis of Plasma Cell-Free DNA by Ultradeep Sequencing in Patients With Stages I to III Colorectal Cancer. JAMA Oncol. 2019.
3. Nakamura Y, Watanabe J, et al. ctDNA-based molecular residual disease and survival in resectable colorectal cancer. Nature Medicine. 2024. doi: 10.1038/s41591-024-03254-6.



piyaset / Getty Images

5 BEYOND THE GENOME: FIVE EMERGING LEADERS IN EPIGENETICS DIAGNOSTICS

by Jonathan Smith, PhD

Epigenetics is increasingly powering cancer diagnostics and liquid biopsies. These emerging private companies are spurring the market with structural DNA, fragmentomics, and DNA methylation tests.

Our understanding of the role of epigenetics in disease is growing rapidly, driven by rapid advances in sequencing technology and computing.

Epigenetic processes such as DNA methylation, histone modifications, and non-coding RNA expression can interact with genomic changes to cause cancer. Therefore, diagnostics can detect early signs of disease by screening for these epigenetic signals.

Players including Illumina, Agilent Technologies, and Roche Diagnostics are leading the global market for epigenetic diagnostics, which is expected to swell by 15.5% per year from $17 billion in 2024 to $39 billion by 2030.

Growth is being driven by the increasing affordability of genome sequencing; the integration of AI tools in data analysis; growing investments; and soaring demand for liquid biopsies—noninvasive cancer tests based on blood and urine samples.

One of the first diagnostics with an epigenetic component to be approved by the U.S. Food and Drug Administration (FDA) was Exact Sciences' (now part of Abbott Laboratories) ColoGuard® noninvasive stool test for colorectal cancer in 2014.

Since then, epigenetics diagnostics have already been generating M&A activity, with deals in the space including Cardio Diagnostics of the U.S. going public via a merger with special purpose acquisition company Mana Capital in 2022; the takeover of Ireland's EpiCapture by compatriot Trinity Biotech in 2024; the 2023 acquisition of Germany's Epigenomics AG by U.S.-based New Day Diagnostics; and U.S. Agilent's acquisition of Avida Biomed, also in 2023.

There is also corporate venture interest with giants like Illumina Ventures, the Labcorp Venture Fund, and Lilly Asia Ventures making investments in small startups.

Check out below for our take on the most promising privately-owned players in the epigenetics diagnostics space, based on their investor attraction and market potential.

1 ARIMA GENOMICS

Arima Genomics

Founded: 2015 | **Headquarters:** Carlsbad, California

Arima Genomics was spun out of UC San Diego and developed research tools to pinpoint the 3D structure of DNA in cells.

However, the company pivoted to cancer diagnostics after its assay discovered vital clues on how to treat a teenage girl with glioblastoma in 2022.

Arima's Hi-C technology involves locking the DNA structure in place via crosslinking. DNA strands are then cut with enzymes and labeled with a marker called biotin. Arima uses a process called proximity ligation to connect DNA strands that were physically close together into a single strand, and then sequences the resulting molecule.

Last year, Arima launched a lymphoma test that is delivered via the firm's laboratory testing service, certified by the U.S. Clinical Laboratory Improvement Amendments (CLIA) program. The test is designed to be used to help patient management by discovering gene fusions and rearrangements for 417 genes in different types of lymphoma.

The test helps to fill in the gaps left by the gold standard, fluorescent *in situ* hybridization, which can be time- and resource-intensive and lead to conflicting results.

Arima raised $22 million in a Series C round led by Illumina Ventures in 2025 and appointed a former venture partner from Illumina Ventures as CEO. The firm is using the proceeds to launch a pipeline of clinical assays in cancer.

Arima also closed a partnership with Fox Chase Cancer Center earlier this year to co-develop diagnostic tests for lymphoma and sarcoma.

2 DELFI

DELFI Diagnostics

Founded: 2019 | **Headquarters:** Baltimore, Maryland

DELFI Diagnostics was founded on an "aha" moment at Johns Hopkins University School of Medicine when a group of researchers aimed to overcome the high costs and low sensitivity of traditional liquid biopsies.

The breakthrough involved hunting for the certain way cell-free DNA fragments appear in the blood. Healthy cells and cancer cells package their DNA in different patterns, reflecting changes in the cell's genomic and epigenomic machinery.

Using this method of "fragmentomics," DELFI's technology can tap into orders of magnitude more data than traditional methods.

DELFI's product FirstLook Lung uses artificial intelligence (AI) and fragmentomics technology to screen a blood sample for signs of lung cancer. It is designed as an adjunct tool to check whether patients are eligible for lung cancer screening, and is regulated under the CLIA program.

The startup's other product, DELFI-Tumor Fraction (DELFI-TF), allows pharmaceutical companies to track the effectiveness of a cancer therapy based on a sample of less than one milliliter of plasma.

DELFI raised $5.5 million in a seed round when it was founded, with investors including Menlo Ventures and Illumina Ventures.

The startup subsequently raised a $100 million Series A round led by OrbiMed in 2021, a $225 million Series B round led by DFJ Growth in 2022, and a $34 million debt round last year.

3 Element Biosciences

Element Biosciences

Founded: 2017 | **Headquarters:** San Diego, California

Element Biosciences was co-founded by three former Illumina employees who dreamed of democratizing access to genomic sequencing.

The company markets devices designed to sequence genetic information at a lower cost and higher performance than traditional next-generation sequencing. These include AVITI™—its flagship benchtop sequencer—and AVITI24, which can simultaneously analyze DNA, RNA, proteins, and phosphorylated proteins.

The company generated $25 million in revenue in 2023, partly driven by orders of AVITI.

The technology, based on a process called Avidite Base Chemistry (ABC™), uses a dye-labeled polymer to bind genetic material and produce sequencing data with the need for fewer reagents than traditional sequencing.

Element is working with epigenetics specialists to boost their research offerings, including Dovetail Genomics and biomodal.

The company has also formed collaborations with diagnostics providers to enhance their offerings, including Revvity's neonatal genetic tests and Medicover Genetics' tests for hereditary cancers, metabolic and cardiovascular disorders, infertility, and neonatal diseases.

The company plans to market a clinical diagnostics-focused sequencing product called AVITI Dx, with EU approval expected this year in the form of a CE In Vitro Diagnostic (IVD) mark.

(continued on next page)

(continued from previous page)

Element Biosciences has raised more than $680 million since it was founded, including a $277 million Series D round in 2024. The asset manager, Wellington Management, led the oversubscribed round, with participation from Samsung Electronics, Fidelity, and more.

This year, Element plans to commercialize a benchtop device, called VITARI, that can sequence a whole genome at high quality for just $100.

4

Nucleix

Founded: 2008 | **Headquarters:** Rehovot, Israel

Nucleix was initially founded to use epigenetics to trace falsified DNA in forensic investigations. Although the technology worked well, the management team decided to pivot to cancer screening.

Nucleix's kits involve screening for specific cancer-linked DNA methylation patterns using polymerase chain reaction (PCR) tests.

The company also uses machine learning to construct biomarker panels best suited to the application of interest.

Nucleix's Bladder EpiCheck® urine test is designed to detect the recurrence of bladder tumors based on changes in DNA methylation. It can also be used to support standard diagnostics when detecting bladder cancer in cases where malignancy is suspected.

The test has a CE mark in Europe and FDA 510(k) clearance in the U.S. for bladder cancer recurrence, meaning it can be marketed as substantially equivalent to another device in the U.S. market.

Nucleix is also developing a blood test for detecting lung tumors based on their DNA methylation signatures.

The company raised a $55 million funding round led by RA Capital Management in 2021, with participation from investors including BlackRock and corporate venture firm Lilly Asia Ventures. It followed up with a $22 million extension round in 2022.

In 2024, Nucleix sealed a strategic partnership with A. Menarini Diagnostics, part of the Italian Menarini Group, to bring its Bladder EpiCheck test to the European market.

5

Precede Biosciences

Founded: 2021 | **Headquarters:** Boston, Massachusetts

Precede was established by a team comprising Dana Farber Cancer Institute researchers and the venture capital firm 5AM Ventures.

Precede is developing blood tests that measure signals of disease based on the genomic and epigenomic characteristics of cell-free DNA shed into the blood by tumors.

For example, the company tracks gene transcription activity and DNA methylation based on as little as one milliliter of plasma. It can then use machine learning to interpret the results and predict the optimal treatment for each patient.

Precede collaborates with drugmakers to harness its technology to inform the development of next-generation radioligand therapies and antibody-drug conjugates, which depend on the knowledge of target expression and pathway activity rather than single genomic alterations.

The research-focused product Precede Bio Insight™ is designed to track the progress of cancer, with data spanning breast and prostate cancer.

The second product, Precede Bio Dx™, also allows clinicians to select patients for clinical trials based on the blood test results.

The company emerged from stealth mode with $57 million in 2023, and followed up with a Series B round worth $83.5 million in January this year to fund the scaling of its technology as it gains commercial traction.

Among the B round's syndicate were corporate venture investors Labcorp Venture Fund and Lilly Asia Ventures, and existing investor Illumina Ventures.

Jonathan Smith, PhD, is a freelance science journalist based in the U.K. and Spain. He previously worked in Berlin as a reporter and news editor at *Labiotech*, a website covering the biotech industry. Prior to this, he completed a PhD in behavioral neurobiology at the University of Leicester and freelanced for the U.K. organizations Research Media and Society of Experimental Biology. He has also written for *medwireNews*, *Biopharma Reporter*, and *Outsourcing Pharma*.

berya113 / iStock / Getty Images Plus

BEHIND THE BREAKTHROUGHS Podcast

Hosted & Produced by: Jonathan D. Grinstein, PhD

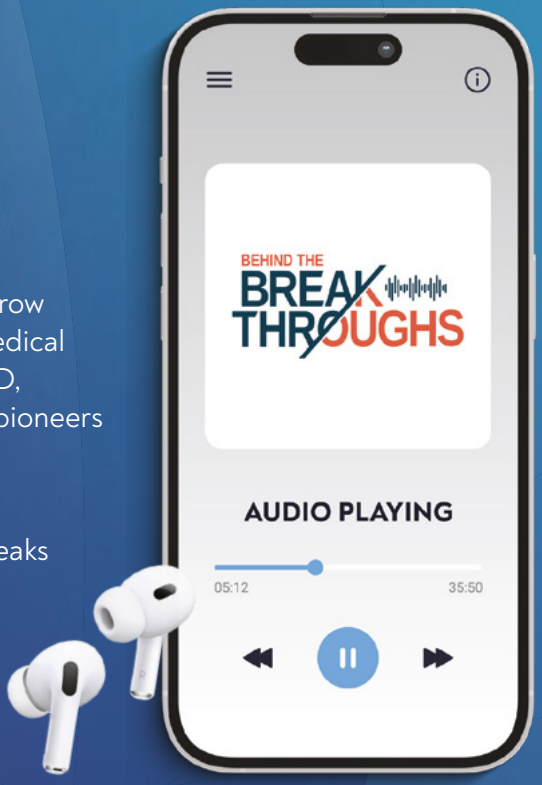
North American Editor, *Inside Precision Medicine*

New Episodes Every Other Wednesday

30–40 minutes

Step into the minds shaping the future of medicine.

Behind The Breakthroughs is more than a podcast—it's a front-row seat to the stories behind the science. Hosted by former biomedical researcher turned master storyteller Jonathan D. Grinstein, PhD, this series brings you candid, insightful conversations with the pioneers of precision medicine.



- **UNFILTERED ACCESS**
  From biotech trailblazers to clinical innovators, Jonathan speaks their language—asking the questions others don't.
- **THE HUMAN SIDE OF SCIENCE**
  Discover the personal journeys behind the breakthroughs. From career-defining moments to unexpected detours, these stories make the science real.
- **BIG IDEAS, GLOBAL IMPACT**
  Explore cutting-edge topics like AI in diagnostics, gene editing, and equitable access to care—across cancer, rare diseases, and more.
- **FOR THE CURIOUS & THE COMMITTED**
  Whether you're in pharma, biotech, healthcare, or just passionate about the future of medicine, this podcast delivers practical insights and fresh perspectives.

NOTABLE GUESTS INCLUDE:

- Geoff Oxnard, MD (Lilly)
- Helen Sabzevari, PhD (Precigen)
- Michael Severino, MD (Tessera)
- Kate Sasser, PhD (Tempus)
- David Liu, PhD (Harvard/Broad Institute)
- and many more.

TUNE IN.
GET INSPIRED.
STAY AHEAD.

Subscribe to *Behind The Breakthroughs* on your favorite podcast platform!

INSIDE PRECISION MEDICINE

Paper Mills and The Fight Against Scientific Fraud

by Laura Cowen

Scientific publishing is facing a growing challenge from fabricated research produced by industrial-scale paper mills. But researchers and publishers are fighting back through technology and collaboration to protect the integrity of the scientific record.

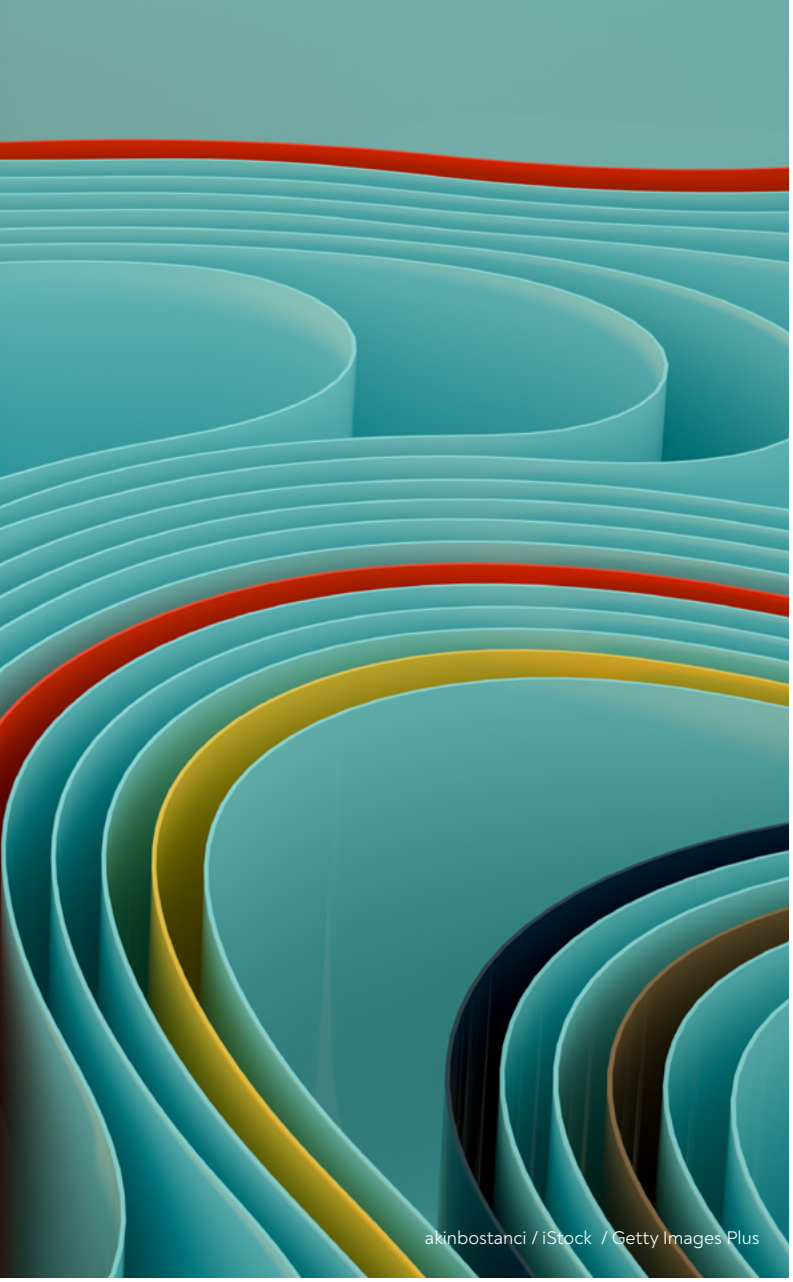
Scientific publishing is based on the trust that the data are real and that peer review ensures quality. But that trust is being eroded by commercial enterprises known as paper mills—coordinated commercial operations that sell authorship slots in fraudulent or manipulated manuscripts, then submit those manuscripts to journals.

Unlike traditional misconduct, these are not lone researchers cutting corners but businesses producing research at scale, often tailored to meet the demands of specific fields, journals, and career incentives.

A recent analysis of almost 19,000 online adverts for paper mills revealed authorship slots being sold for between $36 to $5,600 depending on the position of the slot, highlighting how commercialized the market is. The average for a first author position was $1,030 and, although the study did not examine which adverts resulted in published papers, another investigation traced approximately 1,000 authorship adverts to more than 400 published papers.

Adrian Barnett, PhD
Professor
Queensland University of Technology

The magnitude of the problem is difficult to estimate. A 2022 report by the Committee on Publication Ethics (COPE) and the International Association of Scientific, Technical & Medical Publishers (STM) found that the percentage of suspect papers submitted to journals was around two percent overall but increased sharply to as high as 46% in journals targeted by paper mills.



akinbostanci / iStock / Getty Images Plus

The pressure to publish

For honest researchers, it might be difficult to understand why paper mills even exist. At the heart of the issue is what Adrian Barnett, PhD, a professor in the Australian Centre for Health Services and Innovation at Queensland University of Technology, described as the "publish or perish" phenomenon.

"If I could do one simple thing tomorrow, I would ban all the university league tables," said Barnett. "They're just encouraging corruption." Ranking systems that prioritize publication volume can push researchers toward quantity over quality, making paper mills an easy way to meet expectations.

Furthermore, publication is often not just a measure of success but a requirement for career progression. "For the clients, it's believed that they need publications that they can't achieve through their own efforts, either because they don't have the time, the facilities, the training, or the money to do research and yet, for whatever reason, their employers expect them to," explained Jennifer Byrne, PhD, a professor of molecular oncology and lead of the Publication and Research Integrity in Medical Research group at the University of Sydney.

Byrne has published extensively about paper mills and publication integrity; she got into the field accidentally when she came across some papers about a gene that her team discovered many years earlier. "In 2014–2015, we realized that five or six different groups suddenly published very similar papers about this gene in different journals," she said. "And I just thought, that doesn't really make a lot of sense."

Upon investigation, Byrne found that the papers, and a further 48 similar publications, showed features consistent with mass production. She has since proposed that human gene research in general is highly vulnerable to paper mills. "You can hide fake research quite effectively in experimental fields, because it's very difficult and time-consuming to reproduce experimental studies," she said.

Why paper mills matter

Aside from the obvious fraud, paper mills are problematic for several reasons. Byrne describes them as "a billion-dollar problem" with few resources devoted to tackling it. And although she and others have advocated for scaled investments, progress so far has been slow.

Jennifer Byrne, PhD
Professor
University of Sydney

The publishing system can also reinforce the problem. Paper mills are profit-driven, but journals also benefit through article processing charges and citations, creating what Byrne describes as a "circle" in which "everyone gets what they want."

The consequences of paper mill papers being published can influence real research. The papers are cited, reused, and built upon, wasting both time and money for all involved.

More broadly, the erosion of trust can drive researchers away from entire fields. In Byrne's case, she stopped doing preclinical cancer research. "I left because there were a lot of papers that I couldn't trust. When you get to the point where you can't trust most of the recent literature, it's very difficult to continue," she said.

There are also more sinister risks. Barnett recalled reports of paper mills exploiting their clients, including instances of potential blackmail. "If you've been a regular customer and then you suddenly stop, they might try and squeeze more money," he said. "They've got absolutely no scruples."

Despite these impacts, deterrents are limited. "There are almost none," said Byrne.

Retractions are often slow, meaning damage is done before action is taken, and retraction rates are far below where they should be.

(continued on next page)

(continued from previous page)

In an April 2026 report to a U.S. Congress hearing on the state of scientific publishing, Kate Travis, managing editor of *Retraction Watch*, showed that the retraction rate was around 0.2% in 2025, up from 0.02% in 2016. Yet, the report states that *Retraction Watch* "are confident that the rate [...] should be about two percent—10 times what it is today."

How to tackle the problem

Concerns about problematic papers are often raised by individual researchers or so-called science sleuths on platforms such as PubPeer. Although they have become skilled at spotting telltale signs of a paper mill, like manipulated images, distinct layouts, author affiliations that might not match the topic of the paper, unusual patterns of coauthors, and fake peer reviews, it is difficult for the untrained eye to detect problems from a single paper.

This is why there have been calls for increased awareness. "Awareness is always the first step," said Byrne, who is working with The Lancet–World Conferences on Research Integrity Foundation commission to address critical issues related to research integrity.

Efforts to extend awareness are also being coordinated through initiatives such as United2Act, which brings together stakeholders from research institutions, publishers, sleuths, and universities to develop shared guidance and educational resources.

Marie Soulière, PhD
Elected Trustee
COPE

But even with greater coordination, human detection has limits. As paper mills scale, automated tools are becoming essential.

Earlier this year, Barnett, Byrne, and colleagues published a paper in the *BMJ* showing that their large language model (LLM) could flag papers suspected of being from paper mills by analyzing sentence-level patterns. The model identified 9.9% of more than 2.6 million cancer research papers for further review. Many of the papers were linked to regions with strong publication incentives, including China.

However, Barnett emphasized that the model "is not a 100% proof, it's a quick and simple flag that should encourage reviewers to look at those papers and look for other signs of paper mill activity."

Other paper mill detection technologies are also available. Platforms such as Clear Skies, which is used by the STM Integrity Hub, use machine learning to detect patterns across large bodies of literature, while image-forensics tools and cross-publisher data sharing help identify duplicated figures and submissions.

Alongside these tools, Barnett suggested that researchers may increasingly need to provide a "breadcrumb trail," through preregistration of hypotheses and transparent workflows to demonstrate the authenticity of their work.

Adya Misra, PhD
Associate Director
Sage

Platforms such as PubPeer and *Retraction Watch* also play a role, enabling researchers to flag concerns and share evidence about suspect papers after publication. These flags then prompt journal retractions and investigations, making it a critical component in the fight against paper mill activity.

A call for tighter regulation

Aside from technology, Byrne would like to see tighter regulation for the commercial publishing industry, akin to something like the ISO 9001 quality management standards that have been widely adopted across industries like manufacturing, engineering, and healthcare.

> "Our research integrity team acts centrally to support editors and internal journal teams with both prevention of suspicious or problematic research and the correction of the scholarly record ... in line with COPE guidance."

"We need a regulatory framework that rewards journals that do the right thing and that care about publishing quality," she said. "And we need to disincentivize the current commercial drive towards publishing anything for money."

Byrne believes that funders and researchers should be demanding these standards. "They pay for the research, the journal subscriptions, the article processing charges, and give their research for free," she said. "They don't ask anything in return, in terms of quality standards, and that's unacceptable."

Marie Soulière, PhD, an elected trustee of COPE and chair of the COPE Paper mill Working Group, acknowledged that "a standard such as ISO 9001 could help with process consistency, documentation, and accountability." But she said, "it would not be a direct solution to publication fraud or paper mills" and "would need to sit alongside integrity-specific controls, not replace them."

How publishers are responding

Publishers are increasingly shifting from isolated responses to coordinated action. Initiatives like the STM Integrity Hub and United2Act are driving cross-industry collaboration and shared detection approaches.

Soulière said that several recommendations from the COPE/STM 2022 "have been put into practice, particularly around cross-publisher collaboration, shared screening approaches, and investment in integrity infrastructure."

A central strategy, highlighted in a publication from the United2Act working groups, uses the "Swiss Cheese Model," a move toward layered screening that combines tools such as plagiarism screening, image forensics, citation analysis, and author verification. "Each safeguard has limitations, but multiple checks together make it harder for fraudulent papers to pass through," said Soulière.

Publishers are also strengthening internal processes. As Adya Misra, PhD, associate director of research integrity at Sage, described: "Our research integrity team acts centrally to support editors and internal journal teams with both prevention of suspicious or problematic research and the correction of the scholarly record … in line with COPE guidance."

A spokesperson for Taylor & Francis highlighted their work on external collaborations designed to address the root causes of integrity issues. They are partnering with the National Science Library at the Chinese Academy of Sciences to develop research integrity and publishing ethics training programs, designed to ensure that students and researchers at all levels receive adequate support and to help them avoid exploitation by unethical third-party services such as paper mills.

AI changes the game

Even as safeguards improve, artificial intelligence (AI) is moving the goalposts. Many current detection strategies were developed to target structured forms of fraud; template-driven papers, recycled images, and repeated patterns across manuscripts. But these signals are beginning to disappear. "Our system worked because the paper mills would have a template, but now with AI, there is no template," said Barnett. "It's going to absolutely change everything."

Barnett and his colleague Matt Spick, PhD, a lecturer in health and biomedical data analytics at the University of Surrey, recently demonstrated this by generating a complete scientific paper in just under 30 minutes using publicly available data and the OpenAI platform PRISM.

"All we did was give it the dataset and said write a paper for an Elsevier journal," Barnett explained. "If an honors student had given me this paper, I would have been pretty pleased."

Paradoxically, AI could also be bad news for paper mills as people realize they can create the papers themselves at little to no cost.

Reasons for cautious optimism

With AI adding to the challenges that publishers and researchers already face, the future could appear bleak. Barnett recalled an analogy describing the AI problem as an oil spill in a digital ocean, "We don't know how deep it is, can't get to the bottom of it, and it's very difficult to clean up."

Even removing a single problematic paper can require significant time and effort, while thousands more remain undetected. But Byrne remains positive that the work being done can have an impact.

Hispanolistic / Getty Images

"I'm actually really positive, because I think the biggest thing is awareness," she said, noting that when she gives talks, she asks if the audience has heard of paper mills. "In 2023, that might have been five percent of people, and yet by 2025 it had increased to 30%–50%," she said.

Soulière added that increased collaboration and transparency within scholarly publishing is another positive takeaway.

"Publishers, editors, institutions, and other stakeholders are no longer treating these issues as isolated problems," she said. "They are investing in stronger screening systems, clearer policies, and better cross-sector coordination. In that sense, this moment is also driving progress and innovation.

"While the risks are serious, the response from the sector shows that trust can be reinforced, and that the system is becoming better equipped to detect problems earlier and protect the scholarly record more effectively," Soulière concluded. ■

Laura Cowen is a freelance medical journalist who has been covering healthcare news for over 10 years. Her main specialties are oncology and diabetes, but she has written about subjects ranging from cardiology to ophthalmology and is particularly interested in infectious diseases and public health.

IN CONVERSATION *with*

Olga Colgan & Darren Treanor

Digital Pathology and the NHS: Overcoming Barriers to a More Connected Future

As demand on National Health Service (NHS) U.K. pathology services continues to rise, the shift toward digital pathology has never been more critical. While the NHS 10 Year Plan identifies it as one of the system's most transformative enablers, digital pathology adoption remains uneven. Damian Doherty, Editor in Chief of *Inside Precision Medicine,* sat down with Olga Colgan, PhD, strategic marketing director at Leica Biosystems, and Darren Treanor, MB BCh, PhD, consultant histopathologist at Leeds Teaching Hospitals NHS Trust, to explore the pressures facing today's pathology departments, the transformative potential of digital workflows, and how collaborative partnerships are helping accelerate progress and unlock the full value of digital diagnostics.

Q: The NHS 10 Year Health Plan identifies digital pathology as one of three fundamental shifts, yet adoption remains limited. What are the key barriers?

Olga Colgan: Many pathology departments today are already stretched thin by managing growing workloads, which can make it difficult to pause and do a thorough workflow examination and consider process improvements. Transitioning to digital pathology requires an investment and openness to change. For decades, pathology has been optimized for glass slide review under a microscope, so moving to digital is not just a technology upgrade, but a cultural shift for laboratory staff and clinicians who value the familiarity and comfort of traditional methods.

Proper capital allocation and investment are critical to unlock the benefits of digital pathology. For example, information technology (IT) infrastructure must be capable of supporting high-resolution imaging, secure storage, and rapid sharing of thousands of slides. Regulatory needs must also be considered, as each lab must validate digital workflows to ensure appropriate compliance.

While these upfront hurdles can seem daunting, they lead to significant long-term gains. Digital workflows enable faster slide sharing, improve access to subspecialists, and ultimately improve turnaround times—delivering real benefits for both laboratory teams and patients eagerly waiting for critical results.

Q: What are the key benefits of digital pathology that make it such a crucial step for modernizing NHS pathology services—particularly in terms of workflow efficiency, diagnostic accuracy, and collaborative decision-making?

Colgan: Digital pathology is the quintessential modernization of a pathology laboratory, driving efficiencies in workflows, accuracy, and collaboration. Centralized digital storage provides instant access to prior cases and supports predictive analytics. Eliminating physical slides from the workflow after scanning reduces breakage risks and concerns, misidentification risks, along with space and storage needs.

Beyond efficiency gains, digital pathology unleashes the power of remote collaboration. The ability to share whole-slide images instantly means pathologists can quickly leverage remote expertise within their network, or obtain second opinions in minutes rather than days, accelerating diagnostic confidence and treatment decisions. It also extends expertise beyond geographic boundaries, removing the "postcode-lottery" and providing a basis for equity in pathology diagnostics. This enables rural or underserved regions to access pathologists without the delays, costs, and concerns of physical slide transport. This connectivity transforms

Olga Colgan, PhD

pathology into a truly networked resource, ensuring that expertise is available whenever and wherever it's needed, even after hours.

Further, although in the early stages of routine usage, artificial intelligence (AI) models can add another layer of support by bringing greater quantification and reproducibility to slide analysis, highlighting subtle patterns or abnormalities that may be difficult to identify by eye. Effectively, AI can act as a second set of eyes to further build diagnostic confidence and augment—rather than replace—pathologist review.

Q: How are companies like Leica Biosystems supporting NHS trusts in overcoming digital pathology adoption challenges?

Colgan: It starts with listening. We understand that every laboratory and every pathology department has unique workflows, bottlenecks, and priorities, so our first step is a conversation and analysis to identify those needs and design a tailored roadmap for transformation. This isn't just about technology; it's about creating solutions that make the pathology workloads more sustainable, especially at a time when the profession faces significant workforce shortages.

Leica Biosystems partners with labs to deliver systems that meet their demands today, while anticipating future growth and scalability. A great example is Leeds Teaching Hospital and the National Pathology Imaging Co-operative. Combined, they make up the largest national integrated digital pathology network in Europe for routine diagnostics—a milestone that demonstrates what's possible when technology and collaboration come together. *The Leeds Guide to Digital Pathology*, volume one and volume two, is packed with practical tips and pragmatic approaches to support successful digital pathology adoption.

Q: What influenced Leeds Teaching Hospital to adopt digital pathology, and what transformation have you experienced?

Darren Treanor: We've been involved with digital pathology since the very early days of the technology, and it has become the essential foundation of our teaching and research work at the University of Leeds. We had taken a cautious approach to clinical adoption until we were convinced that the technology was ready—both in terms of clinical safety and technical readiness—and we could ensure that it worked and was safe.

We decided that the threshold for adoption for clinical use was reached in 2015, when we established that the clinical safety was acceptable and that the scanners and viewing software were fit for purpose and would not slow us down. Working in partnership with Leica Biosystems, we adopted a phased approach to 100% digital scanning, starting with a "meaningful pilot" with our four breast pathology colleagues. This group was the most pro-digital in the department and, being located in a separate building, had experienced frustrating delays in the delivery of glass slides between the main lab and their offices. They actively pursued us to "go digital." The pilot with them was critical for us in planning the laboratory and clinical workflow reconfigurations needed to go digital and, importantly, developing a verification and validation process that allowed us to transition from glass to digital slides while maintaining safety. This process became the foundation of the U.K. Royal College of Pathologists guidelines for digital pathology, which have been adopted in many other countries as well.

Darren Treanor, MB BCh, PhD

We then looked toward the further summit of "100% digital" and took a phased approach, starting with immunohistochemistry (IHC). As a separate part of the lab, this activity could be separately digitized. With digital review of IHC being a lower-risk activity clinically, it allowed us to introduce the rest of our over 40 pathology consultants to the idea of diagnosis on a digital image. Once that was completed, we moved in one final big step to 100% digital scanning, reaching that milestone on a summer's day in 2018.

Q: What lessons can other NHS trusts learn from your digital transformation journey, and what should be considered as they examine their current workflows?

Treanor: Because of our academic background and partnership with Leica Biosystems, we were very keen to share our experiences of going digital and how to do it. Too many deployments would talk of the great success in using whole-slide imaging, but gloss over the challenges and effort involved in getting there.

We wrote the Leeds guides to provide really simple general-purpose assistance to other labs that are new to digital pathology and didn't have the benefit of in-house expertise yet.

Looking back, being early adopters, we had the unique challenge of being one of the first centers to go fully digital and pave the way at a time when scanners, displays, and software were just good enough, and the combined global experience of digital pathology was low. We have run many workshops to share our experiences, and it has been interesting to see how the field has evolved in recent times and how much easier it is now to go digital. There are far fewer "unknowns" when going digital now, and modern scanners and workflows are significantly better. For example, our current setup has a very smooth transition from H&E [hematoxylin and eosin] stainer to scanner, which saves a lot of time in the lab and removes a major obstacle to lab operation that we had to work around in the early years. In our early workshops, a deployment was often a multi-year project with a lot of uncertainty and need for a lot of preparatory work; nowadays, labs are much more digital-ready, the timelines are much shorter, and success rates are much higher! ■

Damian Doherty has been in media and publishing for over 30 years, beginning at News Corporation. Damian has managed, edited, and launched life science titles in drug discovery and precision medicine. He was features editor of *Drug Discovery World* and founded the *Precision Medicine Leaders Summit* and the *Journal of Precision Medicine*. He edited *AIMed* magazine before launching Photo51Media, a platform for illuminating untold, compelling stories in precision healthcare. Damian joined Mary Ann Liebert in 2021 to help steer the new rebrand and relaunch of *Clinical OMICS* to *Inside Precision Medicine*.

Organs-on-a-Chip Offer "Elegant Solution" to Quandary of Animal Models in Drug Design

Tomorrow's drug trials hinge on biotechnology that not only eliminates the need for animal testing, but also ushers in opportunities for individualized treatments

Lindsey Leake

To the untrained eye, the chip is a piece of clear silicone about the size of a AA battery. Crisscrossing chambers within house hot pink and electric blue liquids that neatly cascade toward the device's beveled edges.

Yet inside, invisible without a microscope, is the replicated microenvironment of a human liver. The pink and blue rivulets, each a millimeter wide, are endothelial and epithelial channels, respectively. Between them dance immune, stellate, and endothelial cells, complete with extracellular matrices and a membrane, hepatocytes galore. Together, they comprise the quad-culture model of Emulate's Liver-Chip S1.

Lorna Ewart, PhD
CSO
Emulate

"When you first look at it, you're like, '*That does this*?'" said Lorna Ewart, PhD, CSO at Emulate, a Boston-based biotechnology firm specializing in organs-on-a-chip. "The engineering behind it is fairly complex."

The chip, a marvel of photolithography, is assembled in layers of polydimethylsiloxane. A porous membrane separates the blue upper channel, which has a height of 1 mm, from the pink lower channel, which stands a mere 0.2 mm tall. Emulate prepares the multicellular framework for purchase and from there, researchers are free to experiment on the tissue-tissue interface in three dimensions.

"It's a very elegant solution," Ewart said. "When you place the cells in this device, you are starting to create an environment that feels like home for those cells."

In the world of drug development, the advantages of organs-on-a-chip over traditional Petri dish cultures go beyond their 3D design, Ewart stressed. Microfluidics are at play, with perfusion the "secret sauce" that mimics human physiology.

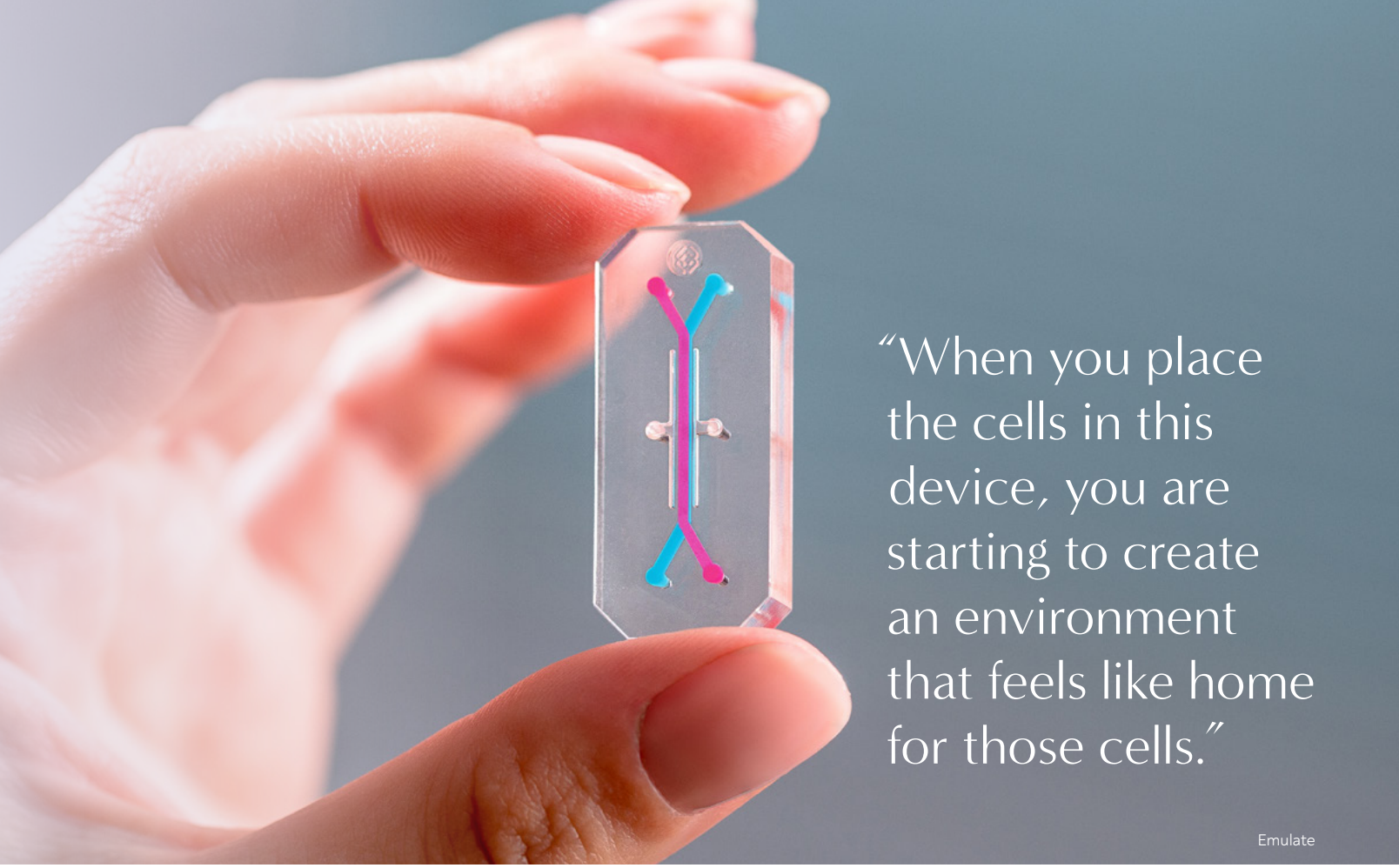
"All of your tissues in your body are perfused," Ewart said. "Recreating that *in vivo*-like environment is what makes these cells function as if they're in the body, and therefore gives greater or more predictive data to the user."

Emulate, whose founders began their work at Harvard University's Hansjörg Wyss Institute for Biologically Inspired Engineering, is a key player in the explosion of the organ-on-a-chip industry. Valued at $227 million last year, the global market size is projected to soar to $3.4 billion by 2034, according to market research firm Straits Research.

This growth, Ewart said, comes down to one driver: Animal models are poor predictors of drug safety and efficacy in humans.

Ancient problem meets futuristic solution

The vast majority of drug candidates—90%—fail in clinical trials, according to a 2022 report in the journal *Acta Pharmaceutica Sinica B*. That doesn't include those that don't make it past



preclinical testing. The few drugs that are successful typically take more than 10 to 15 years each, and upward of $1 billion to $2 billion to go from discovery to market.

One reason for drugs' limited success in this costly, lengthy pursuit is the inability of animal models to adequately simulate drug responses in humans.

Since antiquity, humans have relied on animals to help them understand their own anatomy and physiology. Though French chemist Louis Pasteur famously tested the rabies vaccine on animals before successfully doing so in humans in the 1880s, it wasn't until the passage of the Food, Drug, and Cosmetic Act in 1938 that animal testing became the gold standard in U.S. clinical drug trials.

More than 80 years later, in 2022, the bipartisan Food and Drug Administration (FDA) Modernization Act 2.0 made animal testing optional. The new law encourages drug developers to conduct testing "*in vitro*, *in silico*, or *in chemico*, or a nonhuman *in vivo* test." Organs-on-a-chip, which the FDA considers a type of microphysiological system, were listed as one such technology.

The FDA has continued to move away from animal testing. In March 2026, the agency issued draft guidance highlighting new approach methodologies (NAMs)—including organs-on-a-chip—that may be used instead.

"This draft guidance advances our commitment to replace animal testing with human-relevant, scientifically rigorous methods," Secretary of Health and Human Services Robert F. Kennedy Jr. said in a recent statement. "Clear validation expectations will help modern tools earn regulatory confidence and speed safer, more effective therapies to patients."

It's a global effort. The U.K.'s Medicines and Healthcare products Regulatory Agency announced a commitment to "replace, reduce, or refine animal use in medicinal product development." In Japan, the Pharmaceuticals and Medical Devices Agency established a NAMs Working Group. The Indian government recognizes NAMs as a valid preclinical endeavor.

Donald Ingber, MD, PhD, the scientific founder at Emulate and founding director of the Wyss Institute, has been a step ahead for the better part of two decades. In 2010, he and Dan Dongeun Huh, PhD, now a professor of bioengineering at the University of Pennsylvania and the co-founder and CSO of biotech firm Vivodyne, developed a "breathing" lung-on-a-chip. Their research, published in *Science* that year, is considered a seminal work in the organ-on-a-chip space.

In a video accompanying a 2010 Harvard Medical School news release about the research, Ingber described the chip as a "little, flexible device" designed "hopefully, someday, to replace animal studies." Someday has arrived.

The FDA launched the pilot program, Innovative Science and Technology Approaches for New Drugs (ISTAND) in 2020 and adopted it as a permanent initiative in 2025. Part of Ewart's job

(continued on next page)

(continued from previous page)

is to steer Emulate through this regulatory pathway. In doing so, she confronts one of the biggest hurdles in organ-on-a-chip expansion: standardization.

Weiqiang Chen, PhD
Professor
NYU Tandon School of Engineering

"When a tool is qualified, it can be used in a regulatory document without the FDA needing to reconsider or reconfirm its suitability," Ewart said. "It saves the sponsor a lot of time, and it's an acknowledgement that these tools perform very well. … The data that comes from them, they will use in their risk assessment of a drug as it moves into the clinic."

Emulate was the first organ-on-a-chip company granted acceptance to ISTAND, Ewart said. The FDA noted its Liver-Chip S1 is designed to predict drug-induced liver injury, a major reason why drugs fail safety testing in trials and are withdrawn from the market.

"We're in the final phase now of the program," Ewart said. "Looking forward to trying to obtain qualification in 2027."

Faster results for patients in need

As they continue their metamorphosis from futuristic concept to laboratory standard, organs-on-a-chip offer researchers and patients an unprecedented bench-to-bedside timeline.

While drugmakers and the general public alike stand to benefit from accelerated drug discovery, Weiqiang Chen, PhD, designs chips for patients who lack the luxury of time. Chen, a professor of biomedical, mechanical, and aerospace engineering at NYU's Tandon School of Engineering in Brooklyn, helped develop the first immunocompetent leukemia-on-a-chip.

"It's quite a different type of cancer," Chen said. Most cancers form solid tumors, but leukemia, a liquid cancer, develops in the bone marrow. "It's more challenging to generate the microenvironment for leukemia. … It involves a lot of immune cells, immune functions, and immune interactions."

The leukemia-on-a-chip, commissioned by NYU Langone Health, is circular, roughly the size of a quarter. Green and vermilion pools surround a blue ring at the center. Within that lies a red liquid dot.

"Outside, we have one layer of osteoblasts, the bone cells, and inside are the central sinus and the vasculature and some mesenchymal stem cells," Chen said. "All the immune cells are located within the vascularized niche, similar to real bone marrow."

The technology allows Chen and his team at NYU's Applied Micro-Bioengineering Laboratory to interrogate single cells. They can also observe how the cancer responds to chimeric antigen receptor T-cell therapy in real time—within a patient's unique immune system.

The chips are constructed using a leukemia patient's own cells. Meaning, Chen said, the observed therapeutic response is not only more accurate than it would be in an animal model but also patient-specific.

"We can help to identify responders, non-responders, or we can help screen out more efficient combination therapy for the specific patient for precision medicine purposes," Chen said.

He acknowledged that the process is imperfect, yet strong enough to swiftly guide treatment. The chips take just half a day to build and yield results within weeks.

"We can fill the gap, providing a high throughput and also accelerated screening in three weeks," Chen said. "We can screen many drugs at the same time."

Avathamsa Athirasala, PhD
Assistant Staff Scientist
Oregon Health
and Science University

Chen pointed out that some patients have a weeks-long window in between chemotherapy and immunotherapy—a time crunch the leukemia-on-a-chip can accommodate.

The lab is also exploring other immunologic uses for organs-on-a-chip, including a lymph node-on-a-chip that can help validate new vaccines. In addition, in March, the NYU Grossman School of Medicine and Sage Bionetworks received a $25-million grant to launch the data hub and coordinating center for the National Institutes of Health's (NIH) Complement-Animal Research in Experimentation program.

Though Chen will leave NYU in June to become the dean of the new School of Biomedical Engineering at Nanjing University in China, the work continues.

"It's exciting for us to expand our research in the future to make a real impact," Chen said.

Bone-deep discoveries, millimeters thin

Nearly 3,000 miles to the west, Avathamsa Athirasala, PhD, an assistant staff scientist at the Oregon Health and Science University (OHSU) in Portland, is studying other aspects of the bone in miniature.

"The bone is different from other tissues in how it feels and what it's made up of," she said. "It's highly mineralized, it's mechanically stiff, and it's constantly being remodeled. It has a lot more forces being put on it."

Athirasala works in the Precision Biofabrication Hub, part of the OHSU Knight Cancer Institute, under founding director Luiz Bertassoni, DDS, PhD. Through their bone-on-a-chip, hub researchers are studying cancer metastasis.

For example, more than 80% of people with advanced prostate cancer experience bone tumors. A $2.5-million NIH grant awarded in April will help Athirasala's team discover how.

"Some of these tumor cells—why are they attracted to bone? And why do they thrive in bone?" she asked. "Because they have never experienced an environment like bone."

She added, "Using this model, we are able to try and maybe even understand how cancer progresses, or how it changes as it goes to a new environment."

Athirasala is also investigating potential uses for the bone-on-a-chip in regenerative therapies. Soldiers, for instance, may have debilitating bone injuries that heal differently from fractures. A scaffold designed to regenerate bone may be a better treatment than a metal implant, and the chip could help evaluate patient reaction.

"What are the first things that the body starts doing in response to a foreign object? There will be inflammatory signals, there will be host stem cells that want to infiltrate in there and start remodeling it," Athirasala said. "You can actually recreate the temporal aspects of this—what comes first, what comes later—in a chip."

Problem and promise of precision

Athirasala delights in seeing solutions to biological problems play out before her. Within organs-on-a-chip, cells hold answers. Still, the devices' possibilities aren't endless—yet.

Precision medicine applications, in particular, face logistical roadblocks, she said.

"You have to get all the pipelines in place to be able to get patient cells, preserve them long enough, and get them to where the engineers are making these chips and incorporate them in the devices," Athirasala said.

Preclinical drug testing that replaces animals with organs-on-a-chip is projected to curtail costs in the long run. Emulate, for example, expects its Liver-Chip alone to increase annual research and development productivity in the small-molecule drug development industry by $3 billion. But as with any new technology, for now, the chips themselves and the infrastructure required to sustain them aren't cheap.

Market intelligence platform IndexBox estimates that in the U.S., single-chip readers cost about $10,000 each, while comprehensive systems that manage microfluidics run as high as $200,000. Chips are priced between $50 and $2,000, with assay kits and reagents hovering around $100 to $500.

Ewart, of Emulate, said the company doesn't typically publish costs, which vary depending on customer needs.

What's more, with each institution that builds its own organ-on-a-chip, standardization becomes harder to attain.

"Each one may have their own advantages, but no one can convince each other which one's better," said Chen, of NYU. "Without standards, we cannot really push this technology into practical use."

In the absence of device uniformity, Vivodyne, the Penn Engineering spinoff with offices in Philadelphia and outside San Francisco, is tackling the issue of reproducibility. CEO and co-founder Andrei Georgescu, PhD, saw a solution in end-to-end automation.

"If it is possible to scale up the production of these lab-grown tissues, then we have ourselves a substrate for solving what is the most challenging problem now in medicine," he said, "which is, we don't know how human biology responds very well to the perturbations that we make on it."

The result not only eliminates human variation in lab technique but also allows Vivodyne to test more than 10,000 lab-grown tissues at once.

"We shrink what is like a state-of-the-art biotech lab into the footprint of a large desk," Georgescu said. "Within each of these systems, we have complex confocal microscopy and a fridge and freezer and a robot arm with multiple tools for liquid handling, dispensing, and dosing these tissues, and we grow them within this platform."

Andrei Georgescu, PhD
CEO and Co-founder
Vivodyne

Vivodyne pairs its automated labs with artificial intelligence to create a feedback loop in experimental design, Georgescu said. The idea is to quickly identify druggable targets and pinpoint which drug candidates are most likely to succeed.

While complete bodies-on-a-chip remain a pipe dream, Vivodyne is among the companies investigating how different organs-on-a-chip interact with one another. Orlando-based Hesperos, for one, manufactures a Human-on-a-Chip® that can replicate several organs on a single device. TissUse, of Berlin, is developing multi-organ chips to mirror male and female environments: the HUMIMIC ChipXY and HUMIMIC ChipXX.

The burgeoning field of organ-on-a-chip drug testing lies at the intersection of bioengineering, pharmaceutical regulation, and data science. To Georgescu, at its heart, it's also reassuringly straightforward.

"Just because biology is complex," he said, "does not mean it is not already as simple as can be." ■

Lindsey Leake is an award-winning, independent health reporter based outside Washington, D.C. She spent 15 years as a staff journalist at outlets including *Fortune*, the *USA TODAY* Network and Sinclair Broadcast Group. She holds an MA in Science Writing from Johns Hopkins University, an MA in Journalism and Digital Storytelling from American University, and a BA from Princeton University.

entrePRECISIONeur

Cyclana Bio Is Exploring the Extracellular Matrix to Treat Endometriosis

A Discussion with Léa Wenger, PhD

by Helen Albert Senior Editor

Despite an estimated 190 million women and girls around the world living with endometriosis, a chronic and painful gynecological condition, no disease-modifying therapy has yet been approved to treat it. Léa Wenger, PhD, and her colleagues at Cyclana Bio are aiming to fix this.

Endometriosis occurs when endometrial tissue grows outside the uterus, causing inflammation, pain, and sometimes scarring and fertility problems. Although this condition was historically neglected in terms of research and development, Cyclana is now one of a small but growing group of companies trying to develop more effective endometriosis treatments. After completing a veterinary degree, Wenger shifted away from clinical practice when she discovered a passion for biomedical research during her PhD at the University of Cambridge. During this time, Wenger was diagnosed with endometriosis, which led her to co-found Cyclana Bio in 2024 with Kevin Chalut, PhD, who was her colleague at Altos Labs at the time.

The company joined the Babraham accelerator program last year and has already raised an oversubscribed £5 million ($6.8 million) pre-seed round. Wenger spoke to *Inside Precision Medicine*'s senior editor, Helen Albert, about her inspirations, career, and what she and her colleagues are hoping to achieve at Cyclana.

Léa Wenger, PhD

Q: What inspired you to become a scientist?

Léa Wenger: I was always very curious as a child. What drove me directly to science, rather than going for any other subjects, was my desire to be a vet. I wanted to be a vet and knew vets needed to know about science, so I decided to learn all the science I could. The irony of that was that I didn't end up practicing a single day of veterinary medicine, but it got me into the doors of institutions where they teach you veterinary medicine in a way that was very scientific and research-driven. I really discovered a passion for science at that point, a passion for actually understanding things that we don't know. I was exposed to this idea of driving knowledge where it isn't present, and that was really what got me excited about research. That's when I effectively shifted from the veterinary medicine career to the more traditional biomedical research route.

Q: What made you decide to go into biotech rather than staying in academia?

Wenger: I think the frustration I had in academia was that the system was set up to do a one-person, one-project type of research. That can be fun in some ways, but for me, it didn't really address impact in the way that I really wanted it to. I wanted to feel like I was working towards creating discovery, translating it, and being able to improve patient lives. I just felt that biotech was a better conduit for that because it was based on faster-moving collaborative teamwork.

I was working in neurodegeneration at the time and on

Cyclana Bio scientists working in the LiveLabs laboratory, from left to right, Kevin Chalut, PhD, CSO and co-founder, Léa Wenger, PhD, CEO and co-founder, Siiri Salooma, PhD, founding scientist, and Tom Wyatt, PhD, founding scientist.

organoid models made of 3D stem cell-derived complex architectures. Organoid models are incredibly good at reproducing human development. But when you're looking at neurodegenerative diseases that happen with age, it's a lot harder. Aging in a dish is really hard to reproduce.

It was at exactly then that I wanted to go down this research route in more detail that Altos Labs opened in Cambridge. The company had a thesis of "Let's try and do real discovery science, deep, groundbreaking science," but in a biotech environment where you're much more collaborative. That really attracted me at the time, and so I applied to work there after my PhD. Luckily enough, they took a chance on me and believed in me.

I loved it and I learned a huge amount. Not just in terms of how you build discovery programs from the ground up, but also how you work in a team, how you focus, and how you align incentives in biotech. I think it completely shifted my mindset away from simple academic curiosity to, "How do we drive that curiosity towards impact as quickly as possible?" The bar, in my opinion, is somewhat higher than in academia because you're not just saying, "Is this good enough to publish?" You're saying, "Is this a therapy? Is this actually good enough to put into a human and help them and not harm them?"

Q: What made you decide to found Cyclana Bio?

Wenger: I was in an epigenetics lab within Altos, and my co-founder was actually one of the group leaders there working on the extracellular matrix. The more I worked with him, the more I realized how massively important it is in guiding how cells behave. You can get completely different responses from a cell depending on what environment it's in. I got really interested in that interface between the epigenetics, the gene level regulation, and the [extracellular] matrix.

I was doing a lot of discovery science there, but during that time, I also developed endometriosis. I was in my mid-to-late 20s when my symptoms started, and they got worse very quickly.

Like every scientist who gets diagnosed with a condition, I nerded out on the disease. In my spare time, I downloaded all the data and looked into what research was there, and very quickly realized that there wasn't much information available.

There's not much that we know about the disease and how it happens. People are still debating the causes and drivers of endometriosis. That was interesting and another area of unknown, which has always been what I was attracted to. I'd always been passionate about women's health, but never really had the opportunity to do something about it.

There's an easy, non-invasive way of getting access to cells to study endometriosis because menstrual fluid is built and shed every month from your endometrium. It's built and shed in healthy women, in women with endometriosis, and in women with other conditions. On top of that, biopsies are actually way more common in gynecology than in a lot of other conditions. So I realized this was a huge opportunity to do this tissue-level discovery that we were so passionate about, but for a cause that I really believed in, in a field that was unknown.

I spoke to the CEO at Altos at the time and explained what I wanted to do. He was supportive and thought it was an interesting idea, but ultimately, the indication didn't align with the priorities of Altos—of looking into age-related diseases. So that's when we left and started Cyclana Bio.

Q: How easy was it to start the company?

Wenger: We were very lucky in that we got into the Babraham accelerator program very quickly, last May. That was important because not only did it give us validation that someone had actually picked us and said this is a good idea, but it also gave us lab space and access.

We did take quite a bit of a risk. Both my co-founder and I left without having raised funding or grants to start the company. For a short while, we were living off our savings and also paying

(continued on next page)

(continued from previous page)

for some very preliminary science and our first scientist to try and get some data going. That was in May [2025], but quite quickly, we got a bit of traction. By July, we had our first investment term sheet because we started fundraising immediately. Then by September, we were oversubscribed. We finalized the closing in October–November for a £5 million pre-seed round.

I think along the way, we basically just had to assume it was going to happen. We were building the company as if we had the money already, although we were always very open with Tom [Wyatt], the scientist who joined us first, about how much funding we had when he joined.

We're nine people now and have some amazing scientists who have joined the team, including a great CTO who was also at Altos beforehand. We are still growing as we speak. It's funny how science brings so much more science.

Q: What are you trying to achieve at Cyclana?

Wenger: Our main aim is to get at least one therapy that's truly disease-reversing to the clinic. Based on a lot of research, we know that the extracellular matrix can guide how cells respond. It can act as a sink for particular signal factors. Sometimes it can sequester or deliver things like growth factors or inflammatory signals, but it also massively changes how the cell is interacting with its neighbors.

It's a key component of a positive runaway effect that happens in lots of chronic inflammatory diseases and in some cancers. A lot of the time, when trying to develop treatments, we focus on the cells and whether we can stop that inflammation. What we think is, if you don't address problems with the matrix, you are not going to cure the disease. You're effectively just going to mitigate the side effects, and this matrix is going to act like a memory of the disease. This means that if you stop the treatment, it comes back because the matrix issue hasn't been solved.

We think that that's a big element of what's going wrong with endometriosis. Lesions are removed surgically and then they come back. We really think the diseased extracellular matrix is very much driving the pro-inflammatory phenotype, and that if we don't address that, we don't actually get to the point where we are curing the disease. We want to see if we can effectively reverse the phenotypes and if we can effectively get to a cure by stopping this recurrent feedback loop.

We haven't settled on an exact target or modality yet. We're exploring a few different targets, and I think based on exactly what mechanism we want to go after, we will determine what the best modality is. We want to be sure about the science, very sure about the target, and then make that target work.

Q: Where does precision medicine come into your strategy?

Wenger: Our overall strategy is based on how we see endometriosis as a whole, but I think endometriosis hopefully won't be viewed like that much longer. We hope that there's going to be much better stratification and classification of the disease, because it manifests very differently in different women.

Although we think the extracellular matrix might be a common mechanism, we're building a research platform where we will hopefully find out for sure because we're collecting data. We've got an ongoing observational clinical study where we're collecting biopsy tissue, menstrual fluids, clinical data, and blood from women, either with or without endometriosis.

> "I've met many people who have helped me along the way and who have shared their opinions with me. I walked in expecting academia to be way more collaborative than the biotech industry, but actually, I've been very pleasantly surprised with my experience."

We're collecting that data, looking at the tissue, the proteins, and the architecture, but also isolating cells to test in our models. Then, when we start perturbing with particular interventions that we think might reverse the disease's impact on the matrix or have different effects on the cells, we might start seeing patterns as to which types of women with endometriosis respond well to different treatments.

It's going pretty well so far, thanks to our clinical collaborators and participants who have donated samples. Menstrual fluid is a very good way of getting samples from seemingly healthy women, because they don't need to go to the doctor, [they] just send us a sample. We are also collecting tissue biopsies during routine gynecological procedures to minimize invasiveness and inconvenience.

So far, there's lots of variability, which was what we expected and which is why we want to collect [samples from] a high number of donors. Not because we think that variability is noise, but because variability is signal. It can tell us more about the nuances of the disease in these different manifestations.

Q: What has the experience of being a CEO and biotech founder been like so far?

Wenger: It's definitely been a steep learning curve. I think that's also why it's been so fulfilling, because I do love being in an environment where I'm not complacent, where I'm always learning.

To some extent, because we had so much freedom at Altos to drive our own projects, I had exposure already to the pure project management side of science, so that didn't seem quite as much of a step up.

Obviously, there's a huge business, commercial, and legal dimension that I never had thought about before. But I have been trying to learn as much as I can, as quickly as I can, from others. One thing that the biotech field is quite good at is volunteering information. You go to any sort of networking event, or you meet someone from the industry, and they are often very willing to talk to you about what they're interested in, but also about what you're doing, and give any advice they might have.

I've met many people who have helped me along the way and who have shared their opinions with me. I walked in expecting academia to be way more collaborative than the biotech industry, but actually, I've been very pleasantly surprised with my experience.

Q: Can you share any key learning experiences from the last year?

Wenger: If you have scientific training or you can think in a scientific way, going into the field of business or building a company is somewhat similar. There's lots of information and lots of alternative paths that you can take, just like in scientific discovery, and there is differently weighted evidence as to which paths are the best ones to take. Once you have a certain amount of information, you can then take the best educated guess. That's how I've gone about building the company. For example, when I started, I was told by a friend, "If you're starting a biotech, you're going to need to raise venture capital." They gave me a book called *Venture Deals*, which is a very good book that explains how funds work. I read that book and felt I was better equipped to talk to people at the fundraisers. I think the first thing I'd say is, when going into any sort of field, try to really understand how and why that field exists and what are the structures that define its environment. Then you can put context into how people work. As a first-time founder, you might think, "I'm going to find investors, and if they believe in me, they'll invest." But there's so much more to running a venture capital fund. Those things are important to know when framing your discussion.

Something I would do differently is not do everything at once. I left my job, started the company, started the science, started building the network, and started fundraising at the same time. There was always this pressure when I was meeting people that I also had to get them to invest. I think looking back on it, if I could start over, I probably would have spent a few more months trying to build my network and understanding the field better before I started having those investment conversations. It still worked out for us, we still raised funds, but it was stressful. Networking events were very high stakes!

Q: How has the endometriosis space changed in recent years?

Wenger: Gedeon Richter purchasing the Celmatix portfolio and backing FimmCyte are very good signs that people are trying again. I think endometriosis has been plagued by failures in clinical trials, and I think now we're finally seeing some non-hormonal options being tested, which makes me hopeful. Some will fail, some will succeed, and the successes will drive more interest and availability of funding and hopefully, more successes in the future. I'm really looking forward to seeing the results from some of those clinical trials because I think the more solutions we have for women, the better.

Q: Is funding in the overall field of women's health changing for the better?

Wenger: Absolutely. I think the funding environment is more open to women's health. I think that's been helped by the World Economic Forum and McKinsey Health Institute driving the message of value there. There is excitement, I think, and more funding, especially privately.

I'm not sure about public funding. I do think that on the public funding side, we have a trend of saying, "We should fund women's health, let's look for quick wins." I think that's a bit of a problem with any field that's been somewhat left behind, once we realize that we need to bring it back. The risk will be funding the wrong things or putting too much of the money into solutions that may not be revolutionary because they don't have the foundational science to back them up.

It can also be easy to get stuck in the valley of death between seed and late-stage funding. But I do think that there are incredible scientists moving into the field, and there are some great companies starting up. So even if there is this bias towards pre-seed or seed funding, you only need a couple of those companies to have some really promising data, and they will be funded. The bar might be higher than in other fields, but if you produce groundbreaking discoveries, there will be money.

Q: What advice would you give other new founders starting to build their companies?

Wenger: Just follow your gut and your dream. That's the most important thing. I started Cyclana because I thought this needed to happen and we needed to look into endometriosis. I thought it was a bit hypocritical of me to think we needed to do something and not do it, despite having the training and the skills to try and find a solution. If you really believe something needs to happen in the world, startups are the best way to feel like you are driving that change and contributing to seeing the change that you want to happen. Whether it succeeds or not, you won't wake up thinking, "What am I doing this for?" You'll just be thinking, "I really hope that we don't fail!" ■

Helen Albert is senior editor at *Inside Precision Medicine* and a freelance science journalist. Prior to going freelance, she was editor-in-chief at *Labiotech*, an English-language, digital publication based in Berlin focusing on the European biotech industry. Before moving to Germany, she worked at a range of different science and health-focused publications in London. She was editor of *The Biochemist* magazine and blog, but also worked as a senior reporter at Springer Nature's *medwireNews* for a number of years, as well as freelancing for various international publications. She has written for *New Scientist, Chemistry World, Biodesigned, The BMJ, Forbes, Science Business, Cosmos* magazine, and *GEN*. Helen has academic degrees in genetics and anthropology, and also spent some time early in her career working at the Sanger Institute in Cambridge before deciding to move into journalism.

COMPANY INDEX

ADVERTISER INDEX

GO DIGITAL

READ OR LISTEN TO EACH ISSUE OF INSIDE PRECISION MEDICINE ANYWHERE, ANYTIME.

TRY THE NEW DIGITAL EDITION

INSIDE PRECISION MEDICINE

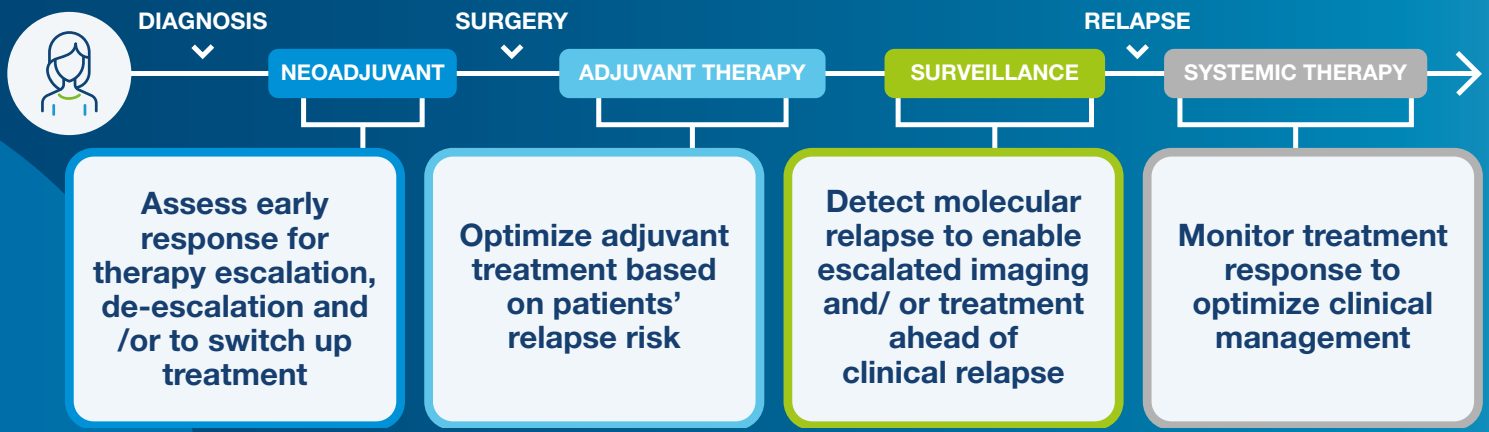
natera™ | Signatera™
Residual disease test (MRD)

Shaping the future of MRD testing

The most comprehensively validated and widely used MRD assay available

Informing critical decisions along the continuum of care

- Does my patient need adjuvant therapy?
- Is my patient's cancer recurring?
- Is my patient responding to therapy?



Signatera™ is the only MRD assay that leverages the distinct advantages of multiplex PCR for highly targeted selection of clonal variants and ultra-deep sequencing

Discover more at natera.com/oncology

13011 McCallen Pass, Building A Suite 100 | Austin, TX 78753 | natera.com