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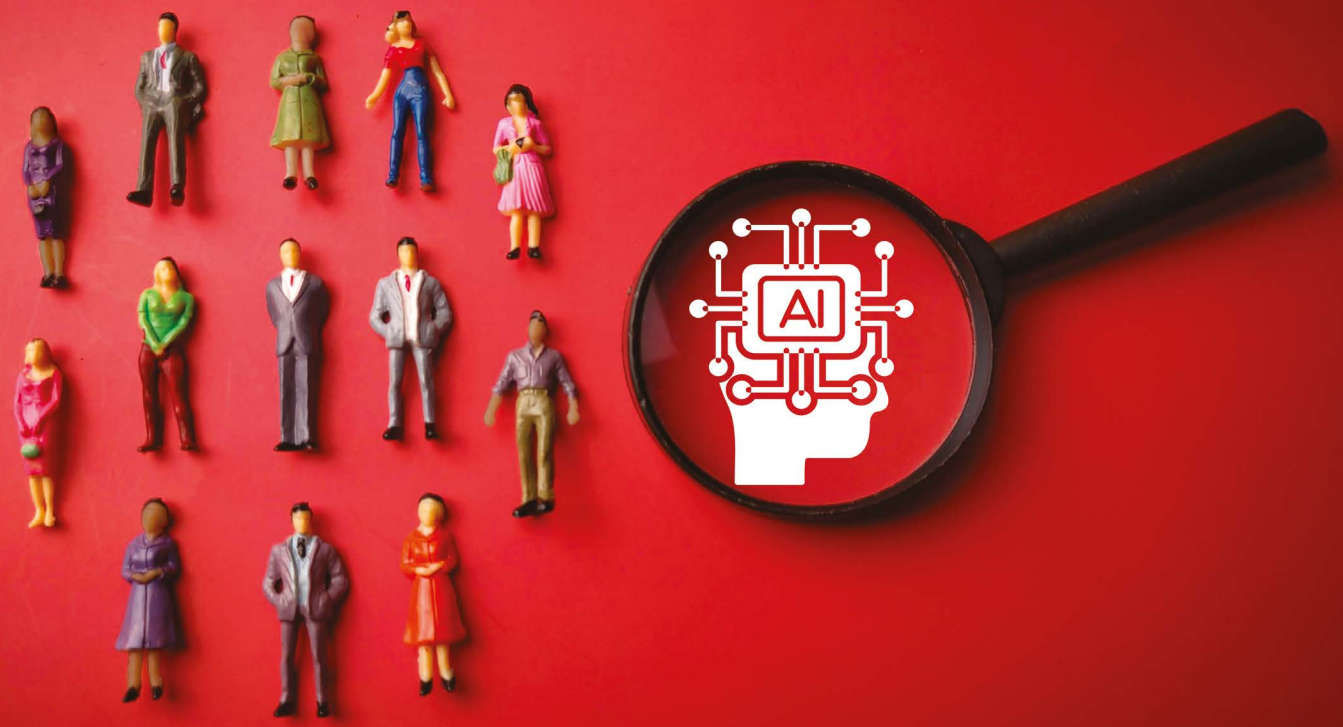

Harnessing AI Innovation to Modernize Clinical Trials

Assembling the Brain—Modeling Disease at Its Core

CDx for Gene and Cell Therapies

mRNA Vaccines—A Brain Game Changer?

Psychedelics—Reshaping Mental Well Being

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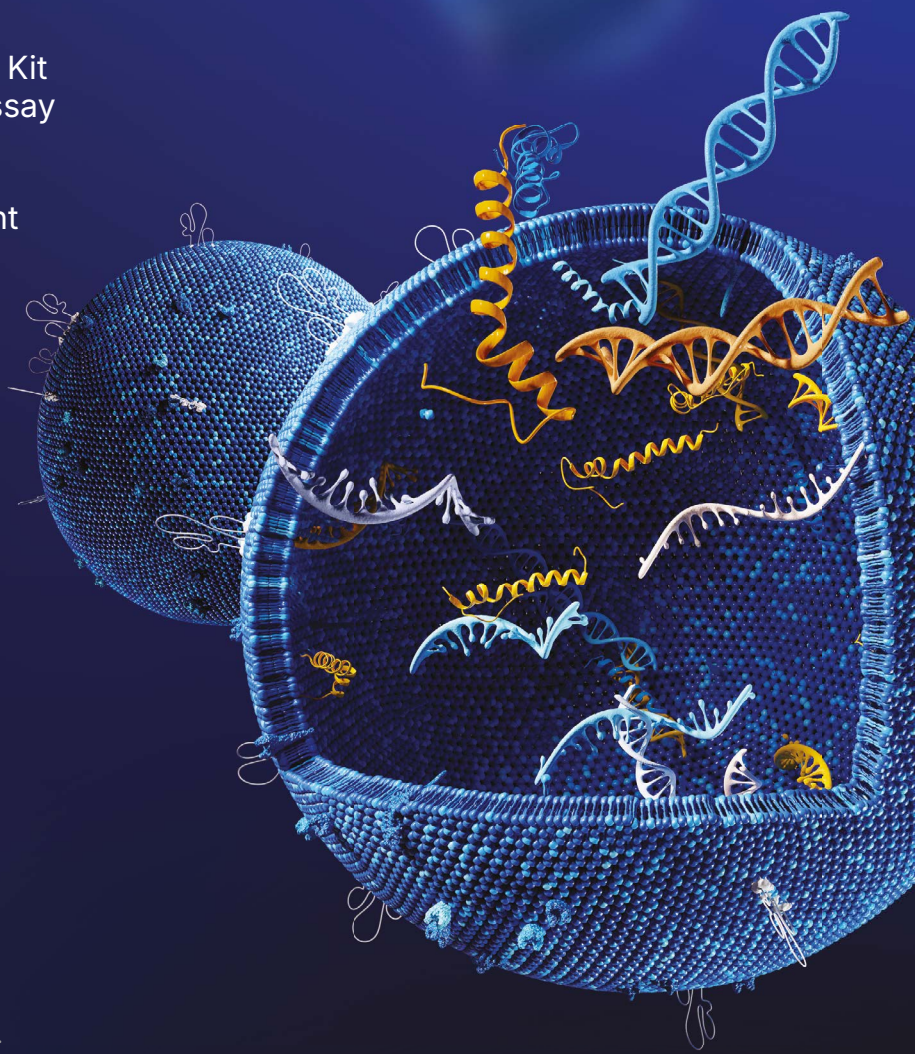

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Editor's Note

"It is common sense to take a method and try it; if it fails, admit it frankly and try another."

—Franklin D. Roosevelt

For decades, the bedrock of bringing life-changing medicines to patients—the clinical trial—has been a notoriously slow, costly, and often rigid process. From the seminal streptomycin trial in 1946 through to the dawn of the new millennium, many fundamental aspects remained largely unchanged. Twenty plus years ago, clinical research was a veritable paper mountain of case report forms, faxes, and endless shipping of physical documents. Even today, despite a significant push towards digital transformation, health systems still face challenges of interoperability, perceived issues of security, and in many cases, a distinct inertia to rethink long-established workflows. Despite these issues and inefficiencies, AI has been steadily reshaping the clinical trial landscape, transforming what was once a cumbersome bottleneck into a dynamic, more efficient, and inclusive pathway. It has cost too much to bring a drug to market, but we're at an inflection point in how clinical trials are not only being designed, but how we recruit the right patients for those trials. AI is able to meticulously sift through vast datasets to identify optimal candidates and sites, enhance patient engagement and adherence, and be used in digital pathology and imaging biomarkers to select the right patients and monitor responses with unprecedented precision.

The clinical trial landscape is rapidly evolving and moving towards more flexible, adaptive trials which can be modified based on interim data. However, regulatory challenges and the need for specialized expertise present significant barriers, with a survey finding that many trial sponsors lack the necessary in-house knowledge and tools. Furthermore, overly restrictive inclusion criteria can disproportionately exclude minority patients and lead to recruitment bottlenecks. As we look over the horizon, the integration of AI and machine learning is expected to further streamline trial design, data analysis, and regulatory processes, ultimately leading to faster approvals, lower costs, and more patient-centric clinical trials.

In the midst of a mental health crisis, with health systems struggling to keep up with the increasing demand, and patients' health conditions deteriorating as they wait long periods for treatment, the field of psychoactive therapeutics, long relegated to the shadows of research following widespread prohibition in the 1970s, are experiencing a powerful resurgence. The is driven by a growing understanding of their profound potential to "reset the mind" and offer significant improvements in mental health and neurological conditions. While work still needs to be done in optimal dosing strategies and navigating regulatory hurdles—the shifting public perception, decriminalization efforts, and the compelling promise of fast-acting, profound effects are propelling these compounds to the forefront of mental health innovation.

Beyond the technological marvels we champion, we must never lose sight of the profound stigmatization that all too often afflicts those battling mental health challenges. Just as we're now ingeniously redesigning clinical trials to foster greater inclusion and diversity cohorts, we carry a parallel imperative: to ensure these powerful new therapies, once proven, aren't just innovations for the few, but accessible solutions for every patient who desperately needs them. By continuously challenging the status quo and remaining agile in our pursuit of change, we truly can forge a healthcare system that benefits everyone, not just a select few.

Damian Doherty
Editor in Chief

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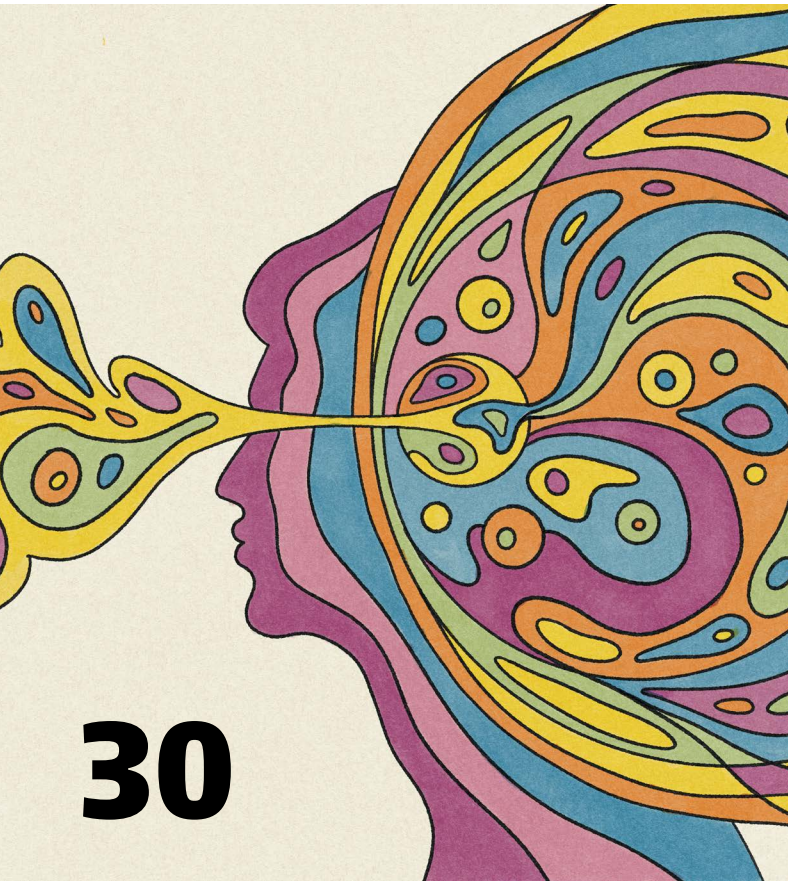

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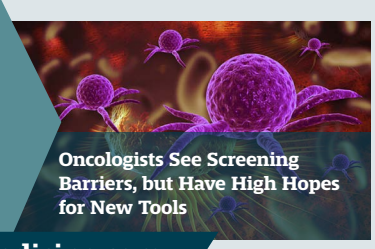

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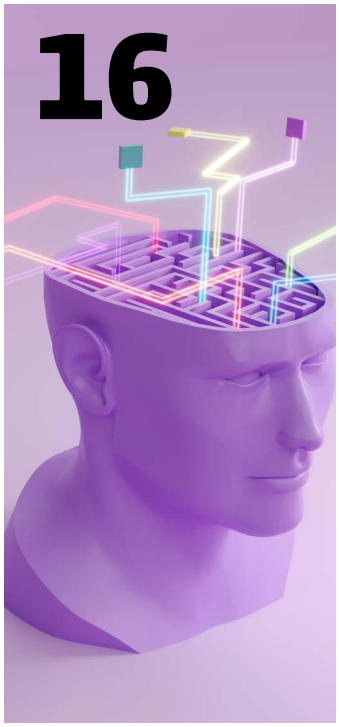

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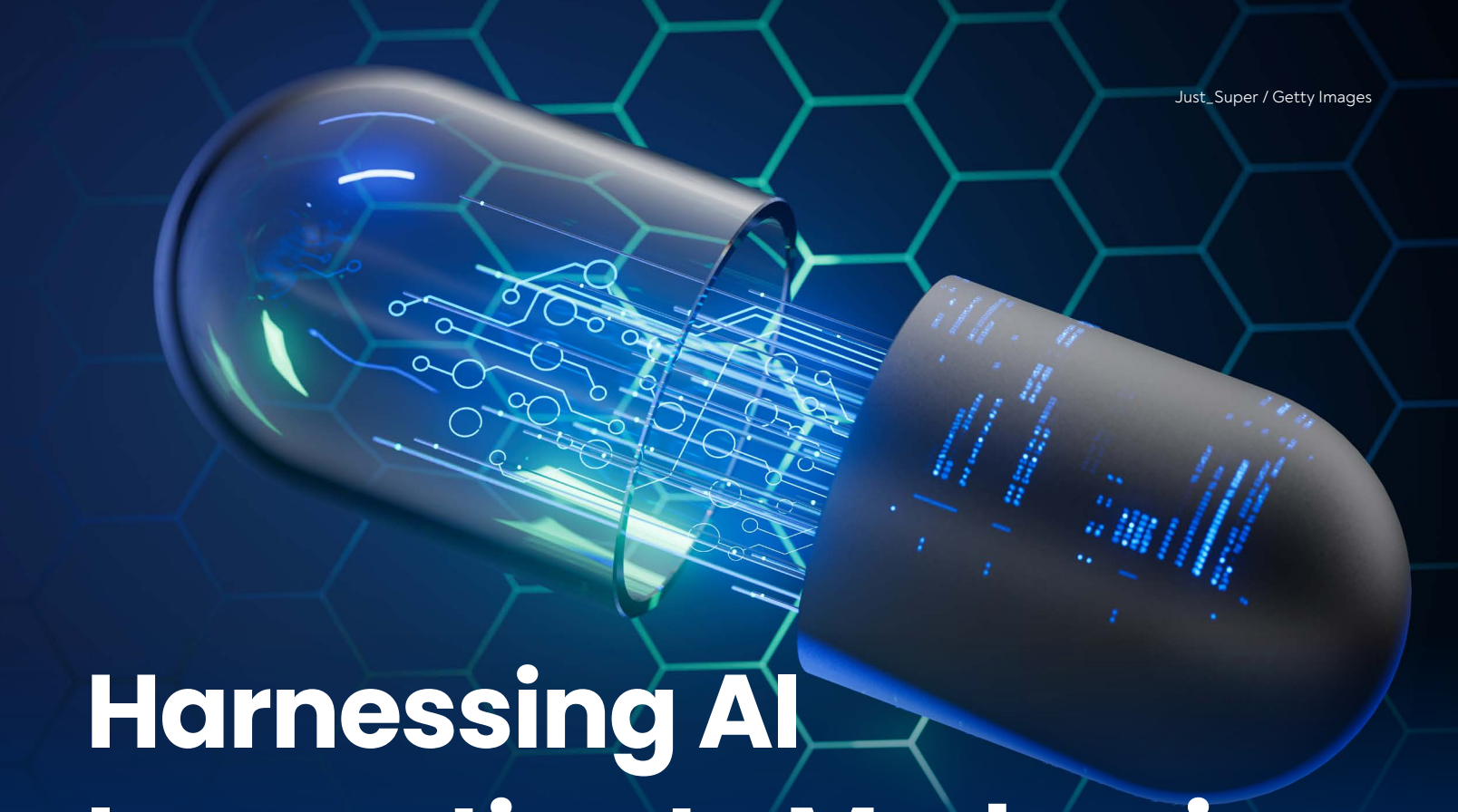

Just_Super / Getty Images

Harnessing AI Innovation to Modernize Clinical Trials

by Helen Albert Senior Editor

Clinical trials are an essential part of bringing new medicines to patients but are often slow and expensive to complete. Innovations in artificial intelligence (AI) over the last two decades are already having a positive impact on the way these trials are run and have the potential to improve them further in many ways, ranging from simple economics to more diverse trial cohorts.

The first randomized controlled clinical trial is generally agreed to have taken place in 1946 in the U.K. to test the antibiotic streptomycin for the treatment of pulmonary tuberculosis. Although some changes and improvements to the trial processes were instituted, like better informed consent procedures, many aspects of the system did not change significantly until the late 1990s.

The fast pace of technological development in the early 2000s did not leave clinical trials behind. "When I first started working in the clinical research space in the early 2000s, we were processing paper case report forms, paper queries, faxing data back and forth with sites, or worse, shipping paper back and forth," said Joshua Wilson, the chief operating officer at AiCure, a New York medtech company that uses computer vision and machine learning to aid patient engagement and medication adherence in clinical trials.

"Some of the most transformational changes have been in the many ways that technology has evolved and been used to revolutionize the way the industry thinks about and conducts clinical trials. … Technology and logistical challenges still exist, but the progress we've made would have been hard to imagine 20 years ago," he added.

Since the launch of the public facing generative AI chatbot ChatGPT in late 2022, AI seems to be everywhere. In reality, the technology had been quietly advancing in the background for some time before this. In particular, key advances in image recognition were highlighted in the so-called AlexNet paper published in 2012. In addition, Word2Vec, developed by Google in 2013, signaled the beginning of a big change in natural language processing that eventually led to more public facing technology such as ChatGPT.

Tom Doyle
Chief Technology Officer
Medidata Solutions

In a similarly quiet fashion, a number of companies like AiCure have been developing AI-based technology to make clinical trials less risky, shorter, cheaper, and more effective.

Medidata Solutions is one such company. Also based in New York, it was founded in 1999 at the beginning of the digital revolution and develops software that can improve the clinical trials process, from design to completion. Tom Doyle is the chief technology officer at the company and thinks that more can still be done to enhance clinical trials.

"After 25 years, it takes still $2 billion to bring a new product to market," he emphasized. "We think that as an industry we can do better at that. We can design trials that execute faster, have higher probability of success, are targeted to the right populations, but are also more inclusive of more patients."

Start as you mean to go on

AI-based technology can enhance trial design and help researchers and companies find the right patients for their studies. Tempus is a large health tech company based in Chicago and one of its focus areas is enhancing clinical trial design and recruitment.

"When it comes to trial design, AI excels at analyzing vast datasets from previous studies and real-world datasets to uncover patterns or characteristics that human researchers might overlook," noted chief operating officer Ryan Fukushima.

"This capability lets us design more tailored inclusion and exclusion criteria and be more predictive of those patients that will likely benefit from a novel treatment."

Medidata works on all aspects of clinical trials, including recruitment, and also uses AI to help researchers running trials find the best sites. "Today, there's competition for studies. Sites can't run everything. They make selections about what compounds they'll pursue, what partnerships they will enter into … and one of the factors is what is the burden of a study," explained Doyle.

"We can also look at the scientific side of that protocol and help tune inclusion and exclusion criteria, so we are targeting the population that's most likely to respond to a medicine. Similarly, we are not excluding people unnecessarily from treatment."

Using more precise patient measures in combination with AI allows people who might have been previously defined as 'borderline' and therefore excluded to be admitted to clinical trials. Tempus has a platform called TIME that can look for real-time, relevant patient matches for clinical trials that are currently recruiting. It is designed to facilitate precision oncology by matching cancer patients to nearby trials focusing on their cancer type.

Ryan Fukushima
Chief Operating Officer
Tempus

"The impact is significant. Over 1,000 clinical trials have been active in the TIME program and over 40,000 patients were identified for potential enrollment into clinical trials in our network," emphasized Fukushima.

There are typically two types of data in patient records: structured data, which includes predefined and organized facts such as date of birth or address, lab results, billing codes, and vital signs; and unstructured data, which includes freeform content such as doctors' notes, patient narratives, audio recordings, and imaging.

"One of our newest innovations is particularly exciting," said Fukushima. "Our Patient Query capability allows our team to rapidly analyze unstructured patient data, unlocking detailed information not typically captured in structured

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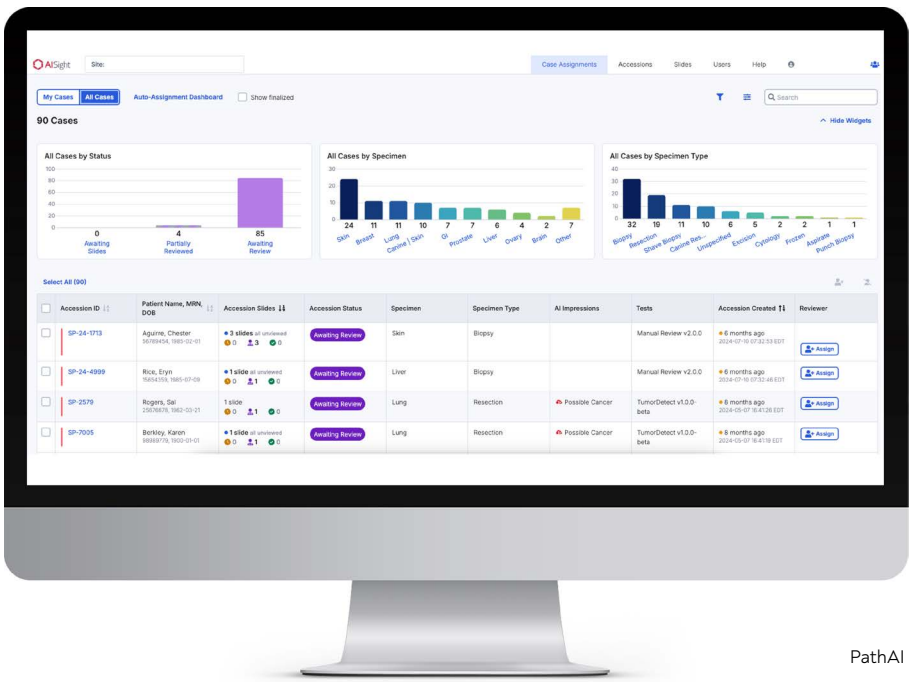

PathAI

AISight™ is a cloud-native intelligent enterprise workflow solution used by the world's leading laboratories and research centers to power their digital pathology workflows and AI applications. It serves as a central hub for case management, image management and viewing, and best-in-class AI tools to enable multiple histopathology use cases.

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data but critical to assessing trial eligibility, such as hospice status, presence of exclusionary comorbidities, and current line of therapy."

Tempus's recent acquisition of clinical trial matching platform Deep 6 AI will also help the company identify more eligible patients for clinical trials and improve the TIME platform.

"We're leveraging AI and natural language processing to mine millions of patient records—including that critical unstructured data hiding in physician notes, pathology reports, and lab results—pinpointing eligible study participants in near real-time," explained Fukushima. "This isn't just faster; it is critical technology needed to allow more patients to benefit from novel treatments."

George Harston, DPhil, MBBChir
Chief Medical and Innovation Officer
Brainomix

Improving the process

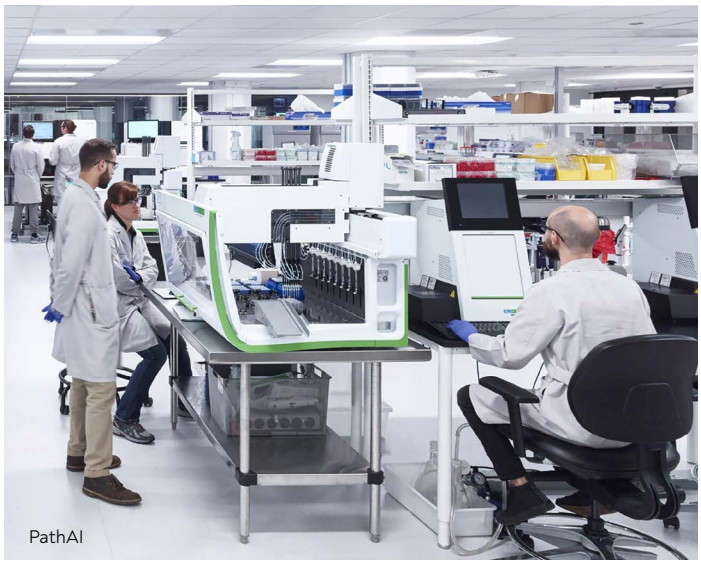
Following improvements in AI-based image recognition, many digital pathology or image analysis-based medtech companies have been founded. Two success stories in this area are Oxford-based Brainomix, which specializes in AI-powered computed tomography and magnetic resonance imaging analysis primarily for diagnosing stroke and lung disease, and Boston-based PathAI, which analyses histology images for cancer, inflammatory bowel, and liver diseases.

Both these companies have developed diagnostic tools that can be utilized to better diagnose stroke or conditions such as cancer, but also work in the clinical trials space.

"It was clinical trials that really drove the creation of Brainomix," explained the company's chief medical and innovation officer George Harston, DPhil, MBBChir, who is also a consultant physician in Oxford.

"One of our co-founders derived a scoring system for looking at stroke scans. He was running clinical trials at the time, and he realized there was this big heterogeneity of different of patients. Some of the patients had big strokes, some small strokes, and they were all being lumped together. He came up with a scoring system, but doctors weren't very good at using it. There was a lot of inconsistency, so he saw an opportunity with the other co-founders to use technology to try and automate the assessment of these brain scans and so Brainomix was born."

In addition to helping clinicians diagnose stroke and lung disease, Brainomix continues to support people running clinical trials, both in selecting suitable patient populations and biomarkers before trials begin and in monitoring trial endpoints during the trials.



PathAI

"One of the biomarkers that's really interesting at the moment is we can assess how much life the brain has lived before the person had a stroke," said Harston. "Let's say you've got two 60-year-old people. They both have a stroke. One of them has high blood pressure and is a heavy drinker and smoker and could have a very atrophic brain with lots of small vessel disease established. The other patient could be fit and healthy and have a pristine brain. Those patients will respond differently to the same stroke because the outcome is determined not just by the stroke, but also by the brain and indeed the body it happens in."

Similarly, PathAI is working on creating imaging biomarkers that can be used in clinical trials in cancer and liver diseases such as metabolic dysfunction-associated steatohepatitis (MASH).

Andrew Beck, MD, PhD
CEO and Co-founder
PathAI

In MASH liver trials, patients must have a certain disease activity score, which is determined by how much inflammation, fat, and ballooning hepatocytes are in the tissue, to get into the trial. To assess whether the treatment was effective for the patient, the pathologists manually look at the slides and assess whether there were significant changes.

"What AI can do, and what we recently received biomarker qualification from the European Medicines Authority in late March for, is to show that a single pathologist, assisted by AI, could both enroll and assess primary endpoints," said Andrew Beck, MD, PhD, CEO and co-founder of PathAI.

Beck and colleagues have also experimented with exploratory biomarkers in a number of different studies, where they have used their technology to look for small changes in imaging data to see which patients respond best to different therapies. This

information can be particularly helpful in early-stage trials as it can help show researchers what to look for in later stages of drug development.

"Often this data can be used in conjunction with other exploratory methodologies like RNAseq to really better understand the biology of why patients are responding or failing to respond to therapy," said Beck.

AiCure uses computer vision and machine learning in combination to track both adherence to medication and patient behavior in the clinical trial setting. For example, using a smartphone camera and app, the company's technology can verify that a trial participant has taken their medication and also confirm that the correct person has ingested the medication using facial recognition technology.

Malaikannan Sankarasubbu
Chief Technology and AI Officer
Saama Technologies

"Our H.Code platform offers patients a flexible solution that is specifically designed to fit into a trial participant's life," noted Wilson. "Our proprietary AI sits within the platform to assess what a participant may be having difficulty with, whether it is dosing compliance, questionnaire completion, or side effects, providing specific guidance to sites and patients to assist them in a customized way."

Medidata is using real world data combined with its AI-based technology to help run trials in rare diseases by creating synthetic control arms. For example, they previously worked with a company called Medicenna to run a Phase III trial in the rare brain cancer glioblastoma using a synthetic control arm.

"Recruiting for the standard of care is very difficult in rare diseases because there's only so many patients, but also in areas where there's serious significant unmet need, putting someone on a standard of care means they likely won't survive," explained Doyle.

"We have sufficient data that allows us to build a synthetic cohort of patients that are representative of the control arm. Then we use the experimental arm to match against that to see the uplift or the performance of the new therapy."

It all depends on the data

One of the most important parts of a clinical trial is the data that is collected and analyzed during and at the end of the trial. Making sure that the best possible data is collected as quickly and efficiently as possible and analyzed effectively without errors is something that AI-based technology is already helping implement.

"It is not sexy, but it's important," said Malaikannan Sankarasubbu, chief technology and AI officer at Saama Technologies. "When you look at a clinical trial, it's like a continuum. If you think of it like project management, there are multiple milestones you have to hit. … You have to plan for patient recruitment, you have to set up sites, you have to get the patients in, collect the data, clean the data, and then you have to lock the database."

Saama is an AI-driven clinical data analytics company based in Campbell, California, that was an early player in the field in the late 1990s. During the pandemic, the company showed the value of its technology by participating in the Pfizer/BioNTech COVID-19 mRNA vaccine trial and helping it become the first vaccine to get to patients.

The company did this through use of its AI-driven clinical data management platform, Smart Data Query, which allowed the team working on the trial to flag potential errors in real time. They also cut the amount of time needed to clean data obtained from more than 40,000 trial participants from the standard 30 days down to 22 hours.

"The data cleaning is a very huge part. The entire hypothesis is you run a clinical trial to prove that your medicine works. … For you to actually do that, the data you collect has to be clean," explained Sankarasubbu.

"A pharma company cannot modify the data in clinical trials. It's dealing with patient lives. You have to send a question back to the hospital or the site where the data has been collected for them to actually modify it if there is any issue … and that's what we did for the COVID vaccine."

> "There are AI agents that are identifying anomalous data that are pointing you in the direction of things that need further review."

Medidata also launched a data analysis tool called Clinical Data Studio last year. It provides a single space for all trial data such as wearables, electronic health records and lab information, automatically organizes the data, and flags potential issues that need to be checked.

"There are AI agents that are identifying anomalous data that are pointing you in the direction of things that need further review. There's also a more gen AI experience for interacting with data like audit trails to help you uncover potential risks in data that was entered out of sequence," said Doyle.

"There is fraud in all industries, inclusive of clinical research. Sponsors and contract research organizations work very hard to make sure that that isn't happening. It's important for the veracity of the data that's collected, and we can help be a part of that effort through the use of technology like these AI approaches."

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Of course, data quality is also important to optimize AI systems. "If you put rubbish data in, you get rubbish data out of your algorithm," said Harston. "We have very large datasets that we've grown over many years that we use to build, develop, and also, most importantly, validate our models. Those data not only have to be good quality, but they also have to be really heterogeneous populations from around the world so we don't have too much bias."

A sign of things to come

AI certainly seems to be well on the way to becoming an integral part of the clinical trials ecosystem. "In the same way that in healthcare, we're starting to see AI becoming a sort of standard of care. I suspect we'll see this in clinical trials as well," said Harston.

"In the coming years, the use of AI will become more imbedded in every aspect of how trials are planned, conducted, and incorporated into participants' lives. We will see that clinical trial participation will become much more commonplace, and more people will be able to easily join trials, reducing barriers to access and improving the quality of trials," added Wilson.

A few things still need to happen before use of AI in clinical trials becomes ubiquitous. The AI technology needs to be widely available, which is not the case at the moment. Regulators like the FDA also need to keep up with and adapt to fast changes in the technology.

> "There are certain endpoints that regulators like the FDA use as standard for pivotal registrational trials. Now, if you want to use your AI biomarker the regulator has to be willing to accept that that's an alternative surrogate outcome"

"There are certain endpoints that regulators like the FDA use as standard for pivotal registrational trials. Now, if you want to use your AI biomarker the regulator has to be willing to accept that that's an alternative surrogate outcome," said Harston.

"For example, in the lung space, where we work, we do analysis of change in AI imaging biomarkers over time to look at how effective a drug is in pulmonary fibrosis trials. That's probably a more direct measure of how well the drug is working, but at the moment the FDA insists on using a test where you blow into a machine to see how much air you blow out of your lungs, which is incredibly noisy and sub optimal."

PathAI

Although manual data entry in the clinical trials space is slowly being reduced, many trials still include large amounts of paperwork. "Automated electronic data capture submission isn't just a convenience—it's eliminating the error-prone transcription process that has plagued trials for decades," said Fukushima.

"This shift means clinical research staff at sites can refocus on patient care rather than paperwork management, creating ripple effects throughout the entire clinical trial ecosystem."

Another potential issue is making sure that AI systems are trusted by non-experts like healthcare professionals and that they are checked for mistakes and bias by those with relevant expertise.

"It's always about trust that you build with medical providers," notes Sankarasubbu. "Generative AI models can hallucinate quite a bit. You ask it a question and it can make up random things … you need to ground it first for that particular clinical trial or therapeutic area."

Like Saama, Medidata has been investing in AI technology for more than 10 years now. "In the beginning, we learned a lot of ways not to make a light bulb. But over the last few years, we've really begun to pick up the pace on how to make really good light bulbs," emphasized Doyle.

"I would say we are at an inflection point right now where, yes, of course, there's still a lot of hype and expectations, but real use cases that are demonstrating measurable value are starting to appear and are gaining real acceptance." ■

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.

Advances in Antibody Engineering for Therapeutic Applications

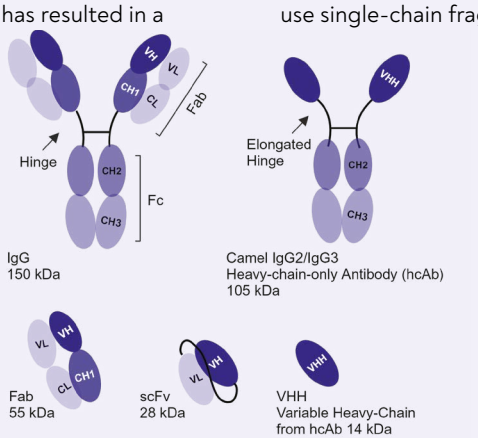
Approaches to Antibody Engineering

The gold standard method of monoclonal antibody (mAb) production is a recombinant approach, which reduces the need for animal involvement and increases the consistency between production lots of the antibody. In recent years, the discovery and manufacturing of small non-canonical antibody types, such as variable heavy domain of heavy chains (VHH), have also enabled new avenues of research. These single-domain antibodies (sdAbs) offer significant benefits due to their small size, high affinity and stability, low immunogenicity, good solubility, and enhanced tissue penetration.

The cumulative effect of these advancements has resulted in a new generation of enhanced mAbs and VHH, now positioned at the leading edge of diagnostics and therapeutics.

Antibodies for Therapeutics

Due to their ability to closely target some cancer cell surface proteins without the systemic drawbacks of standard chemotherapy, mAb therapies are widely used in cancers that express known targets like EGFR and HER2. Antibody therapies are also well established for treating infectious diseases and autoimmune disorders like inflammatory bowel diseases, type 1 diabetes mellitus, and multiple sclerosis.



Comparison of canonical IgG molecules, hcAb camelid IgG molecules, common Fv formats Fab and scFv, and the monomeric VHH domain. *Image created with BioRender.com*

• Bispecific antibodies

To enhance efficacy and reduce risk of drug resistance and toxicity from combination therapies, bispecific antibodies are engineered to target two antigenic epitopes. By performing two functions in one molecule—binding tumor cells and recruiting cytotoxic immune cells, for example—bispecific antibodies can do more with less drug and potentially fewer side effects.

Bispecific antibodies can be either IgG-based or fragment-based. The known advantages of VHH, including increased solubility and thermal stability, can be harnessed into bispecific or even trispecific VHH, in which two or three VHH domains are connected by a flexible peptide linker. Multispecific VHH are undergoing investigation for treatment of solid tumors and conditions like psoriatic arthritis and psoriasis.

• Antibody-drug conjugates

Advances in antibody engineering have enabled more precise payload targeting, allowing for highly specific therapies that deliver treatments directly to disease sites. Beyond standard mAb treatment, antibody-based therapy has expanded to include other types of drug products, such as antibody-drug conjugates (ADCs). ADCs combine a mAb with a cytotoxic payload and a linker that releases the payload once inside a tumor cell.

• CAR-T for cancer therapy

For the treatment of hematological malignancies, chimeric antigen receptor T-cell (CAR-T) therapy provides new second- or third-line treatment options for some patients. Six CAR-T therapies have been approved in the U.S., and most of these use single-chain fragment variables (scFvs) as targeting domains. However, use of scFvs for CAR-T engineering may have limitations, such as the potential for folding instability and changes in binding affinity when engineered into a CAR using a linker. To overcome some of these issues, VHH are being explored for numerous CAR-T therapies and offer advantages in stability, low immunogenicity, binding affinity, and modularity that could lead to improvements in CAR-T efficacy.

Immunohistochemistry for Companion Diagnostics

Multiplex immunofluorescence (mIF) is a specialized type of immunohistochemistry (IHC) that addresses the need in personalized medicine to assess multiple biomarkers simultaneously. Using fluorescently labeled antibodies, mIF can detect up to 40 or more biomarkers simultaneously, reducing the need for tissue and enhancing the amount of diagnostic and prognostic information that can be obtained. IHC is used in several FDA-approved companion diagnostics to help select appropriate mAb therapies.

Conclusion

At Fortis, we believe that your research deserves more than a one-size-fits-all approach—it deserves a partner who empowers you. Our recombinant monoclonal antibody and VHH development services and spatial biology CRO services are supported by a team with over 50 years of experience.

Navigating Emerging Challenges in Clinical Trial Design

by Clara Rodríguez Fernández

With technological advances continuing to break new ground in medical research, the pressure is on for clinical trials to adapt at an unprecedented pace. As the field forges ahead, researchers, clinicians and sponsors alike have to face increasingly complex challenges when undertaking a clinical study.

Aman Khera
President
TOPRA

"Gone are the days of simple trial designs," said Aman Khera, regulatory science and innovation advisor, and president of The Organisation for Professionals in Regulatory Affairs (TOPRA). "With the rise of precision medicine, biomarkers, and cell and gene therapies, studies must now account for intricate biological variations. The industry is rethinking traditional methods to adapt to an increasingly complex and dynamic landscape."

In such a rapidly shifting environment, conventional randomized trials can often fall short. Investigators and sponsors must navigate a slew of continuously evolving challenges, from ensuring timely patient enrollment to complying with ever-changing regulations, which, in turn, consume increasing amounts of time and resources.

"Clinical trials are more expensive than ever," said Khera. "The demand for advanced technology, extensive data collection, and compliance measures all contribute to escalating financial burdens. To successfully tackle these challenges, sponsors need to embrace innovation, fine-tune regulatory strategies, and keep patients at the heart of it all."

Integrating adaptive trial design

Adaptive clinical trials allow protocol modifications during the study based on data findings. This type of study design enables researchers to modify parameters such as sample size, treatment regiments, and selection criteria in response to interim results, offering much more flexibility compared to traditional randomized clinical trials, which follow a rigid protocol from start to finish.

Edward J. Mills, PhD
Professor, McMaster University
Associate Professor, Stanford University School of Medicine

Edward J. Mills, PhD, professor of health research methods, evidence, and impact at McMaster University and associate professor at the Stanford University School of Medicine, has been working on adaptive trials for the past decade. While this type of trials garnered little attention 10 years ago, he saw interest spike during the COVID-19 pandemic, as it allowed researchers to run fast, efficient studies for an indication about which little was known at the time.

Demand has continued rising for adaptive study designs, such as basket trials, where patients are selected based on predictive biomarkers rather than indications, and umbrella trials, where multiple targeted interventions are tested against a single disease. Also growing in popularity are platform trials, which evaluate multiple treatment regimens against the same control group, allowing flexibility to drop and add arms over the course

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of the study. Some notable examples include the RECOVER trial for COVID-19 and the I-SPY2 trial for breast cancer.

However, running adaptive trials requires extensive and complex preparation, which creates additional challenges at the organizational, funding, and regulatory levels. In addition, designing adaptive clinical studies requires specialized knowledge that not many scientists or clinicians have, said Mills. Therefore, sponsors should carefully consider the right type of adaptation for each prospective study and ensure that they have a team with the right expertise to carry it through.

Between 2010 and 2020, more than 300 trials reported employing at least one form of adaptive design. Most of these clinical trials were in the field of oncology, making up 53% of all trials using adaptation strategies. Dose-finding trials, which seek to identify the most effective dose for each patient group, were the most popular form of adaptive design and used in nearly 40% of all adaptive studies. Approximately a third of trials employed Bayesian statistics, which are specifically designed to incorporate pre-existing data in clinical trial design, analysis, and decision making.

Lessons from the industry

The growing popularity of adaptive studies highlights some of the shortcomings of traditional randomized trials. For instance, adaptive design can have important ethical implications as they can reduce the number of participants who are exposed to ineffective or poorly tolerated treatments. Novel approaches to trial design can also cut costs across patient recruitment, data collection and, most importantly, trial duration.

"If a drug doesn't work, the sooner we know the better," said Dan Goldstaub, PhD, scientific co-founder of PhaseV, a provider

Dan Goldstaub, PhD
Scientific Co-founder
PhaseV

of machine learning tools for clinical trial design and analysis. With more than 25 years of experience in the pharmaceutical industry, Goldstaub has seen his fair share of clinical trial failures over the years. In some cases, failure may have been clear long before the study ended, but patients still had to be treated with ineffective drugs for the entire duration of the trial.

One example of a successful adaptive trial was the KEYNOTE-001 study, which evaluated Merck's now blockbuster cancer drug Keytruda (pembrolizumab) in patients with advanced solid tumors expressing the programmed death-ligand 1 (PD-L1). The trial went through nine protocol amendments that enabled the addition of multiple expansion cohorts, ultimately enrolling over 1,200 patients. Its adaptive design was instrumental in the approval of pembrolizumab for melanoma, which took place within four years of the investigational new drug (IND) application, setting a new precedent for clinical development in the oncology field. Using a more traditional development approach, the development would have likely taken more than twice as long.

Goldstaub, who worked as executive director of clinical research at Merck at the time the trial took place, highlighted how an adaptive approach allowed the pharma company to achieve in a single trial what, in the past, would have required multiple separate studies. At Merck, he was directly involved

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with many adaptive trials, including KEYNOTE-158, a tumor-agnostic trial that pooled patients based on a biomarker for DNA mismatch repair. “This was one of the early and most successful basket studies that led to a label expansion based on Phase II.”

However, integrating adaptive designs comes with its own set of challenges. A survey run by PhaseV, of studies published at the National Library of Medicine (clinicaltrials.gov), found that trial sponsors still face significant barriers to the adoption of adaptive clinical trial design. “Despite the fact that these tools are recommended by regulatory authorities, most of the trials do not use them,” said Goldstaub. “In our analysis, this was mainly because they do not have enough expertise in-house and they do not have good enough tools.”

Tiantom Jarutat, PhD, MD
Chief Medical Officer
iOmx Therapeutics

Ultimately, the specific needs of each trial sponsor must be carefully considered. This is one of the lessons that Goldstaub has learned by working with developers across a broad spectrum of backgrounds and sizes. When it comes to big pharmaceutical companies, avoiding mistakes and creating a full-picture plan that addresses every possible question, from clinical to statistical, and operational and regulatory aspect of the trial, is essential. On the other end of the spectrum, speed is of the essence for biotechnology companies, which are typically smaller, younger, and more agile. For them, says Goldstaub, the priority is finding quick answers to every question so decisions can be taken at an extremely fast pace.

Recruiting a diverse, representative population

Conventional clinical trial designs accommodate patient heterogeneity poorly, which has hindered progress in clinical translation across a wide range of indications. The implementation of biomarkers and digital assessment tools can enable novel experimental designs that better deal with this inherent heterogeneity while providing statistically robust data.

“It is sometimes worthwhile to opt for a more precise development path, even if that results in a numerically lower patient segmentation,” said Tiantom Jarutat, PhD, MD, chief medical officer of Munich-based immuno-oncology drug developer iOmx Therapeutics. “If you get a higher percentage of the selected patients to respond and benefit from treatment and be spared from side reactions, this is certainly a valuable proposal to the physician.”

However, patient recruitment remains a huge challenge. With inclusion criteria becoming increasingly harder to fulfill, many trials end up failing due to low enrollment. Retaining participants through the entire length of a study can also prove challenging, placing the onus on sponsors and contract research organizations (CROs) to proactively address the barriers patients face to continued participation.

“When developing protocols, careful attention is needed to avoid overly restrictive exclusion criteria that may unintentionally disqualify minority patients, especially those with common comorbidities,” said Khera, noting that broadening inclusion criteria can make trials more representative and ease recruitment bottlenecks. “Diversity must be prioritized from the very start of clinical trial planning—ideally even before protocol development begins. Integrating diversity early on isn’t just beneficial, it’s essential for ensuring trials are representative, inclusive, and aligned with real-world needs.”

From the choice of trial locations to partnering with community organizations, sponsors and CROs need to consider strategies to bring down barriers to trial participation within historically underrepresented and underserved communities. These can include financial and logistical challenges as trials often require participants to commit significant amounts of time and can incur travel costs and unpaid time off.

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“Several standout trials and initiatives are paving the way for greater diversity in clinical research, setting benchmarks for the industry to emulate,” said Khera. She pointed at the example set by the Clinical Trials Transformation Initiative, which has developed practical recommendations to increase diversity in clinical studies with an emphasis on systemic, long-term change over short-term fixes.

Navigating the regulatory maze

One of the greatest challenges to initiating a clinical study is the burden of administrative work required to obtain a regulatory authorization, said Mills. “That’s by far the largest impediment, and often a bigger problem than accessing money.”

While regulations are necessary to ensure safety, a lack of clarity from the authorities can result in delays and require

investigators to allocate additional time and resources to ensure compliance. Mills noted that this became clear during the COVID-19 pandemic, when administrative hurdles slowed down recruitment in many studies that had already been funded.

"One of the biggest challenges is the variation in approval requirements across countries," said Khera. "Different regions, such as the FDA in the United States and EMA in Europe, have distinct regulatory standards, which leads to delays, additional costs, and difficulties in harmonizing protocols. In some areas, local patient data is mandatory, forcing companies to conduct extra studies before seeking approval.

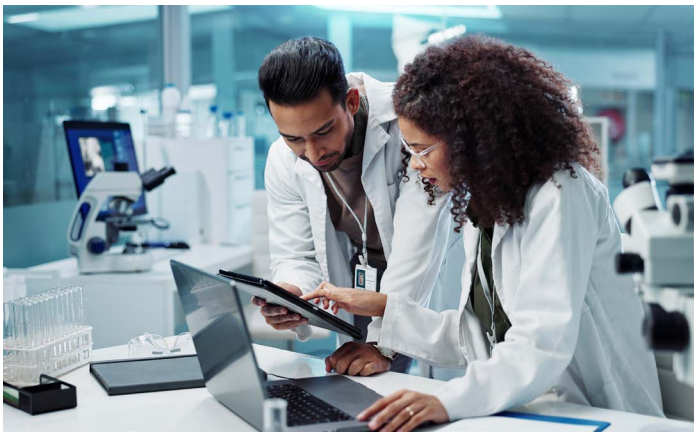
"Adaptive trial designs, while efficient, require detailed predictive modeling to gain regulatory approval. Similarly, the integration of real-world evidence has been encouraged to enhance valuable insights, but it demands rigorous validation before acceptance." Khera is also expecting to see emerging AI technologies designed to aid with trial design facing heightened scrutiny from regulators in coming years, driven by their growing concerns about data integrity and algorithmic bias.

"Choosing and managing the right CRO, adopting risk-based monitoring to focus oversight on higher-risk sites, and automating data management with AI and machine learning are all ways to cut down on unnecessary expenses."

"My top advice to trial sponsors is to prioritize early engagement with regulatory agencies," she added. "Sponsors must make full use of every available pathway for agency interactions to facilitate smoother approvals. With differing tones from agencies, AI governance policies, and stricter data security requirements constantly evolving, reaching out to regulators before finalizing protocols and development plans can prevent costly delays, foster compliance, and build trust with authorities. While regulatory requirements can feel like moving targets, proactive efforts can help companies build compliant trials that advance innovation while protecting patients."

Looking ahead

The fate of clinical research seems uncertain in today's political climate, with the FDA undergoing massive changes under the current U.S. government. "There is a good likelihood that the political nationalism that's happening around the world right now will have an impact on clinical trials," said Mills. With public funding being diverted away from medical research, he believes investigators will need to become smarter and more selective about choosing the right questions to ask and finding the most efficient way to answer them reliably.



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"With trial costs soaring, smarter budgeting becomes crucial," said Khera. "Choosing and managing the right CRO, adopting risk-based monitoring to focus oversight on higher-risk sites, and automating data management with AI and machine learning are all ways to cut down on unnecessary expenses."

In addition to integrating adaptive design into their clinical trials, she recommends that sponsors look into model-informed drug development, a computational approach used to predict outcomes and reduce patient enrollment needs, as well as synthetic control arms, a strategy that relies on real-world data and historical controls to strengthen efficiency and ethical practices.

Khera is confident that we are moving closer to faster approvals, lower costs, and more patient-friendly trial experiences that can improve engagement along with the quality of the data collected. This will be enabled by the introduction of AI technology, wearables, and digital biomarkers, which are already starting to drive a shift in the industry towards automation and decentralization.

"I think machine learning and AI are going to play a big part in clinical trials," said Goldstaub. He highlighted the potential of this technology to streamline not just study design and early decision-making, but also retrospective analyses, making it easier to stratify patient populations across multiple parameters at once.

In years to come, he expects to see a significant reduction in the amount of time it takes a drug candidate to move from a first-in-human study to entering the market. Goldstaub also believes that innovative tools and study designs will benefit many orphan disease indications, for which it has historically been a challenge to reach the market due to the small number of eligible patients that can be found at any given trial location.

Khera concluded: "Looking ahead, clinical trials are ripe for transformation in all manners, set to become smarter, faster, and more inclusive, transforming drug development into a process that's not only technologically advanced but also deeply patient-centered." ■

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.

Modeling the Human Brain

Organoids and assembloids open new opportunities to explore the nervous system and potentially develop treatments for a range of conditions, from pain to schizophrenia

by Mike May, PhD

Eoneren / Getty Images

No one knows when humans first pondered how knowledge of the brain could be applied to medicine. What we do know is that it happened long ago. As one example, a papyrus from the 17th century B.C. found in an Egyptian tomb tried to connect head injuries with brain damage. Thousands of years later, though, scientists still face obstacles to learning more about the human brain.

Stanislav Zakharenko, MD, PhD
Director, Division of Neural Circuits and Behavior
St. Jude Children's Research Hospital

When I ask Stanislav Zakharenko, MD, PhD, director of the division of neural circuits and behavior at St. Jude Children's Research Hospital in Memphis, TN, about the primary benefits of using models in neurobiological research, he said, "That's very easy. We don't have access to the human tissue, and we don't have easy access to human neurobiology."

Scientists have examined post-mortem brains, recorded electric signals through the skull in living people, and applied various imaging techniques in people performing tasks, but all of these techniques have difficulty answering a key question: how do circuits of neurons work in a human brain?

To explore this question, scientists often studied the brains of model organisms such as mice and rats. Still, scientists wondered how much these models taught us about the human brain. Although rodents and humans are "not that different on the basic level, we are definitely different in many, many, many aspects: our brain is bigger; we're making more complex calculations and decisions than mice do during the whole day," Zakharenko said.

Beyond the curiosity about basic brain functions, scientists hope to use this information to better understand brain-related diseases and how to treat them. In some cases, exploring the neurobiology of diseases requires a close look at neurons. So, in addition to studying the brains of rodents, scientists grow cultures of brain cells. This started with 2D cultures, like a single layer of brain cells, and progressed to 3D cultures of cells. In the early 2000s, scientists developed brain organoids, which are 3D cultures of brain cells intended to mimic the human brain. In 2017, Sergiu Pasca, MD, director of the Stanford brain organogenesis program, and his colleagues described simultaneously culturing different types of neural cells to produce assembloids, which are 3D models of more than one brain region, such as two areas of the cortex. Now, scientists face a new question in neuroscience research: how closely do organoids or assembloids replicate the natural structure and function of a brain?

How to make a human brain organoid

Making a human brain organoid starts with pluripotent stem cells, which can make any kind of cell. Although such cells can be obtained from human embryonic tissue, scientists usually start with adult human cells and turn them into induced pluripotent stem cells (iPSCs) through chemical or genetic processes.

Next, 3D culturing methods are used to grow those iPSCs. With the properly timed addition of growth factors and other molecules, the iPSCs develop into specific kinds of brain cells. Instead of growing randomly, these cells self-organize. As a result, the cells build structures, such as specific regions of the human cortex or other brain areas. "The great promise of organoids is the self-organization," Zakharenko said.

An assembloid is produced by developing and combining organoids that replicate different regions of the brain. With this method, for example, more than one kind of cortical region can be combined to study how the regions interact.

Organoids are usually made through unguided or guided approaches. An unguided protocol "generates different brain regions in a disorganized fashion," and a guided protocol "generates only one brain region," explained Alysson Muotri, PhD, professor of pediatrics and cellular and molecular medicine at the University of California San Diego School of Medicine. In addition, Muotri mentioned a third, semi-guided method, which "can be achieved by giving embryonic cues according to human neurodevelopment."

The basic idea behind organoids and assembloids is that they self-organize in ways that are similar to the normal human brain. "About 50% of biologists believe this is true, and about 50% believe it's not true," Zakharenko said. At best, he believes that brain organoids or assembloids make a "very rudimentary model of how these neurons from one brain region connect to the neurons of other brain regions and represent what's happening in our brain." Rudimentary or not, he called it "a good first step."

Alysson Muotri, PhD
Professor
UC San Diego School of Medicine

Synaptic plasticity and schizophrenia

Although Zakharenko did not know it at the time, his first step toward organoids started with his interest in the biology of schizophrenia. For example, he pointed out that the 22q11.2 deletion syndrome, often called DiGeorge syndrome, which arises because a chunk of DNA—25 to 40 genes—is missing on chromosome 22, underlies a high risk of developing schizophrenia. According to Zakharenko, this syndrome creates "a tremendous increase in risk, like 25- or 30-fold" of developing schizophrenia.

The section of DNA deleted in DiGeorge syndrome can also be deleted in mice. In these mouse models of schizophrenia, Zakharenko studied brain circuits, but they seemed normal.

"I was very, very frustrated," Zakharenko said. "How is it that the deletion of 30 genes can have no consequences whatsoever?"

Eventually, Zakharenko's team found one consequence. The deletion disrupted circuits between the thalamus, deep in the center of the brain, and the auditory cortex. Moreover, anti-psychotic drugs rescued this disruption. This made sense to Zakharenko, because hallucinations are a common symptom

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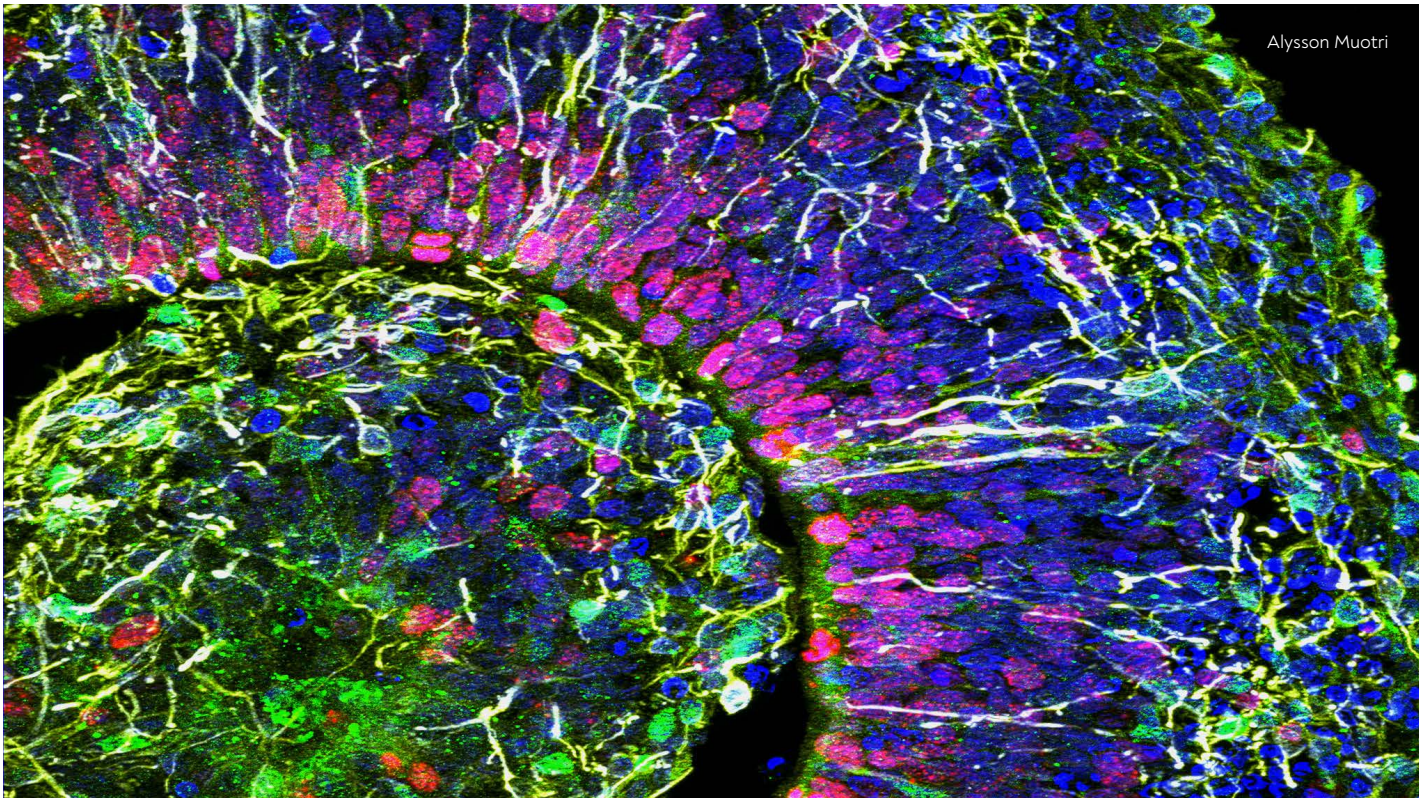

Human embryonic tissue or induced pluripotent stem cells can be cultured to create brain-like collections of cells, which are known as brain organoids. As shown here, brain organoids appear to self-organize into structures that resemble brain tissue.

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of schizophrenia, and "85% of all of these hallucinations are auditory," he said.

To look for similar changes in circuits in people with schizophrenia, Zakharenko's team used a guided protocol to make human thalamic and cortical organoids and then combined them to make human thalamocortical assembloids.

So far, Zakharenko and his colleagues have used these assembloids to study synaptic plasticity, which is the stimulus-based strengthening or weakening between connections that play a role in forming memories. As Zakharenko and his colleagues pointed out: "Aberrant synaptic plasticity is well documented in animal models of autism, schizophrenia, and other psychiatric disorders, but full insight into these disorders requires a human model system." To use thalamocortical assembloids to study schizophrenia, though, the scientists face a crucial obstacle: schizophrenia-driven hallucinations usually arise in adolescents or young adults, but the assembloids consist of young cells. So, the neurons in these assembloids will not mature enough to allow Zakharenko to study the underlying cause of these hallucinations, "unless we really just wait for 20 years," he said.

In the meantime, Zakharenko can use the assembloids to study synaptic plasticity. Eventually, similar assembloids might tell scientists more about schizophrenia. "Who knows?" asked Zakharenko. "Maybe people will come up with a model that contains more mature neurons."

Various techniques can be used to create organoids that mimic specific regions of the brain, such as these cortical organoids.

Searching for signals

To help other scientists employ brain organoids, Muotri and his colleagues published a protocol for making semi-guided cortical organoids. As Muotri says, "In my opinion, semi-guided protocols are the future of the organoid technology."

In semi-guided human cortical organoids, Muotri's team found various cortical cells, including glial cells and neurons in various stages of development. The performance of a brain, though, is about more than the presence of cells. The neurons form circuits that create patterns of electrical activity across the brain, which can be recorded with electroencephalography.

To find out if such activity developed in Muotri's organoids, the team grew them on an Axion Biosystems Maestro Pro system, which includes a microelectrode array (MEA). Based on recordings from this platform, Muotri said, "Neural oscillations generated by semi-guided protocols are indistinguishable from the oscillations found in the human brain." That is, the shapes of the waves look the same, or as Muotri put it: "the ones that can be compared are strikingly similar, confirming the functional advantages of semi-guided organoids." Nonetheless, Muotri added that "it is important to note that the human brain produces more oscillations than these organoids."

Eugenio Martinelli, PhD
Professor
University of Rome Tor Vergata

Other scientists also study the electrophysiology of organoids or assembloids. For instance, Eugenio Martinelli, PhD, professor of electronic engineering at the University of Rome Tor Vergata, used MEAs to explore various features of assembloids. "We monitored the distribution of neuronal spikes over time to study the evolution of network dynamics, including in the presence of specific diseases," Martinelli said. "By applying targeted external stimuli, we also investigated how neuronal activity patterns responded to perturbations, using novel AI algorithms developed specifically for this application." This work produced useful information, including "insights into the development of functional connectivity and responsiveness in brain organoids, highlighting their potential as in vitro models for studying neural network behavior and disease modeling," Martinelli said.

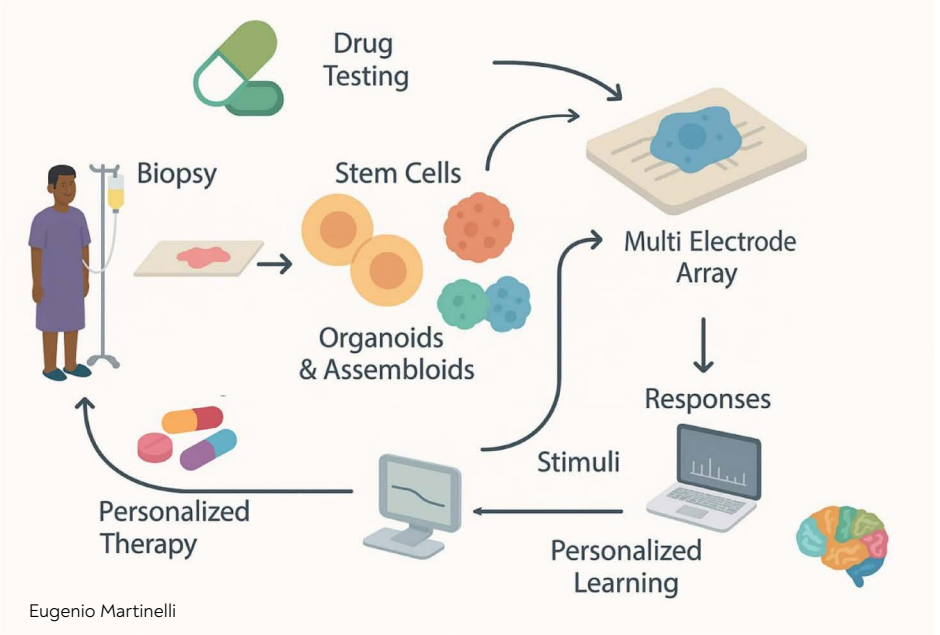
Martinelli plans to dig even deeper into the electrophysiology of brain-related assembloids by using high-density MEAs. With this technology, Martinelli expects his lab to "achieve greater spatial resolution in capturing neuronal signals." In fact, he plans to combine electrical and optical techniques to study how a neuron's structure impacts signaling at synapses in these brain assembloids.

"We aim to explore inter-electrode array correlations to gain deeper insights into functional connectivity and information flow within these complex 3D neural models," Martinelli said. "This research is crucial for advancing our understanding of brain development and for modeling neurological disorders in more physiologically relevant systems."

Even with unguided protocols, human brain organoids "exhibit spontaneous electrophysiological activity in both stable firing and burst firing patterns," according to Feng Guo, PhD, associate professor of intelligent systems engineering at Indiana University Bloomington, and his colleagues, but "high variability as well as the heterogeneity of [these] organoids are stumbling blocks for quantitative studies."

A guided protocol produces more consistent human brain organoids. In these organoids, "periodic oscillatory network activities are observed in 8-month-old organoids," Guo's team noted. "Although these neural network activities do not recapitulate the full temporal complexity in adults, synchronous network events exhibit characteristics comparable to those seen in preterm neonatal electroencephalography."

To make human organoids even better models of the brain, as Guo's team pointed out, other features, such as a vascular system, need to be added.



Eugenio Martinelli

Organoids or assembloids, which include organoids of different types, can be used to develop personalized therapies.

Reproducing pathways to pain

Organoids and assembloids can also be used to learn more about one of the most common ailments—pain. In particular, scientists are searching for non-opioid treatments that are effective, but not addictive. Assembloids could provide a crucial model system for testing new treatments for pain. However, pain arises from a complex network of neural pathways. So, model assembloids need to mimic multiple peripheral and central regions of the nervous system.

That's just what Pasca and his colleagues achieved. These scientists developed a human ascending somatosensory assembloid (hASA) by combining human somatosensory, spinal, thalamic, and cortical organoids. Such an assembloid models pathways from neurons in the spinal cord to ones in the brain, and transmits signals related to pain and other sensory information. As Pasca's team showed, noxious chemical stimulation produced coordinated neural signaling in hASAs.

In the human peripheral nervous system, specific voltage-gated sodium channels, particularly $Na_v1.7$ and $Na_v1.8$, play key roles in processing pain. Pasca's team used CRISPR-based editing to decrease the levels of $Na_v1.7$ channels in hASAs. As these scientists reported: "Notably, loss of the sodium channel $Na_v1.7$, which causes pain insensitivity, disrupted synchrony across hASA." Increasing the expression of *SCN9A*, which encodes the proteins that build the $Na_v1.7$ channels, increased stimulus-induced synchrony of neural activity in the hASAs.

So, this assembloid model of pain could be used in many ways. As Pasca's team put it: "These experiments demonstrated the ability to functionally assemble the essential components of the human sensory pathway, which could accelerate our understanding of sensory circuits and facilitate therapeutic development." In particular, the hASAs could be used to screen novel, non-opioid treatments for pain.

Pasca's team also works on other potential therapies. As one example, Pasca and his colleagues included organoids and assembloids in the development of a model of Timothy syndrome, which they described as "a severe, multisystem disorder characterized by autism, epilepsy … and other neuropsychiatric conditions." According to Pasca, this work "led to the first potential therapeutic developed exclusively with stem-cell models." In addition, organoids and assembloids might one day be created from a patient's disease cells and used to develop a specific treatment for that person.

Most scientists would probably agree that organoids and assembloids reveal much more information about the brain than can be gleaned from a 2D culture of cells. How closely that information correlates with a living human brain, though, remains a matter of debate. ■

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Cell Therapy at a Crossroads

Over the past decade, cell therapy has emerged as one of the most transformative forces in precision medicine, delivering astonishing clinical results—particularly in hematologic malignancies and autoimmune diseases. But the triumphs have not come without caveats. Toxicities remain a serious concern, and the logistical complexity and cost of autologous manufacturing have turned access into a luxury few patients can afford. Cell therapy, for all its promise, has largely remained an option for the privileged few.

Enter Artiva Biotherapeutics, a clinical-stage biotech pushing to democratize cell therapy by reimagining its very foundations. At the heart of their strategy is AlloNK®, a non-genetically modified, cryopreserved natural killer (NK) cell therapy designed to bypass the inherent constraints of autologous approaches. AlloNK isn't just a scientific bet—it's a scalable platform aimed at broad, off-the-shelf application across cancer and autoimmune diseases.

Currently, AlloNK is in clinical development for systemic lupus erythematosus (SLE), including patients with lupus nephritis, and in an investigator-initiated basket trial spanning multiple autoimmune indications. Beyond autoimmunity, Artiva is also targeting non-Hodgkin lymphoma and exploring synergistic potential with Affimed's acimtamig, an innate cell engager, for patients with relapsed or refractory CD30-positive lymphomas.

Artiva is part of a growing wave of innovators challenging the status quo of cell therapy—seeking not just deeper responses, but also faster, safer, and more equitable access for patients in need. *Inside Precision Medicine's* editor in chief sat down with Subhashis Banerjee, MD, chief medical officer at Artiva to discuss the company's vision and aspirations for this burgeoning field.

Subhashis Banerjee, MD

Q: Artiva is advancing multiple clinical trials in autoimmune diseases—including company-sponsored studies in refractory rheumatoid arthritis, Sjögren's Disease, idiopathic inflammatory myopathies, systemic sclerosis, and lupus nephritis, as well as an investigator-led basket trial in some autoimmune indications. What's the broader strategy behind this parallel trial approach, and how do these studies inform one another?

Banerjee: Our approach is grounded in understanding how targeted B-cell depletion that is deep and durable can address immune dysregulation across a range of autoimmune diseases using a treatment platform, AlloNK, that is potentially better tolerated and more convenient to administer in an outpatient setting than other cell therapy approaches. Artiva's strategy is to explore the potential of AlloNK across a spectrum of autoimmune diseases

characterized by B-cell dependence for many of their clinical manifestations. By conducting both company-sponsored and investigator-initiated trials for AlloNK in parallel, we can evaluate safety, tolerability, and efficacy across a broader range of indications in a timely manner. This approach allows us to identify commonalities in disease mechanisms and patient responses across a variety of B-cell dependent chronic inflammatory diseases, informing our understanding of AlloNK's therapeutic potential and guiding future development priorities.

Q: You've described AlloNK as a scalable, off-the-shelf immunotherapy product designed for outpatient administration. How is that vision influencing your trial design and site strategy across autoimmune indications?

Banerjee: Our development program is rooted in more real-world accessibility of cell therapy approaches for autoimmune diseases than is currently available. AlloNK is designed to be cryopreserved, ready to infuse, and combinable with approved and widely used monoclonal antibodies—making it well-suited for community-based infusion centers. This has allowed us to partner with both academic and community sites, reducing logistical burden and enabling broader patient participation. For example, the investigator-initiated trial is led by a community rheumatology practice where patients receive the treatment regimen entirely in an outpatient setting. Our goal is to bring forward a modality that behaves more like a biologic in terms of ease of delivery, while delivering potent and durable B-cell depletion with a well-characterized safety profile.

Q: What was the rationale for incorporating a basket trial into your development plan for autoimmune diseases, and how does that approach help validate AlloNK across multiple immune-mediated conditions?

Banerjee: Basket trials offer a powerful tool for evaluating a therapeutic agent across multiple indications that share a molecular mechanism targeted by the agent. In our case, it allows us to explore the safety and efficacy of B-cell targeting across indications like rheumatoid arthritis, Sjögren's Disease, idiopathic inflammatory myopathies (IIM), and systemic sclerosis—all within a single protocol. These conditions are commonly managed by the same specialists, so the basket structure also gives us the ability to enroll rheumatology practices that routinely treat a broad range of autoimmune indications. The operational efficiency of a basket trial helps maximize site interest and enrollment potential while allowing us to generate safety, translational, and early activity data across multiple diseases that share molecular mechanisms. This strategy also allows us to gather comparative translational and safety data across indications that will inform both regulatory strategy and future trial designs.


Artiva Biotherapeutics

Q: Artiva is taking a dual-track approach with both company-sponsored and investigator-initiated trials. What are the strategic advantages of running these in parallel across different autoimmune diseases?

Banerjee: Our company-sponsored trials are focused on generating robust clinical and translational data towards eventual marketing authorizations in priority indications. In parallel, the investigator-initiated trial (IIT) provides an important proof of concept for how our product can be used in a disease population in a real-world, community rheumatology setting using entry criteria that may differ somewhat from company-sponsored trials to simulate real-world use. By evaluating our therapy in diseases commonly seen in community clinics—and pairing it with an anti-CD20 antibody already familiar to treating physicians—the IIT allows us to test feasibility, operational fit, and initial patient experience outside of academic centers. This real-world perspective is critical as we think about eventual access and broader adoption by healthcare practitioners in the community.

Q: Looking ahead, what are the key upcoming milestones across your autoimmune programs, and how are you defining success in the next 6 to 12 months?

Banerjee: Over the next year or so, we expect to share initial safety and translational data from both our company-sponsored studies, including the Phase 2a basket trial, and ongoing investigator-initiated research. We're focused on assessing safety, tolerability, and efficacy, evaluating for deep and sustained peripheral B-cell depletion, and identifying disease-specific signals of activity. We expect to validate our mechanism in autoimmune settings, narrow in on a lead indication, and set the foundation for registrational development with a modality that can be delivered broadly and reliably in the community outside of hospital settings. ■

Damian Doherty has been in media and publishing for over 30 years, beginning at News Corporation. Damian has managed, edited, and launched life science titles in drug discovery and precision medicine. He was features editor of *Drug Discovery World* for fourteen years and founded, established, and edited the *Journal of Precision Medicine* in 2014. In parallel, Damian founded and organized the Precision Medicine Leaders' Summit, a global, immersive 3-day senior leadership conference that still runs today. He edited *AIMed* magazine in 2019 before launching Photo51Media, a platform for illuminating untold, compelling stories in precision healthcare. Damian joined Mary Ann Liebert in 2021 to help steer the new rebrand and relaunch of *Clinical OMICs* to *Inside Precision Medicine*.

STORIES *from the* FRONT LINES

Practicing Medicine in the Age of AI

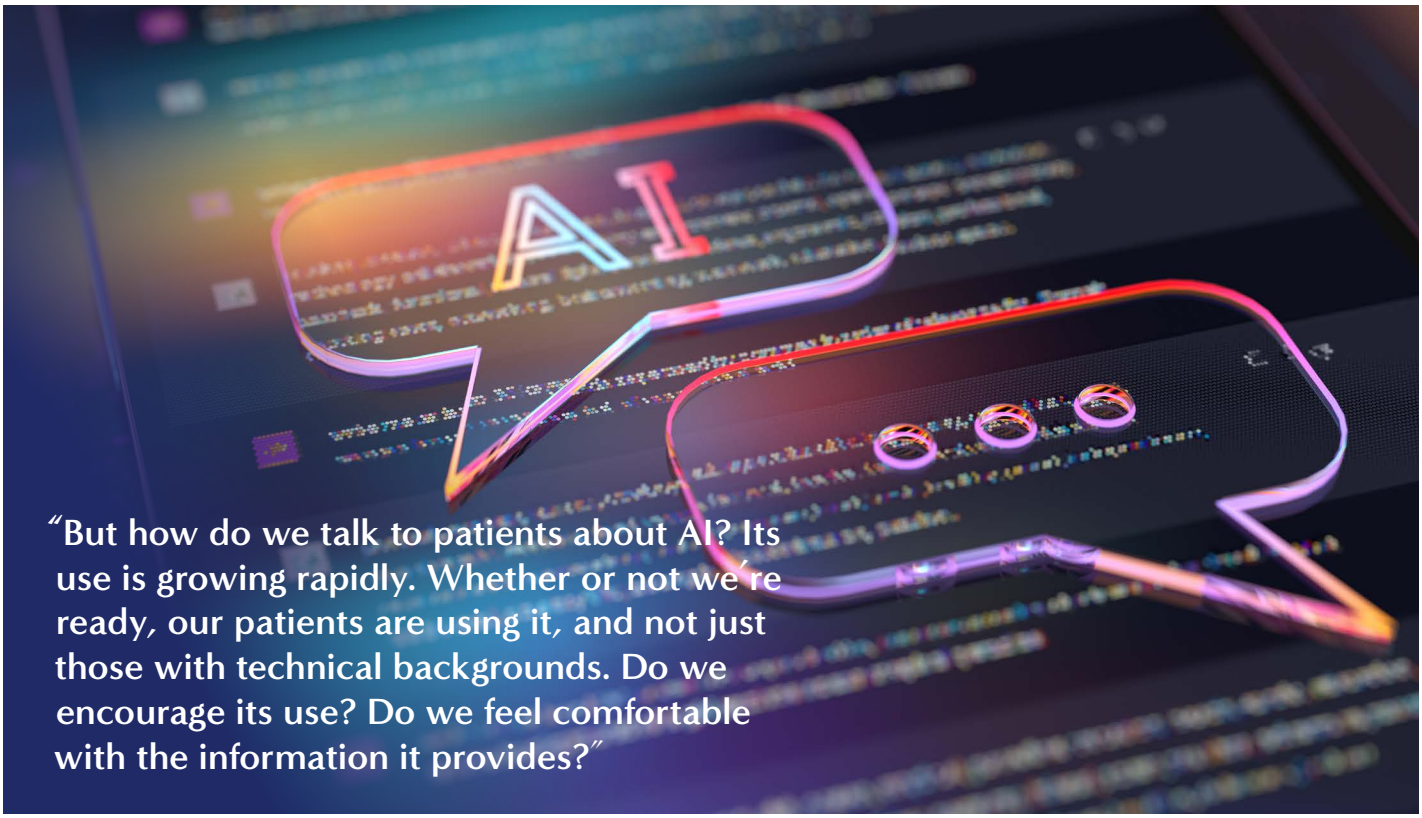
by Nephi Walton, MD

As I was preparing for my clinic the following day, I noticed one of the patients had already undergone genetic testing through another specialty and been diagnosed with a rare genetic disorder. Given the breadth of conditions we encounter as clinical geneticists, it's common to come across disorders we've never seen before. I did my homework: reviewed the literature, learned the condition, and outlined a management plan.

The next day, I walked into the room to meet a healthy-appearing, intellectually sharp software engineer who worked professionally in artificial intelligence (AI). As I collected his history, he explained that he had self-diagnosed his condition using a large language model (LLM), inputting lab results and clinical features. Initially, the specialist managing the condition (outside of genetics) refused to order the test he requested. Eventually, he convinced them to send the genetic test—and the LLM was right.

After gathering his history and completing the exam, I sat down across from him to explain the condition, the management plan, and its implications for family planning. He listened thoughtfully, then smiled and said, "Great, that's exactly what the LLM told me."

Not long ago, we only had to contend with "Dr. Google," "Dr. Facebook," and "Dr. TikTok." The first often fueled anxious patients with unreliable information. The latter two frequently left patients convinced that common symptoms pointed to rare and exotic diseases—and don't even get me started on Methylenetetrahydrofolate reductase. These platforms created con-



"But how do we talk to patients about AI? Its use is growing rapidly. Whether or not we're ready, our patients are using it, and not just those with technical backgrounds. Do we encourage its use? Do we feel comfortable with the information it provides?"

ertigo3d / Getty Images

fusion, but the physician remained the anchor; someone who could thoughtfully interpret, correct, and guide with grounded medical expertise.

Now, the challenge is different. We're being compared directly to a digital superintelligence that can rival, and sometimes exceed, our ability to synthesize information. These models have an advantage: they retain and access vast stores of knowledge instantaneously, which is something the human brain can't do. Yet, we still hold a unique role, particularly in our ability to examine, empathize with, and physically connect with patients.

I've always encouraged my patients to research their conditions, offering guidance and trusted sources to avoid misinformation. I often recommend online patient communities to help them learn from others with lived experience while cautioning them to steer clear of miracle cures and consult me before trying any "exotic berry" elixirs.

But how do we talk to patients about AI? Its use is growing rapidly. Whether or not we're ready, our patients are using it, and not just those with technical backgrounds. Do we encourage its use? Do we feel comfortable with the information it provides?

As I reflect on that patient's parting words—"you told me exactly what the LLM told me"—what I didn't share is that I had used AI too. It wasn't my only tool, but it was part of my process. I've been using it for a while now and I am consistently impressed.

Some modern LLMs go beyond regurgitating memorized content and fabricating references. They can reason, hypothesize, and synthesize insights in useful ways. In one recent case, I saw a patient with an extremely rare disorder, only documented in a few dozen individuals. Unlike reported cases, this patient had hearing loss. I wondered whether this was part of the syndrome or an unrelated finding. I asked an LLM if hearing loss could be associated with the disorder. It found a single case, one I had missed despite thorough searching, and even proposed a plausible biological mechanism based on the gene's function.

Despite that, I still ordered further testing to rule out other causes. We're not being replaced just yet. But we must embrace these tools and not fear them. Because whether we like it or not, every day our patients are comparing our knowledge and decisions to that of our digital counterparts.

It's a high bar. And when you can't beat them, join them. ■

Nephi Walton, MD, completed his MD and MS in biomedical informatics with a focus on machine learning/artificial intelligence at the University of Utah School of Medicine. He completed a combined residency in pediatrics and genetics at Washington University in St Louis, Missouri. He is board certified in both clinical genetics and clinical informatics. He has worked with two of the largest population health sequencing programs in the U.S.: MyCode at Geisinger and HerediGene at Intermountain Health. He was past chair of the American Medical Informatics Association Genomics and Translational Bioinformatics Workgroup a former program director at the National Human Genome Research Institute and has presented at several meetings on translating the use of genomics and artificial intelligence into general medical practice, something he is actively pursuing in clinical practice.

Unpacking the Complexities of Companion Diagnostics for Cell and Gene Therapies

by Laura Cowen

In a world of increasingly precise therapies, companion diagnostics (CDx) are gaining importance. Yet the need for a CDx is often unclear, particularly for emerging cell and gene therapies (CGT) where patient eligibility may not simply depend on the presence or absence of a targetable mutation.

A CDx is defined by the U.S. Food and Drug Administration (FDA) as a medical device that provides essential information for the safe and effective use of a corresponding drug or biological product. CDx are used to identify patients who are most likely to benefit from a particular therapeutic product or those likely to be at increased risk for serious side effects from that treatment. They can also be used to monitor treatment responses to achieve improved safety or effectiveness.

At present there are 188 CDx listed as "cleared" or "approved" by the FDA. All but two of these are for use alongside drugs, typically targeted immunotherapies, to treat cancer. In addition, there are currently 44 FDA-approved cell and gene therapy products. Of these, just three have a CDx.

The question is, why are there so few CDx for CGT when so much investment goes into creating these precision treatments? The answer, according to experts in the field, is nuanced and reflects unique scientific, regulatory, and business challenges.

> "Many AAV gene therapies approved with a CDx requirement include the CDx approval as a post-market commitment to the Biologics License Application, meaning the CDx is approved after the gene therapy itself."

"It's important to emphasize that determination of whether a CDx is required for cell and gene therapy products is made by the FDA's Center for Biologics Evaluation and Research," said Monica Veldman, director of global regulatory policy at the Alliance for Regenerative Medicine.

She explained that the "FDA's enforcement of this requirement in the cell and gene therapy space has evolved over time and, in the specific context of adeno-associated virus (AAV)-based gene therapies, has shifted from not

Westend61 / Getty Images

requiring a CDx to generally requiring one for the safe and effective use of the CGT product."

Veldman added that "many AAV gene therapies approved with a CDx requirement include the CDx approval as a post-market commitment to the Biologics License Application, meaning the CDx is approved after the gene therapy itself."

She said that, overall, the limited number of CDx for CGT products largely reflects the fact that CGT is still an emerging field, unlike non-CGT oncology products which have a much longer regulatory history.

Monica Veldman
Director
Alliance for Regenerative Medicine

CDx for gene therapies

The rationale for gene therapy was first described in *Science* in 1972 by Theodore Friedmann, MD, and Richard Roblin, PhD. In simple terms, it is the use of genetic material to treat disease. Gene therapy can involve gene addition, where a functional gene is inserted into a cell to make more copies of a specific protein; gene silencing, in which the genetic material inhibits genes that may be overproducing proteins; and gene editing, which is used to correct pieces of DNA by changing or deleting the information within the affected individual's gene.

Gene therapies are usually delivered to cells via a genetically engineered virus vector. The virus of choice is often AAV due to its minimal pathogenicity and ability to establish long-term gene expression in different tissues.

However, a potential limitation for recombinant (r)AAV vectors is pre-existing anti-AAV antibodies that may be present in a patient following natural AAV infection. It is estimated that approximately 30–60% of individuals have pre-existing anti-AAV antibodies, but this varies across different AAV serotypes, by geographic region, and with the age of the individual. Anti-AAV antibody levels can also change over time within an individual.

Anti-AAV antibodies are problematic for companies developing gene therapies using rAAV vectors because they have the potential to reduce the efficacy of the treatment or trigger an adverse immune response.

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This is where a CDx can help. The test can be used to screen for patients with anti-AAV antibodies. Indeed, both CDx currently approved for use with gene therapies measure anti-AAV antibody levels.

The first, AAV5 DetectCDx® is a bridging immunoassay, developed by ARUP Laboratories, that detects antibodies to AAV serotype 5 in plasma specimens. It is used to determine eligibility for treatment with ROCTAVIAN (valoctocogene roxaparvovec-rvox), Biomarin's gene therapy for severe hemophilia A. Only patients who demonstrate no detectable anti-AAV5 antibodies can be treated.

The second, LabCorp's nAbCyte™ Anti-AAVRh74var HB-FE Assay is a CDx to determine patient eligibility for treatment with BEQVEZ™ (fidanacogene elaparvovec-dzkt), Pfizer's FDA-approved gene therapy for patients with moderate-to-severe hemophilia B. The cell-based assay detects pre-existing neutralizing antibodies to AAV serotype Rh74var. A negative test result indicates that an individual can be considered for BEQVEZ therapy.

Deborah Phippard, PhD
Chief Scientific Officer
Precision for Medicine

Seven of the remaining 13 FDA-approved gene therapies also use AAV vectors, while the others use either a herpes simplex virus vector, a lentiviral vector, autologous stem cell transplantation, or encapsulated cell-based gene therapy. None have a CDx.

"It comes down to the risk profile of the therapy, the route of administration, and the expected age of the patients," explained Deborah Phippard, PhD, chief scientific officer at Precision for Medicine. "You can't just say every gene therapy must have a companion diagnostic, because that is not the case."

She points out that treatments being delivered at immune-privileged sites such as the eyes, brain, and central nervous system are less likely to be exposed to anti-AAV antibodies than those being administered systemically. In addition, younger patients, who are often candidates for gene therapies to treat rare diseases, are less likely to have antibodies than an adolescent or adult with an evolved immune system. Pre-existing immunity may also depend on the type of AAV vector. The amount of virus being delivered is another consideration.

Overcoming hurdles and driving forward

Ultimately, it is up to the company developing the therapy to work with the FDA and other regulatory authorities to determine the requirement for a CDx.

Yet manufacturers would argue that there is a need for more guidance on when a CDx is compulsory.

Christos Petropoulos, PhD
Vice President
Labcorp Research and Development

"I'd like to know what the rules are, what boxes to check," said Christos Petropoulos, PhD, vice president of LabCorp. "In other industries, you have guidelines for consideration from the FDA and I think we need to get there with CGT."

LabCorp's nAbCyte assay was the first CDx to use a cell-based format. "We didn't have a playbook, we had to figure it out as we went along," said Petropoulos. "Hopefully, in the future we'll have that playbook."

Irene Bacalocostantis, PhD, executive director of regulatory affairs, CDx, at LabCorp, added that it would be useful for the FDA to consider industry feedback on the challenges involved in developing CDx, particularly in the early stages.

"There have been instances where the FDA has required significant amounts of data to be submitted in an Investigational Device Exemption prior to clinical trial, but this can be difficult to obtain in the early stages," she remarked.

Petropoulos agreed: "These are rare diseases, so there's not a lot of study subjects and not a great opportunity to generate the data that you need to understand how the CDx should be regulated or how it should be used."

The process is also expensive, which can be a sticking point with CGT manufacturers. "They have an early phase, non-registrational trial and don't yet know if their drug is going to succeed, but they've been asked to pay a few million dollars for the development of a CDx," said Bacalocostantis. "I think that's a huge hurdle."

Irene Bacalocostantis, PhD
Executive Director
Labcorp

Although the FDA is there to guide and regulate the use of CDx for CGT, they are not the only stakeholders when it comes to the development of new treatments. The payers may also have an impact.

"Payers may well be a driver in the future, because they don't want to pay for an expensive treatment if somebody's not going to respond due to significant levels of pre-existing immunity," said Phippard. This may mean that they require a CDx before they will consider reimbursement.

Phippard noted that CDx development adds significant cost to early phase studies, but would encourage the gene therapy developers to work with a CDx partner early in the process.

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Top Trends Driving Priorities for Companion Diagnostics Development

Companion diagnostics (CDx) have become an essential tool to identify patients that benefit from targeted therapies in the precision medicine landscape. Recent shifts in the pharma pipeline and diagnostic strategies as well as regulatory requirements are transforming the current CDx development paradigm and prompting pharma companies to think differently about drug development.

Antibody-drug conjugates are redefining CDx priorities

Antibody-drug conjugates (ADCs) comprise the lion's share of oncology pipelines today, and pharma companies are having to rethink their strategies for biomarker testing. "The number of ADCs has risen dramatically in the past three years," said Gulzar Sandhu, PhD, chief business officer, companion diagnostics at Agilent, a trend that has reignited interest in immunohistochemistry (IHC) as a key platform for developing CDx solutions.

The high potency and toxicity profiles of ADCs make selecting the right patients for exposure critical, prompting a push for the use of biomarkers, more precise biomarker thresholds, and sensitive assays.

Earlier decision-making on CDx development is increasingly important

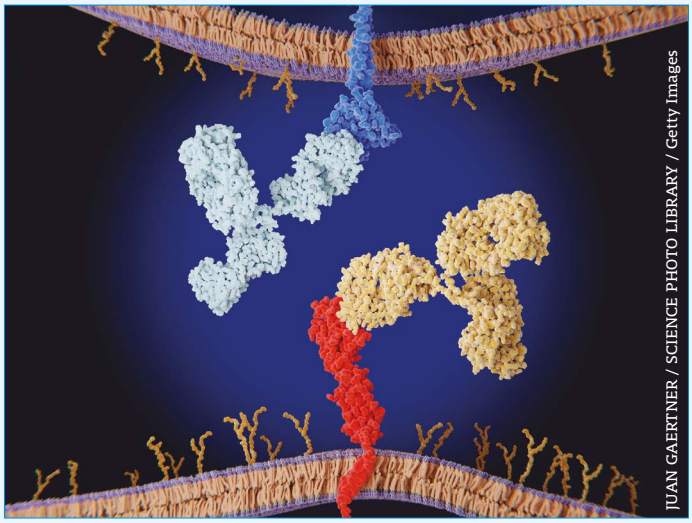
Targeted therapies constitute a large proportion of oncology drugs in development and most of these require an understanding of the relationship between therapeutic response and biomarker status. Given the high costs of developing a CDx, pharma companies adopt a "fail fast" approach and utilize low-investment assays in early clinical development to assess biomarker utility. This enables greater focus and optimal investment in robust assay development for assets requiring a CDx. Agilent offers solutions for both early assays and full CDx development and helps pharma optimize efforts and investments with a range of assay offerings.

Karina Kulangara, PhD, associate vice president, R&D, companion diagnostics at Agilent, noted that this trend is both a strategic shift and a fundamental change in how biomarkers are integrated into trial design. "We're seeing the role of biomarkers evolving, not just to define who should get the drug, but whether the drug should even move forward."

Digital and AI-enabled diagnostics are the future

Digital pathology and artificial intelligence tools are increasingly being evaluated as part of the CDx ecosystem. While not yet widely adopted in commercial diagnostics, their potential to quantify subtle biomarker expression patterns and support internal workflows could be transformative.

Digital tools can improve definition of the biomarker characteristics for safe and effective use of therapeutics including ADCs and cell therapies. "There's intense interest in whether digital solutions can help identify low-expressing patients who still benefit from therapy," said Sandhu. "At Agilent, we incorporate digital tools for image analysis and in our development workflows so that we have the necessary foundational elements and could support any digital CDx development if warranted."



JUAN GAERTNER / SCIENCE PHOTO LIBRARY / Getty Images

The present uncertainty around regulatory pathways, reimbursement models for digital CDx and global access to necessary technologies has slowed adoption. Furthermore, the infrastructure needed to support digital and AI applications "is not there yet and will need to be established," Sandhu acknowledged. And it will require significant support from pharma companies. "But when a major therapy requires it, we will see a significant step change to make that infrastructure accessible."

The way forward

Companion diagnostics are no longer niche tests but critical levers in the success or failure of targeted therapies. External forces such as evolving regulatory expectations will likely continue to reshape the CDx field for some time. Whatever shifts occur, pharma companies will need to adapt quickly. As Mark Verardo, PhD, head of the science office at Agilent summed up, "from the perspective of patients, there's never been a more hopeful time" but the complexity is growing, and Agilent is focused on creating solutions to address the challenges.

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Companies like Precision for Medicine and LabCorp have been supporting various gene therapy developers for many years. Both Phippard and Petropoulos said that they have often been approached for CDx support when the drug developer has already planned a clinical trial timeline that does not allow for the development of validated assays. If a regulatory agency then requires a validated assay, this can result in costly delays to a clinical study while the CDx is developed and manufactured.

> "As a pathology community, we have seen the effects of not looking ahead to the therapies coming down the pipeline and essentially scrambling to keep up with all the changes that are happening, so we're really intent on getting ahead of the curve."

"I would say companies get caught blindsided regularly, and then they're shocked with how long it takes to make a CDx," Phippard remarked. "I always say, 'Engage with the regulatory system and ask for a significant or a nonsignificant risk determination,' because if the FDA says there's significant risk, that puts you on a very different pathway. If you need a CDx, it's going to take you a year or more to find a company and make one."


Suriphon Singha / Stock / Getty Images Plus


Fabienne Lucas, MD, PhD
Assistant Professor
University of Washington

Planning for an increase in CDx for cell therapies

Gene therapies have been a focus for CDx because of the potential impact of anti-AAV antibodies on efficacy and safety, but CDx for cell therapies is also a growing area. Cell therapy involves the transfer of intact, live cells into a patient to treat or cure a disease. The cells may originate from the patient (autologous cells) or a donor (allogeneic cells) and may be unmodified or gene edited. Chimeric antigen receptor (CAR) T cell therapies are an example of gene-edited cell therapies that have been successfully used to treat some cancers.

Among the 19 CAR-T and other cell therapies that have FDA approval, only one has an approved CDx so far. TECLERA® (afamitresgene autoleucel) is a genetically modified autologous T cell immunotherapy for synovial sarcoma that targets melanoma-associated antigen A4 (MAGE-A4), a cancer-testis antigen overexpressed in various cancers. In August 2024, the treatment, developed by Adaptimmune, became the first approved engineered cell therapy for a solid tumor indication in the United States.

Two CDx are associated with TECLERA. The first, SeCore™ CDx HLA A Sequencing System from One Lambda, uses a sequence-based typing method to screen for human leukocyte antigen (HLA)-A alleles in genomic DNA purified from whole blood samples to ensure that the modified cells are not rejected by the patient's immune system. The second, Agilent's MAGE-A4 IHC 1F9 pharmDx, is an immunohistochemistry assay used to detect MAGE-A4 expression in synovial sarcoma tissue.

There are currently no FDA-approved CDx for allogenic cell therapies (ACTs) but a recently published article by The College of American Pathologists (CAP) highlighted patient selection and compatibility as a potential challenge in the development and implementation of ACTs. They say that "HLA matching of the allogeneic cell product may be required to avoid GvHD [graft versus host disease] or to ensure efficacy."

"The article was written to try and prepare the pathology community for what is to come with regards to diagnostic tools for CGT," explained Fabienne Lucas, MD, PhD, assistant professor of hematopathology at the University of Washington, Seattle, and Matthew Anderson, MD, PhD, executive vice president and chief medical officer at Versiti. Together, they lead the ACT project within the CAP Personalized Health Care Committee.

Matthew Anderson, MD, PhD
Executive Vice President
Chief Medical Officer
Versiti

"As a pathology community, we have seen the effects of not looking ahead to the therapies coming down the pipeline and essentially scrambling to keep up with all the changes that are happening, so we're really intent on getting ahead of the curve," said Anderson.

Lucas added: "One promise of this type of therapy is their 'off-the-shelf' availability, meaning that patients can be treated or monitored more widely. We therefore want to prepare the pathology community at large, including the labs and pathologists not necessarily involved with specialized diagnostic or monitoring tools, in how to handle patient samples and what they might show."

This will be increasingly important as the CGT market grows, and thus by default the need for diagnostic testing and tools, including CDx, expands.

Sharing the development burden

"As CGT therapies become more common, there is likely to be a significant expansion in the field of CDx, driven by new scientific discoveries, evolution of technologies, and advancements in non-viral gene editing methods, allogeneic therapies, and applications beyond cancer," said Gulzar Sandhu, PhD, chief business officer of the companion diagnostics division at Agilent.

Gulzar Sandhu, PhD
Chief Business Officer
Agilent

Companies like Agilent, Precision for Medicine, and LabCorp are already seeing a growing demand for diagnostic support related to CGT trials and commercialization, with therapy areas expanding from oncology and rare diseases to more common conditions like congestive heart failure with a genetic component and neurological conditions such as Parkinson's disease. Phippard believes these new additions could "change the paradigm for how you think about CDx for gene therapy and making that accessible globally."

Stígur Már Karlsson /Heimsmyndir / Getty Images

There is also interest in standardizing or streamlining the approach to developing CDx. "As more therapies utilize shared delivery systems, the ability to use one CDx across multiple products, such as AAV-GTs that share a common vector, could reduce duplicative development efforts and lower overall regulatory and financial burdens," said Veldman.

Karina Kulangara, PhD
Associate Vice President
Agilent

However, Karina Kulangara, PhD, associate vice president of the companion diagnostics division at Agilent also cautions that "a more standardized CDx approach for the CGT pipeline necessitates a CDx technology that addresses the broad need of CGT and flexibility to incorporate specific biomarkers. It would require robust regulatory frameworks, continuous innovation in diagnostic technologies, and collaboration between biopharma companies and diagnostic developers."

With this in mind, the CGT field will be closely monitoring how regulators handle early CDx implementations. "The Alliance for Regenerative Medicine is actively working with stakeholders to recommend regulatory approaches that support broader CDx applicability," said Veldman. "These approaches will be critical to enabling a scalable, efficient CDx infrastructure that keeps pace with innovation in the CGT space." ■

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.

Reshaping Minds

Therapeutic psychedelics promise to reset the mind, offering potentially massive improvements in mental health and neurological conditions

Eugene Mymrin / Getty Images

by Chris Anderson

Some of the first pieces of knowledge of how psychedelics affect perception and benefit mental health date back to the late 1800s. Significant research was spurred by the synthesis of lysergic acid diethylamide (LSD) in 1938. The mid-20th century saw a range of clinical studies of LSD and other psychedelics, including psilocybin—the active compound in "magic mushrooms"—and their use as treatments in psychiatry in the U.S. and Europe.

But in the late 1960s and early 1970s, the increased use of psychedelics as recreational drugs and concerns about safety and potential for abuse led to their prohibition. The U.S. government even declared that psychedelics had no potential for use as therapeutics. As a result, psychedelics remained in a research purgatory for decades until a handful of scientists began revisiting their potential in the early 2000s. Today, there are no less than 130 clinical trials being conducted worldwide on potential therapeutic uses of psychedelics, although most are in early stages. Psilocybin is the most studied of a range of a range of drugs that includes LSD, ketamine, and methylenedioxymethamphetamine (MDMA), among others. The bulk of research centers on their use for mental health treatments such as major depressive disorder, post-traumatic stress syndrome (PTSD), anxiety, and substance abuse, with other studies focused on neurological disorders such as Parkinson's disease.

Rotem Petranker
Director
Canadian Centre
for Psychedelic Science

The resurgence of interest in these drugs is likely influenced by shifting public opinion of psychedelics and ongoing efforts to legalize, or at least decriminalize, the use of psilocybin. Australia became the first country to officially recognize psilocybin as a medicine in July 2023. In the U.S., Oregon was the first in 2020, followed by Colorado in 2022, to enact laws that allow the supervised use of psilocybin for therapeutic purposes.

"Public interest in psychedelics has increased, perhaps exponentially," said Rotem Petranker, director of the Canadian Centre for Psychedelic Science, whose early research in the 2000s focused on mindfulness. "Psychedelics was always interesting to me, but I never thought that the moment would come when it would be a legitimate research interest."

Leading research institutions have now made significant commitments to psychedelic inquiry, including the Johns Hopkins Center for Psychedelic and Consciousness Research, the U.K.'s

Imperial Centre for Psychedelic Research, and the University of California, Berkeley Center for the Science of Psychedelics.

Ginger Nicol, MD, a clinical investigator and professor of psychology at Washington University (WashU), St. Louis, sees a couple of other factors influencing this surge in research. "Psychedelics offer so much hope and promise because they work so fast and they have such a profound effect," she noted, "and the pandemic really brought it into full relief and showed us just how mental health is impacting all people."

Ginger Nicol, MD
Professor
Washington University

How psychedelics work

Psychedelics like psilocybin work on the brain primarily by interacting with the serotonin system, particularly the 5-HT_{2A} receptor. Once in the body, psilocybin is converted into psilocin, which closely resembles serotonin. Psilocin binds to 5-HT_{2A} receptors in areas of the brain such as the prefrontal cortex, which is a center of cognition, mood, and perception. It enhances communication in the brain between regions that typically do not communicate as much. It also suppresses the default mode network (DMN) in the brain, which was discovered ins 2001 by Nicol's colleague at WashU, neuroimaging expert Marcus Raichle, MD. The DMN is a group of regions in the brain that are most active when the brain is at rest. Research suggests that DMN dysfunction may lie at the heart of a number of mental health conditions.

In this way, psychedelics lead to a state of neuroplasticity, which is what essentially allows the brain to grow and form new connections. Research by Nicol and colleagues sought to better understand the differences in brain activity when a person has and has not taken psilocybin. To do this, they recruited seven healthy individuals between the ages of 18 and 45 and dosed them with 25 mg psilocybin or 40 mg methylphenidate (brand name Ritalin; used as a control drug). The participants underwent magnetic resonance imaging (MRI) scans during both drug and non-drug sessions. The images showed that the psychedelics desynchronize brain activity both regionally and globally.

"We actually saw changes that give us an indication that this change might be one of the mechanisms by which psilocybin helps people with depression," Nicol noted.

Significantly, their research showed that after a person took the psychedelic, the brain connectivity changes persisted for 3–4 weeks after dosing. This finding suggests potential for a longer therapeutic window.

These findings were echoed by research from the University of Michigan (UM), conducted in the lab of Omar Ahmed, PhD, an assistant professor of psychology. The researchers used microdoses of the drug 25CN-NBOH, a psychedelic known for being a highly selective agonists of the serotonin 5-HT_{2A} receptor. The UM team evaluated the behavioral effects of 25CN-NBOH on flexible learning in mice, a cognitive function regulated by the prefrontal cortex. An important aspect of this study was its design to isolate the long-term effects of the psychedelic by conducting testing only after two weeks had passed since the drug was administered. This helped avoid potential confounding effects from acute psychoactive impacts.

To measure flexible learning, the investigators used a novel automated reversal learning task, in which mice were trained to poke their noses into two holes in sequence to get a treat. The sequence in which to poke the holes was then reversed to track how well mice could adjust to changes in learned rules. Mice were given either a single dose of 25CN-NBOH or a saline control. After a two-week delay, both male and female mice that received the psychedelic showed significantly greater adaptability in the reversal phase of the task, as measured by poke efficiency, accuracy of trials, and number of rewards earned.

"Psychedelics such as 25CN-NBOH alter the neuroplastic structure of neurons in many parts of the brain, increasing the connectivity between key neurons," Ahmed said. "These results show that these biological changes lead to sustained behavioral learning benefits that are still evident many weeks after a single psychedelic dose, highlighting why clinical trial designs using only one or two doses may reveal long-lasting benefits in terms of flexible learning. This is important because the fewer the doses one has to take to see long-lasting benefits, the lower the risks for potential side effects."

Omar Ahmed, PhD
Assistant Professor
University of Michigan

Dosing psychedelics

The WashU and UM studies show the long-lasting effects of both a higher dose and a lower dose in producing brain plasticity that lasts for weeks. But might higher doses and accompanying psychoactive effects be necessary to gain maximum benefit? Current research indicates it might not be an either/or question.

Petranker noted that larger doses, while more expensive because they require therapist assistance, can be psychologically intense and provide a depth of experience, leading to a profound sense of connectedness or new personal insight that can benefit people suffering from major depressive disorder or PSTD. "Some researchers and practitioners would argue that this experience is part and parcel, perhaps necessary, for the healing process," he

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said. "Once you reintroduce a sense of connection … from connectedness emerges meaning, and from meaning emerges better mental health."

There is a need for better dosing data, Nicol added, which would include optimal dosing frequency and a better definition of the role of psychotherapy in the treatment regimen. "Right now, we don't know what the right dose is and where do we place the psychotherapy in the context of that."

> "If these substances require psychotherapeutic support, then either the mandate of the FDA and other similar regulatory agencies needs to be amended, or these drugs will not pass the threshold."

Microdosing, where a small amount of psilocybin or other psychedelic that won't produce a psychoactive response is used, potentially has many benefits. Some psychiatric and other health conditions, like bipolar disorder and cardiovascular conditions, may preclude a higher dose as it elevates the heart rate and blood pressure.

Looking ahead to a future with psychedelic treatments that have regulatory approval, microdoses could improve acceptance as the treatment will be less expensive and people will not feel impaired. Petranker prefers to prioritize doses that do not impair daily activities. "As long as you can do everything you normally do, you can drive, you can take care of kids, you can work, then that is an okay dose."

Gaining regulatory approval

Hopes ran high in 2024 as clinic-stage psychedelic therapy company Lykos seemed poised to be the first company to gain regulatory approval for its MDMA-assisted therapy for PTSD. But news from the FDA was not good as the agency declined approval and requested an additional trial to support the therapy's safety and efficacy.

Although the FDA had issues with the trial design, which included the psychotherapy portion, some in the industry hoped the treatment would gain approval, but with restrictions on how it would be administered and requirements for the company to conduct a post-approval study.

Lykos contended that many of the FDA's requests could have been addressed with existing data or through reference to the scientific literature. The company continues to maintain close contact with the agency to work toward approval. Lykos declined an interview while it works through these issues.

Currently, two other psychedelic drugs are in Phase III trials: CYB003 from Cybin, a deuterated analog of psilocybin for the treatment of major depressive disorder; and COMP360 from COMPASS Pathways, a synthetic formulation of psilocybin for treatment-resistant depression.

The Lykos setback has not dampened enthusiasm in the field. If anything, it can provide valuable lessons to other companies pursuing regulatory approval for treatments that include both a psychedelic agent and therapy assistance.

Petranker sees the psychotherapy component of some clinical trials as a sticking point with the FDA, as evaluating and regulating therapy is outside the normal bounds of how the agency operates.

"If these substances require psychotherapeutic support, then either the mandate of the FDA and other similar regulatory agencies needs to be amended, or these drugs will not pass the threshold," he said.

Further, the industry standard double-blind trial structure designed to keep people in a trial unaware if they are receiving the drug or a placebo is a challenge as many receiving the drug will feel its psychoactive effects. Nicol laid out ways to get around this hurdle.

"One way is to not have a full placebo arm, but to have your comparison arm be a very low dose of the same agent or of another drug, where you know that people can tell that they're taking it," Nicol said. Two agents that fit the bill are niacin, which elicits warmth and flushing, and benzodiazepines, which have noticeable effects on the central nervous system. Nicol also noted that trial participants will likely have tried many other drugs that did not work before enrolling in a psychedelic drug trial, so a model that has different dosing levels for the two cohorts could attract more trial participants.

"Why would a person who is really, really depressed and desperate for relief enroll in a trial if they could potentially get a sugar pill?" she asked. Further, a trial with such a design could help establish dosing levels if the low-dose cohort exhibits the same, or very similar, benefits compared with the higher dose group.

Nicol noted that continuing research and clinical validation is needed as self-dosing with these substances is increasing, even without the necessary scientific proof of safety and efficacy. "We do need the rigorous research and [to] get federal drug approvals," she said. "But meanwhile, decriminalization is already happening, so can those two processes happen in a complimentary way?"

She also sees how the approval of these drugs could represent a sea change in mental health management. "When these become legitimate medical therapies, then the medical system will have to figure out how it's going to accommodate delivering this care," Nicol concluded. "It will require us to rethink our clinical care delivery in mental health." ■

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*.

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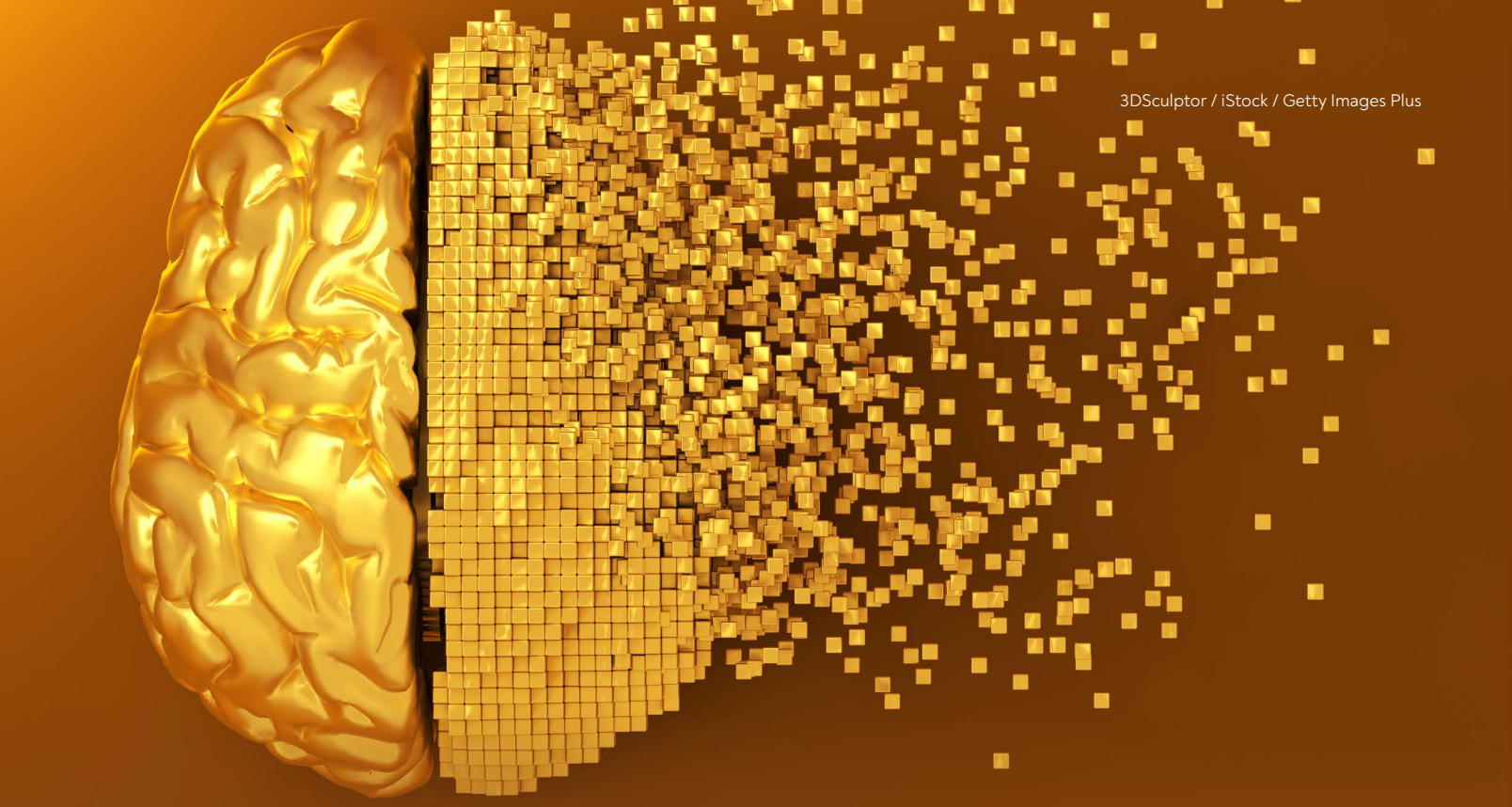

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From Rejection to Revolution: mRNA Vaccines Go Beyond Infections to Diseases in the Brain

The Nobel Prize–winning technology behind mRNA vaccines is now training the immune system to treat and prevent glioblastoma and Alzheimer's disease

Jonathan D. Grinstein, PhD North American Editor

Katalin Karikó, PhD, who is now a professor at the University of Szeged, Hungary, had one goal in mind when she was working with messenger RNA (mRNA) to develop therapeutics. It had nothing to do with vaccines—whether for viruses, cancer, or any other condition in which it would make sense to bring in the immune system. "I never thought it would be immunogenic because I was only thinking about using mRNA to produce proteins inside of cells … or more receptors already found in the body," Karikó told *Inside Precision Medicine*.

Then, while knee-deep in research literature, the lightbulb moment came. "I was thinking about why the mRNA therapeutics were failing, and then I realized that the body was fighting it with an inflammatory response," said Karikó. So, in the early 2000s, Karikó teamed up with immunology expert Drew Weissman, MD, PhD, now a professor and the director of vaccine research at the University of Pennsylvania, and the rest is history. Together, they discovered that adding chemical modifications to synthetic mRNA prevented inflammatory immune responses and boosted protein production. By incorporating these modifications, they transformed mRNA into a safe, efficient tool for therapeutic use. This innovation paved the way for cost-effective and scalable mRNA-based vaccines, including

Katalin Karikó, PhD
Professor
University of Szeged, Hungary

the COVID-19 vaccines, revolutionizing medicine and global health. For this work, Karikó and Weissman were awarded the 2023 Nobel Prize in Physiology or Medicine.

The impact of Karikó's research has taken an even more unexpected turn from her initial work: mRNA vaccines are now being developed beyond infectious diseases to tackle non-communicable conditions. While vaccinating against cancer and neurodegenerative diseases is not a new idea, progress with traditional viral-, peptide-, and cell-based vaccines has been limited. With mRNA vaccines, the ability to mobilize the immune system to fight non-infectious diseases could be headed for a renaissance—especially for treating (and possibly preventing) devastating diseases of the brain.

Inside Precision Medicine spoke with several experts who shared their progress in utilizing mRNA vaccines for treating glioblastoma and Alzheimer's disease.

Beware: microenvironment

Elias Sayour, MD, PhD, an associate professor of neurosurgery and pediatrics at the University of Florida, was treating cancer patients with immunotherapy during his fellowship at Duke University, where he encountered pediatric oncology's harsh realities. "We often talk about great outcomes and improved cure rates, but the truth is, curing one child often means harming others," Sayour told *Inside Precision Medicine*. "You're poisoning ten to cure three, four, or five children with cancer, and for those you don't cure—you're just hurting them. It's a brutal equation, one that breaks the 'do no harm' rule in every patient we treat." That's when Sayour first began to look into mRNA vaccines.

Elias Sayour, MD, PhD
Associate Professor
University of Florida

By programming immune cells to recognize and attack cancer as a foreign invader, mRNA vaccines not only combat the disease but also imbue the immune system with a memory that lasts for life. "The immune system doesn't just fight for you," Sayour explained. "It remembers. That memory is one of its most powerful features."

One of the most difficult cancers that Sayour has treated is glioblastoma, a brain tumor that is aggressive and infamously resistant. "If we could cure glioblastoma with mRNA vaccines, I think we could cure all cancers," he said. "It's not the easiest target—it's the hardest—but its complexity offers a blueprint for overcoming even the most resilient cancers."

According to Sayour, the tumor and its hostile ecosystem pose a great challenge to any immunotherapy. To illustrate the concept of a hostile microenvironment, Sayour tells his students about a situation in which a civilian with no survival training is dropped into the Everglades at night to hunt the invasive Burmese python.

Sayour said, "Go shoot the Burmese python. Bring three of your friends, but good luck. I don't think you're going to survive. Even if you do have training, you still need food and shelter. You're probably going to freeze. That's what happens to T cells when they get into these environments: they're frozen. The T cells become anergic—they lose energy—and you find them right near the glioblastoma in the blood vessels as if they can't penetrate the hostile environment. That's glioblastoma; it's not just surviving, it's reprogramming the immune system to defend it."

Myriam Mendila, MD
Chief Scientific Officer
and Head of R&D
CureVac

This is where mRNA's versatility becomes a game-changer. Unlike traditional treatments that rely on toxic chemotherapy or radiation, which Sayour compared to "dropping a nuke on the Everglades," mRNA trains the immune system to target cancer with precision. It is software for the body's hardware, capable of adapting to cancer's relentless evolution. "Cancer is an organism within an organism, constantly reshaping its environment," he explained. "RNA can fight evolution with evolution, reprogramming the immune response in ways we've never been able to before."

The mRNA vaccine approach to cancer is risky, especially for aggressive glioblastoma, Sayour warned, as extreme immune responses can cause serious side effects. However he believes the pros outweigh the cons in the long-term. "The immune system is like fire," Sayour said. "Controlled, it's powerful. Unchecked, it's destructive. But if we can harness it effectively, the possibilities are endless."

Dancing to the algorithm

During the COVID-19 pandemic, CureVac, a pioneer of mRNA vaccine technology, failed to deliver its first-generation vaccine candidate. "We weren't lucky with our initial mRNA backbone used during the pandemic," Myriam Mendila, MD, chief scientific officer and head of R&D at CureVac, told *Inside Precision Medicine*. But as the saying goes, it is not whether you fall, but whether you get up. "Since then, our team has refined our platform using cutting-edge skills in protein design, mRNA formulation, and—most importantly—proprietary algorithms."

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At the heart of CureVac's updated approach to designing their second-generation mRNAs is a sophisticated system of artificial intelligence (AI) for stimulating an immune response. CureVac's process begins with identifying the cancer antigen, typically a protein or smaller peptides, that is then designed to behave exactly as needed within the cell, irrespective of whether it is secreted, presented on the cell surface, or anchored through major histocompatibility complexes. The optimal antigen presentation design is determined by advanced computational tools and iterative testing.

Once the protein design is finalized, CureVac uses another algorithm to optimize how the designed protein will be encoded in mRNA. "Our proprietary mRNA design algorithm ensures optimal codon usage for translational efficiency," Mendila said. "By selecting the perfect combination of nucleotide triplets, the algorithm maximizes protein production from the mRNA sequence. That's our secret sauce."

Rebecca Nisbet, PhD
Research Head
The Florey Institute

CureVac is developing two arms for their mRNA vaccine programs: personalized cancer vaccines (PCVs) and shared antigen cancer vaccines (SACVs), each with its own benefits. Commercially available SACVs that target common patient antigens are faster, cheaper, and easier to make than the customized approach, which theoretically maximizes vaccine efficacy. PCVs involve sequencing a patient's tumor to identify unique antigens, which are ranked for their ability to provoke an immune response. To expedite mRNA vaccine production, CureVac has also developed an mRNA printer—a fully automated system that can transcribe mRNA for PCVs in mere days. "We can go from sequence to vaccine in about four to six weeks," said Mendila. "For cancer patients, that speed can be life-saving."

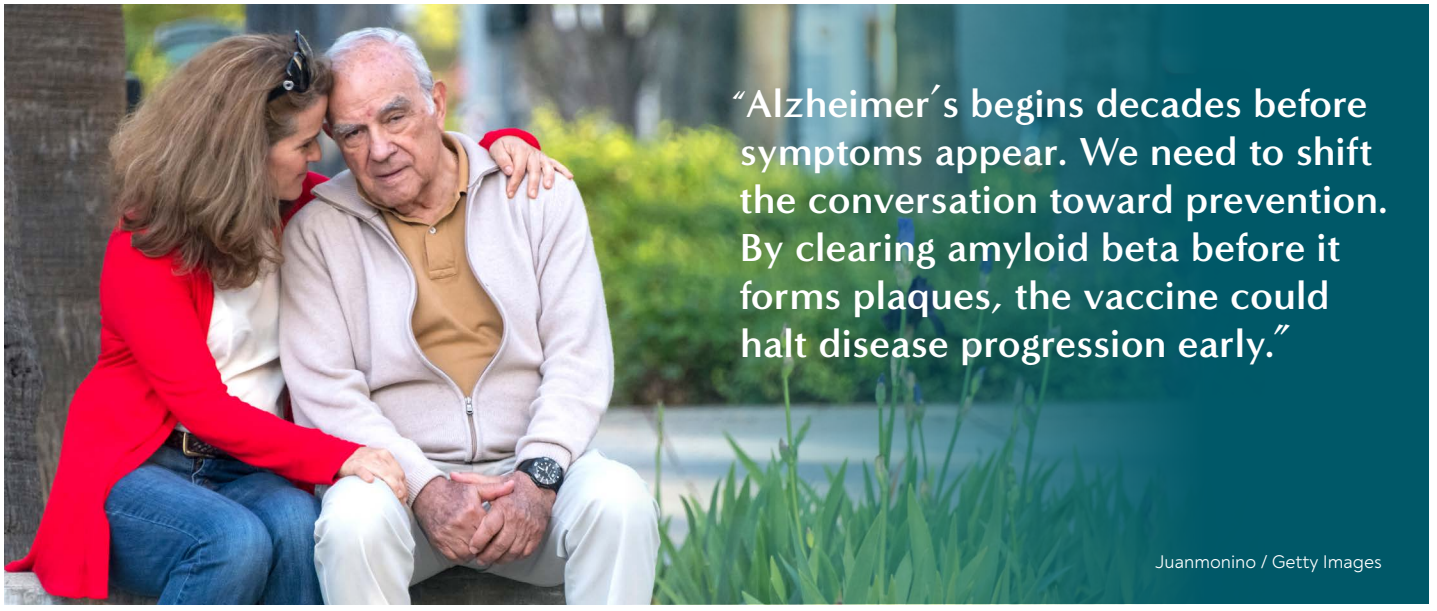
CureVac's efforts are still in the earliest stages of clinical testing, but the results they have presented on their vaccine for glioblastoma, CVGBM, have been promising. CVGBM encodes eight carefully chosen antigens, offering a ready-to-use option for patients who need immediate treatment.

> "We're striving for a therapeutic strategy that is accessible, effective, and preventive, making this as simple as a flu shot. Many people with Alzheimer's live in rural areas without access to infusion clinics, so intramuscular vaccines could revolutionize treatment."

At the European Society for Medical Oncology 2024, CureVac demonstrated that the CVGBM mRNA vaccine made with lipid nanoparticles (LNPs) for glioblastoma was safe at the highest dose tested, with no serious side effects, and successfully triggered an immune response in 77% of patients. Of these immune responses, 84% were *de novo*, seen in patients who did not have any previous T cell activity against the cancer antigens. It's still early days, as the trial is currently in Phase Ib, but it looks like CureVac, which recently won a patent battle in court against BioNTech, may be back on track.

Alzheimer's disease, not today, not tomorrow

During her graduate studies, Rebecca Nisbet, PhD, who was fascinated by prion protein mechanics, encountered a harsh reality: funding for prion disease research was scarce, so she pivoted to Alzheimer's disease, for which there was—and still is—greater financial support. This pragmatic decision marked



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the start of a distinguished career, largely centered on Alzheimer's and related tauopathies like frontotemporal dementia. During her time as a postdoctoral researcher in antibody engineering at the Commonwealth Scientific and Industrial Research Organisation in Australia, Nisbet fell in love with antibodies and immunotherapy.

Since monoclonal antibodies have high production costs, require large doses, and need intravenous infusion infrastructure, the COVID-19 pandemic piqued Nisbet's interest in mRNA technologies. At The Florey, Australia's leading brain research center, Nisbet heads the Antibody Therapeutics Group, which focuses on mRNA vaccines that encode amyloid beta antigens, stimulating the immune system to produce antibodies against this hallmark protein of Alzheimer's disease. "I believe the future of immunotherapy for Alzheimer's lies in vaccines," Nisbet said. "We're striving for a therapeutic strategy that is accessible, effective, and preventive, making this as simple as a flu shot. Many people with Alzheimer's live in rural areas without access to infusion clinics, so intramuscular vaccines could revolutionize treatment."

Overcoming the blood-brain barrier (BBB) is one of the greatest obstacles to treating Alzheimer's, and Nisbet is taking two mRNA approaches to get around the problem. One involves using LNPs conjugated to BBB-penetrating peptides to deliver mRNA encoding an antibody towards tau. The other approach does not require the mRNA itself to traverse the BBB, but uses mRNA encoding an amyloid beta peptide to stimulate the immune system to generate anti-amyloid beta antibodies that can reach the brain. Nisbet's team has shown that this mRNA vaccine does stimulate an immune response that generates high levels of anti-amyloid beta antibodies circulating within the serum in wild-type mice.

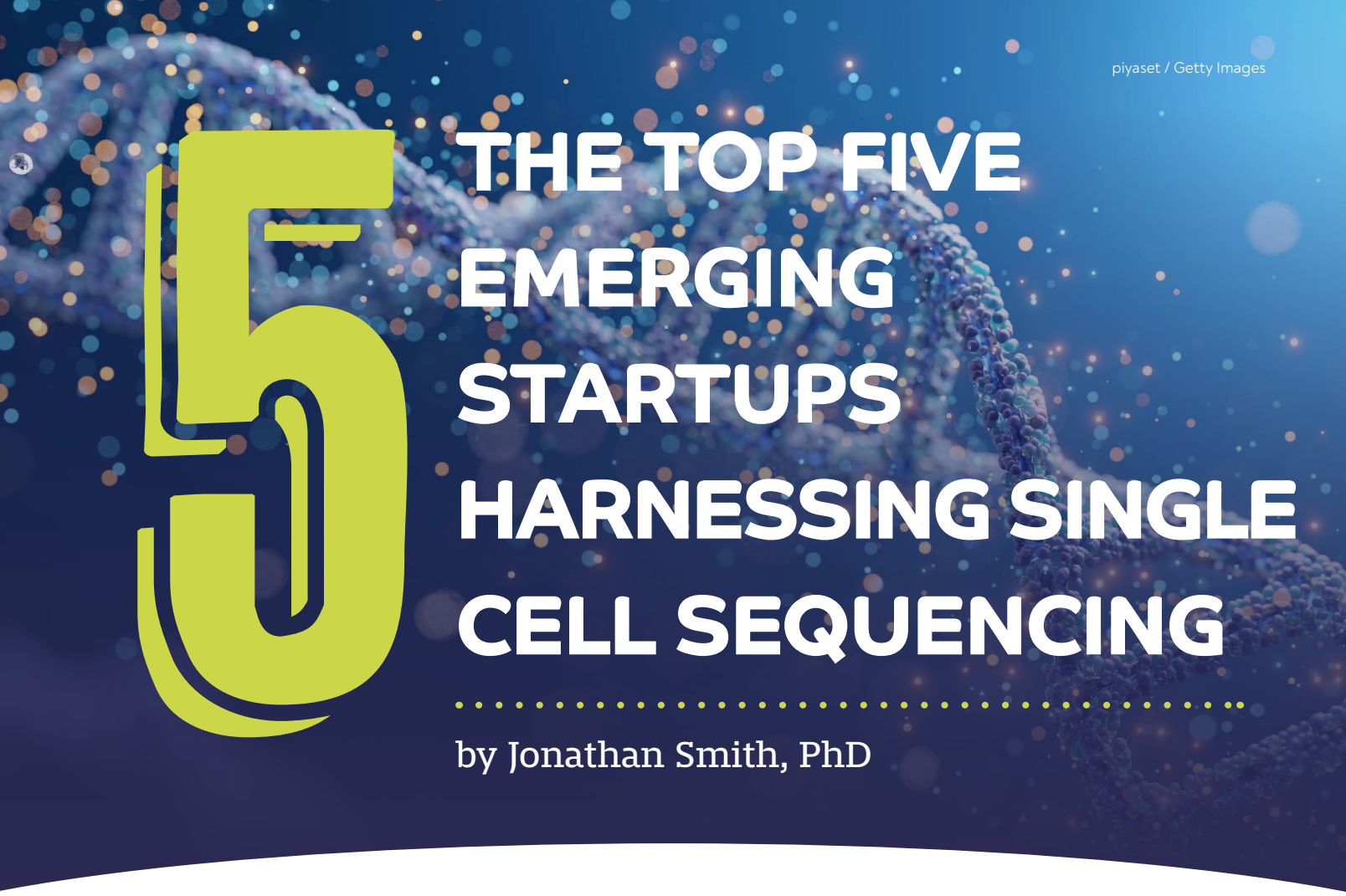
The major unknown now is how many of these anti-amyloid beta antibodies can cross the BBB and stimulate an immune response to clear out amyloid beta plaques. "What we don't know is how much of these antibodies get into the brain once they're made," said Nisbet. "The estimate is that about 0.1% of those antibodies can transverse the BBB naturally. So, we're relying on the endogenous low level of antibodies to cross the BBB. If we're using our vaccine as more of a preventative, I don't think we'll need that much to get into the brain to clear the increased amount of amyloid beta there before it forms plaques. We're quite optimistic that although these antibodies aren't designed to cross the BBB, we'll still get brain amyloid beta clearance."

Nisbet is adamant that the neurodegeneration field needs to shift focus, and she is working tirelessly to develop a vaccine that will stop the progression of Alzheimer's and save millions of lives. "We've spent too long targeting late-stage pathology when it's already too late—neurons are essentially dead by then," Nisbet said. "Alzheimer's begins decades before symptoms appear. We need to shift the conversation toward prevention. By clearing amyloid beta before it forms plaques, the vaccine could halt disease progression early."

It remains to be seen whether the mRNA vaccine approach will be able to muster a therapeutic response in animal disease models and Alzheimer's patients. This approach, if successful, could pave the road to other neurodegenerative diseases driven by toxic peptide buildup in the brain, such as those caused by alpha-synuclein in Parkinson's disease. If so, an entirely new movement in precision medicine could be launched involving personalized genomics and prophylactic neurodegenerative diseases, where people with pathological mutations or high-risk variants could opt for protective mRNA vaccines far before neurodegenerative processes take hold. That would be quite the leap for neurodegenerative diseases, going from a lack of therapeutics to stopping or slowing down disease and then to population-level prevention.

The paradigm of preventing complex noninfectious diseases with mRNA vaccines appears to be expanding into fields where immunotherapies are being explored, such as the treatment and prevention of atherosclerosis and myocardial infarction. Amongst all this speculation, one thing is clear—that Karikó, when beginning her work on mRNA over 30 years ago, absolutely did not see this coming. As such, her work on mRNA is a testament to the value of "basic science" as a springboard for therapeutic innovations. Karikó's persistence has sent reverberations through the world with mRNA vaccines, and that's just one of the many tools provided by this Swiss Army Knife-like platform provided by the single-stranded genetic molecule. ■

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, genome engineering, and AI/ML for drug discovery for publications like *Scientific American* and *Genetic Engineering and Biotechnology News* (*GEN*). Jonathan earned his PhD in biomedical science from the University of California, San Diego, and a BA in neural science from New York University.



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5 THE TOP FIVE EMERGING STARTUPS HARNESSING SINGLE CELL SEQUENCING

by Jonathan Smith, PhD

From semi-permeable capsules to engineered yeast: check out five promising startups that could ride the soaring single-cell sequencing market.

Researchers have been quantifying gene expression in cells for decades using traditional approaches like real-time polymerase chain reaction (RT-PCR), whereas single-cell sequencing has only emerged in the last 20 years.

Unlike RT-PCR, single-cell sequencing allows investigators to explore the entire genome of a cell, generating rich datasets to understand disease in more depth.

Technological advances in genomics are driving rapid growth in the market for single-cell sequencing, which is expected to climb by 15% per year, from $2.8 billion in 2025 to $9.9 billion in 2034. However, the high costs of single-cell sequencing methods generally limit the uptake of the technology, with users navigating trade-offs between analyzing single cells and using broader spatial methods.

Alongside key players like Thermo Fisher Scientific, 10x Genomics, and Illumina, newer players are gunning to enter the space, including Parse Biosciences and Singleron Biotechnologies. There is also wide industry interest in startups developing technology based on single-cell sequencing, especially in the U.S., with the acquisition of Fluxion Biosciences by Cell Microsystems in 2023 and the takeover of Fluent BioSciences by Illumina in 2024.

Many smaller startups are using single-cell sequencing to develop therapies and democratize access to users across the life sciences by lowering cost and scaling barriers. See our list of the top five rising stars in the field, with a focus on those at the Series A stage and below.

Alethiomics

Founded: 2021 | **Headquarters:** Oxford, U.K.

Alethiomics was spun out of the University of Oxford, U.K., by two hematology professors and launched with £6 million ($8 million) in seed funding from Oxford Science Enterprises.

The company—whose name includes the Greek word for "truth" (aletheia)—is focused on a group of blood cancers called myeloproliferative neoplasms (MPNs), which arise from mutations in bone marrow stem cells. There are currently no treatments for MPNs that can eliminate the stem cells that drive the disease.

To overcome this challenge, Alethiomics crunches transcriptomic and proteomic data from cancer stem cells to pinpoint disease targets for treatments like antibody-drug conjugates (ADCs), which consist of an antibody chemically attached to a toxic drug.

Last year, Alethiomics secured seed extension financing and is in an optimization phase for its lead program. The company aims to nominate a candidate by the end of the year and to be in the clinic by 2027. The firm also plans to land research collaboration deals to spur the development of its pipeline.

Atrandi Biosciences

Founded: 2016 (previously Droplet Genomics)
Headquarters: Vilnius, Lithuania

Atrandi—which means "you discover" in Lithuanian—was founded to bridge a gap between two traditional methods of single-cell sequencing: droplet-based microfluidics and plate-based methods.

Droplet-based methods allow the processing of thousands of cells at a time in tiny capsules but with limited libraries of molecules per cell. Plate-based methods let users analyze cells in tiny wells in close detail but with less throughput.

Atrandi has developed semi-permeable capsules (SPCs) that are formed by mixing two polymers in a microfluidic chip. The capsules sequester cells and nucleic acids while proteins and small molecules enter and leave the capsule freely. This allows users to process cells in a single tube and generate complex datasets from each cell.

The company's products include the Flux microfluidic device to encapsulate cells in SPCs, the Onyx droplet generator, and Styx, a high-throughput device that uses fluorescence to screen and sort droplets.

Atrandi raised $4.8 million in a seed round in 2023, followed by a $25 million Series A round in February this year. The A round was led by Lux Capital and will help the startup bankroll its expansion into the U.S. market, with the goal of setting up a base in Boston. Atrandi also aims to further develop its technology and launch new products into the market.

BioSkryb

Founded: 2018 | **Headquarters:** Durham, North Carolina

BioSkryb was founded based on the licensing of single-cell genomics technology from a group at St. Jude Children's Research Hospital. In 2020, the company raised $11.5 million in seed funding led by Anzu Partners to accelerate product development and commercialization.

The company's technology platform, dubbed Primary Template-directed Amplification (PTA), is designed to capture more than 95% of the genome of a single cell and detect variations in the genome more accurately and cheaply than existing methods.

BioSkryb's offerings using PTA include its ResolveOME™ whole genome and transcriptome amplification kit, ResolveDNA® genome sequencing kit, and BaseJumper platform to analyze the data from the kits. The firm also launched the ResolveSEQ MRD service this year to characterize residual cancer cells that remain after treatment, helping users understand how cancer cells resist treatment.

In the last few months, BioSkryb inked a deal with the U.S.-based Ultima Genomics to collaborate and run a joint grant program to advance cancer research with free sequencing. BioSkryb also teamed up with the Swiss company Tecan Group to add more automation and speed to its ResolveOME product.

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4

PARTILLION BIOSCIENCE

Partillion Bioscience

Founded: 2020 | **Headquarters:** Los Angeles, California

Partillion was co-founded by a microfluidics researcher at the University of California, Los Angeles, as his team grappled with a key problem with existing lab-on-a-chip devices: the gadgets involved tend to be expensive and hard to use in a commercial setting.

In response, the company developed a so-called "lab-on-a-particle" in the form of hydrogel-based capsules called nanovials. The capsules have a cavity that can hold a single cell and capture a protein secretion of interest. Researchers can then cheaply use existing equipment such as flow cytometers to sort hundreds of thousands of cells captured within the capsules and analyze their behavior and genetics.

Partillion now offers a range of kits for single-cell analysis and custom research services. The startup also launched kits for accelerating antibody discovery in 2023, and can help cell therapy developers predict the potency of their candidates.

In the same year, Partillion raised $5 million in a seed financing round with new investors like ND Capital, Vertical Venture Partners, and Paladin Capital. The firm also sealed a pact with Alloy Therapeutics that would allow the latter to carry out antibody discovery services using Partillion's nanovial technology.

5

sampling HUMAN

Sampling Human

Founded: 2016 | **Headquarters:** Berkeley, California

The techbio player, Sampling Human, was first founded in the Czech Republic before branching out to the U.S. to benefit from the entrepreneurial spirit of the San Francisco Bay Area.

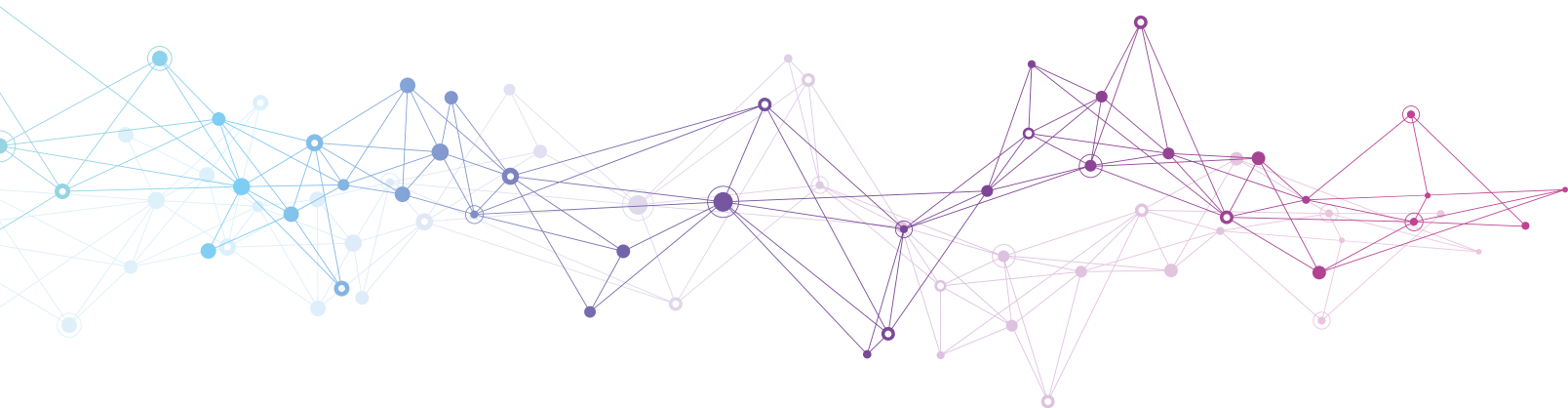
Sampling Human genetically engineers yeasts to detect and classify specific cells such as cancer cells hidden within millions of other cells. They also allow users to measure RNA and protein levels in the target cells.

This has the potential to supercharge liquid biopsies—the ability to detect cancer cells in the blood—by making them faster and more precise. Unlike traditional approaches, it does not require expensive equipment and specialist staff to use.

Sampling Human raised $2 million in 2022 in a round led by i&i Biotech Fund to fuel its research and hire new staff.

The startup sent out its first biocytometry kits to early-access customers last year to help researchers and students measure apoptotic cells present in complex samples. ■

Jonathan Smith, PhD, is a freelance science journalist based in the U.K. and Spain. He previously worked in Berlin as 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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- The state of cell and gene therapy in Africa with Julie Makani, MD, PhD (Tanzania) and Johnny Mahlangu (South Africa)
- A conversation on base editing and more with Alexis Komor, PhD (UC San Diego) and Nicole Gaudelli, PhD (Google Ventures)
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In Conversation with Chris Loose

by Helen Albert Senior Editor

Current therapies targeting multiple sclerosis (MS) primarily target the symptoms of the disease but do not repair neurological damage caused by the condition. This is something that Chris Loose, PhD, CEO and co-founder of Progentos Therapeutics, and his colleagues are hoping to remedy.

MS is a chronic, immune-mediated condition that results in the demyelination of neurons in the central nervous system. Some people have a relapsing-remitting version of the condition and others have a gradual progression of neurological symptoms with increasing disability over time.

Although many treatments, like anti-CD20 monoclonal antibodies, sphingosine-1-phosphate receptor modulators, and Bruton's tyrosine kinase inhibitors, are available for treatment of MS, they almost exclusively target abnormal immune activity and do not repair tissue damage caused by the condition.

Progentos Therapeutics was founded last year by Loose and colleagues and is aiming to develop small molecule, oral drugs that can stimulate the regeneration of myelin in people with MS. Loose spoke with *Inside Precision Medicine* senior editor Helen Albert about his career, about building Progentos in a challenging time for the industry, and what he hopes to achieve going forward.

Chris Loose, PhD

Q: What inspired you to become a scientist?

Loose: For as long as I can remember, I've been interested in helping to develop new medicines. I thought about whether I should be a doctor, or an engineer who can have a broader impact rather than seeing one patient at a time. Could I help create something that could help a great number of people? That's been inspiring me for the last 20 years.

Q: What made you decide to move into the biotech industry?

Loose: After college, I had the chance to work in Merck's research labs and loved the mission and being around smart people doing important work. I had the realization that to have a real impact, getting into a smaller environment like a startup would be a way to really maximize what I could contribute. And so, I came up to MIT with the goal of working with Bob [Robert] Langer, who became my PhD advisor. He has been so successful entrepreneurially, and I had the opportunity to just immerse myself in that culture. I was able to do two startups with Bob, and Progentos is now a spin-off of the last startup.

Q: Did attending MIT help you to become an entrepreneur?

Loose: I think it's why I wanted to go there. From the middle of my graduate work, it was clear there could be a startup opportunity arising from my project. Immediately, I could find people from all different backgrounds, from finance and business, to marketing, to biology and chemistry. They all came together very quickly to join me and to try to move ahead with our idea.

We had success winning the business planning competition at MIT to get our start. It was fun and a good validator. It turned into a device company making safer vascular catheters called

zeljkosantrac/ Getty Images

Semprus BioSciences that got two FDA approvals and also got to an acquisition.

That's how I got started, but my heart had always been in making new medicines. That's where I wanted to go, and so that's where I started to pivot to.

Q: The second startup you founded was called Frequency Therapeutics, how was that experience for you?

Loose: It was working in drug development, so a very different world. We were focused on hearing restoration, which is a big unmet need, and we were able to carry a new approach into the clinic that looked very promising early on. Ultimately, while that didn't pan out, we made a discovery relating to multiple sclerosis that was very encouraging.

While Frequency didn't continue, we were able to spin that out into Progentos, where we think we're working on what could be the first restorative therapy for multiple sclerosis, as well as a broader vision for regeneration in the body.

Q: This is your first CEO role, how has that been for you so far? Has it been a big change or was it the next logical step?

Loose: These startups are all teamwork. From the earliest days of my first startup, it's all about a small group of people figuring out how to raise the money, how to set the strategy, how to recruit the right people. So, I think there's been a lot of continuity in that regard. Obviously, I have a different set of responsibilities now, but I think I have been moving in that direction for a while.

It helps that I have a great co-founder in Sanjay Magavi, PhD, our CSO, who is an excellent scientist, and also just a great business partner as well.

Q: How did treatments for hearing restoration turn into a possible treatment for MS?

Loose: The science is actually quite distinct between the two. I think the connection was that we were looking for ways to achieve cellular regeneration inside the body. How do you trigger the body to restore a tissue? The reason we started working on multiple sclerosis is because inside the brain about 5% of the cells are oligodendrocyte precursor cells, or OPCs. They're the regenerative cells that are there to repair damage. When someone has MS, what that is, is the body's immune system attacking the myelin covering their nerves. You get degeneration, but the system can repair that. The problem is that in the state of disease, it doesn't keep up with the damage.

We discovered distinct targets that could very effectively turn on this regenerative system. We're really pushing a system that's designed to be active, and really has been proven to be active, because when you look at MS, that system is why you have relapses, where patients get worse, but then go into remission—they get better as repair happens. We know that happens naturally, but we want to essentially turbo charge that system.

Q: Why is it important to have new therapies for MS?

Loose: There's around 20 drugs for MS that all slow the body's attack on the myelin. They slow down the immune attack, but nothing rebuilds the structure that's been lost, and that is the enormous unmet need.

If you look at the best drugs that are out there, they slow down progression, and they very much reduce the relapses that happen. But none of them make you better. They don't restore any function. And when you talk to patients and clinicians, that is absolutely clear, their number one need is restoration of neurological function that is impacted by the disease.

Q: I know the company is at a fairly early stage, but what are your future goals?

Loose: We discovered a new target that, to our knowledge, no one else is working on, that is giving some really profound preclinical efficacy. If you look at the history of remyelination, there have been attempts in the past that people have taken to clinic, and they have seen some signals of efficacy.

Our view was that we needed a much more effective target, and that's what we have found. I think what sparked the interest of Progentos investors was the striking improvements in the degree of remyelination. We're thinking with this much more effective target; we can make it clinically meaningful for patients.

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The enormous goal is getting to human proof of concept. I think with the level of efficacy we've seen preclinically, our goal is to make sure we have the best candidate that we can to move into patients to demonstrate safety and get to that human proof of concept. Of course, we'll be building backups, as you'd expect, but it's really about getting to that big end point. We don't have a specific timeline yet, but we're working very swiftly, and I think we have a lot of good candidates to move ahead into clinical trials.

Q: Is anyone else doing anything similar to Progentos?

Loose: There are competitors in the space, one of which is in the clinic called Contineum Therapeutics. There are others who are pursuing some different pathways. We've been very excited by the preclinical data we've been able to produce head-to-head with the other pathways that are really being pursued. We think we have a really distinct approach with robust efficacy, and we're excited to get into the clinic.

Q: How has the fundraising environment been for you since founding Progentos?

Loose: We were able to raise a $65 million Series A last year from some wonderful investors. That gives us support all the way through to human proof of concept, which is an enormous milestone for patients, as well as for the company. We're very focused on driving to that.

It has been a very tough fundraising environment. I think people are looking for big advances right now. This would be a new category of medicine. It'd be the first restorative in MS. That'd be a big deal. I think investors are looking for big ideas that could have a large patient impact, a lot of value creation, and proven teams.

Q: Are you interacting with any MS patient groups?

Loose: Absolutely. We spend a lot of time, through the major conferences, working with both the key opinion leaders and patient spokespeople. It's been striking that if you do surveys amongst patients the number one thing on their list is restoration of function. It's what everyone wants.

The existing drugs have got about as good as immune modulators can get. They slow down attacks and progression, but patients still decline over time. Everyone wants to gain function back. By the time you've been diagnosed, you've likely already had some loss of function and people really want to get better.

Q: What have you been your biggest learning experiences since you've taken over this role?

Loose: I think it's an interesting environment we're operating within, notably in the current funding climate. I think figuring out ways to be very efficient and scrappy and creative is at a premium right now. We've been operating with a very lean team, while engaging the right experts to help us make efficient progress and stay very nimble.

I think that's been a transition that a lot of companies are going through. It's also a lot of just staying very focused and driven. I think there are times when big platform stories are exciting, and there are times when a specific product story that you have just got to execute on is attractive. We've just had to be very disciplined and push very hard to get to where we want to be.

Q: What advice would you give young biotech founders trying to succeed in the industry right now?

Loose: Having really good advisors and supporters around you who've been successful and seen a lot of ups and downs solves a lot of problems. For example, we had the good fortune of recruiting Andrew Miller, the founder of Karuna Therapeutics, to chair our board. He founded that company and helped it progress all the way for 14 years through FDA approval and the acquisition by BMS. He has a ton of CNS drug development experience.

I think finding people like that in your environment who've been down the road you're trying to go down and can give you real advice is super helpful, and it's great to have such an experienced operator on the board. It is a big resource, both for me as well as the venture capitalists around the table.

Finding people who you can trust and have known for many years is also key. One of the advisors I continue to talk to most days was my advisor during the MIT business plan competition, starting in 2005. Having decades of history with someone where you can float new ideas, and they can push you and can give you super direct feedback are really important things to have around you. I encourage young entrepreneurs to keep assembling great people who will give them direct feedback and help them look around corners.

It's also about focusing on fundamentals. Really strong science is still getting funded in the venture community. Make sure you have really good conviction in the targets you're going after. They're going to have a big impact for patients and investors. If you can articulate that, and you have a clear, differentiated approach, those deals are still getting done.

Q: Is there anything that you would do differently if you had to go back to the beginning?

Loose: I feel very fortunate about where we are. We've got great backers; we've got a great team. We're working on a big problem that I think can have a real impact for patients. Science always adds ups and downs, but I think we're in a great spot and I'm really excited to move ahead. ■

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.

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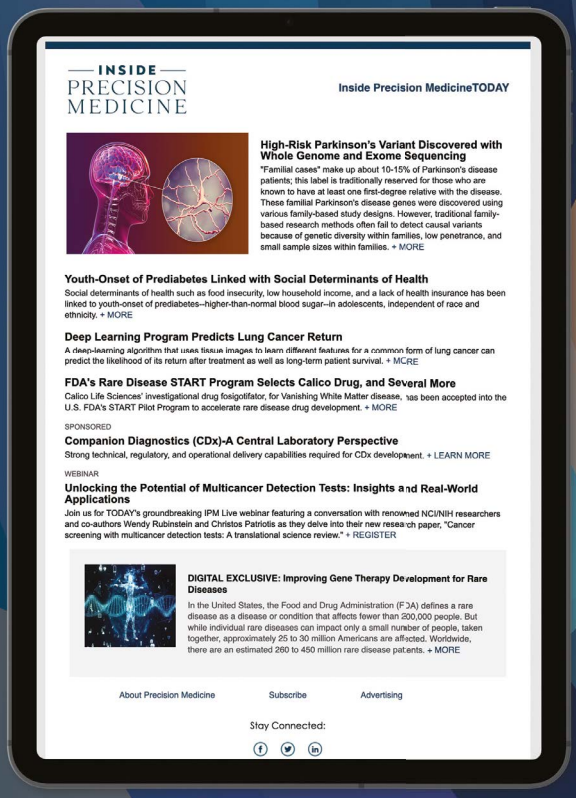

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Illumina Ventures

Tam Nguyen
St. Vincent's Hospital Melbourne

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