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References:

1. Dowdell, A. K., Meng, R. C., Vita, A., Bapat, B., Hanes, D., Chang, S.-C., Harold, L., ... Piening, B. D. (2024). Widespread adoption of precision anticancer therapies after implementation of pathologist-directed comprehensive genomic profiling across a large US health system. JCO Oncology Practice, 20(11), 1523–1532. https://doi.org/10.1200/OP.24.00226

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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

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National Society of Genetic Counselors

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Editor's Note

"I have nothing to offer but blood, toil, tears and sweat."
—Winston Churchill

These immortal words, spoken to Parliament in May 1940 as Britain faced its darkest hour, were a rallying cry for sacrifice in pursuit of victory. Read them again, however, and one might easily mistake them for a dispatch from the front lines of modern diagnostics—particularly the bruising, decade-long campaign to transform a simple blood draw into a window on human disease. Blood, toil, tears and sweat: the field of blood-based diagnostics has witnessed all four in abundance.

The power of blood as a diagnostic medium is as old as medicine itself. From Hippocrates observing the colour and consistency of humours to the 20th century's biochemical revolution, physicians have long understood that circulating within our veins lies a narrative of health and disease waiting to be decoded. Yet the modern era's pursuit of this promise has been anything but linear.

We need not rehearse the Theranos debacle in exhaustive detail; the fraudulent claims duped political elites, captivated investment circles, and seduced a public desperate for medical miracles. The "miracle blood draw" would diagnose everything from diabetes to cancer from a finger-prick—except, of course, it couldn't. The scandal left legitimate researchers scrambling to distance themselves from the wreckage, and blood-based diagnostics acquired an unfortunate whiff of snake oil.

More recently, we have witnessed similarly inflated claims from certain corners of the multi-cancer early detection (MCED) market—promises of stopping cancer at its earliest stages. The recent NHS trial results have tempered such enthusiasm, though we should be careful not to throw the baby out with the bathwater. Others continue making genuine inroads in this sphere.

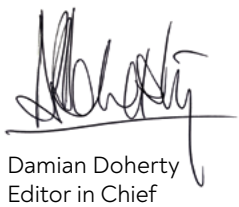
But while these high-profile ventures captured headlines and, in Theranos's case, criminal indictments, another field has been quietly, diligently advancing. Minimal residual disease (MRD) testing has gone about its business with considerably less hype and considerably more rigour—and it is beginning to demonstrate precisely the clinical utility that blood-based diagnostics have long promised.

As this issue illustrates, MRD is maturing from a research endpoint into a genuine clinical tool. The technology has evolved from its well-established foundations in haematological malignancies—where it could detect one malignant cell among millions—to solid tumours through increasingly sophisticated liquid biopsy platforms.

What distinguishes this progress is its measured, incremental nature and the FDA's January 2026 draft guidance supporting MRD negativity as a clinical trial endpoint for multiple myeloma signals regulatory confidence built on evidence, not enthusiasm.

The applications are multiplying: earlier detection of residual disease, informed de-escalation of therapy for patients who have cleared cancer at the molecular level, and real-time monitoring of treatment response. The expanding ecosystem of complementary technologies all point toward a future where longitudinal molecular monitoring becomes routine rather than exceptional.

The field is on the right trajectory. Blood-based diagnostics are finally delivering on their foundational promise. It seems only fitting that, as the latin root of "blood" suggests, I remain sanguine about the future.



Damian Doherty
Editor in Chief

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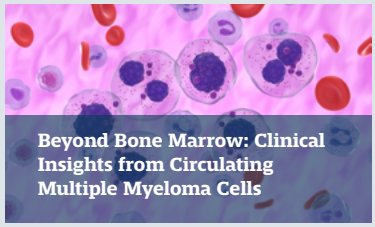

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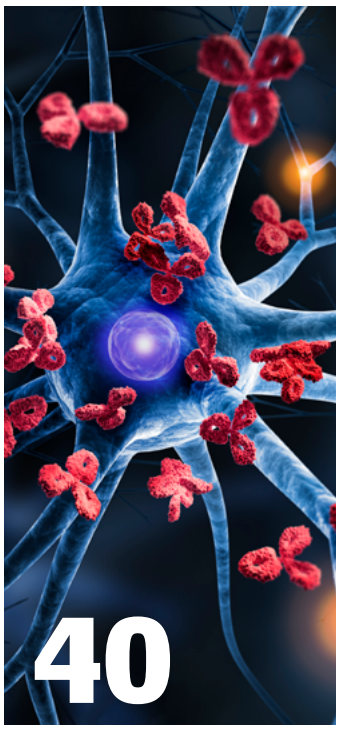

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Chasing the Zero That Matters

How MRD testing is reshaping cancer care, research, and survivorship

by Mike May, PhD

Mary Royal almost skipped her mammogram.

At 51, the mother of four from Wichita Falls, Texas, was busy, tired, and juggling the overlapping demands of work, family, and everyday life. The appointment felt routine—easy to reschedule and easy to dismiss. In a decision that would change everything, she went.

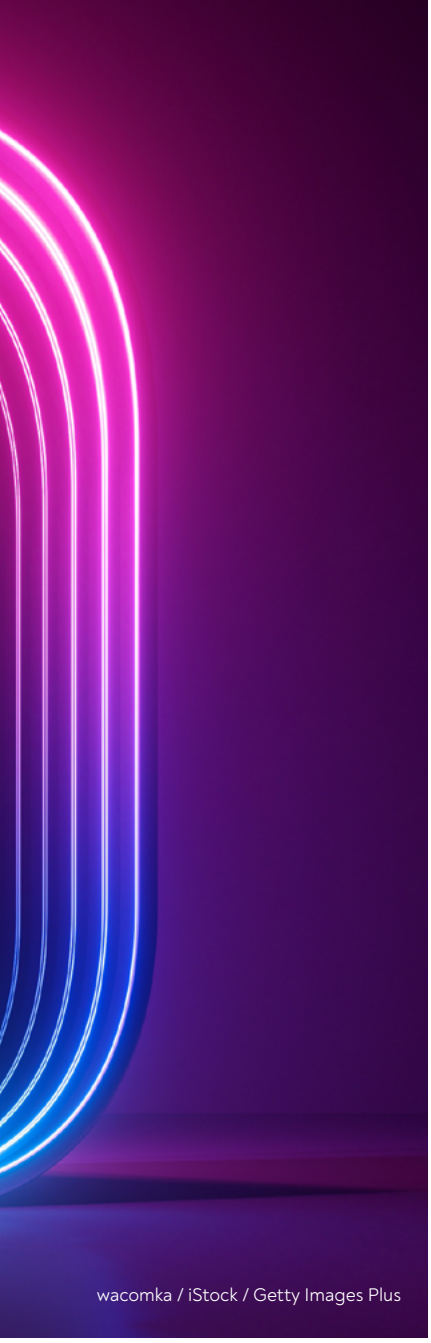
In 2023, Royal was diagnosed with stage 2B multicentric invasive lobular and ductal carcinoma. What followed was a cascade familiar to many cancer patients but deeply personal in its toll: a double bilateral mastectomy, months of chemotherapy and radiation, and the discovery of a nodule in her chest cavity. Another scan later revealed a mass on her ovary, prompting a preventative radical hysterectomy. By the end of the year, Royal had endured positron emission tomography (PET) scans, injections, fasting, and what she called "all that nuclear medicine."

For many patients, completing treatment is supposed to signal relief. In reality, it often marks the beginning of a new phase—one defined by uncertainty. Surveillance imaging, blood tests, and follow-up visits can feel like checkpoints in an endless waiting game. Every scan carries both hope and fear.

Royal knows this phase well. Like many survivors, she lives with what patients and clinicians call scan anxiety. "I've never met a person diagnosed with cancer who did not live with scan anxiety," she said.

That anxiety eventually led her to consider a different way of monitoring her disease—one that looks not for tumors large enough to be seen on a scan, but for microscopic traces

Mary Royal, Patient



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of cancer that may remain in the body after treatment. These traces are known as measurable, or minimal, residual disease (MRD).

MRD basics

MRD refers to the small number of cancer cells that can persist after treatment, even when imaging and conventional tests show no evidence of disease. These cells are often invisible to computed tomography (CT), magnetic resonance imaging (MRI), or PET scans, yet they can drive relapse months or years later.

Historically, MRD testing has been best established in hematologic malignancies such as leukemia, lymphoma, and multiple myeloma. In these diseases, molecular and flow-based techniques can detect one malignant cell among tens of thousands, or even millions, of normal cells. In solid tumors, however, detecting MRD has been far more challenging. That is now changing.

Advances in liquid biopsy technologies allow researchers to analyze circulating tumor DNA (ctDNA): tiny fragments of DNA shed by cancer cells into the bloodstream. With increasingly sensitive assays, it is now possible to detect residual disease at levels far below what imaging can reveal.

MRD matters because cancer recurrence is often a race against time. The earlier residual disease is detected, the greater the opportunity to intervene—whether by intensifying therapy, switching treatments, or, in some cases, sparing patients from unnecessary additional therapy if no disease is detected.

Regulators are taking note. In January 2026, the U.S. Food and Drug Administration (FDA) issued draft guidance supporting the use of MRD negativity as an endpoint in clinical trials for multiple myeloma. The move signaled growing confidence in MRD as a meaningful surrogate for long-term outcomes, potentially accelerating clinical trials and access to new therapies.

Deciding to look closer

When Royal's oncologist suggested the Personalis NeXT Personal® test, a blood-based MRD assay, her initial reaction was hesitation.

"I said, 'Let me think about it,'" she recalled. As she researched the test online, her anxiety rose. "I thought, 'No, thank you. I have had so much anxiety already.'"

Her husband disagreed. "You are insane," he told her, "Why would you not want to do that?" Her oncologist offered a different perspective: "What is the point of science if we don't use it?"

"That really resonated with me," Royal said.

She agreed to the test and had her first ctDNA draw in early 2024. Since then, she has taken it 13 times.

"Seeing that zero in the results is a huge relief," she said. "I really appreciate how much easier the test is on me, both mentally and physically. Now, I cannot believe anyone would say 'no' to this. It brings me so much comfort. And I want to know what to do next. I don't want to just sit around waiting for something when I have the ability to see things early on."

Her experience reflects a growing shift in survivorship—from episodic imaging to continuous molecular monitoring.

Richard Chen, MD
Chief Medical Officer
Personalis

An ultrasensitive approach

For Richard Chen, MD, CMO at Personalis, the goal of ultrasensitive MRD testing has always been to address the uncertainty patients live with after treatment.

"Our NeXT Personal test pioneered 'ultrasensitive MRD' down to about one part per million of ctDNA, designed to be a leap forward in detecting very small traces of cancer from a blood sample earlier," Chen said.

The test is tumor-informed, meaning that it begins with whole-genome sequencing of a patient's tumor. From that data, up to approximately 1,800 tumor-specific mutations are identified to create a personalized molecular signature. Blood samples are then analyzed for that signature.

"The groundbreaking clinical data that we have published in lung and breast cancer shows that the ultrasensitive capabilities of NeXT Personal enable it to detect cancer many months to years ahead of imaging," Chen said, "potentially allowing for earlier intervention and treatment of the patient." Equally important, he added, is the reassurance that a highly sensitive negative result can provide.

Personalis is expanding MRD testing beyond simple detection. A new opt-in feature, the Real-Time Variant Tracker®, allows clinicians and patients to view potentially actionable mutations detected in ctDNA, including those associated with treatment resistance.

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MRD testing is increasingly viewed not just as a prognostic tool, but as a way to actively guide care. Chen outlines three major applications: earlier detection of residual or recurrent disease; earlier de-escalation of therapy for patients who have cleared their cancer at a molecular level; and real-time monitoring of treatment response.

"Cancer is often a race against time," he said. "If you can detect cancer that's coming back much earlier than before, then you have the opportunity to intervene earlier with additional treatment for the patient."

Adding biological precision

Sensitivity alone, however, is not the only challenge in MRD detection. Biological precision—understanding which cells persist and why—is equally important.

Zivjena Vucetic, MD, PhD, CMO at Mission Bio, points to the limitations of bulk sequencing approaches, which average signals across mixed-cell populations.

Mission Bio's single-cell MRD assay simultaneously detects genetic mutations and surface protein expression across thousands of individual cells in acute myeloid leukemia. This approach reveals whether mutations coexist in the same cell and how they relate to cellular phenotypes.

Zivjena Vucetic, MD, PhD
Chief Medical Officer
Mission Bio

"Our integrated single-cell approach provides a more biologically precise definition of measurable residual disease," Vucetic said, which might improve risk stratification beyond conventional molecular or flow-based methods.

By identifying rare, therapy-resistant clones, single-cell MRD technologies offer insight into clonal evolution and emerging resistance. This information can guide treatment selection and drug development.

Decentralizing monitoring

Accessibility and turnaround time are also shaping the MRD landscape. For example, QIAGEN is advancing MRD monitoring by pairing tumor-informed assay design with decentralized digital polymerase chain reaction (dPCR), aiming to make longitudinal molecular monitoring faster, more accessible, and more informative for research and drug development.

In June 2025, QIAGEN announced a partnership with Tracer Biotechnologies to integrate Tracer's tumor-informed assay design with QIAGEN's QIAcuity dPCR platform. The approach begins with sequencing a patient's tumor, often leveraging existing next-generation sequencing (NGS) data, to identify somatic mutations. Tracer then designs personalized multiplex dPCR assays to detect ctDNA carrying those mutations in blood samples.

Running these assays on QIAcuity enables absolute quantification of rare tumor-derived molecules by partitioning samples into thousands of reactions. According to Richard Watts, vice president of partnering for precision diagnostics at QIAGEN, "The result is a decentralized, high-frequency monitoring solution," with turnaround times measured in hours to days rather than weeks. He noted that this model significantly reduces cost and logistical complexity compared with centralized NGS-based MRD testing while enabling earlier detection of molecular recurrence, often before radiographic changes are visible.

Richard Watts
Vice President
QIAGEN

While currently intended for exploratory research use, the platform has clear implications for oncology drug development. By allowing assays to be run on standard dPCR instruments at clinical trial sites, sponsors can avoid centralized sample shipping, simplify global study design, and more rapidly generate data. Frequent sampling also provides detailed insight into tumor kinetics and treatment response, potentially enabling earlier assessments of drug activity.

Looking ahead, QIAGEN anticipates MRD evolving beyond detection toward biological characterization. Emerging single-cell technologies, supported by QIAGEN's recent acquisition of Parse Biosciences, could reveal why residual disease persists by distinguishing resistant cell populations and non-genetic resistance mechanisms. Watts emphasized that future clinicians will not only ask whether MRD is present, but "why it persists and which pathways sustain it," signaling a shift toward more precise, biology-driven intervention strategies.

The expanding ecosystem

Beyond ultrasensitive and single-cell approaches, a growing number of companies are contributing complementary technologies that are broadening how MRD is detected, characterized, and monitored across cancer types.

Twist Bioscience, for example, has developed scalable target enrichment solutions for MRD monitoring that support highly personalized approaches to disease surveillance. Its MRD Rapid 500 Panel enables fast design and manufacture of customized capture panels using silicon-based DNA synthesis. By offering panels that range from dozens to hundreds of tumor-specific probes and fast turnaround times, this approach allows researchers to assess adjuvant treatment response at a genomic level while remaining compatible with established NGS library preparation and hybrid capture workflows.

Whole-genome sequencing-based plasma assays are also playing an expanding role in solid tumor MRD detection. Labcorp offers a plasma-based assay for colorectal cancer that uses whole genome sequencing to identify ctDNA associated with MRD. This approach enables the detection of recurrence at a molecular level before clinical symptoms, biological markers, or radiographic evidence emerge, creating an opportunity for earlier and more proactive intervention.

In hematologic malignancies, ultrasensitive liquid biopsy platforms are demonstrating the ability to dramatically shorten the time required to detect residual disease. For instance, Foresight Diagnostics has developed a ctDNA-based MRD platform that achieves exceptionally high sensitivity across multiple cancers. In patients with large B-cell lymphoma, this approach can detect ctDNA immediately after treatment, rather than waiting for months or even years for disease recurrence to become apparent through PET or CT imaging.

Comprehensive NGS-based MRD solutions are also advancing in myeloid malignancies. Thermo Fisher Scientific offers an integrated research-use testing solution that combines highly sensitive DNA and RNA assays on a single sequencing platform. This enables the simultaneous assessment of single-nucleotide variants, insertions and deletions, and gene fusions alongside streamlined informatics and reporting designed to simplify MRD data interpretation in research settings.

Meanwhile, dPCR continues to play a crucial role in MRD monitoring, where absolute quantification and extreme sensitivity are required. Bio-Rad Laboratories has long supported droplet dPCR technologies that are well suited for tracking low-abundance disease markers. These capabilities are particularly valuable in both hematologic malignancies and solid tumors, where MRD signals in blood can be vanishingly small yet clinically meaningful.

Pre-analytical precision

As MRD assays push detection limits ever lower, pre-analytical steps such as sample collection and cell-free DNA (cfDNA) extraction become increasingly important.

As one example, Anagha Kadam, PhD, applications and product development scientist at New England Biolabs (NEB), highlights how the Monarch Mag Cell-free DNA Extraction Kit addresses crucial challenges in liquid-biopsy workflows and MRD research.

This kit is a magnetic bead-based solution designed for the reproducible isolation of circulating cfDNA from biofluids like plasma, urine, and cerebrospinal fluid. “The kit can be used to isolate cfDNA for discovery and detection workflows, including ctDNA profiling, cancer biomarker discovery, and oncology diagnostics research,” Kadam explained. This technology efficiently recovers cfDNA fragments in the typical sizes of 150–300 base pairs, and even as small as 50 base pairs, while remaining compatible with common anticoagulant and preservative collection tubes. According to Kadam, “The silica-coated magnetic beads, combined with optimized buffer chemistry, help ensure maximum binding and recovery of cfDNA in manual or automation formats.”

Anagha Kadam, PhD
Scientist
NEB

Sensitivity and reproducibility are especially crucial for MRD applications. “A cfDNA isolation method that is compatible with different sample types, and that faithfully isolates cfDNA, is a key consideration when establishing MRD workflows,” Kadam noted. She added that the kit delivers “reproducible, high-quality cfDNA yields from different biofluid samples, without additional post-extraction cleanups,” enabling consistent fragment profiles while saving time. When integrated with NEB’s sequencing and amplification tools, the kit supports streamlined, end-to-end workflows for generating high-quality data from challenging clinical samples.

From waiting to watching

For Mary Royal, MRD testing has not eliminated uncertainty, but has transformed it.

Instead of waiting passively for scans, she feels engaged in her care. Instead of fearing every appointment, she has access to information that helps her understand what is happening inside her body in near real time.

“I want to know what to do next,” she said. “I don’t want to just sit around waiting for something when I have the ability to see things early on.”

As MRD technologies continue to mature, the desire to replace waiting with knowledge is becoming central to modern oncology. MRD is no longer just a research endpoint or laboratory metric. It is becoming a bridge between science and survivorship, offering patients, clinicians, and researchers a clearer signal in the noise of uncertainty.

And sometimes, that signal is a simple zero—small, powerful, and profoundly reassuring. ■

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.*

Moving *In Vivo*: Next Steps For CAR T-Cell Therapy

by Helen Albert Senior Editor

Umoja

There is no doubt that autologous chimeric antigen receptor (CAR) T-cell therapy has revolutionized the treatment of serious blood cancers. A significant proportion of advanced-stage blood cancer patients who failed to respond to previous therapies now go into remission with this treatment, with some remaining cancer-free in the long term.

However, despite their success, these immunotherapies have significant disadvantages. Although CAR T-cell therapies have essentially rescued advanced-stage patients who previously would only have been offered palliative care, serious side effects such as cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome (ICANS) are associated with the treatment.

All seven CAR T-cell therapies approved by the U.S. Food and Drug Administration (FDA) since August 2017 are autologous cell therapies, wherein the patient's own T cells must be extracted and genetically engineered in the lab to produce cancer-targeting CAR T cells that are reinfused into the patient to fight the cancer.

Unless they live near a major cancer center or company with the relevant expertise and lab capacity in-house, many eligible patients miss out on the therapy because the wait time is too long or the whole process is too expensive. Patients must also be admitted to the hospital to undergo lymphodepletion chemotherapy before receiving the final infusion to allow the infused cells to expand, persist, and work better.

Maurits Geerlings, MD
Co-founder, CEO
NanoCell Therapeutics

"It's just simply too expensive, too complex to manufacture, and has all kinds of logistical issues that translate to limited patient access," explained Maurits Geerlings, MD, co-founder, CEO, and president of *in vivo* CAR T-cell therapy biotech NanoCell Therapeutics, which has offices in Pennsylvania and Utrecht.

"Also, importantly, the batch capacity in highly specialized hospitals is so limited that altogether maybe 10% of patients that are eligible effectively get access to CAR T-cell therapy in the Western world."

Initially, after the first *ex vivo*, autologous CAR T-cell therapies like Novartis's Kymriah and Kite's Yescarta were approved in 2017, the field looked to develop "off-the-shelf" allogeneic

therapies made from donor cells that would overcome some of the issues with autologous CAR T-cell therapies.

Despite the best efforts of a number of companies and researchers, no allogeneic CAR T-cell therapies have yet reached the market, although some companies like Allogene have reached Phase II trials. This is likely due to a few factors, such as adverse events linked to the rejection of donor cells, complex engineering problems, and the small margin of benefits of allogeneic over autologous CAR T-cell therapies.

Instead, over the last couple of years, the focus of the field has moved towards developing next-generation *in vivo* CAR T-cell therapies. Until recently, vectors or nanoparticles that could hit T cells precisely, safely, and predictably enough in humans to justify skipping *ex vivo* engineering were simply not available, but this is now changing.

Kevin Friedman, PhD
Co-founder, CEO
Kelonia Therapeutics

In vivo CAR T-cell therapy uses the patient as a bioreactor. Upon injecting an engineered treatment carried by a vector such as a lentivirus or a lipid nanoparticle (LNP), it programs the patient's T cells to attack either the cancer or autoreactive B cells in the case of autoimmune disease.

The field is still young, but initial clinical results reported last year in multiple myeloma blood cancer by Kelonia Therapeutics and in the B cell-driven autoimmune disease systemic lupus erythematosus by MagicRNA, as well as from EsoBiotec and academic labs, are promising.

"It's early days, so I don't want to overinterpret the data. It's also only in four patients, but what we are seeing is substantially better than what *ex vivo* CAR T cells have shown from an efficacy perspective," emphasized Kelonia CEO and co-founder Kevin Friedman, PhD.

Indeed, this early success seems to have prompted intense investor and big pharma interest in the field. Since March 2025, when EsoBiotec was acquired by AstraZeneca, at least four other *in vivo* CAR T cell biotechs have been acquired, including Capstan Therapeutics by AbbVie and Interius BioTherapeutics by Kite/Gilead.

Whether *in vivo* CAR T-cell therapy will truly be the future of the field remains to be seen, but its convenience, economic viability, and the fact that it is effectively an "off-the-shelf" therapy that does not require lymphodepletion make it an attractive prospect for many.

Lentiviral vectors: Sticking with a known quantity

Five of the seven FDA-approved autologous CAR T-cell therapies, including Kymriah, use lentiviral vectors in the lab to engineer a patient's T cells and transform them into CAR T cells.

Kelonia

Many of the most advanced companies in the *in vivo* CAR T-cell therapy space are applying similar technologies and using lentiviral vectors to target and transform T cells, but inside the body rather than in the lab.

Kelonia, which is based in Boston, is a leader in the *in vivo* CAR T-cell space and has already started clinical trials with its lead candidate KLN-1010 for the treatment of patients with relapsed and refractory multiple myeloma.

"It's essentially delivering a fully human anti-BCMA (B cell maturation antigen) CAR to T cells, to reeducate them by expressing this anti-BCMA CAR inside the body to fight their tumor cells. Just like Abecma, or Carvykti, but it's all done inside the body," explained Friedman.

At the American Society of Hematology Annual Meeting in December last year, the company presented early Phase I results from four patients with relapsed and treatment-resistant myeloma who were treated with KLN-1010.

Ryan Larson, PhD
Senior Vice President
Umoja Biopharma

Although the study was small, the results were promising, with all four patients showing 100% minimal residual disease-negative response rate at follow-up and a lower rate of side effects than approved autologous CAR T-cell therapies.

"With our data and the efficacy and the safety profile that we're seeing, this has a real shot at getting out of the major medical centers and into the community hospitals where the patients live, so they don't have to travel to major medical centers," said Friedman.

"Doctors can potentially treat patients in their own community and get access to the 90% of myeloma patients who, right now, despite the profound clinical benefit that CAR T cells provide, cannot be treated."

Umoja Biopharma is another biotech using lentiviral vectors to develop *in vivo* CAR T-cell therapies. "We have three different

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products in the clinic currently. Two of those products are in B-cell malignancies, and one of the products is in autoimmune disease. And we're making really great progress in enrolling patients across those studies," said Ryan Larson, PhD, senior vice president and head of research at Umoja, although the Seattle-based company has not yet released any results from its Phase I studies.

Although Umoja is using lentiviral vectors, it has built in a rapamycin-activated cytokine receptor, which essentially acts as a booster switch for the engineered T cells in cancer patients while slightly dampening the rest of the immune system.

Priti Hegde, PhD
Senior Vice President
Kite Pharma, a Gilead Company

"It allows us to deliver a controlled pro-survival signal selectively to our CAR T cells *in vivo*," explained Larson. "We're able to potentiate persistence in a controlled manner in our *in vivo* generated CAR T cells with this rapamycin-activated cytokine receptor to drive persistence and ongoing immune surveillance, thus driving the key durable outcomes in oncology specifically."

The requirements for autoimmune disease patients are different from those of advanced cancer patients, with a greater focus on safety. Long-term depletion of B cells is also not ideal, with the aim being to reset the immune system by getting rid of autoreactive B cells and replacing them with healthy ones.

"You're eliminating all of the autoreactive repertoire and replacing it with a normal B cell repertoire, thus driving, ideally, a durable response wherein those autoimmune disease patients are no longer reliant on all the various immunosuppressants that are typically used to treat autoimmune disease," said Larson.

Kite Pharma, now owned by Gilead and headquartered in California, was a pioneer in the autologous CAR T-cell therapy space. It developed Yescarta, one of the first two autologous CAR T-cell therapies approved by the FDA to treat blood cancers in 2017. Kite recently acquired Interius BioTherapeutics, a biotech in the lentiviral *in vivo* CAR T-cell space, for $350 million.

"The reason why we moved forward with Interius was that the clinical proof of concept for lentiviral-based delivery systems is far more advanced than for LNP-based systems," said Priti Hegde, PhD, senior vice president and global head of research at Kite. "We were really excited to see that translation of the pharmacokinetics from an *ex vivo* platform to an *in vivo* platform."

Kite, a Gilead Company

While lentiviral vectors are arguably "tried and tested" in the CAR T-cell space, there are some disadvantages associated with using them. For example, they can be hard to produce, implying that it is expensive and challenging to scale up manufacturing.

This is something both Umoja and Kelonia seem to have addressed, however. "We actually are quite unique from a biotech perspective in that we have our own, wholly owned manufacturing facility … It's really allowed us to have a true pipeline from an *in vivo* cell therapy development perspective," said Larson. "We're actively working in our early phase clinical trials in a manufacturing setting that we know is scalable to commercial readiness."

Kelonia does not do all its manufacturing in-house, but Friedman said that they have worked hard to develop a system that can be scaled. "Manufacturing is complicated. We like to think that we were thoughtful about our manufacturing approach, but it's challenging generating these particles, these complicated medicines for Phase I use. We did it, though, and we now have a very reliable and scalable manufacturing process."

Another potential risk linked to lentiviral and other viral vectors is that there is a small but significant risk of the vector inducing unwanted mutations in the DNA of target cells.

"Viral vectors have a propensity to integrate in transcriptionally active gene regions where you don't want to go, because that enhances the mutagenesis risk," noted NanoCell's Geerlings.

Taking the non-viral route

Not everyone working to develop *in vivo* CAR T-cell therapies is using viral vectors. The second main route that companies and researchers are following to develop these cell and gene therapies is to use mRNA encapsulated in an LNP.

Last September, Shenzhen-based Chinese biotech MagicRNA published data from a Phase I trial of its *in vivo* mRNA and LNP-based CAR T-cell therapy in five patients with systemic lupus erythematosus. Similar to in Kelonia's cancer trial, the results were promising. However, larger studies are needed for more conclusive results, as the sample size was small. But

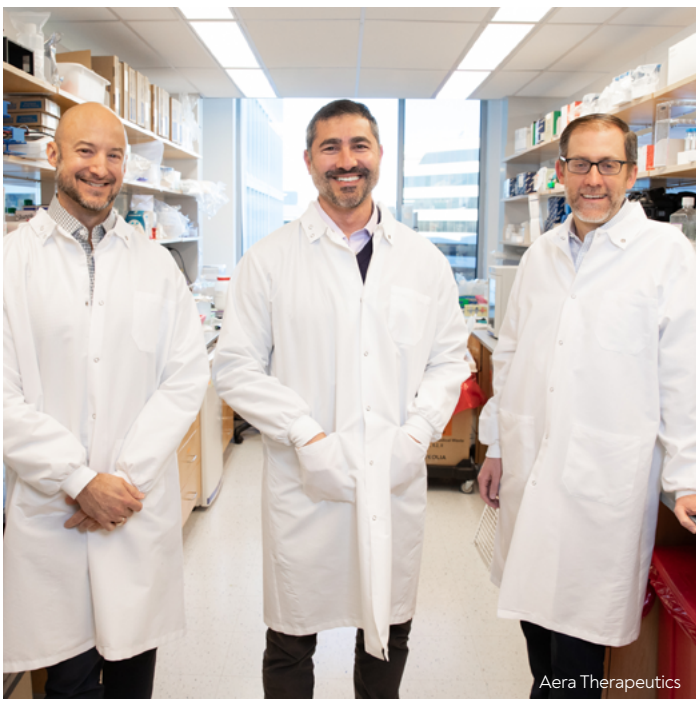
rapid, near-complete B cell depletion was seen for up to 10 days with no significant side effects like serious cytokine release syndrome or ICANS.

Since the pandemic, the use of mRNA therapeutics has become much more mainstream. For example, both of the prevalent vaccines against COVID-19 use a combined mRNA–LNP approach. In *in vivo* CAR T-cell therapy, the LNPs are used to take CAR-encoding mRNA to the right target cells in the body. Once inside a T cell, the LNP breaks apart and releases the mRNA into the cytoplasm. The cell's protein synthesis machinery reads the mRNA and makes the correct CAR protein, which is then added to the surface of that T cell.

Aera Therapeutics, founded by CRISPR pioneer Feng Zhang, PhD, and based in Cambridge, Massachusetts, takes a combined mRNA–LNP approach to *in vivo* CAR T-cell therapy development, with a focus on treating B cell-mediated autoimmune disease.

"We were really focused on autoimmune indications, so we said, 'Let's try to build a product profile that's a great fit for that,'" explained Akin Akinc, PhD, who is CEO at Aera.

"You have the risk of insertional mutagenesis with lentiviral vectors. Even if those rates are small, they're not zero … So that's why we thought an mRNA–LNP approach, where there's no chance of insertion, is theoretically a more attractive approach."



Scott Barros, Head of Early Development, Akin Akinc, Chief Executive Officer, Bill Querbes, Chief Scientific Officer

Aera has not yet moved into clinical studies but reported preclinical data for its therapy candidate AERA-109 in non-human primates at the American Society of Hematology Annual Meeting at the end of last year. They showed potent and durable B cell depletion across different tissues in the body.

One potential disadvantage of using a combined mRNA–LNP approach, particularly for treating cancer, is that it is unlikely to last as long as a lentiviral approach. As this could be potentially advantageous in people with autoimmune disease, where B cell depletion does not need to occur over such a long period of time, it seems to be the most common method followed by companies designing *in vivo* CAR T-cell therapies for autoimmune conditions.

Akin Akinc, PhD
CEO, Aera Therapeutics

"Our therapeutic goal is to go in and clear out the B cells that exist in the body, both in the periphery and the tissues, and then allow them to repopulate. If we achieve that immune reset, then that's all that we can do," said Akinc.

"Then the question is, is there going to be a relapse 12–18 months later? But so long as we clear out all the B cells, which happens pretty quickly, I think there's no benefit to having the CAR T cells hanging around for longer, because at that point you've done the job. Then it's about whether or not that remission is going to persist."

NanoCell Therapeutics is also taking a non-viral approach to developing *in vivo* CAR T-cell therapy for treating B-cell malignancies, but is using DNA instead of RNA. The candidate has not yet reached the clinic, but it has achieved good preclinical results and will soon be tested in non-human primates.

Similar to Aera, NanoCell packages its therapy in targeted LNPs. However, these carry a minicircle DNA that encodes the CAR information and an mRNA transposase that allows the DNA to integrate into the target cell genome.

"We still remain, I think, pretty much in the lead as a company delivering non-viral DNA, because it is very difficult … We see an opportunity for us to actually make a breakthrough there," said Geerlings.

"The nuclear membrane of the cell is such a barrier. You need to find an opportunity to open it up and to be just in time with your DNA in a way that is not triggering an innate immune response. You also need to have a mechanism by which that DNA can integrate, because otherwise, you will end up having an episomal expression of your DNA."

The approach taken by NanoCell is definitely at an earlier stage than the lentiviral and mRNA–LNP approaches that are already generating clinical data, but there are a couple of other companies working on similar products, like Stylus Medicine and CPTx. If it works, then this approach has the promise of ruling out problems with viral vectors, such as manufacturing difficulties. It would also theoretically generate longer-lasting and more durable treatment effects than could be achieved with mRNA.

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What's next for CAR T-cell therapy?

It seems that we are on the cusp of next-generation *in vivo* CAR T-cell therapies, although the studies published so far have all been small and it remains to be seen if the current buzz in the space is based on hype or reality.

"I do think that *in vivo* will go from a platform with initial proof-of-concept to broad applicability faster than perhaps *ex vivo* platforms did," said Hegde. "But we have a lot of scientific questions. For example, in the absence of lymphodepletion, can an *in vivo* platform give you the depth and durability of response that an *ex vivo* platform does?"

There is a lot of interest in whether safer and more accessible *in vivo* CAR T-cell therapy can make this treatment approach more appealing to people with B-cell-mediated autoimmune conditions than autologous CAR T-cell approaches. The initial clinical results are good, but questions remain about how long the results will last.

"I think these are going to work, but we're going to learn things that allow us to make second-generation products that are even better and even more potent," said Akinc.

On the cancer side of things, most companies developing *in vivo* CAR T-cell therapies for oncology indications are sticking with blood cancers against which autologous CAR T-cell therapies have already been shown to be efficacious.

"I think we'll continue to see strong proof of concept in de-risked indications like the hematologic malignancies over the next year," said Larson. "Over the next two years, I think we're going to be closely watching the field for durable outcomes in oncology and the ability to drive immune reset in autoimmune disease that then translates to durable remissions in autoimmune disease patients."

A big question on everyone's mind is whether this new technology could help overcome some of the hurdles that prevent CAR T-cell therapy from being successful at treating "solid" tumors, such as working out how to overcome diverse tumor microenvironments.

"I think there's great potential in solid tumors. One reason why we went with Interius was [that] we think that the application of the *in vivo* platforms could really break open the problems that we perhaps had in solid tumors with *ex vivo* CAR T cells," said Hegde.

"The nice thing about the *in vivo* space is you can put whatever targeting antigen you want on the virus to go to a specific cell type. So it's really up to your imagination, how you want to design an *in vivo* CAR T cell."

Dispatch Bio is also in the CAR T-cell therapy space, but is targeting solid tumors rather than developing *in vivo* CAR T cells. The company is based in Philadelphia and was co-founded by Carl June, MD, one of the pioneers of CAR T-cell therapy.

The technology they are developing is a two-component system, in which a human-specific adenovirus designed to infect cancer cells, but not healthy tissue, is used to "paint" the tumor cells so that a CAR T cell can more easily home in on the cancer and destroy it.

"The virus gets into the tumor microenvironment and then, because it's a virus, creates an inflammatory condition. When it does that, it's immediately more supportive for T cells," explained Dispatch chief scientific officer Barbra Sasu, PhD.

Barbra Sasu, PhD
Chief Scientific Officer
Dispatch Bio

"We're doing what T cells can't do for themselves. We're expressing a target and directing them to kill what we want them to kill. We're also adding a cytokine to support them and, actually, the endogenous immune system too."

The two-part approach is very new, so Sasu and colleagues are testing the system using a known autologous CAR T-cell therapy approach. But she says that the system is potentially very flexible and could allow a wide range of therapies, including *in vivo* CAR T-cell therapies, to be combined with the viral targeting approach if they prove effective.

"What we wanted to do was to start with something that we felt we understood very well. We also had the benefit in our first program of being able to work with people who've already developed CAR T-cell therapies," said Sasu. "That's a big advantage because [when] coming in with a two-component system, it's good if you don't have to refine both parts at once."

Another CAR T-based approach being developed by Kite and others in this space is logic gating, which is the development of IF, AND, and NOT switches to allow much more refined control of CAR T-cell therapies by clinicians and potentially increase effectiveness in complex solid tumors.

"We're really interested in exploring the logic gating space and what it can do to deliver CAR T cells more safely, especially in solid tumors, where the antigens aren't as broadly homogeneously expressed," said Hegde. ■

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.

TARGA Imager: Accelerating Mechanistic Profiling Beyond Cell Painting

Cell painting is a multiplexed imaging assay introduced by Gustafsdottir and colleagues in 2013. As originally envisioned, six chemical stains are used to fluorescently label and image eight distinct cellular constituents: DNA, cytoplasmic RNA, nucleoli, actin, Golgi apparatus, plasma membrane, endoplasmic reticulum, and mitochondria. The assay provides insights into the mechanisms of action underlying phenotypic changes and has been widely adopted in drug discovery and preclinical safety pharmacology (Gustafsdottir et al., 2013. PLoS ONE, 8:e8099).

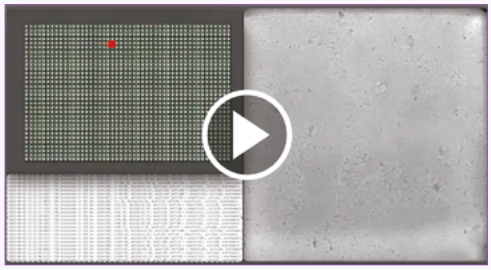

Figure 1. TARGA imaging 1,536-well plate in under two minutes.

As the drug discovery community has demanded improvements to throughput and fast acquisition of time-course data from single microwell sample plates, the technique continues to evolve and mature. Increasingly high-resolution, Z-stacked brightfield imaging and *in silico* processing as a complement to traditional, fluorescence multiplexed assays for cell painting is being developed and adopted. For example, researchers at the University of Cambridge and AstraZeneca (Cambridge, U.K.) demonstrated that machine learning algorithms can generate cell painting in the form of level insights from merely three optical slices in a Z-stack combined with label-free brightfield imaging (Cross-Zamirski et al., 2022. Sci Rep, 12:10001). More recently, the research team at Recursion Pharmaceuticals (Salt Lake City, UT) demonstrated improvements to machine learning algorithms, which achieved image analysis quality up to 95%, equivalent to that of fluorescence cell painting results (Baker et al. 2024). The costs associated with fluorescence cell painting are known and high: including but not limited to expensive fluorescent reagents, extensive staining time (often three hours or more), the destructive nature of repeated staining and stripping steps in highly ordered multiplexed fluorescence protocols, large file sizes from five-plex and higher imaging, and the single-use nature of fixed and permeabilized samples. Brightfield imaging presents a more efficient, scalable, and cost-effective alternative.

To address the hardware imaging needs for brightfield-based cell painting, Lumencor has developed the TARGA Imager for high-throughput screening of multi-well plates. TARGA's workflow includes laser-based autofocus on every well, acquisition of a three-slice Z-stack centered on the autofocus plane, and high-resolution brightfield imaging. The resulting 16-bit TIFF image stacks can be analyzed with machine learning algorithms to achieve mechanistic profiling performance comparable to cell painting. TARGA's data competes with more complex, destructive, and costly fluorescence cell painting while eliminating the need for complex fluorescent staining and extended sample preparation and destruction. Moreover, TARGA is fast: it can image a 1,536-well plate in under two minutes. This represents a 120-fold improvement in time-to-data compared with conventional five-color cell painting workflows (two minutes using TARGA vs. typical 240 minutes) for high-content cell painting (Cimini et al., 2023. Nat Protoc, 18(7):1981–2013). Additionally, because TARGA requires fewer images than fluorescence cell painting, the downstream data storage requirements are significantly reduced by 16-fold (11.52 GB vs. 192 GB).

Figure 2. TARGA Imager

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THE DIGITAL PATH TO AI IN CANCER CARE

by Chris Anderson

As cancer care becomes data-driven, artificial intelligence (AI) will play an increasingly central role across the treatment continuum, from biomarker identification and drug development to clinical trial recruitment and diagnostics. In this corner of healthcare, the ability of AI to interpret and annotate tumor sample slides that have been digitized is taking center stage. While the promise is great, and AI interpretation is already influencing some clinical care, it has not yet reached critical mass.

David West
CEO, Proscia

"There's something like a billion slides created every year for diagnostic purposes, and today most of those, about 85%, are still read by a pathologist with a microscope on physical glass slides," said David West, CEO and co-founder of digital pathology company Proscia. In practice, that means pathologists manually examine slides, identify cancer, grade tumors, and dictate reports in a traditional approach to diagnosing cancer that has seen little change in decades.

BlackJack3D / iStock / Getty Images Plus

But that foundation is now shifting. Advances in slide scanning, cloud storage, and AI are turning digital pathology images into data that can be analyzed at scale. At Memorial Sloan Kettering Cancer Center, large archives of digitized slides helped launch Paige AI, one of the earliest companies to train deep learning systems on pathology images linked to clinical and genomic outcomes. This yielded the first U.S. Food and Drug Administration (FDA)-approved diagnostic using AI and digital pathology: Paige Prostate Detect. The company, which was acquired last year by AI-enabled precision medicine company Tempus, now combines Paige's digital pathology-based AI with Tempus's broad genomic sequencing data platform.

Mohamed Omar, MD
Associate Professor
Cedars-Sinai Medical Center

Researchers in the field say the implications of AI in digital pathology extend beyond image analysis. Mohamed Omar, MD, an associate professor of computational biology at Cedars-Sinai Medical Center, Los Angeles, noted that large language models can help clinicians navigate a research landscape that produces "hundreds of papers every single day" to inform ongoing cancer research. Multimodal AI tools promise to unlock even more insights from digital pathology data by combining it with genomic, radiomic, and clinical data to build powerful new models of both common and rare cancers for diagnosis, drug development, and clinical trial enrollment.

While adoption is in its early stages, the advent of faster and less expensive scanners is bringing digital pathology within reach of both regional and rural hospitals. Razik Yousfi, senior vice president and general manager of AI products at Tempus, and a co-founder of Paige, predicts that within the next 10 years, the majority of pathology workflows will be digital. The ultimate goal of the application of AI here is not to replace human pathologists, but to empower them with a capable assistant while spreading adoption beyond major medical centers.

Razik Yousfi
SVP and GM
Tempus

Building the foundations

As the field of applying AI to digital pathology progresses, it needs to build the groundwork for a wider range of potential applications that could address rare cancers and other areas without an abundance of data. One such project is called Atlas, a collaboration between researchers in Korea, Germany, and the United States to build a foundation model trained using 1.2 million histopathology whole-slide images from 490,000 cases sourced from the Mayo Clinic and Charité - Universitätsmedizin Berlin.

Foundation models like Atlas allow large-scale pre-training of data to develop numerical representations called embeddings that capture both the structural and contextual features of slides in the dataset. Atlas incorporates a diversity of diseases, staining types, and scanners, and uses multiple image magnifications during training. This broad approach confers power and utility. It allows the digitized representations of the histology to be adapted, queried, or fine-tuned to very specific

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downstream tasks using much less data than would be needed to build a one-off model.

As such, a foundation model provides a reusable digitized computational backbone that can be tapped across a wide range of uses, like tumor classification, detection of morphologic structures, biomarker quantification, and outcome prediction. In short, foundational models make the process of querying digital pathology images more efficient compared with past approaches.

Andrew P. Norgan, MD, PhD
CMO, Mayo Clinic

"In the case of pathology, the successful AI models developed using 'conventional' neural network approaches before the advent of FMs (foundation models) typically required huge amounts of training data to achieve high performance and generalizability—the ability to work across datasets distinct from the training data," said lead Atlas researcher Andrew P. Norgan, MD, PhD, CMO of Mayo Clinic Digital Pathology and assistant professor of laboratory medicine and pathology. "We think of FMs as [an] enabler that allows model development in pathology … to move from artisanal or craft processes to more scalable and reproducible processes that should allow for the rapid development of high-quality models to address problems in pathology."

At Paige AI, the company's early work resulted in the first FDA-approved AI diagnostic, Paige Prostate Detect. Its algorithm was built using a technique called multiple instance learning instead of traditional supervised neural network techniques that require detailed human annotation of slides, a time-consuming and expensive method that could expose the learning to human error. The difference between the two methods is that traditional neural networks expose AI to a slide with cancer and tell it that there is cancer present. In multiple instance learning, the model is shown unannotated slides and is tasked with finding the cancer.

Even this approach, however, required a very large dataset. It became apparent to company leaders that the heavy lifting required to get Paige Prostate Detect to work wasn't scalable.

"We had kind of cracked this recipe," said Yousfi. "We know how to use a lot of GPU (graphics processing unit) compute, and if we get a ton of data and a lot of compute, we can build anything. But GPU infrastructure is very expensive, and it takes a lot of time to train a very large system."

Perhaps the most important factor moving Paige away from this model is that it will not work when there is only a small amount of data available. This blocks the ability to train AI to recognize rare cancers for which sample counts are low. The company needed a different approach.

"We had this idea [for] a new system that was basically trained on all of the images we had access to, independent of the organ and indication and tissue and task," Yousfi said. "Back then, we didn't know what that thing was called. But ultimately, that became what everyone is calling today a foundation model."

Originally trained on 200,000 slides, Paige's new model now includes 3.5 million images and roughly two billion parameters, making it the backbone for other downstream applications the company builds today. This ability to use foundation models as the AI and data encyclopedia for smaller applications will ultimately propel the field of digital pathology forward by widening the playing field.

Going multimodal

To address more complex predictive problems, additional data types can be integrated. Clinical, radiologic, or genomic data can be combined with morphologic embeddings or used during training to help the model learn which tissue features carry a signal of disease or identify a biomarker. These approaches aim to support precision oncology by making morphologic data computable and aligning slide-derived features with other cancer-focused datasets. "These approaches can surface subtle or 'latent' patterns in pathology slides and align them with other data sources," Norgan said. Pathologist and oncology care teams can then evaluate and interpret the features identified by the models within the clinical and biological context.

> "Digital pathology and AI will allow us to extract far more information from tissue samples, making our diagnoses more actionable for the clinical team and ultimately improving patient care."

"In this way, pathologists and oncology teams use these outputs as decision-support tools, while clinical judgment remains central to diagnostic interpretation and therapeutic decision making," Norgan added.

Atlas has now been succeeded by Atlas2, which was trained on 5.5 million pathology images and is now a two billion-parameter model, making it one of the largest pathology foundation models to date. The team has explored distilling methods to create smaller, more efficient, and targeted versions of the model that retain performance, with an eye toward finding a balance between scale and deployability.

Proscia is embarking on a different multimodal approach that combines vision models with language models, with the intent of creating methods to query the morphology of digitized slides. Their efforts in vision-language models (VLMs) combine

textual data with visual data and allow the model to describe the morphology of a slide, answer questions about what it contains, find images in a database based on a text query, and even follow multimodal instructions such as "circle the tumor area on this image."

In short, a VLM can be engaged in the same way you can engage a human. "I could go ask a pathologist to point out all the areas of tumor-infiltrating lymphocytes," West said. "Now, because language-vision models are encoding language and images in the same space, they can do that, too. You can ask the model to describe what is happening in an image, and it will tell you exactly what it sees."

At Cedars-Sinai, Omar's work with large language models takes a less direct route of leveraging queries to gather information from research studies or even images. "Basically, you could go to the tool, ask questions, and the tool will provide you with pieces of code," he explained. "These pieces of code are what you use on the slide to get more information."

Atlas provides a similar function at the Mayo Clinic, Norgan noted. Because the model-generated embeddings in the digitized slide also encode semantic information, the Atlas team is now building a slide search function, which would allow researchers or clinicians to identify and access slides, or regions of slides, with related features.

Democratizing care

Although it will take time to disseminate the tools needed for AI-enabled digitized models of cancer care to smaller health systems, the future is now at Moffitt Cancer Center, where the research hospital is engaged in a top-to-bottom digitization of its system.

According to Marilyn Bui, MD, PhD, senior member of the departments of pathology and machine learning, the comprehensive cancer center plans for full digital adoption across clinical and research labs by 2027. Last August, it entered a multi-year collaboration with integrated AI and digital pathology company PathAI to deploy its cloud-based digital pathology image management system for both research and clinical applications.

Within the pathology department, the transition will mean that all glass slides will be scanned and reviewed digitally, providing the basis for applying AI computational tools to assist pathologists. Bui said that the cancer center is accelerating its move toward clinical AI adoption: "Just today I received an email asking which AI algorithms we plan to incorporate for clinical utility—prostate cancer, breast cancer, general tumor detection," she said. "For us, it's no longer just research."

Moffitt is taking a hybrid approach to algorithm development and deployment within the system. Some AI tools will come from commercial vendors and will be validated internally, while others will be developed by investigators through the center's translational pathology work. Taking this approach will allow it to apply AI to both common cancers and the rare tumor types Moffitt frequently encounters.

While the digital initiative will be transformational, Bui emphasized that the goal is not to replace pathologists but to enhance their capabilities. She prefers to refer to AI as augmented intelligence to reflect this. "Artificial intelligence suggests a robot replacing us," she said. "But what we mean is augmented intelligence—tools that assist and enhance our ability to make clinical decisions."

Further, Moffitt intends to integrate digitized slide data with genomic, proteomic, and clinical outcome data to build a multimodal data environment that could advance precision oncology. "Digital pathology and AI will allow us to extract far more information from tissue samples," Bui said, "making our diagnoses more actionable for the clinical team and ultimately improving patient care."

The promise of AI in oncology isn't just better algorithms, it's broader access. The maturation of computational pathology and its dissemination from large cancer centers like Moffitt to regional and rural health systems has the potential to provide levels of care typically only available at large research hospitals in community settings as well.

Marilyn Bui, MD, PhD
Senior Member
Moffitt Cancer Center

"It's about democratizing access to care," said Omar. "For a person in Maine or Wisconsin or another place to have access to the same high-quality care that you would get from a larger academic medical center in LA or New York, slides have to be digitized."

Over the next 10 years, there could be a compelling business case for hospitals to embrace digital pathology. As the cost of scanners comes down and a broad range of diagnostic tools becomes available, digitizing routine H&E slides could become common.

While genetic cancer testing can cost hundreds of dollars, Omar pointed out that pathology slides "cost $5 [and] they are available universally, in all patients with cancer." As AI models increasingly identify genomic-level insights directly from those inexpensive images, it represents a "huge win for accessibility, making AI work for patients who cannot afford genetic tests," Omar said. If there is broad adoption of digital pathology "it is very easy to roll out any kind of AI models and computational tools across the board, across situations and locations that don't have access to care."

"At the end of the day, all slides will be digitized," he concluded. "It's just a matter of time." ■

Chris Anderson, a Maine native, has been a B2B editor for more than 25 years. He was the founding editor of *Security Systems News* and *Drug Discovery News*, and led the print launch and expanded coverage as editor in chief of *Clinical OMICs*, now named *Inside Precision Medicine*.

From Reactive to Proactive: Reimagining Hypertension Management in the Precision Medicine Era

by Laura Cowen

Hilo

According to the World Health Organization, an estimated 1.4 billion adults aged 30–79 worldwide had hypertension in 2024, representing around one-third of the global population of that age. Of these, 44% were unaware that they were living with a leading risk factor for premature death and poor health worldwide due to its association with myocardial infarction, stroke, and kidney disease.

Despite the size of the hypertension problem, its diagnosis and treatment pathway has remained largely the same for decades.

A 60-year-old pathway

"The current pathway in hypertension diagnosis and treatment has really not changed in over 60 years," said Sandosh Padmanabhan, MD, PhD, chair of pharmacogenomics and professor of cardiovascular genomics and therapeutics at the University of Glasgow in Scotland.

He explained that it is based on opportunistic detection of hypertension, which has traditionally been defined as a blood pressure (BP) of 140/90 mmHg in the clinic, although thresholds vary by measurement method and guideline. For example, out-of-office measures typically use lower cut-points (e.g., home/daytime ambulatory averages) of 135/85 mmHg.

Sandosh Padmanabhan, MD, PhD
Professor
University of Glasgow

Diagnosis typically occurs when a patient visits their primary care physician (PCP) or has a pharmacy BP check. Confirmation follows, ideally with out-of-office BP monitoring to avoid misclassification caused by one-off measurements.

Patients are then stratified by predicted 10-year cardiovascular risk, using risk calculators such as Q-risk or the PREVENT score, and treatment is based on a stepwise algorithm. First, patients are generally given lifestyle advice like reducing salt, alcohol, and caffeine intake, improving sleep, managing stress, and

increasing exercise. This may give them a chance to reduce their BP without pharmacologic intervention.

If unsuccessful, depending on local guidelines, patients may be offered an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker if under 55 years of age. Those over 55 years or of Black African or Caribbean origin are started on a calcium channel blocker. The next steps combine ACE inhibitors and calcium channel blockers, then add a thiazide-like diuretic, followed by spironolactone or other drugs.

However, this approach uses "a population-level logic," said Padmanabhan. Although age and ethnicity are considered, "these are broad demographic proxies that don't include any understanding of the individuals' underlying pathophysiology or the genetic makeup."

He stresses that, on a public health basis, the system works. There are multiple effective, low-cost antihypertensive drug classes and many generic options available that effectively lower BP. Despite this, control rates are poor. "Fewer than one in four hypertensive adults globally have their BP adequately controlled," he said.

The measurement problem

Part of the issue lies in how BP is measured. "To give you an idea about the scale of inertia, we diagnose BP using a device that was introduced in the late 19th century," Padmanabhan noted, referring to the sphygmomanometer invented by Scipione Riva-Rocci in 1896. Not only that, the technique can also be flawed. Variables such as incorrect cuff size, improper positioning, and patient movement can distort readings. Even talking during measurement can increase BP values by 5–9 mmHg or even higher.

Crucially, a single measurement provides little insight into cumulative lifetime exposure to high BP and can be skewed by issues like white coat hypertension or masked hypertension. "We look at the BP number, but the patients don't experience that number. What they experience is a lifelong vascular risk," Padmanabhan explained. "Treatment is not about a short-term reduction in a number. It's about long-term sustained risk reduction."

Yet the current system remains reactive and is not working well enough. "We have to move away from reactive diagnosis to proactive identification," Padmanabhan said. "The earlier we measure accurately and respond systematically, the fewer surprises we'll see later."

Continuous monitoring

The pitfalls of opportunistic, or even planned, BP measurement are driving the emergence of new technologies capable of continuous monitoring.

Josep Solà, PhD, began working on optical sensing technology in 2004 at the Centre for Electronics and Microtechnology in Switzerland. By analyzing subtle changes in reflected light caused by arterial dilation, it became clear that BP could be measured using these light signals. In 2018, this research was spun out into Aktiia, where Solà is CTO and co-founder. The company has developed and commercialized the Hilo™ band: a CE-certified wearable medical device designed for continuous, cuffless, BP monitoring that has been clinically validated against traditional ambulatory BP monitoring.

Josep Solà, PhD
CTO and Co-founder
Aktiia

The band tracks BP and heart rate automatically, about 25 times per day, without requiring any action from users. Paired with an app, the device shows users daily, nightly, and long-term BP trends. It is currently available as a certified medical device across Europe, Australia, and Canada, and, following FDA approval in July 2025, the company is preparing for a U.S. launch.

Solà said he and co-founder Mattia Bertschi, PhD, were convinced they could change how hypertension is being managed today. He believes there is no good reason why most people with hypertension cannot control the condition. The medication is cheap and effective; the problem is that there has been no technology that patients can use to properly manage their condition.

"No one wants to use a cuff every day for the next 30 years," said Solà. "They're just so inconvenient, and you cannot expect people to proactively measure something they don't feel."

The Hilo band gives wearers a feedback loop that has historically been missing from BP measurement. Users can

Hilo

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immediately see that reducing their salt or alcohol intake, for example, lowers their BP. "We are empowering people," said Solà. "We are empowering them to look at the intervention, or combination of interventions, with or without medication, to see what is effective for them, and this reinforces their willingness to continue with the changes they are making."

Adam Bress, PharmD
Researcher
University of Utah

Data published by Aktiia has shown that this approach works. A study of 8,950 U.K.-based Hilo users indicated that individuals who monitored their BP continuously showed better control over time. Specifically, users over 50 years of age appeared able to prevent the age-related rise in systolic BP typically seen in the general population, which the researchers say "may reflect greater awareness, stronger treatment adherence, and lifestyle changes prompted by continuous feedback."

Wearables at scale: Opportunity and caution

Beyond dedicated monitoring devices like the Hilo band, smartwatches and other devices are increasingly capable of detecting physiological signals associated with cardiovascular risk. The Apple Watch can detect potential signs of chronic hypertension by analyzing heart rate sensor data over 30-day periods, the Huawei Watch D provides on-demand and 24-hour ambulatory BP monitoring using an air-filled strap, while the team behind the Oura ring is developing a "Blood Pressure Profile" feature to detect early signs of hypertension.

Although this represents a significant step toward embedding cardiovascular monitoring into everyday life, the increasing use of these devices raises important questions about accuracy, interpretation, and clinical integration, particularly as they often rely on indirect signals rather than direct BP measurement.

As Adam Bress, PharmD, from the Spencer Fox Eccles School of Medicine at the University of Utah, and colleagues have recently shown, translating wearable-derived signals into meaningful clinical information is not straightforward.

They evaluated the hypertension alert feature of the Apple Watch, which has a published sensitivity of 41% and specificity of 92%, meaning that approximately 59% of individuals with undiagnosed hypertension would not receive an alert, while about eight percent of those without hypertension would receive a false alert.

"The problem there, is that this data only tells you how the alert works in a very controlled, limited population," said Bress. "In order to understand how it's going to work in the real world, we need to know how the true prevalence of undiagnosed hypertension varies in the population and in subgroups and to what degree."

Using data from nearly 4,000 adults in the U.S., Bress and colleagues showed that the pretest probability of having hypertension has a significant impact on the reliability of the alert. For example, among adults under 30 years of age, the pretest probability of having hypertension is 14%. A positive alert on the Apple Watch would increase this probability to 47%, whereas no alert reduces the probability to 10%.

However, for adults aged 60 years and older, an alert increases the probability of an individual having hypertension from a pretest level of 45% to 81%, whereas the absence of an alert only lowers it to 34%. This translates to large numbers of false negatives when applied across millions of users.

In Apple's validation study, the company stresses that the watch is not intended to replace traditional diagnosis methods or to be used as a method of BP surveillance, and that the absence of a notification does not indicate the absence of hypertension.

"The concern is, if you're not getting an alert, will people interpret that as them not having hypertension," said Bress. "That's the worry. … The groups in which the negative alert is the least trustworthy contain the people with the highest risk. We're most worried about people being falsely reassured."

At the same time, he is clear that wearables should not be dismissed. "This technology is an important step forward; we need more wearable tech that can screen," he said.

Unfortunately, access to these devices is not universal. Advanced monitoring technologies are often first adopted by the "worried well"—people who are more affluent and health-conscious—rather than those at highest risk.

"The only thing that can change this is a clear political decision to make awareness of hypertension large scale," said Solà. Devices like the Hilo band could be used much like the continuous glucose monitors for diabetes. The difference is that if someone with diabetes doesn't keep their blood glucose levels under control through regular monitoring, they can become ill very quickly. With hypertension, the effects of poor control don't become apparent for decades.

"We need the policymakers to understand that investing in this technology today will have a return on investment in 10 years from now, not in one year from now," Solà remarked.

Targeted drug selection

Even when hypertension is detected early and monitored closely, treatment remains largely empirical and can lead to therapeutic inertia, one of the biggest current challenges in hypertension care. "BP is not like diabetes, it doesn't cause symptoms, and because of that, we don't escalate treatment often enough," said Padmanabhan.

(continued on page 22)

Integrating BP Monitoring With Precision

Laura Cowen interviewed Teresa Castiello, MD, a cardiologist and healthcare prevention advocate, to discuss her insights on hypertension management in the era of precision medicine. Castiello shared her perspectives on the need for a proactive approach to hypertension care, the role of precision medicine and pharmacogenomics, and the potential impact of digital health Hilo in transforming how hypertension is diagnosed, monitored, and treated.

Teresa Castiello MD

Q: Do you think there needs to be a shift in how hypertension is diagnosed and treated?

Teresa Castiello, MD: Without a doubt. We must move from reactive medicine—treating damage once it has occurred—to proactive medicine. Hypertension is frequently underdiagnosed because it often remains asymptomatic until organ damage is already underway. Furthermore, traditional office readings are often biased by the "white coat" effect, which is why clinical guidelines, including those from the ESC (European Society of Cardiology), are moving away from them. Current monitoring also has limitations; nocturnal readings from standard cuffs often wake the patient, and sporadic readings fail to reflect the true, dynamic daily blood pressure response.

Q: Are there any "uncomfortable truths" about hypertension care that we don't talk about enough?

Castiello: A significant "uncomfortable truth" is the lingering bias that considers a rising blood pressure to be a normal part of aging. It isn't. Data from the Yanomami population in the Amazon shows that systolic blood pressure can remain constant at approximately 100 mmHg throughout life. In our Westernized society, blood pressure increases as a response to environmental and stressful "insults" rather than as a physiological necessity. Unfortunately, current clinical practice in the U.K. has not yet fully implemented recent ESC changes. We still see values defined as "normal" when guidelines now identify them as elevated (anything above 120/70 mmHg). Cardiovascular risk actually begins to climb much sooner than most realize, often at systolic levels as low as 110–115 mmHg.

Q: Is there a risk of current treatment strategies controlling blood pressure numbers without addressing underlying mechanisms?

Castiello: Yes. Labeling most cases as "essential hypertension" is essentially admitting we are treating a multifactorial condition of unknown cause. We often fail to assess the individual holistically. Stress, hormonal shifts, poor work-life balance, diet, and physical inactivity are profound drivers of blood pressure increases. While medical therapy is a vital tool, we must not forget that humans are multifaceted and complex. We need a healthcare approach that treats the person, not just the metric.

Q: Is there a need for increased precision medicine in hypertension, e.g., with the use of pharmacogenomics? Could this information redefine high-risk?

Castiello: We are in an era where precision medicine is the only way to deliver effective care. The power of data is enabling us to target prevention and early diagnosis like never before. Pharmacogenomics is a key part of this; by understanding how a patient's genetic profile influences their metabolism of a drug, we can move away from "trial and error." This information redefines "high-risk" from a generic population score to an individual biological reality. It allows us to define optimal doses that maximize efficacy while minimizing the toxicity that often leads to treatment non-compliance.

Q: Are healthcare systems ready to integrate continuous blood pressure monitoring into routine care?

Castiello: Probably not yet, but they will be forced to be. COVID-19 showed that we can adapt to global interconnection and remote monitoring in a very short time when we have no choice. Prevention is the only way for healthcare systems to survive the rising burden of chronic disease. Philosophically, if we wait until we feel "ready" to take action, we will never act. The time to implement these preventive strategies is now.

Q: In ten years' time, how do you hope hypertension will be managed differently?

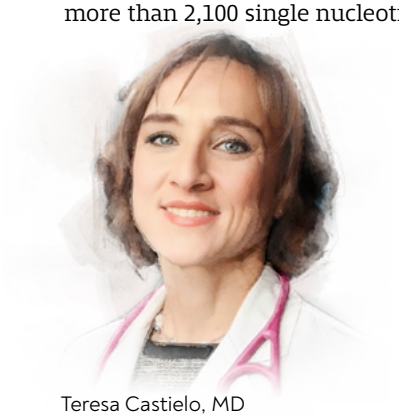
Castiello: I hope every individual has access to a medical-grade wearable—whether a band, ring, or chip—empowered by AI to feed data into a proactive health system. This data will be filtered to flag those requiring care at a pre-pathological stage. We can no longer afford to wait for a crisis to occur before we treat it; global healthcare systems cannot handle that burden. We must prevent what is possible and focus our hospital resources on the conditions that occur despite our best preventive strategies ■.

(continued from page 20)

At the same time, treatment selection remains largely trial-and-error. Clinicians cycle through medications sequentially, adjusting regimens based on response rather than underlying biology. The issue is that failed attempts risk side effects and can erode trust. That lack of trust can then impact adherence and, therefore, cardiovascular risk.

Instead, Padmanabhan believes that we need to move toward mechanistically informed drug selection.

This approach is common in oncology, where targeted therapies have been matched to specific mutations, but the picture is more complex for BP. Genome-wide association studies (GWAS) have identified more than 30 genes associated with monogenic forms of hypertension or hypotension and more than 2,100 single nucleotide polymorphisms linked to BP regulation, underscoring its highly polygenic nature.



Teresa Castiello, MD
Director
MIAL Healthcare

This, combined with the strong influence of environmental factors, means that there is no single pathway or biomarker that can be easily targeted to reduce BP.

Padmanabhan's work on the uromodulin gene (*UMOD*), however, shows that GWAS data can translate into therapy. His team identified a signal on chromosome 16 linked to uromodulin, a protein that is only expressed in one part of the kidney and plays a role in salt regulation. In a clinical trial comparing people with low BP to those with high BP, they found that people with the *UMOD* allele that increases protein expression experienced a sustained reduction in BP when treated with the loop diuretic torasemide, whereas the effect was only temporary and followed by rebound in those carrying the *UMOD* allele that lowers protein expression.

Approximately two-thirds of the population carry the *UMOD* allele that increases protein expression, meaning that loop diuretics like furosemide or torasemide, which are more commonly used to treat heart failure, could potentially be used in hypertension personalized by the patient's genotype.

So far, "this is the only clinical trial from a GWAS-identified genetic variant in hypertension," Padmanabhan noted, highlighting both the promise and challenge of pharmacogenomics in hypertension.

Although clinical translation from GWAS of hypertension has been limited, research has shown that genetic variation in drug-metabolizing enzymes can significantly impact hypertension treatment efficacy and toxicity. For example, variants of *CYP2D6* affect metoprolol metabolism whereas those in *CYP2C9* influence responses to losartan. Research is needed to determine whether testing for these variants or others could reduce trial-and-error prescription, minimize side effects, and thus increase patient confidence and long-term engagement.

On a more fundamental level, biological sex differences remain a significant consideration in cardiovascular medicine. "Biological factors are an integral part of the clinical picture," noted Teresa Castiello, MD, consultant cardiologist and director of MIAL Healthcare in London. She points out that clinical trials have historically seen a predominance of male participants; as a result, many standard medication dosages are based on data primarily derived from men.

This can lead to challenges with tolerability and a higher incidence of side effects in women as the therapeutic dose required for efficacy often tends to be lower in female patients.

Castiello suggests that this area of management warrants further refinement in clinical practice. She also emphasizes that key aspects of female cardiovascular risk, including reproductive history, menopause, and conditions like polycystic ovary syndrome, are nuances that may not always receive the necessary focus in routine care.

Toward a precise, preventative system

Ultimately, transforming hypertension care will require more than new technologies or therapies. It will require a fundamental change in how care is delivered.

Padmanabhan argues that hypertension should be managed through a "precision prevention service," that integrates early detection, continuous monitoring, and personalized treatment, and involves more than just PCPs.

This approach recognizes that the disease is not just a clinical condition but a societal one, influenced by factors such as diet, socioeconomic status, work patterns, and access to care. Equity remains another critical issue. "We treat the ideal average patient under ideal circumstances but that's not reality," said Padmanabhan.

There also needs to be a cultural shift, said Castiello. "It's not just the doctor's responsibility; we also need to take responsibility for our own health."

Solà shares a similar vision for the future: he would like to see BP measurement to become as routine as brushing your teeth, supported by technologies that empower individuals and reduce the burden on healthcare systems.

If realized, this shift could transform hypertension from a silent, progressive disease into a manageable, preventable condition, saving millions of lives in the process. ■

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.

Powering the Organoid Revolution with Scalable, Human-Based Systems

The strategic shift to 3D biology

Organoids[1], or miniature organ-like structures derived from stem cells, have emerged as transformative tools in biomedical research. Unlike traditional two-dimensional (2D) cell cultures, organoids possess a three-dimensional (3D) architecture and multiple cell types, closely mimicking the structural and functional properties of native organs. This makes them highly versatile, scalable platforms for studying human biology in a controlled laboratory environment.

As regulatory landscapes evolve, the demand for these models is surging. In April 2025, the U.S. Food and Drug Administration (FDA) announced plans to phase out certain animal testing requirements, explicitly promoting organoids as superior, human-based alternatives for drug development. With over 180 organoid-related clinical studies registered by mid-2025, the industry is rapidly transitioning toward these high-fidelity systems for drug sensitivity testing and precision medicine.

Technical hurdles in organoid culture

Despite their potential, the path from bench to bedside is hindered by persistent technical challenges:

- Batch-to-batch variability that compromises experimental reproducibility.
- Insufficient tissue maturation and limited scalability.
- Restricted access to clinically compatible, high-performance reagents.
- Endotoxin contamination, which can activate innate immune signaling, alter cellular metabolism, and induce stress responses, ultimately confounding drug response data.

Sino Biological's 3D organoid research solutions

To address these bottlenecks, Sino Biological offers a comprehensive portfolio of high-quality cytokines, growth factors, small molecules, and marker antibodies that are essential for organoid culture and characterization. Our research solutions are optimized for nearly 30 popular physiological and tumor organoid models, providing robust support for oncology, disease modeling, and drug screening.

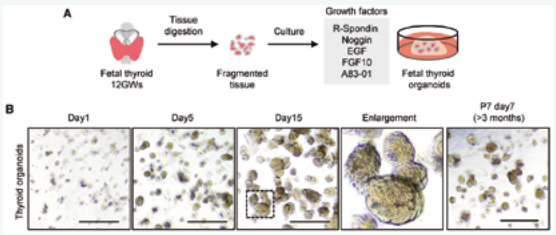


Figure 1. Generation of reproducible human fetal thyroid organoids (hFTOs)[2]. (Image from Liang et al. used under CC BY 4.0. https://doi.org/10.1002/advs.202105568)

For example, Fudan University's Jianqing Liang, PhD, and his colleagues[2] used Sino Biological's recombinant human EGF protein (Cat#: 10605-HNAE) to establish an optimal culture system for human fetal thyroid organoids (hFTOs). Figure 1A depicts the schematic diagram of the digestion and seeding of fetal thyrocytes, and the culture medium of hFTOs, while Figure 1B represents the time point bright field images of hFTOs.

The ProPure™ advantage: ensuring culture integrity

In organoid culture systems, recombinant cytokines and growth factors play central roles in directing stem cell differentiation, maintaining tissue identity, and sustaining long-term growth. However, trace levels of endotoxin contamination can profoundly disrupt three-dimensional cultures by activating innate immune signaling pathways, altering cellular metabolism, and inducing stress responses or cell death. Such unintended effects compromise experimental reproducibility, obscure true disease phenotypes, and confound drug response data, particularly in sensitive, patient-derived organoid models.

Sino Biological provides ProPure™ endotoxin-free proteins for researchers to establish robust and translationally relevant organoid platforms. Highly purified preparations minimize inflammatory artifacts, reduce batch-to-batch variability, and enable consistent lineage specification across large-scale cultures. In high-throughput drug screening and preclinical studies, these reagents help ensure that observed biological responses arise from therapeutic candidates rather than culture-induced artifacts, supporting confident data interpretation and regulatory-facing research workflows.

ProPure™

Conclusion

Organoid technology is reshaping disease modeling and drug discovery by providing physiologically relevant, human-based platforms. Overcoming challenges such as variability, limited scalability, and endotoxin interference is essential to fully realize their translational potential. With high-quality, endotoxin-free reagents and comprehensive technical support, Sino Biological empowers researchers to build robust, reproducible organoid systems that accelerate scientific innovation and therapeutic development.

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IN CONVERSATION *with* Haijiao Liu, PhD

As a postdoctoral researcher at the University of Pennsylvania, Haijiao Liu, PhD, helped advance tumor-on-a-chip technology, a feat of bioengineering that mimics the microenvironment of malignant human tumors. Led by Dan Dongeun Huh, PhD, a Penn Engineering professor and trailblazer of organ-on-a-chip technology, Liu and his team explanted lung adenocarcinoma tumors onto the transparent chips to test their perfusion with chimeric antigen receptor (CAR) T cells. Their findings were published in October in *Nature Biotechnology*, with Liu as first author.

Now on paternity leave in Toronto, Liu spoke with Lindsey Leake about the implications of this work, the challenges inherent to tumor-on-a-chip studies, and his plans to launch a lab of his own this fall.

Q: Walk me through the creation of the tumor-on-a-chip. What went into its design?

Haijiao Liu: It's essentially inspired by the need for alternative tumor models. This is speaking to the traditionally used animal tumor models and some existing *in vitro* tumor models, especially for the study of immunotherapies.

For example, when I started at Penn around 2018, Penn Medicine was pioneering this immunotherapy called CAR T-cell therapy, which is basically aiming to harness the patient's own immune system, specifically the patient's own T cells, to help fight the cancer. Penn Medicine was demonstrating huge clinical success using this CAR T therapy to treat blood cancers, such as leukemias and lymphomas. In a huge contrast to this, the solid cancer arena has seen a limited response from this new immunotherapy. So there's this great need to study why this has not been successful, and that comes down to the consensus that the solid tumor has this really complex microenvironment.

In the category called tumor-on-a-chip, people try to control the cultural environment, the biochemical and biophysical environment of tumor cell cultures. We can use this for simple drug testing—see how the tumor growth will be affected or how effectively they can be killed. However, these existing tumor-on-chip or *in vitro* tumor models are still very simple. They don't usually recreate or reproduce the complex structure of the human solid tumors that I described, like where they often include complex vessel networks.

I took the lead to address the need and the challenges of reproducing and then investigating, or probing, the dynamic interactions between those CAR T cells and human solid tumors entirely *in vitro*.

Q: How does the vascularization work on the chip?

Liu: It took several years to start, from the idea of building this more advanced tumor-on-a-chip technology toward proving it's actually useful. I started by focusing on this one aspect, which is the CAR T-cell trafficking and their functions after they traffic to fight the tumors, and that will involve the recreation of the structural interface between the tumor and this complex vascular network that's present in human tumors.

I was inspired by *in vivo* tumor transplantation, where traditionally, people take human tumors and then transplant them in a bulk, intact format into animal models. So my idea was, if we want to focus more on the human biology, if we want to engineer this entirely *in vitro*, how about we design a vascular bedding, like a miniature living model?

We basically took advantage of the self-assembly capability of human-sourced endothelial cells, combined with certain

Haijiao Liu, PhD

stromal fibroblasts, or stromal cells. With a bit of optimization, engineering, tweaking, then we can allow them to form capillary-like vascular networks in our engineered models.

Q: What are the advantages of recreating the tumor microenvironment in this way? That is, is the Petri dish becoming obsolete in cancer research?

Liu: The unique advantage of this way of engineering is to have a higher level of control over the structures of the tissue-tissue interface that we can build. For example, we can engineer different culture chambers. We can engineer different access windows with this model. That allows us to construct, step by step, the vascular bedding and then the tumor transplantation. Also, by forming these perfusable vessels—by the way, we can provide the infusion and flow of the CAR T cells, just like they are infused and flow in the patient—that gives us the leverage to reconstruct, probe, and then control these tissue functions in a highly precise manner.

Q: How did you and your colleagues at Penn explore CAR T-cell activity on the chip?

Liu: We first used different functional assays, like immunostaining and ELISA (enzyme-linked immunosorbent assay) assays, to characterize how the CAR T cells are doing and how they are interacting with the tumors in our engineered model. Then we disassembled this engineered tissue to extract all the cells for flow cytometry, to further characterize their functional phenotypes.

With the help of our collaborators and other people in the lab, I took advantage of this engineered model of vascular tumors interacting with CAR T cells for multi-omics analysis. For example, I was able to extract all the cells and send them for single-cell RNA seq[uencing]. We were able to look at the gene expressions of each individual cell from all the cell types that we included in this model. In this way, we have almost like a superpower to probe and read into how each cell—including the CAR Ts and tumors and the vessels—how they are responding and interacting with each other at the molecular gene levels. This is so powerful that it helped me to discover novel interactions between these parties and also new druggable targets.

The message is that through the development of this more advanced tumor-on-a-chip technology—combined with advanced multi-omics analytics and advanced computational analysis—we were able to provide this powerful *in vitro* technology to apply to accelerate the development of cell therapies, such as the CAR T immunotherapies for cancer, but also other complex diseases.

Q: What are the overall implications of this latest research?

Liu: With a growing understanding of human biology at the cellular and tissue levels, I think we're seeing that our ability to engineer and design biological systems is also growing. More than ever, we have these advances in the ability to precisely construct, investigate, and then eventually control very complex tissue functions, and even organ functions. For example, our demonstrated tumor-on-a-chip technology is like presenting a miniature sandbox; we can literally see and predict the battlefield of CAR T therapy in cancer.

If we combine these advanced engineering technologies with emerging technologies in spatial multi-omics and the unprecedented productivity of the AI revolution, we will be able to accelerate the understanding of more complex human biology and extract more biological insights, and then apply that to accelerate the development of safer and more efficacious drugs and therapies, such as immunotherapies in cancer.

Q: What are the limitations of organ-on-chip technology that need to be overcome?

Liu: I think there are challenges on two fronts. The first limitation is the lack of complexity. We're claiming that what we just published is a sufficiently complex system for us to deeply probe and understand the dynamics of CAR T tumor interactions. Still, if we're speaking next level of translational power or potential, then we need to pursue a higher complexity that incorporates the missing but critical components from *in vivo*.

The other side of the coin is that if you make this engineered model more complex, you make it more challenging to reproduce or to scale up or to translate to other labs. But also, that points to an opportunity and growing room for translation, to standardize every single step, from the construction to the analysis of these engineered models, and to automate these processes as much as possible.

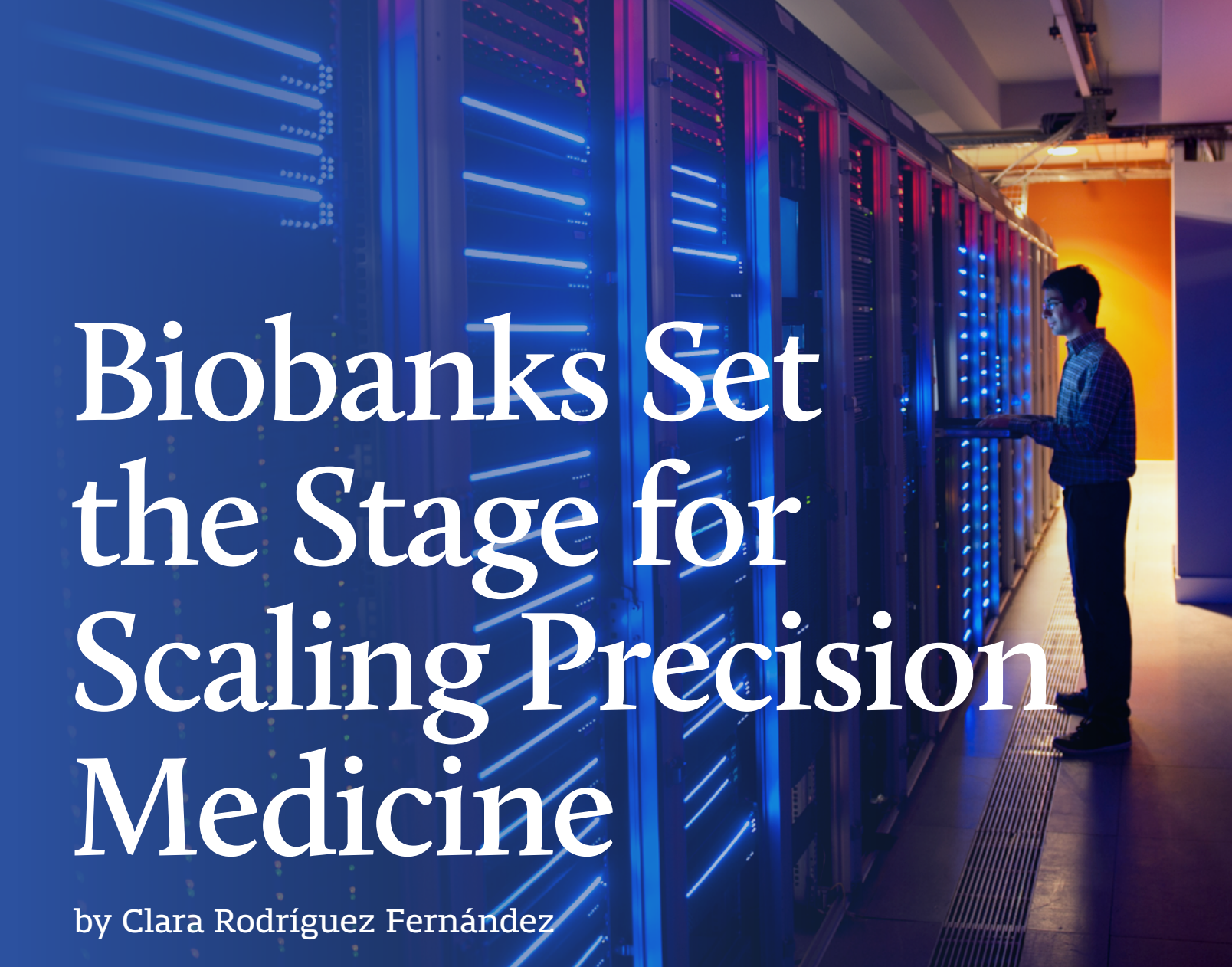
Q: What do you envision for your new lab?

Liu: I have a lot of things I want to do. I'm eager to establish my own team. The overarching and the unifying theme of the new lab will be to develop the next generation of *in vitro* complex tissue models, or I call it assembloid tissue models. Assembloid basically means there's a stem cell-based, three-dimensional complex tissue model that intentionally incorporates different cell types, to emulate the critical tissue-tissue interactions that determine the tissue- and organ-level functions. I still need to make a big decision where the lab could be; it could be in Canada and it could also be in China.

Q: What impact might tumors-on-a-chip have on the future of precision medicine?

Liu: It's attracting a lot of attention from biologists and clinicians who are heavily focused on using the traditional tissue models—animal models, for example, or the simple dish cultures—for their studies of interest. So the biggest impact I can foresee with our technology is that now it's more mature. I can see it being gradually, and maybe quickly, adapted into more traditional biological labs, to help them dissect the complex biological questions they're asking, or to accelerate the evaluation of the exciting new drugs or therapies they're developing. Overall, I can see that accelerate this development pipeline of new drugs and therapies in precision medicine. ■

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.



Biobanks Set the Stage for Scaling Precision Medicine

by Clara Rodríguez Fernández

Dating back more than a century, biobanks have outgrown their beginnings as small, local collections to become large, global facilities that store and handle millions of samples and serve thousands of researchers at any given time. Over the years, biobanks have transformed from passive repositories into active research infrastructures that are increasingly bridging the gap between medical research and clinical applications.

"Today's biobanks have evolved far beyond sample storage," said Yan Zhang, PhD, president of proteomic sciences at Thermo Fisher Scientific. "They are automated, digitally connected systems integrated with hospitals and health networks to ensure appropriate consent, longitudinal clinical context, and the ability to re-engage participants over time."

As safeguards of clinical samples, biobanks fulfill a central role in the advancement of precision medicine. Access to the right samples can make or break a research project, with most researchers reporting that they have had to limit their scope of work because of difficulties obtaining the samples they need.

Yan Zhang, PhD
President, Proteomic Sciences
Thermo Fisher Scientific

"Robust, population-scale biobanking enables precision medicine to move from isolated findings toward broader clinical relevance," said Zhang. "Modern biobanks combine genomics, proteomics, and other high-dimensional omics platforms with robust data architecture, high-performance computing, and artificial intelligence (AI)-driven modeling. Dedicated data science teams integrate molecular data, longitudinal health records, and curated public datasets to generate biologically meaningful interpretations."

Biobanks now provide the infrastructure needed to support population-scale, longitudinal studies that allow scientists to uncover molecular drivers of disease and understand their

baranozdemir / Getty Images Plus

evolution over time to ultimately identify biomarkers, develop targeted treatments, and inform clinical decisions.

"We're seeing researchers design studies with scale in mind," Zhang noted. "They're combining proteomics, genomics, and clinical data to generate insights that are both statistically powerful and relevant to real-world populations. There's also a clear shift from searching for a single biomarker to building a more complete, systems-level understanding of disease."

To navigate today's rapidly shifting landscape and meet their core purpose of supporting cutting-edge clinical research, biobanks have to keep up with fast-moving targets. Going forward, moving from initial discovery to translation will remain the number one challenge in precision medicine. "Generating discovery insight is no longer the limiting factor," said Zhang. "Validating, standardizing, and implementing those insights at scale is."

A matter of scale

One of the most transformative shifts in biobanking over the past decade has been an exponential increase in the scale of data collection and sample storage. At the forefront of this expansion is the UK Biobank, which currently stores around 18 million samples from 500,000 participants, together with imaging and biomarker data, healthcare records, questionnaires, physical measurements, demographics, lifestyle, and environmental data collected over the course of 20 years. This depth of phenotyping is what makes the data so valuable to researchers worldwide, said Martin K. Rutter, MD, professor of cardiometabolic medicine at the University of Manchester and deputy chief scientist at the UK Biobank. "When you link all that together, you can get amazing insights into the biology of disease."

Martin K. Rutter, MD
Deputy Chief Scientist
UK Biobank

To keep up with increasing storage needs and researcher requests, the UK Biobank is now getting ready to move more than 10 million samples currently stored in its main laboratory to a new building in central Manchester by the end of the year. The new storage facility is designed to quadruple sample retrieval speed while making the whole infrastructure more energy-efficient and environmentally friendly.

The scale at which facilities like the UK Biobank operate today would have been unthinkable when it was established two decades ago. Such massive growth has been driven by rapid technological advances across genomics, transcriptomics, and proteomics, with costs continuing to fall while coverage, speed, and accuracy keep surging.

Partnerships with the pharmaceutical industry have also been instrumental in nurturing this exponential growth. This can be seen in initiatives like the UK Biobank Pharma Proteomics Project (UKB-PPP), a collaboration between the UK Biobank and 14 biopharmaceutical companies with the goal of analyzing proteomics data from 600,000 samples.

In the long run, scale provides the backbone to enable increasingly ambitious, statistically powerful studies. However, as they grow, biobanks face the challenge of navigating a constantly shifting landscape while making sure the samples and data they collect, store, and maintain are valuable to the entire research community they serve.

"Our job is to make the data available to researchers," said Rutter. "We are involved now more than ever in connecting with research teams and trying to understand what their needs are."

Through surveys and consultations, the UK Biobank actively gathers information to design prospective data collection programs that anticipate researcher needs. Next year, the

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biobank is planning a repeat assessment of its whole cohort, focusing on measurements of aging. The goal is to support researchers looking into causal pathways and mechanisms driving age-related diseases, empowering the development of preventive interventions and new diagnostics and treatments for age-related conditions.

Keeping pace with the evolving demands of researchers, industry, and the broader public is essential for biobanks to secure the funding necessary not only to operate but also to expand such vast enterprises, which remains a major challenge across this resource-intensive field.

Diversity takes the spotlight

Historically, samples collected by biobanks are biased in favor of participants who are white, middle-class, and have a higher education. This creates major disparities in the applicability of clinical research. In fact, studies have shown that patients from non-European ancestry backgrounds have not benefited equally from precision drugs approved by the U.S. Food and Drug Administration (FDA) to treat a range of cancer indications.

Even within biobanks dedicated to sampling the population of a specific region, ethnic minorities, low-income, or elderly people are often underrepresented, skewing results against the real-world populations they strive to serve. As the research community increasingly recognizes the importance of more diverse and representative patient cohorts, demand is rising for resources that address these barriers.

Joshua C. Denny, MD
CEO
All of Us

Representation is at the heart of All of Us, a program launched by the National Institutes of Health in 2018 to address the gap present at the time in many biobanks and sample repositories. This precision medicine initiative was designed to enroll participants who reflect the full range of populations found within the U.S., including individuals of varied ancestry backgrounds as well as those living in rural commmunities, which are rarely represented in biorepositories due in part to longstanding barriers to research participation, such as the logistical challenges of collecting samples and data from participants in remote locations.

"A lack of diversity impoverishes discovery and applicability of findings for all," said Joshua C. Denny, MD, CEO of the All of Us Research Program.

For instance, data collected by All of Us has been used to investigate *APOL1* gene variants linked to kidney disease, which are more common among people of West African ancestry. This research led to the identification of a novel *APOL1* variant that can reduce the risk of kidney disease in individuals carrying high-risk variants.

> "Over the next decade, biobanks are expected to become increasingly integrated into clinical and translational workflows."

The program has so far enrolled about 870,000 participants across all U.S. states, with about 80% of them representing communities that have historically been underrepresented in biomedical research. This has been achieved by emphasizing accessibility and flexible participation models; participants can enroll digitally and choose whether to share access to their electronic health records, donate biospecimens, and complete demographics and lifestyle surveys. They may also opt to provide saliva samples, simplifying logistics in rural areas with limited access to blood collection facilities.

"What works in a rural location is different from what works in a big city like New York," said Denny. Whether it comes to location, age, or language, he emphasized the importance of adapting how the program approaches and engages each population.

Democratizing access to patient data across the research ecosystem is another major biobanking challenge that All of Us is committed to addressing. The program has established a streamlined access model that enables researchers to access the data they need in less than two hours if they belong to one of the 1,300 already approved institutions across the world. Together with central data storage and cloud-based analysis tools, their setup is designed to make the data accessible to researchers lacking the resources and local infrastructure for high-performance computing.

Towards global integration

With precision medicine studies steadily escalating both in size and complexity, researchers increasingly seek to bring together data stored across diverse biobanks to power larger, more ambitious studies with broader scientific and societal impact. However, building the infrastructure needed to enable cross-biobank studies is still a challenge, starting with convening stakeholders to harmonize data collection standards and establish international guidelines.

Anticipating this need, in 2013 the European Union established the Biobanking and Biomolecular Resources Research Infrastructure - European Research Infrastructure Consortium

(BBMRI-ERIC), which currently coordinates the activity of about 500 biobanks across 32 countries.

"Precision medicine can only move forward with a strong starting point for research," said Jens K. Habermann, MD, PhD, professor for translational surgical oncology and biobanking at the University of Lübeck and director general of the BBMRI-ERIC. "It can be very difficult for scientists to get all the information they need in one place, and this is what biobanks can enable."

Pulling together data from all its members, the BBMRI-ERIC has set up a central catalogue for biobanks, biomolecular resources, and other data and sample collections, which users can employ to identify relevant resources and build virtual cohorts tailored to their research needs. The consortium also works with international committees to set guidelines and support members working towards compliance with international standards.

Despite ongoing progress, there are still obstacles ahead when it comes to harmonizing biobanking practices worldwide, including data collection, annotation, storage, and sharing. Tackling differences in data protection, consent, ethical standards, and regulatory requirements across borders will be another necessary step towards broader standardization. Finally, biobanks will need to invest in cybersecurity to ensure patient data can be shared between institutions safely.

Jens K. Habermann, MD, PhD
Director General
BBMRI-ERIC

Funding will be key to successfully addressing all these challenges. On this front, biobanks face the difficult task of maintaining their existing infrastructure, staying up to date and relevant to the research community, and investing in cross-biobank initiatives. All this must be balanced with growing financial pressure on research centers, hospitals, and the governments supporting them.

As part of its 10-year roadmap, the BBMRI-ERIC is setting the goal of forming international networks that bring together more diverse biobank types, such as environmental, wildlife, veterinary, and plant biodiversity repositories. The overarching aim is to move towards a One Health approach to biobanking, where samples and data that expand beyond monitoring human populations are brought together to tackle overlapping challenges that simultaneously affect human, animal, and environmental health.

Data-driven horizons

As the field forges ahead, biobanks are undergoing broad transformations in the way they operate. On the technology side, these changes are being propelled by the rise of multi-omics techniques in precision medicine research, as well as by rising demand from the research community for non-invasive patient monitoring data and longitudinal sample collection. All of these will be critical for the development of the next generation of personalized therapies and diagnostics.

"Over the next decade, biobanks are expected to become increasingly integrated into clinical and translational workflows," said Zhang. "Proteomics, in particular, will play a growing role in helping us understand the dynamic biology of disease, enabling earlier detection, better prediction of recurrence, and more precise therapeutic strategies."

A key driver of this shift will be AI. No longer just a supporting tool, AI is now becoming an integral part of biobank operations, contributing to real-time sample monitoring, predictive maintenance, risk management, and decision making.

On the data analysis side, Zhang has seen how AI is redirecting the focus from data generation to data interpretation. She said, "Biobanking has already enabled the collection of high-quality biospecimens linked to large-scale molecular and clinical datasets. The challenge now is extracting meaningful biological insight from that complexity."

Although still in its early days, AI is becoming central to how researchers make use of biobank data, noted Rutter. Drawing from the UK Biobank data, recent studies have developed AI models that can predict a patient's risk of stroke based on retinal images, calculate the risk of future disease by looking at an individual's disease history, or spot neurodegenerative diseases like Alzheimer's and Parkinson's early using brain scans and physical activity data.

Going forward, Rutter expects to see biobanks moving away from static cohorts and in favor of continuous data collection, enabling more powerful predictions. For example, the UK Biobank is developing a mobile app that can track a participant's physical activity and monitor their location and sleep patterns, offering an in-depth look at how a variety of factors affect their health with much more accuracy than self-reported surveys.

Over time, all these advances will steer clinical practice from treatment to prevention, allowing healthcare professionals to act early in the patient journey, when interventions are most effective, and eventually, even before disease develops. Ultimately, addressing complex diseases will require coordinated contributions from all stakeholders, including AI innovators, drug developers, clinicians, technology providers, and policymakers.

"The next decade will be incredibly exciting," said Denny. "It will be all about leveraging the huge scale of resources that are just emerging today." ■

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.

Structural Variant Monitoring for Ultra-Sensitive Molecular Residual Disease Detection

For early-stage breast cancer patients, the interval between identification of molecular recurrence and clinical relapse is a critical opportunity for intervention to change the trajectory of disease. However, many first-generation Molecular Residual Disease (MRD) tests often miss that window—either because they lack the sensitivity to detect low-levels of residual disease, or their results are too ambiguous to guide confident clinical decisions. As a result, recurrence is often identified only later, when treatment options are more limited and prognoses worse.

SAGA Diagnostics® developed Pathlight™ to change this paradigm; delivering earlier, clearer MRD signals so clinicians can intervene sooner and with greater confidence.

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Pathlight utilizes ultra-sensitive structural variants (SVs) to deliver critical insights into tumor behavior. Unlike traditional MRD approaches that rely primarily on single nucleotide variants (SNVs), which can be limited by sensitivity and specificity, Pathlight leverages truncal structural variants; early, tumor-defining chromosomal alterations that persist as can cers evolve.

Performance that supports clinical confidence

The TRACER study[1] set out to answer a fundamental question: can SV-based MRD detection reliably identify recurrence across the full spectrum of early breast cancer subtypes? Pathlight demonstrated 100% sensitivity and 100% specificity for recurrence detection across all major subtypes, supporting strong confidence in both positive and negative results.

Baseline detection reached 96% overall and 94% in HR+/HER2- disease, one of the most common and challenging subtypes for MRD assessment, where SNV-based assays have reported lower baseline detection rates. Pathlight delivered lead times to clinical recurrence of up to five years, with a median of 13.7 months prior to radiographic relapse. For clinicians, that window represents a meaningful opportunity to consider intervention before imaging-confirmed progressive disease, with the opportunity to positively impact clinical outcomes. Finally, ~80% of validated SVs were retained at progression as patients transitioned from early to metastatic disease, reinforcing the biological durability of SVs under therapeutic pressure.[2]

Early insights in the neoadjuvant setting

Two additional studies in triple-negative breast cancer (TNBC) illustrate how SV-based MRD monitoring can inform decisions before and immediately after surgery, where treatment choices are consequential and time-sensitive.

In a multicenter registry study[3] conducted at Dana Farber Cancer Institute evaluating patients undergoing preoperative systemic therapy, there was a 95% baseline MRD detection rate. Clearance of ctDNA during treatment was strongly associated with pathological complete response (pCR), with 79.5% of patients who cleared ctDNA achieving pCR (87% among those receiving immunotherapy). Postoperative MRD detection had a median lead time of nearly 11 months, and predicted distant recurrences with 100% sensitivity, giving clinicians a window for early intervention.

Similarly, in the Neo-n[4] randomized phase II trial of neoadjuvant nivolumab-based regimens, 91% of patients had detectable ctDNA at baseline. On-treatment DNA dynamics were highly prognostic: patients who remained ctDNA-positive had a 45% three-year event-free survival (EFS), while those who cleared ctDNA achieved ~90% three-year EFS. Baseline ctDNA-negative patients experienced 100% EFS at three years.

Together, these findings suggest that ultra-sensitive MRD assessment can stratify risk earlier than surgical or imaging endpoints alone, complementing traditional measures such as pCR and potentially informing on earlier treatment escalation and de-escalation decisions, and clinical trial strategies.

Designed for real-world oncology practice

Clinical performance only matters if a test can be seamlessly integrated into real-world practice. Pathlight's tissue fingerprints have low sample requirements and deliver results within two to three weeks, while plasma monitoring can return results in as little as one to three days—enabling timely, actionable clinical decisions.

Pathlight has Medicare coverage for Stage II–III breast cancer, including Stage IIA, reflecting rigorous analytical and clinical validation. Early adoption across leading academic and community cancer centers underscores growing clinician confidence in structural variant-based MRD monitoring.

Advancing the standard for MRD testing

Structural variants offer a biologically grounded foundation for ultra-sensitive recurrence detection and longitudinal disease tracking.

By harnessing whole-genome SV fingerprints, SAGA Diagnostics is redefining expectations for MRD testing; equipping clinicians with earlier, more reliable insights to support confident decisions when timing and accuracy matter most.

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SAGA® DIAGNOSTICS

Rewriting Life Before Birth: Entering the Fetal Genetic Intervention Era

The landscape of prenatal testing, care, and ethics is evolving as emerging technologies—such as *in utero* gene therapy and embryo editing—begin to move from research into early clinical application

Jonathan D. Grinstein, PhD North American Editor

A woman lies on an exam table, holding her partner's hand tightly with anticipation, as a technician glides an ultrasound probe across her abdomen. On the screen, shifting staticky shadows resolve into a skull, a liver, and the flicker of a beating heart. For many families, this moment brings joy and relief. For others, it's paralyzing, as doctors detect signs that something is wrong.

A single nucleotide change can cause neurodevelopmental delays and dimorphism, failing livers, and arrhythmia-ridden hearts. For decades, medicine could only identify these conditions, usually after birth. Prenatal screening has made it easier to detect progressive diseases like Duchenne muscular dystrophy, which degenerates and damages muscles before symptoms typically appear in childhood. But treating before birth could preserve tissue prior to the onset of irreversible deterioration.

Once unthinkable, genetic diseases can now be treated before birth. Fetal genetic intervention—including early screening, *in utero* gene therapy, stem cell transplantation, and even embryo editing—aims not just to diagnose disease but to correct it at its earliest stages. It is a rapidly advancing frontier, defined by technological promise and profound ethical questions.

It starts with detection

Jennifer Hoskovec, vice president of medical affairs at BillionToOne, has spent more than 20 years in prenatal genetics, an era dominated by risk assessment rather than intervention.

Jennifer Hoskovec
Vice President
BillionToOne

Historically, prenatal genetic screening has fallen into two main categories. Aneuploidy testing determines the risk of Down syndrome and other trisomies, sex chromosome abnormalities, and specific microdeletions. Screening is essential for these *de novo* mutations, which have no U.S. Food and Drug Administration (FDA)-approved genetic interventions. High-risk Down

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syndrome patients may receive a fetal echocardiogram, closer ultrasound monitoring, or tertiary care delivery with neonatal support. The standard practice is to screen, monitor, and manage.

The second category involves inherited recessive conditions like cystic fibrosis (CF), spinal muscular atrophy (SMA), and phenylketonuria. If both parents are carriers for the same genetic mutation, then their child has a 25% chance of being affected. Testing typically requires samples from both parents. If both are carriers, chorionic villus sampling (CVS) and amniocentesis can detect fetal abnormalities in the first and second trimesters, respectively. However, getting each partner to follow up is a major hindrance. "When people go through a screening process and are found to be carriers, less than 50% of their partners complete the testing," Hoskovec told *Inside Precision Medicine*. "Half of U.S. carriers of these genetic conditions, whether common or rare, don't know what it means for their pregnancy. That limits their ability to get diagnostic testing because we do not have all the pieces of the puzzle."

Hoskovec's team developed a workaround: a single-gene noninvasive prenatal test that analyzes fetal cell-free DNA (cfDNA) circulating in maternal blood. Around nine weeks into pregnancy, fragments of fetal DNA shed from the placenta can be sequenced and quantified. If a mother is a carrier for a condition like CF or sickle cell disease, the test looks for a second variant that is not present in her DNA and forms evidence of paternal contribution.

"For example, if a mother has [the] sickle cell trait, we first sequence the full beta-globin gene in the cfDNA, which contains a mixture of maternal and fetal DNA," Hoskovec said. "We look for a second variant not present in the mother that would indicate paternal contribution."

Despite not replacing CVS or amniocentesis, Hoskovec said the result is highly sensitive, identifying 95% of affected pregnancies in the conditions it covers. Crucially, it does not require partner testing. "This is a stepping stone," Hoskovec explained. "This earlier detection will likely accelerate the field by increasing the number of eligible patients for clinical studies and registries, improving equitable access across ethnic groups, and advancing precision medicine in prenatal care."

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Avoiding germline editing

As screening opens the door, fetal surgeons and gene therapy researchers are taking their first steps through it. A pediatric surgeon at the Yale School of Medicine, David H. Stitelman, MD, believes prenatal treatment has benefits. The fetus is small, so it can receive higher doses based on weight. As its immune system is still developing and more tolerant, stem cells are growing quickly and organs are still being formed, so problems can be fixed before they become permanent. Because the placenta exchanges oxygen, lung conditions like congenital diaphragmatic hernia can be treated during fetal life. But once a newborn takes a first breath, defective lungs can spell immediate crisis.

David H. Stitelman, MD
Associate Professor
Yale-New Haven Children's Hospital and Yale School of Medicine

Fetal therapy is not new. Specialized centers have performed open fetal surgery for spina bifida and diaphragmatic hernia lung growth, and blood transfusions for fetal anemia dating back to the 1960s. What is new is the molecular toolkit. Stitelman's lab is investigating gene editing methods that use the cell's repair machinery to fix one- to three-base-pair DNA errors. Another team, led by pediatric and fetal surgeon Tippi MacKenzie, MD, at the University of California, San Francisco, is using viruses to replace genes for lysosomal storage diseases and fetal stem cells for alpha thalassemia.

Some diseases require only modest correction. In hemophilia, one percent normal clotting factor expression improves outcomes greatly. Increasing the expression of functional CFTR protein to 15% of wild-type levels may cure CF or at least make it manageable. Even a small number of liver cells corrected in hereditary tyrosinemia can boost growth and repopulate the organ. However, some situations, such as congenital cancer syndromes, may require nearly 100% correction. At present, Stitelman's team achieves single-digit percentage editing in models of CF and beta thalassemia. "We're in the optimization phase," Stitelman told *Inside Precision Medicine*. "We are testing different nanoparticles and generations of editing strategies to incrementally reach therapeutic levels."

Stitelman draws a clear ethical boundary: this is somatic editing, not germline editing. The aim is to treat the fetus as a patient, not to create heritable genetic changes. Instead of editing embryos *in vitro*, systemic therapeutic agents are delivered to avoid reproductive cell damage.

Unintended germline modification remains a concern. Editing a target gene could inadvertently disrupt developmental genes and affect future generations. But, Stitelman argues, medicine always carries risk. "In 1950, children with leukemia all died," said Stitelman. "Today, some forms have a 98% long-term survival rate with chemotherapy. We know chemotherapy can cause germline mutations, yet we accept that risk because it saves lives. With gene editing, the issue is not zero risk but understanding and quantifying the risk. Ideally, there would be no measurable off-target effects. In the places we have examined, we have not seen off-target effects."

One pregnancy, two patients

In a landmark trial in 2011 known as the Management of Myelomeningocele Study, investigators found that fetal surgery for severe spina bifida (myelomeningocele) achieved better results than postnatal repair. Surgically closing the spinal defect *in utero* improved motor function and reduced the need for shunting to relieve hydrocephalus. The benefit was so clear that the trial was stopped early and influenced how doctors treat structural birth defects.

At the University of California, Davis, biomedical engineer Aijun Wang, PhD, is working closely with fetal surgery pioneer Diana L. Farmer, MD, to evolve fetal intervention from heroic surgery to cellular and molecular therapy. Wang and Farmer launched the Cellular Therapy for *In Utero* Repair of Myelomeningocele (CuRe) trial, combining fetal surgery with stem cell transplantation. The goal is to not only close the spinal defect but also restore neural tissue and improve long-term function.

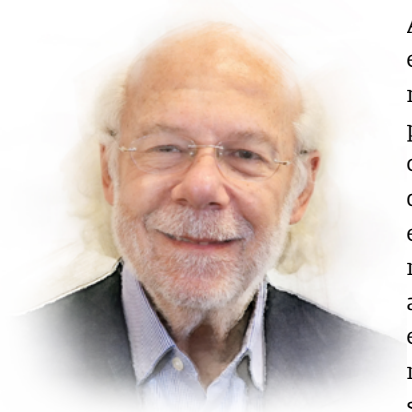
Aijun Wang, PhD
Professor
University of California, Davis (UC Davis)

The lens that Wang has used to focus his research is fetal and maternal safety. "The fetus is the patient, but treatment inevitably carries some risk to the mother," Wang told *Inside Precision Medicine*. "Open fetal surgery, in particular, poses significant maternal risk. Genetic treatments introduce additional uncertainties because the long-term effects of DNA modification are not fully understood. Safety must remain the highest priority."

Genetic medicine delivery is a critical challenge for all life stages, but the stakes are particularly high for a developing fetus. In fetal development, targeting stem cell populations is especially important because these cells are highly active, proliferating, and migrating. If edited successfully at the right developmental window, their progeny will carry the correction. The problem would be if the edit was not just unsuccessful but detrimental.

Wang's lab focuses on delivery systems, particularly lipid nanoparticles carrying mRNA-encoding gene-editing enzymes. For genetic manipulation and high-throughput screening, Wang's lab utilizes mouse models. Fetal sheep are used for scaling and dosing, while human organoids are used for human-specific editing and functional outcomes.

"In our clinical work, we have engaged with the FDA and conducted extensive preclinical studies," said Wang. "Using multiple complementary models is essential. Combining small animal models, large animal translational models, and human organoid systems provides a comprehensive framework for product development, from early screening to human-focused therapeutic design."



Norbert Gleicher, MD
Founder & Medical Director
Center for Human Reproduction

Although the field is highly exciting and progressing rapidly, Wang warns against premature application, which could be dangerous. Safety, developmental biology, ethical considerations, and multidisciplinary collaboration are all essential. "Despite the excitement in the field, we must proceed cautiously," said Wang. "There is strong potential for correcting specific mutations, especially point mutations, using precise gene editing approaches such as base editing. However, safety evaluation must precede rapid clinical application."

Effective progress requires a village of physicians, surgeons, researchers, engineers, and ethicists working together. Scientific progress requires caution, responsibility, and thorough evaluation before clinical use.

The earlier, the better

If fetal intervention treats a diagnosed fetus, embryo editing operates even earlier—at the blastocyst stage in *in vitro* fertilization (IVF). Norbert Gleicher, MD, a fertility specialist known for treating some of the oldest and most difficult IVF patients in the United States, approaches genetic technologies with caution. Due to biological mosaicism, sampling limitations, and his belief that many abnormal embryos self-correct or develop normally, Gleicher opposes preimplantation genetic testing for aneuploidy.

But when it comes to single-gene diseases, he sees a different calculus. Couples with recessive mutations may have one-in-four embryos affected, and in dominant or X-linked diseases, half may carry the mutation. For patients who produce few embryos—especially older women—discarding affected embryos can mean losing precious chances at pregnancy. "If you can cure an embryo rather than discard it," Gleicher told *Inside Precision Medicine*, "that makes a lot of sense."

For single-gene diseases, Gleicher believes genetic editing with CRISPR or other platforms is the most straightforward intervention. He points to the 2025 work at the Children's Hospital of Philadelphia on Baby KJ as a recent milestone. Even partial correction, which Gleicher believes is likely the case with Baby KJ—though no liver biopsies have been extracted—can transform prognosis. Gleicher said, "Correcting some cells was enough to clinically cure the baby, at least for the time being, from symptoms of a disease that historically kills affected children within a few years. However, we do not know whether the treated baby, who likely still has many affected cells, might become symptomatic again later in life."

To Gleicher, success in a newborn is all the more reason to apply genetic intervention to fetal stages. "If this can be successful in a full human being, imagine how much easier it would be at the blastocyst stage, or even earlier at the cleavage stage, when the embryo consists of only six to eight cells," said Gleicher. "If [CRISPR] is applied at that point, correcting those six to eight cells would mean that all their daughter cells would also be corrected. The result would be a normal baby at birth. That is the much stronger argument in this case."

Just because something is possible, it doesn't necessarily mean it should be done, and Gleicher establishes a clear ethical boundary. Editing to prevent a devastating single-gene disease is one thing. Editing for traits—eye color, intelligence, polygenic risk scores—is another. Polygenic predictions explain only a fraction of trait variance, and embryo implantation itself is uncertain. To him, offering polygenic selection in IVF is not only scientifically dubious but also ethically troubling. "It is surprising that professionals, particularly in genetics, would suggest such an approach," said Gleicher. "It is worse than snake oil, because while snake oil may occasionally work by accident, this carries a real risk of causing serious harm."

A pretty penny

What ultimately restricts fetal genetic intervention is timing. Early screening increases experimental trial eligibility, and early treatment may preserve organ development before irreversible damage. In conditions like CF and SMA, where postnatal gene therapies are expensive and delivered after injury, fetal intervention could change outcomes. Frontline screening can identify high-risk pregnancies at 11 weeks without family history or ethnicity, expanding trial access.

Yet, fetal genetic interventions require specialized teams, advanced delivery systems, counseling, and long-term follow-up. Without careful planning and reimbursement policies, only a few top-tier centers could progress, widening the gap. Ethical scrutiny remains inseparable from progress. Innovation must balance maternal risk, fetal benefit, and future consequences with safety, appropriate use, and clear limits. As prenatal care shifts from prediction to prevention, restraint and evidence will determine its future. ■

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.

Igyxos Biotherapeutics is Enhancing Hormone Activity to Treat Infertility

A Discussion with Marie-Christine Maurel, PhD

by Helen Albert Senior Editor

Since the first in vitro fertilization (IVF) baby was born in 1978, the options for couples or individuals struggling with infertility have improved exponentially. However, the core methods that make up this process are still fairly crude and associated with significant discomfort and side effects. This is something that reproductive endocrinologist Marie-Christine Maurel, PhD, chief scientific officer (CSO) and founder of Igyxos Biotherapeutics, is hoping to improve with the company's first-in-class antibody treatment for infertility.

The antibody treatment—IGX12—amplifies the body's own follicle-stimulating hormone (FSH) signal in both women and men, potentially improving production of both sperm and eggs with fewer injections than IVF and more physiological control.

Maurel has a doctorate in reproductive physiology from Pierre & Marie Curie University in Paris and worked as a post-doctoral fellow at the Pasteur Institute in Paris. The idea for the infertility treatment, which achieved promising Phase I results at the end of last year, originated from work at Maurel's first biotech firm ReproPharm, which she co-founded in 2009 after winning a French "national competition for the creation of innovative companies."

Maurel previously worked at the National Institute of Agronomic Research (INRA) near Paris for more than 25 years. Her group studied how gonadotropins affect fertility in animals and developed monoclonal antibodies that impact the activity of these reproductive hormones. ReproPharm initially used this research to improve fertility in farm animals, but when the team realized the same ideas could be applied to human infertility, the initial company was split into ReproPharm Vet and Igyxos in 2017 to focus on animal and human fertility problems, respectively. Alongside serving as CSO at Igyxos, Maurel remains president and CEO of ReproPharm Vet.

Maurel discussed her inspirations, research, and motivations for founding both companies with *Inside Precision Medicine*'s senior editor, Helen Albert, and outlined why Igyxos's antibody could be so important if it achieves market authorization.

Marie-Christine Maurel, PhD

Q: What inspired you to become a scientist?

Maurel: When I was younger, I was passionate about science, and biology in particular. In my teens, I hesitated between choosing to study medicine or biological research. Finally, I chose biological research, but remained very interested in biomedicine. Currently, I mix both topics because we are developing a new medicine to treat infertility problems in humans, so it's a mix of research and medicine. I still enjoy scientific research, so I don't regret my decision.

Igyxos Biotherapeutics

Q: You worked in academia for a long time before you decided to make the move into industry. What inspired you to do that?

Maurel: In nature, there are lots of things that occur. You just have to discover them and know how to ask the right questions to understand how they work. Penicillin is an extraordinary example. And here it's the same thing. We were doing experiments with sheep and goats. When we discovered that the ewes or does that secreted potentiating antibodies were hyper prolific and had high numbers of offspring, we wondered why. Normally, antibodies block the activity of a hormone and never enhance it. But in this case, we discovered that these particular antibodies were able to potentiate the activity of reproductive hormones. It was a marvelous result because it meant [that] it was possible to avoid the use of hormone treatment in animals. When my team and I discovered the existence of these potentiating antibodies, I quickly assessed their potential for application in both human and animal health. I wanted to develop and translate the research. The fact that there are potentiating antibodies for FSH is extraordinary, because antibodies are normally always inhibitory. I wanted to develop a potentiating antibody so we could have much more effective treatments for infertility. I also won a national competition for the creation of innovative companies, which helped with founding ReproPharm. It was a wonderful adventure to create a new biotech with our innovation.

> "I wanted to develop a potentiating antibody so we could have much more effective treatments for infertility."

Q: What did you learn from the experience of founding ReproPharm?

Maurel: I learned a lot of things. It was a human experience. I met a lot of people in medicine and industry who were very important for the development of the company and myself as well. These people helped me to build and to progress the company. Building a good network was important for me when I went into industry. I would also advise this for young people who want to create a biotech company. Meeting good people helps enormously!

Q: What made you decide to split ReproPharm into the two spinout companies, ReproPharm Vet and Igyxos Biotherapeutics?

Maurel: My research group was based at INRA initially. It's a French academic research center focused on animal reproduction. We started with an animal reproduction problem linked to breeding ovine and caprine species, but early on, we tried our innovation on human hormones because we thought it could be an excellent approach to treat infertility problems in women. We developed an antibody against human FSH to see if we could enhance the activity of human FSH and in animal species. We got some money to carry out the first experiments and had very good results. We then decided to develop this innovation in human health, but needed more funds to develop it further. All our existing investors told us that they were unwilling to take the risk of investing in a company developing both veterinary and human medicine. It was impossible for them because it was not separated, so we decided to split the first company into two independent companies in 2017.

Q: Did any of your experiences at ReproPharm help you to do things better at Igyxos?

Maurel: First, I can say that at Igyxos, from the experience

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with ReproPharm, I wanted to do as much research and development on IGX12 as possible using our own funds, and license the therapy as late as possible because that gives us more freedom to develop it as we want to. I think it is necessary to be independent as long as possible for this reason.

Also, during the founding and development of ReproPharm, we developed a lot of animal models, which are very useful now to develop IGX12 for treating human infertility, both in men and women. So it was a very strong basis for Igyxos. All these animal models we developed at ReproPharm were important for developing IGX12 and getting it to clinical trials.

> "We also want to develop a new and innovative treatment for women with infertility, which could be more efficient than current treatments that are burdensome and costly."

Q: Can you tell me a bit more about what you're trying to achieve at Igyxos?

Maurel: FSH is exactly the same hormone in men and women. It has different target cells, but the molecule is the same. So one potentiating antibody could act on FSH either in men or women. It's exactly the same mechanism of action, so we can develop the first treatment in men with oligozoospermia, for example.

We also want to develop a new and innovative treatment for women with infertility, which could be more efficient than current treatments that are burdensome and costly. Now it's necessary to repeat the same hormone treatment four or five times to have a baby with a 50% chance of success. We think that it will not be necessary to repeat our treatment because we have a lot of proof of concept in animals. We have shown we can get better gametogenesis with better quality of ovulation than other methods.

Q: You reported Phase I results in December 2025. Were you happy with the findings?

Maurel: Yes, it was totally successful. We got very nice results. No adverse events, and we have some first efficacy results, so we can start Phase II trials, but we need to raise money first.

The trial results have helped to interest investors, and we are now in contact with several funds. If the fundraising is successful, we hope to be able to start Phase II trials soon.

Q: You mentioned that IGX12, if approved, would be the first such treatment for men with common fertility issues like oligozoospermia. Why have more treatments not been developed for men before?

Maurel: The problem of male infertility was not considered for a long, long time, perhaps because of cultural issues. Now there is a huge problem with infertility in men because sperm counts are decreasing. Numbers decreased from around 100 million per mL to 50 million per mL between 1973 and 2018. So this treatment is very necessary!

Q: Do you think that if your treatment is successful, it could make IVF more accessible?

Maurel: Yes, I think that it would allow a reduction in both time and economic cost, because as I said previously, the treatment will be more efficient, so no need to repeat it. We developed the concept that the antibody could act on the endogenous FSH. So, using our approach, it would not be necessary for women to inject FSH, because the antibody is able to boost the woman's own FSH. In the animal health domain, we use the antibody only. We never inject endogenous hormones, so it's very clean. In humans we will also only inject the antibody. We never inject FSH. So it's a single injection per month. If we succeed, it's a very big market and a very nice treatment for a lot of people.

Q: Could IGX12 make fertility treatment more targeted for specific people or certain population groups?

Maurel: Yes, for example, men with oligozoospermia. That means the sperm count is too low for natural conception. If it's a very low level, it's not even possible to do IVF. So we will target this category of men. In women, we will target those who don't have a good predicted result with IVF, for example, if they have a low follicular count. So we plan to target these two populations, which have few chances to succeed at having children with current treatments.

Q: What are your future plans for Igyxos and ReproPharm Vet?

Maurel: For Igyxos, the current priority is to raise funds to start Phase II clinical trials, both in men and women. For ReproPharm Vet, the objective is to conclude an ongoing collaboration with a big veterinary and pharma partner. ■

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.

Unlocking the Science: Hereditary Cancer Genetic Testing in Cancer Care

A Q&A with Rebecca Previs, MD, MS, Senior Director of Medical Affairs at Labcorp Oncology

Hereditary cancer testing is one of our most powerful tools in the fight against cancer. It enables early detection, personalized treatment decisions, informed surgical decisions, and proactive prevention strategies for patients and their families. Clinical guidelines increasingly support broader use of hereditary cancer testing, and it is becoming more commonly used in clinical practice.

And yet, too many people who meet the criteria for hereditary cancer testing never receive it.

Why is hereditary cancer testing so important in oncology today?

Hereditary cancer testing plays an essential role in precision oncology. For patients with cancers driven by inherited genetic variants such as breast, colorectal, ovarian, pancreatic, or prostate cancers, genetic information can directly shape critical care decisions, such as greater patient awareness of risk, earlier and more frequent screening, and identification of targeted treatments or clinical trials, which can significantly influence health outcomes. Without the insight provided by this testing, clinicians are missing essential data that could guide targeted treatments, affect surgical planning, and inform surveillance approaches for both patients and their families.

If testing plays such a critical role, why are so few patients receiving it?

Even with clear guidelines and strong evidence supporting its value, hereditary cancer testing remains underutilized in routine oncology practice. Its broader adoption is often hindered by logistical, educational, and workflow challenges that make consistent implementation difficult.

Oncologists are navigating increasingly complex diagnostic and therapeutic options. In a busy workflow, selecting the appropriate genetic test, interpreting nuanced results, and integrating them into a patient's treatment plan can be daunting. Limited time, minimal formal training in medical genetics, and the absence of streamlined decision-support tools can further complicate efforts to incorporate testing into everyday clinical care.

What needs to change to improve access of hereditary cancer testing?

To meaningfully expand access, we need to move from isolated ordering to integration at scale. That starts with making hereditary cancer testing a routine part of everyday clinical care, not something reserved for select patients or specialized clinics.

It requires a connected model that brings together genetic insights and diagnostic data, giving every provider information that can guide better care and lead to better outcomes. When genetic testing is fully embedded in clinical workflows, it does what it is designed to do: inform decisions, identify patients who need additional surveillance or preventive strategies, and give individuals clearer, more actionable information about their health.

But improving access is not just about technology; it is also about the people who help patients and clinicians interpret these results. Genetic counselors are essential to this work, yet demand for their expertise often exceeds their availability. To scale their reach, we need to reduce administrative burden through EHR integrations, lab-driven digital support tools, and more transparent coverage and cost information. That allows genetic counselors to focus on what actually improves care: interpreting results, guiding decisions, and supporting patients.

Ultimately, expanding access to hereditary cancer testing isn't just about reaching more individuals. It's a foundational step toward advancing evidence-based, preventative, and personalized oncology at a population level.

FcRn Inhibition in Autoimmune Disease:

2026 Outlook for Graves' Disease, Alloimmune Conditions, and Sjögren's Disease

by Tiffany Yesavage, PhD

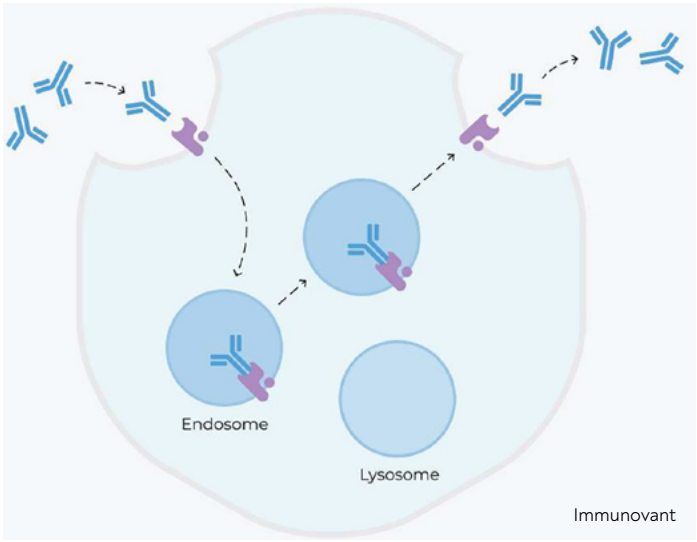
Although immunoglobulin G (IgG) normally protects the body against pathogens, it can become problematic in many autoimmune diseases like lupus, rheumatoid arthritis, Graves' disease, myasthenia gravis, and Sjögren's disease.

"In these conditions, the immune system is creating defective IgGs—called autoantibodies—that are no longer fighting infections," explained Eric Venker, MD, PharmD, CEO of Immunovant. "Instead, they are attacking a part of your normal functioning body and causing dysfunction."

Eric Venker, MD, PharmD
CEO, Immunovant

Historically, autoimmune conditions have been challenging to treat because therapies like steroids rely on broad immune suppression, noted Leonard L. Dragone, MD, PhD, disease area leader of autoantibody and rheumatology at Johnson & Johnson Innovative Medicine. These non-specific approaches are often inconsistently effective and lead to adverse side effects.

"For many autoimmune diseases, there is a need for more targeted strategies that address disease-causing autoantibodies directly, rather than broadly suppressing the immune system," emphasized Dragone. Beginning in 1998, the U.S. Food and Drug Administration (FDA) approved infliximab, a tumor necrosis factor (TNF)-α inhibitor, for the treatment of Crohn's disease. This marked the first approval of a monoclonal antibody for the treatment of a chronic condition. Since then, targeted therapies for autoimmune diseases have expanded to address cytokine signaling pathways (TNF-α, IL-6, IL-17, IL-23), Janus kinase (JAK–STAT) signaling, and immune cell surface markers (CD20).

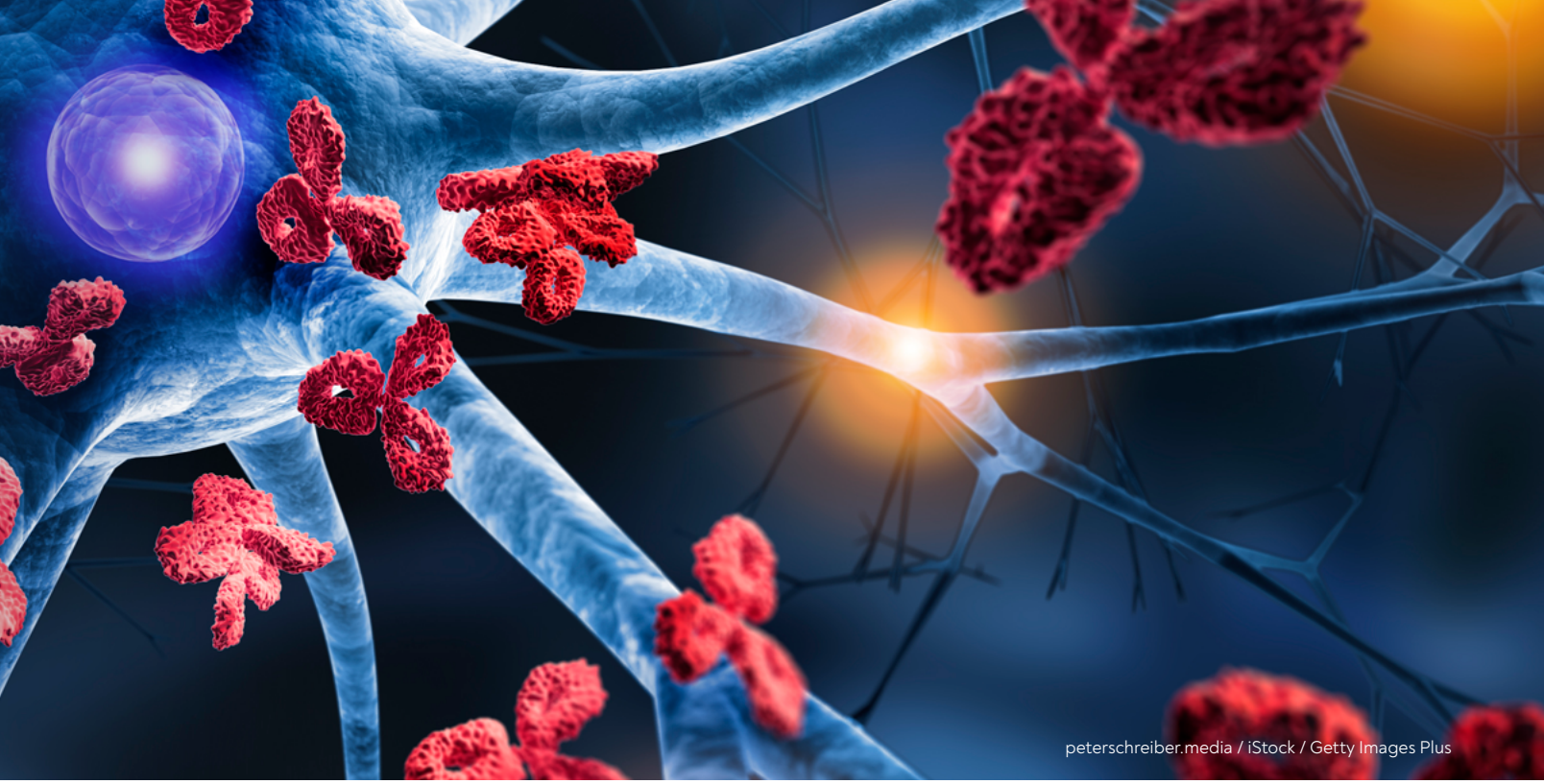


FcRn maintains levels of IgG in circulation by preventing IgG degradation in the lysosomes of cells. However, FcRn drugs block this pathway.

Leonard L. Dragone, MD, PhD
Disease Area Leader
Johnson & Johnson Innovative Medicine.

Another such targeted strategy involves an emerging drug class called FcRn blockers, which are now showing considerable promise in the treatment of certain autoimmune diseases.

FcRn blockers, which typically consist of monoclonal antibodies or antibody fragments, work by



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blocking the function of a protein receptor called FcRn (neonatal Fc receptor). This prevents IgG recycling, thereby reducing IgG levels in the body.

Venker compares FcRn inhibitors to cholesterol-lowering drugs such as statins. "LDL is the disease-causing agent that healthcare providers target to prevent many cardiovascular diseases. Likewise, in the case of FcRn blockade, we are aiming to lower IgG. We believe that deeper IgG reduction may provide improved results."

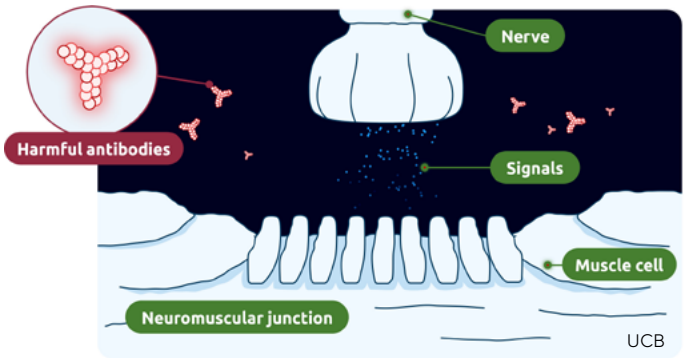
Mark A. Lupo, MD
Founder and Medical Director
Thyroid & Endocrine Center of Florida

As of early 2026, the FDA has approved three FcRn inhibitors for the treatment of myasthenia gravis, a chronic autoimmune disorder affecting up to 100,000 people in the U.S. Efgartigimod (approved in 2021), rozanolixizumab-noli (approved in 2023), and nipocalimab-aahu (approved in 2025) all work by reducing pathogenic IgGs associated with the disease.

"With FcRn blockers, it is exciting to know that there is now a targeted mechanism for patients around the world with autoimmune diseases caused by an IgG autoantibody," said Venker.

Tackling Graves' disease

In Graves' disease, an IgG autoantibody called thyrotropin receptor antibody (TRAb), which targets the thyroid-stimulating hormone (TSH) receptor of the thyroid, is produced. The condition, which is the most common cause of hyperthyroidism, causes elevated heart rate, shakiness, irritability, muscle weakness, and weight loss.



Myasthenia gravis results from harmful antibodies (anti-AChR or anti-MuSK) produced by the immune system that interfere with signaling in the neuromuscular junction.

"TRAb is an IgG antibody, but it is a badly behaving one that is basically hijacking the thyroid system," noted Venker. "It doesn't serve any purpose that is normal at all."

Unfortunately, the toolkit for treating Graves' disease hasn't changed much since 1950, when the FDA approved the drug methimazole, said Mark A. Lupo, MD, founder and medical director of the Thyroid & Endocrine Center of Florida.

Methimazole is an anti-thyroid drug that slows down the production of thyroid hormones. Although Graves' patients benefit from anti-thyroid drugs, Lupo estimates a 50% relapse rate within two years of discontinuing these drugs.

Other options for treating Graves' disease include surgical removal of the thyroid or the use of radioactive iodine to induce destruction of the thyroid gland. However, these approaches result in permanent hypothyroidism, and patients typically require lifelong thyroid hormone replacement after treatment.

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Because TRAb is an IgG, FcRn drugs represent a potential autoimmune solution for Graves' disease. Like all FcRn blockers, they may work by decreasing TRAb recycling and lowering TRAb levels.

Lupo highlights Immunovant's recent proof-of-concept study of an FcRn inhibitor for Graves' disease, the first such study for the condition. "Despite the small number of patients (around 25), the results from this study suggest a potential, durable remission six months off treatment," said Lupo.

Hani Houshyar, PhD
Strategy Team Lead
argenx

While study participants experienced an increase in total IgG levels following treatment, TRAb levels remained low over a six-month period. The thyroid also decreased in size. "To see TRAb levels down six months off the study drug caught the attention of the endocrine thyroid community," noted Lupo.

"What was unexpected was that TRAb, the disease-causing antibody, stayed down for many months after stopping the investigational therapy," added Venker.

"I think we are overdue for a new option in Graves' disease that could help break some of these methimazole cycles and potentially address not the innocent thyroid gland but the underlying immune system issues," concluded Lupo.

But are they safe?

Venker recalls that safety was an initial concern with FcRn inhibition. After all, these drugs work by reducing IgG, an essential part of the immune system. "Any time you are using an autoimmune drug that potentially suppresses your immune system, you have to think about going too far. Am I going to cause an infection or weaken the immune system?

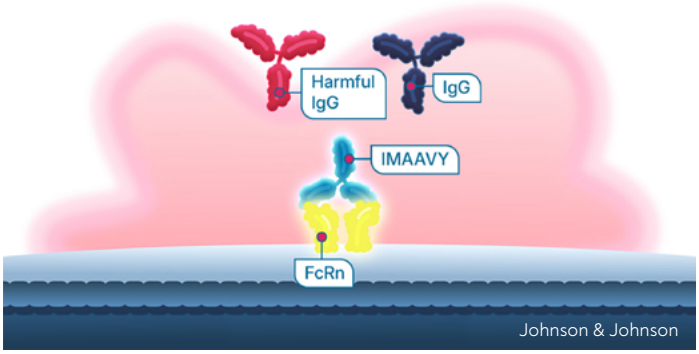
"So far, this investigational drug has demonstrated a safety profile we expected, and appears positive," noted Venker. "That makes sense mostly because FcRn blockade is pretty targeted."

"Although there are no head-to-head comparative safety trials yet, most clinicians and principal investigators view FcRn blockers as relatively safe," added Lupo. "There are FcRn blockers on the market, and they have demonstrated a good safety record in patients." The most common side effect tends to involve injection site reactions with either intravenous or subcutaneous delivery.

Preventing fetal exposure

During pregnancy, maternal antibodies—called alloantibodies—can cross the placenta and attack the organs and tissues of the fetus, explained Dragone.

A distinguishing feature of Johnson & Johnson's nipocalimab is its pH-independent binding to FcRn. This allows it to bind with high affinity in the placenta, a low-pH environment.



Nipocalimab (IMAAVY®) and other FcRn blockers bind to FcRn receptors and reduce levels of both normal and harmful IgG antibodies.

The drug is currently showing potential in the treatment of two alloimmune diseases of pregnancy: hemolytic disease of the fetus and newborn (HDFN) and fetal and neonatal alloimmune thrombocytopenia (FNAIT), said Dragone. These conditions can arise during alloimmunized pregnancies, when the pregnant person's immune system forms alloantibodies against fetal red blood cells (HDFN) and/or fetal platelets (FNAIT). Importantly, published data on nipocalimab suggest minimal transfer of the drug to the fetus or infant. "Therapies like nipocalimab offer a blueprint for how precision medicine can expand to include pregnant people, a population that has historically been excluded from drug development," noted Dragone. "Our approach with nipocalimab has the potential to change how we think about treating autoantibody-driven diseases in people of childbearing age."

Omar Sinno, MD
Medical Strategy Lead, UCB

The FDA has granted a fast track designation to nipocalimab for both FNAIT and HDFN, and Phase III studies are underway to further investigate the drug in both diseases.

Expanding indications

"There are probably 20 trials out there for FcRn blockers, and many are likely to work," noted Venker. "There are a ton of potential new indications under investigation, including rare diseases that have been ignored historically."

He notes that Immunovant's pipeline alone includes potential indications in endocrinology (Graves' disease), rheumatology (rheumatoid arthritis, Sjögren's disease, and cutaneous lupus erythematosus), and neurology (myasthenia gravis and chronic inflammatory demyelinating polyneuropathy).

Venker stresses that no FDA-approved solutions exist for Sjögren's disease, which affects as many as four million Americans. The condition causes severe dry eyes and mouth, fatigue, and joint and muscle pain. Immunovant and Johnson & Johnson are conducting clinical trials to evaluate FcRn blockers for the disease.

Meanwhile, argenx's FcRn inhibitor efgartigimod has been used in 19,000 people worldwide for myasthenia gravis and other autoimmune conditions, said Hani Houshyar, PhD, FcRn asset strategy lead for argenx.

"However, we believe myasthenia gravis is just the beginning," she said. As of 2026, the company has active clinical trials to test the drug's effectiveness in additional autoimmune diseases with high unmet medical need, like myositis, Sjögren's disease, ocular myasthenia gravis, systemic sclerosis, Graves' disease, and autoimmune encephalitis.

Steve Mahoney
President and CEO
Viridian Therapeutics

UCB's rozanolixizumab was the first FcRn blocker to be approved for the treatment of generalized myasthenia gravis in adults who are positive for anti-AChR or anti-MuSK antibodies, who together account for approximately 90% of cases, said Omar Sinno, MD, UCB's U.S. medical strategy lead of rare disease. So far, the drug has been approved in the U.S., Canada, the EU, Australia, Switzerland, China, Turkey, and Korea.

Rozanolixizumab is administered via a convenient subcutaneous infusion rather than intravenously. The company's long-term studies demonstrate robust IgG reductions (up to 75%) with sustained benefit across multiple treatment cycles. UCB is also investigating rozanolixizumab as a potential treatment for a rare autoimmune condition called myelin oligodendrocyte glycoprotein antibody-associated disease.

Finally, Johnson & Johnson's nipocalimab is in mid-to-late-stage studies for Sjögren's disease, lupus, warm autoimmune hemolytic anemia, and chronic inflammatory demyelinating polyneuropathy.

Drugs in development

Viridian Therapeutics is currently investigating two FcRn inhibitors, VRDN-006 and VRDN-008, said Steve Mahoney, president and CEO. Both candidates are designed as subcutaneous products that can be conveniently self-administered by the patient.

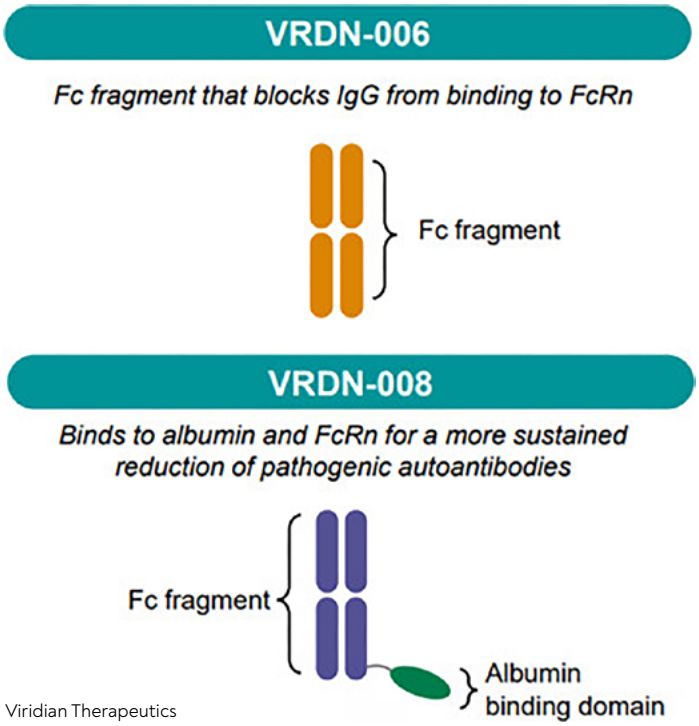
VRDN-006 is an Fc fragment in Phase I trials, while VRDN-008 is made up of an Fc fragment and an albumin-binding domain designed to prolong IgG suppression. Mahoney notes that VRDN-008 showed a longer half-life and more sustained IgG reduction than efgartigimod in a high-dose, head-to-head study in non-human primates.

Clinical trial results of VRDN-008 in healthy volunteers are expected later in 2026. "What we believe differentiates VRDN-008 from other FcRn inhibitors is a longer half-life, which has the potential to support less frequent dosing for patients to enhance convenience," said Mahoney.

Although three FcRn blockers are currently FDA-approved to treat myasthenia gravis in the U.S., Venker notes that Immunovant is continuing to investigate the condition with the company's follow-on FcRn candidate, imeroprubart (IMVT-1402).

In Immunovant's proof-of-concept study for Graves' disease, TRAb stayed low even six months after the investigational treatment was discontinued. But how long will this effect last? "We don't know that yet because our randomized trials with IMVT-1402 are ongoing," Venker said. "However, Graves' disease has given us the first hint that FcRn drugs may be able to put certain autoimmune conditions into permanent remission."

"A key question for autoimmune disease, the holy grail, so to speak, is whether we can reset the immune system so the person can function normally without medication for the rest of their lives," he added.



Viridian Therapeutics

Viridian's VRDN-006 (top) is an Fc fragment, whereas VRDN-008 (bottom) is made up of an Fc fragment and an albumin-binding domain designed to prolong IgG suppression.

Finally, argenx is developing ARGX-213, a next-generation FcRn inhibitor engineered to extend half-life and sustain IgG reduction.

"Looking ahead, FcRn inhibition represents an increasingly important approach across IgG-driven disease," noted Sinno. "By selectively reducing pathogenic IgG, these agents enable more targeted autoimmune care. And as clinical experience with FcRn inhibition grows, treatment paradigms may shift toward earlier intervention." ■

Tiffany Yesavage, PhD is a freelance writer from Denver, Colorado.

Yuichiro Chino / Getty Images

TOP 5 FIRMS ENGINEERING HEALTHCARE IN THE CNS SPACE

by Jonathan Smith, PhD

Central nervous system (CNS) treatments are having a major comeback. These five precision medicine players plan to ride the resurgence.

After a decade of stagnation, the CNS space is seeing a revival in sales and R&D spending as the market was last year projected to surpass $80 billion for the first time since 2013 and hit around $127 billion.

Recent landmark approvals have brought attention back to the CNS, including the U.S. Food and Drug Administration (FDA)'s greenlight of Eisai/Biogen's lecanemab (Leqembi) for the treatment of Alzheimer's disease in 2023, and the FDA approval of Bristol-Myers Squibb's schizophrenia treatment xanomeline/trospium chloride (Cobenfy) in 2024.

At the same time, Johnson & Johnson's depression treatment, esketamine (Spravato), is on its way to blockbuster status, showcasing the growth potential of the CNS market.

These successes accompany an emerging shift in psychiatry clinical trials from subjective rating scales to more objective endpoints, including digital and physiological measures, with the potential to better tailor treatments to a patient's biological makeup.

Startups and scaleups are attracting increasing investor attention for their potential to change the way we treat CNS conditions. Check out our list of the most exciting companies that have netted the biggest investor dollars.

1 aerska

Aerska

Founded: 2025 | **Headquarters:** Dublin, Ireland

Aerska's name is derived from an Irish proverb stating that people survive in each other's shelter, emphasising the strength of its team.

This team includes co-founder Jack O'Meara, previously co-founder of the liver-focused RNA interference (RNAi) biotech Ochre Bio, who is driven by the experience of loved ones suffering from Alzheimer's disease.

Aerska is developing RNAi therapies for neurodegenerative conditions, including Parkinson's and Alzheimer's disease.

While there are already FDA-approved RNAi therapies on the market, such as Alnylam's patisiran (Onpattro), these are typically focused on liver and cardiometabolic conditions rather than the CNS.

Aerska's technology consists of antibody "brain shuttles" that bind to proteins on the blood-brain barrier (BBB). They then carry a payload RNA into the brain.

The payload, which is designed based on data-driven patient stratification and disease biomarkers, then silences specific genes driving the disease.

Aerska has already raised $60 million since its launch, including a $21 million seed round in October 2025 and a $39 million Series A round in February 2026, co-led by EQT Life Sciences and age1.

The company, which has research operations in the U.K., is using the latest funding to drive its pipeline programs toward clinical testing.

2 BEACONBIOSIGNALS

Beacon Biosignals

Founded: 2019 | **Headquarters:** Boston, Massachusetts, U.S.

Beacon Biosignals was co-founded by a team including its CEO—MIT neuroscientist Jacob Donoghue, MD, PhD—and its CTO, the machine learning researcher Jarrett Revels.

Boasting more than 100 employees, the company's goal is to provide objective biomarkers in drug development that neurology and psychiatry have traditionally lacked compared with other areas of precision medicine.

Its FDA-cleared Waveband device measures the brain's activity, known as electroencephalography (EEG), while patients sleep at home. The EEG data is then stored, quality-controlled, and fed into AI models that can guide the design of clinical trials.

For example, Beacon's EEG data can identify patients with Alzheimer's disease who have worse outcomes and might need a more targeted treatment or a different clinical trial than other patients.

Beacon raised $27 million in a Series A round in 2021 and an oversubscribed Series B round worth $86 million in November 2025.

The B round, which included investors such as Innoviva, Google Ventures, and Nexus NeuroTech, will help the startup to accelerate the discovery of neurobiomarkers and broaden clinical adoption of the technology.

Beacon acquired the French sleep monitoring company Dreem in 2023 to access its monitoring data and headband technology. Beacon then acquired the Ohio-based CleveMed in April 2025 to harness technology measuring breathing, oxygen, and other signals.

3 BRAINOMIX

Brainomix

Founded: 2010 | **Headquarters:** Oxford, U.K.

Brainomix was founded by a team including CEO Michalis Papadakis, PhD, who was scientific director of the preclinical stroke lab at the University of Oxford.

Brainomix is dedicated to speeding up patient care in cases of stroke, where speedy treatment is key.

Brainomix's flagship product, Brainomix 360 Stroke, is designed to harness AI to interpret brain scans and detect blood clots in patients with stroke, speeding up clinical decision-making.

The product involves a group of tools that automatically analyze images, including results from computed tomography (CT), CT angiography, magnetic resonance imaging (MRI), and CT perfusion.

Brainomix's technology doubled the rate of thrombectomy treatment in patients with stroke and reduced hospital triage and transfer delays, according to a 2025 study.

The University of Oxford spinout is at a commercial stage, with operations in more than 20 countries, and is expanding into the U.S.

Brainomix raised a $21.2 million Series B round in 2021 and extended its Series C round from $6.5 million in March 2025 to $25.4 million in February 2026, with leading investors including Parkwalk Advisors and Hostplus. The proceeds will fuel the company's expansion into the U.S. market.

Brainomix has also partnered with heavyweights, including Nvidia, Boehringer Ingelheim, Medtronic, and GE Healthcare.

Brainomix also has a product dedicated to disease monitoring in pulmonary fibrosis.

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4

Circular Genomics

Founded: 2021 | **Headquarters:** San Diego, California, U.S.

Circular Genomics was spun out of the University of New Mexico, with its founders including CSO Nikolaos Mellios, PhD, and Alexander Hafez, PhD.

The company later moved its headquarters from Albuquerque to San Diego in March 2025 to access scientific and operational know-how from Eli Lilly at Lilly Gateway Labs.

Circular Genomics aims to equip medical professionals with a blood test to detect CNS conditions early, in addition to stratifying and guiding the treatment of patients.

Its technology involves using a polymerase chain reaction (PCR) test of a patient's blood sample to screen for specific circular RNA molecules produced in the brain that can cross into the blood and be measured as a biomarker of disease in the CNS.

Commercially launched in 2024, Circular Genomics' MindLight SSRI Antidepressant Response Test predicts whether a patient will benefit from common antidepressants called SSRIs with around 77% accuracy. This is designed to predict a patient's most suitable antidepressants without needing months of trial-and-error approaches.

The company is applying its technology in Alzheimer's disease, where the approvals of disease-modifying therapies such as Leqembi have led to demand for tests that can detect the disease at earlier stages than traditional tests.

Circular Genomics raised $15 million in a Mountain Group Partners-led Series A round in December 2025 to finance the development of its technology and expansion of its technology in Alzheimer's disease.

The company also has its sights on other CNS conditions, including multiple sclerosis and Parkinson's disease.

5

Omniscient Neurotechnology

Founded: 2019 | **Headquarters:** Sydney, Australia

Omniscient (o8t)'s founders include CMO Michael Sughrue, MD, a neurosurgeon aiming to improve anatomy maps for other surgeons, and machine learning expert Stephane Doyen, PhD.

o8t's FDA-approved product Quicktome involves using a patient's MRI brain scans and AI models to map out a patient's brain circuitry. These maps, accessible from an electronic tablet, can guide surgery to minimize the risk of brain damage compared to using a generalized anatomical diagram.

Quicktome is already in use at major hospitals around the world, including major centers in the U.S. Its partners include U.S. surgical support firm META Dynamic and the U.S. medical device innovation center, The Jacobs Institute.

o8t has raised more than $60 million, and bagged $14 million (AUD 20 million) in January 2026 as part of a Series D round targeted to reach $25 million (AUD 36 million). The round was led by Australia's National Reconstruction Fund (NRFC) and OIF Ventures, with the aim of keeping the company based in Australia.

The funding is earmarked to fuel the development and commercialization of Quicktome, and grow o8t's Australian workforce by more than 40. The company also has operations in Atlanta, Georgia, U.S.

o8t also plans to expand the technology into high-growth markets, including brain computer interface targeting, stroke and traumatic brain injury. ■

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*.

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