OCTOBER 2025

INSIDE PRECISION MEDICINE

Smarter Diagnoses Ahead: Charting the AI-Powered Path

My Code, My Call: Genomics in the Spotlight

5 Startups Shining the Light on Rare Disease

Breaking the Silence: Reclaiming Reproductive Health

Deep Diagnosis: AI Revolution in Lung and Heart Disease

Mary Ann Liebert, Inc. publishers

bio-techne® / Asuragen®

AmplideX® Nanopore Carrier Plus Kit*

Streamlining carrier screening insights, even for the most challenging genes.

With long-read sequencing technology, labs can achieve greater insight than traditional methods and reduce the need for reflex testing or multiple assays. Experience the transformative power of a streamlined workflow.

Gain Deeper Insights

*For Research Use Only. Not for use in diagnostic procedures.

bio-techne® / **Global Developer, Manufacturer, and Supplier of High-Quality Reagents, Analytical Instruments, and Precision Diagnostics.**

INCLUDES R&D Systems™ Novus Biologicals™ Tocris Bioscience™ ProteinSimple™ Asuragen® ACD™ Lunaphore™

INSIDE
PRECISION
MEDICINE

Founder **Mary Ann Liebert**
Publisher and Commercial Director **Bill Levine**
Editor in Chief **Damian Doherty**
EVP, Strategic Development **Kevin Davies, PhD**
Managing Editor **Corinna Singleman, PhD**
Production Editor **Robert M. Reis**
Online Editorial Manager **Katherine Vuksanaj**
North American Editor **Jonathan D. Grinstein, PhD**
Senior Editor **Helen Albert**
Associate Editor **Savannah Wiegel**
Contributing Editors **Mike May, Clara Rodríguez Fernández, Jonathan Smith, PhD, Susan Kreimer, Chris Anderson**
Art Director **Dianne Paulet**
Senior Graphic Designer **Byron Duque**

Advertising
Strategic Account Executive **Angelo Danza**
adanza@liebertpub.com / 201-230-0733
List Sales **Scott Perillo**
sperillo@insideprecisionmedicine.com / 914-740-2178
Sales Administrator **Fallon Murphy**
Advertising Material **Robert M. Reis**
e-file@insideprecisionmedicine.com

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

In Partnership with
National Society of Genetic Counselors

Cover image: narvo vexar / iStock / Getty Images Plus

Editor's Note

"Trust isn't what we do; it is what results from what we do."
—Richard Fagerlin

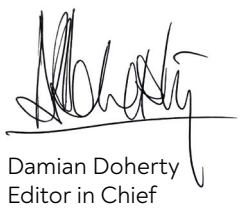
There's no escaping the warp-speed evolution of AI in healthcare. From large language models powering diagnostic support to sophisticated co-pilots navigating patient triage and drug discovery pipelines, AI is not just on our doorstep—it's in the room, actively rewriting how we conceive of care and precision medicine. Yet, as with any disruptive technology, the arrival of AI has stirred both palpable excitement and existential angst.

Among the more doomsday voices, we've heard predictions that AI will render physicians redundant, echoing Geoffrey Hinton's now infamous assertion that radiologists would become obsolete. That simply hasn't materialized. Radiologists are still here, and what's more, they're leveraging AI to sharpen their accuracy, speed, and clinical insight. To frame this as a man-versus-machine dichotomy is a disservice to both. AI is not the death knell for doctors—it is a tool, a partner, and when used judiciously, an enhancer of the human element in medicine, not a replacement.

But let's be clear: we must earn the right to use AI in medicine. We need trust—not just in the technology itself but in the systems, frameworks, and ethical scaffolding we build around it. Any system that fails to keep the physician and the patient at the center of its design will ultimately fail. The clinical setting is already a minefield of complexity, pressure, and emotional toll. Introducing AI tools that add burden, confusion, or opacity only increases risk—not just of inefficiency but of real harm to patients.

Therein lies the paradox: we're witnessing breathtaking advances in AI's application to healthcare—from accelerated drug discovery, where AI models are helping identify novel targets and repurpose existing compounds with unprecedented speed, to predictive analytics in population health and personalized treatment plans tailored in real-time. Yet the infrastructure to regulate, test, and ethically deploy these innovations lags significantly behind. The pace of innovation is outstripping our ability to implement guardrails, and in a domain as high-stakes as medicine, that gap could be catastrophic if left unaddressed.

Trust is the currency of medicine, and right now, it's in short supply—not just between patients and providers, but between society and the systems meant to serve it. Ironically, it may be the machines that gain trust before the humans do. But that trust must be tempered with caution. Machines are only as good as the data that feeds them and the people who build them. We are the architects of these tools—and we must ensure they reflect the best of our intentions, not the blind spots of our ambition.



Damian Doherty
Editor in Chief

INSIDE PRECISION MEDICINE

Contents

Features

View The Latest Online

Dual Screening: MBI Plus Tomosynthesis Finds More Invasive Breast Cancers

Cancer Patients and COVID Vaccine Trials: A Way Forward?

Painkiller Discovery Separates Pain from Inflammation

www.insideprecisionmedicine.com

6

38

46

42

Interview

Columns

34

Imaginima / iStock / Getty Images Plus

Charting a Path to the Right Diagnosis with AI Copilots

by Clara Rodríguez Fernández

The rapid growth and widespread adoption of large language models (LLMs) across real-world applications offer a host of new opportunities for the healthcare sector. Hospitals and clinics are starting to rely on artificial intelligence (AI) assistants for daily administrative tasks, and the technology is expanding to support doctors in making more accurate diagnoses, which remains a cornerstone of effective medical care.

Marc Succi, MD
Founder and Executive Director
MESH Incubator

"AI can improve speed, consistency, and reach while keeping the doctor at the front and center," said Marc Succi, MD, an attending radiologist at Massachusetts General Hospital, associate professor at Harvard Medical School, and founder and executive director of the Medically Engineered Solutions in Healthcare (MESH) Incubator at Mass General Brigham.

His research covers pioneering studies on the potential of using LLMs in clinical decision support and developing and commercializing AI tools across medical specialties. These tools include a real-time AI instructor that can help non-specialists in suburban or rural areas perform techniques like colonoscopies or ultrasounds, and an emergency stroke triage AI that helps doctors prioritize the most likely positive cases, effectively shortening the time to treatment for a condition in which every hour counts.

> "In the U.S. right now there is a significant shortage of radiologists, which is exacerbated by the amount of studies we have to read."

Rapid advances in LLMs also enable them to support doctors with differential diagnosis. This is an iterative process that combines information from the patient's clinical history, physical examination, and test results to create a list of potential conditions, which physicians rely on to decide upon the next steps necessary for diagnosis and treatment.

"The differential [diagnosis] is probably one of the hardest things to do in medicine," said Succi. A major challenge is having to work off very limited information while striking a balance between listing every rare but possible diagnosis and reducing the amount of testing needed to confirm the final diagnosis. In this context, Succi added, "AI is really good at taking a lot of information, synthesizing it, and finding patterns."

Earlier this year, a *Nature* paper published by Google reported that a specialized LLM could help a sample group of 20 clinicians create more comprehensive differential lists, increasing their accuracy from 36% to nearly 52%. As the technology keeps evolving, research suggests that combinations of existing LLMs could significantly improve their diagnostic accuracy when creating differential lists.

This exceptional ability to find patterns in vast amounts of data can make AI a valuable tool for the education of medical professionals by helping them hone their diagnostic skills. While a student will normally only see a few cases of, say, appendicitis, during a typical clinical rotation, AI can give them a chance to practice diagnosing it over and over with varied patient presentations.

Samir Shah, MD
Chief Medical Officer
Qure.ai

"Medicine is all about repetition and pattern recognition, the more cases you see the better you become at diagnosing them," stressed Succi. Both Brigham and Harvard's medical schools have started testing and implementing this technology with their students.

Enhancing diagnostic tools

One of the most promising contributions of AI to diagnostics is its ability to enhance the performance of existing diagnostic tools across medical disciplines. An area where the technology is already spearheading change is radiology, where the demand for diagnostic imaging and turnaround times are growing faster than hospitals can handle, driven by an aging population and the expansion of preventive care.

"In the U.S. right now there is a significant shortage of radiologists, which is exacerbated by the amount of studies we have to read," said Samir Shah, MD, a radiologist with over 20 years of experience and chief medical officer of Qure.ai. "If we can make a radiologist's job easier, that can help us improve [diagnostic] quality without adding time to our work."

Qure.ai has developed several AI solutions to automate the interpretation of X-rays and CT scans, speeding up diagnosis and access to treatments. A major focus of the company is lung cancer, which is a very aggressive condition often diagnosed only at an advanced stage and the leading cause of cancer death in the U.S.

(continued on next page)

(continued from previous page)

Some AI tools can assist with tasks like measuring and identifying lung nodules, stratifying their risk, and monitoring their progression over time, all of which combined typically take a significant portion of a radiologists' valuable time. Others rely on LLMs to mine electronic health records (EHR) for data, finding and flagging patients who may have an actionable nodule in the lungs.

Maulik Nanavaty, PhD
CEO
Anumana

Another area where AI could have a big impact is cardiology, where it can aid established techniques like electrocardiograms (ECGs/EKGs) that have been around for over 100 years. "People can now look at an ECG signal from a wearable device, but what has not really changed much is how you reach a diagnosis from that signal," said Maulik Nanavaty, PhD, CEO of Anumana.

Using EKG and echocardiogram data from millions of patients, the company is creating AI models that can find subtle patterns otherwise invisible to the human eye. Developed in collaboration with the Mayo Clinic, Anumana's AI model has been cleared by the FDA for the detection of low ejection fraction, an early indicator of heart failure that commonly goes undiagnosed.

"AI can take the expertise of the best cardiologists in the world and put it in the hands of any physician," said Nanavaty. Deep learning can assist with difficult diagnoses, such as pulmonary hypertension, which is often confirmed years after onset due to overlapping symptoms with other conditions. For these patients, unlocking early diagnosis and treatment can significantly increase their life expectancy and quality of life.

a-image / iStock / Getty Images Plus

Addressing safety concerns

The growing use of LLMs has brought up concerns about "hallucinations," where the models make information up when responding to a prompt. While newer models have lower error rates, ensuring that these tools provide reliable information is crucial in healthcare. Across the board, experts seem to agree that the reigning challenge to developing highly accurate algorithms is obtaining large amounts of quality data to train AI models.

"At the end of the day, your AI is only as good as your data," said David Spetzler, PhD, president of Caris Life Sciences, a company leveraging molecular profiling techniques and AI to develop next-generation precision medicine tools. He noted that, currently, most patient data is stored in EHR systems, which are often built to collect data for billing and reimbursement rather than to comprehensively track a patient's full history, symptoms, and outcomes over time.

David Spetzler, PhD
President
Caris Life Sciences

To overcome this limitation, Caris Life Sciences has undertaken the task of generating that data in house, using whole exome sequencing (WES) and whole transcriptome sequencing (WTS) to analyze tumor tissue from over half a million cancer patients, essentially tracking their progress and treatment response over the years. Although building such large datasets takes a significant amount of time and resources, the company plans to keep scaling up its data collection. "Because the heterogeneity of cancer is just so big, we will need millions of patients' worth of data in order to find all the nuances possible," said Spetzler.

The company's AI tools are helping identify the tissue of origin in cancers where the primary tumor is unknown, and allowing hundreds of patients who had been initially misdiagnosed access to the right treatment for their condition. From multicancer detection to therapy selection and disease monitoring, this type of technology is unifying and redefining how cancer is diagnosed.

Mindbowser, a healthcare consulting company, is seeking to address the current limitations of clinical data collection by adapting existing systems to meet the needs of AI development. "We are building complete AI-first EHR systems, foundationally correcting how data comes in and what kind of data is extracted," said Ayush Jain, Mindbowser's CEO.

The company is developing multiple features that cover the entire patient's journey, like an assistant that can help physicians check for drug interactions when prescribing a medicine and a chatbot that provides relevant information to patients in between visits. Any LLMs that directly interact with patients can be trained to keep all answers within a knowledge repository created by the organization, eliminating the risk of hallucinations.

Introducing this kind of change can be challenging in an

industry that still relies on fax machines to send and receive information, Jain noted. However, having a single comprehensive solution in place can significantly help hospitals and other healthcare institutions, whose IT teams often struggle to manage software from multiple providers, each covering tasks beyond EHRs such as storing medical images, setting appointments, billing, and filing insurance claims.

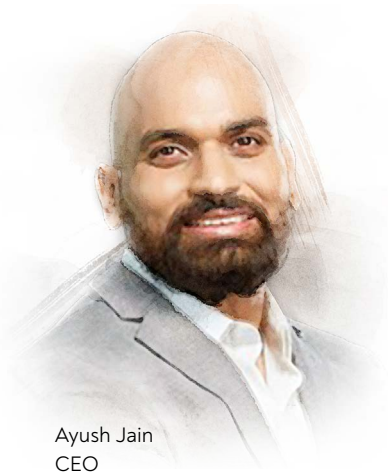
Mastering implementation

Regardless of how well an AI tool performs, improper implementation can turn it into a time sink for clinicians. Understanding and adapting to existing clinical workflows can have a much larger impact on success than the selection of which specific algorithm to use.

While some doctors may be excited to work with AI from the get go, others may be wary of new technology or reluctant to change the way in which they have been working. This can be especially true if they have had unsavory experiences with other tools in the past, like adding unnecessary tasks to their already full schedules and distracting from their job of caring for the patient.

"Great AIs fail all the time because they are not cleanly integrated into existing systems," said Succi. "If you have to leave your medical records screen and open a browser or another program, it is very unlikely to be successful. Anything that adds even two or three extra clicks is really difficult to get adopted."

He added that establishing well-defined evaluation and feedback stages during the implementation process is key to getting doctors on board with any new tools. Accountability is also a concern for patients and doctors alike, highlighting the importance of setting clear guidelines on responsibility for reviewing and approving any decisions made by an AI, and the actions to be taken when adverse outcomes are reported.



Ayush Jain
CEO
Mindbowser

Furthermore, local validation of any new AI tools is essential to ensure the model works as intended for the target patient population. "I think the best approach is to treat AI like a high-risk medical device," said Succi. "You have to prove it works in every single scenario."

"Implementation requires going through a very rigorous process," said Shah. "It touches so many clinicians and patients that we have to make sure that we are doing it ethically and within the rules of the healthcare system."

Any successful implementation needs to account for the needs of the target organization. Shah recalls working with an emergency room in Toronto where the priority was to make sure no patients with bleeds in the head were discharged. This required adjusting the sensitivity and specificity of the AI algorithm to favor false positives over false negatives, and educating doctors working with the AI on where the algorithm was more likely to make mistakes. This helped the doctors make better choices for their patients.

"Different areas have different needs, and the main problem for clinicians is that they are overwhelmed most of the time with features they really do not need," corroborated Jain. "A lot of it goes back to figuring out how to reduce the cognitive burden for the doctors."

For him, the key to success is to never use AI as a temporary bandage to a healthcare organization's problems, but to commit fully to its adoption once a decision has been made. As the technology keeps evolving, he believes that the most successful solutions will be those that can balance the interests of all stakeholders, from upper management to the end users.

Akarapong Chairean / iStock / Getty Images Plus

Stepping into the future

One thing seems clear: AI is here to stay, and its role in healthcare will only continue to grow and evolve. Epic, one of the largest providers of EHR software in the U.S., recently announced the launch of hundreds of AI features like virtual assistants for healthcare providers and patients alike. Others are sure to soon follow in these steps.

Going forward, Nanavaty envisions medicine becoming more precise at the point of care, enabling patients to get tests done much earlier in their health journeys: "Allowing these tools to come in early will change how medicine is practiced." Succi and Shah see AI increasingly moving towards working with multimodal data, integrating information across doctors' notes, lab results, imaging, and more to provide better diagnostic answers. With the rise of wearables and home sensors, continuous monitoring of patients will allow vast amounts of data to be fed into AI models to significantly improve performance.

"We are on the cusp of a revolution where the technology available today can have dramatic effects on patients," said Spetzler. As more drugs become available to patients, the standard of care will shift towards more precise diagnoses earlier in the patient's journey. Ultimately, he envisions a future where diseases can be treated before they even fully manifest in the patient: "Precision medicine is going to turn into precision prevention." ■

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.

Can Large Language Models Transform Healthcare?

These tools work well for easier tasks and less well as tasks become more complicated, but that's likely to improve, and maybe very soon

by Mike May, PhD

Today, it might be harder to avoid using artificial intelligence (AI) than seeking it out. It just comes to you. Web browsers automatically provide AI-generated answers to questions. Word processors entice users to let an AI-driven tool take over to improve a paragraph. And then there's healthcare. AI, especially large language models (LLMs), appears poised to play an increasing role from physicians to patients, and many more players in between. Is today's AI ready for this?

Some patients certainly think so. Recently, in a conversation with someone being treated for cancer, he blurted out: "I love AI!" The comment came out of nowhere, just thrown into the conversation. I guess that he loved it so much that he wanted everyone to know. His love grew, it seems, from AI providing a sense of control in an overwhelming situation. Trying to decide between treatment options? Ask AI. Want to know about a new prescription? Ask AI. That's precisely what he'd been doing.

Given that AI-generated healthcare information provided this patient with some sense of security, a level of access to information that he had not found in his earlier string of cancer diagnoses and treatments, I didn't want to take that from him by asking the question that popped in my head: Is AI providing accurate answers to your healthcare questions?

Some healthcare experts wonder the same thing, especially when LLMs like Med-PaLM, which was developed by Google Research, are used. This tool was designed to answer medical questions. Vivek Natarajan, an AI researcher at Google DeepMind, and his colleagues tested the ability of Med-PaLM 2 to answer questions from the MedQA dataset, which includes questions from professional medical licensing exams. According to Natarajan and his colleagues, "Med-PaLM 2 scores up to 86.5% on the MedQA dataset, improving upon Med-PaLM by over 19%." Perhaps, even more impressive, these researchers found this: "In a pilot study using real-world medical questions, specialists preferred Med-PaLM 2 answers to generalist physician answers 65% of the time."

Although that's an exciting example of applying LLMs to healthcare, even better results lie ahead. To gain a wider perspective, *Inside Precision Medicine* reached out to experts around the world.

AI-driven healthcare basics

Before getting to what I learned, what is a chatbot? That seemed like an easy enough question. So, I'll use an AI-based answer: "A chatbot is a computer program designed to simulate a human conversation through text or voice interactions, automating responses to provide information or perform tasks for users."

This same answer explained that a simple chatbot just regurgitates pre-determined answers, similar to trying to talk with an automated system at, say, a bank or federal agency.

Milan_Jovic / Getty Images

Large language models (LLMs) promise to give clinicians access to far more data and information than imagined a few decades ago.

More sophisticated chatbots rely on LLMs, which make up a subset within the general field of AI. Another AI-based answer noted that LLMs are "a type of AI designed to understand, generate, and analyze human language by learning patterns and rules from vast amounts of text data." After being trained on a dataset, an LLM can answer questions, and much more, like translating the answer from one language to another.

Bright Huo, MD, PhD
General Surgery Resident
McMaster University

In brief, LLMs and advanced chatbots collaborate. The LLMs and chatbots "tend to be coupled together," said Bright Huo, MD, PhD, a candidate in surgical guideline development at McMaster University in Hamilton, Canada. "Chatbots help us interact with LLMs, and natural language processing allows us to communicate with them." The key feature of AI-generated chatbots is that "they generate new output," said Huo. "They generate new information based on their training data."

As Huo added about LLMs and chatbots: "The potential applications in healthcare seem almost limitless, so that's why there's so much interest in them." On adopting AI technology in medicine, Huo added, "We've been lagging behind compared to automotive, avian, and other industries."

Gaps in today's healthcare

LLMs might fill some of the most important gaps in today's healthcare. Currently, patients "struggle to interpret severity of a health issue and to choose the right specialist," said Altuna Akalin, PhD, head of the bioinformatics and omics data science platform at the Berlin Institute for Medical Systems Biology, Max Delbrück Center in Berlin. "Even after their visits, many patients are left alone to understand their test results and details about their diagnosis."

The challenges in today's healthcare, though, go beyond patients because providers struggle as well. "Clinicians face time-pressure and data overload, making it hard to consolidate free-text notes, vitals, and history at speed," Akalin said.

In some ways, patients and providers seek related solutions to existing problems. It's not just about receiving or providing information. "Patients and clinicians need transparent reasoning, with sources and uncertainty, not just answers," Akalin said. In short, they both want to work with the most useful information available, understand the evidence behind

(continued on next page)

(continued from previous page)

that information, and even know the certainty that evidence brings to a particular conclusion.

LLMs in action

How much LLMs can assist healthcare professionals and patients is only beginning to be explored. "So far, the most ubiquitous LLM solution is ambient documentation," said Akalin. "These AI scribes turn clinician–patient conversations into structured notes."

There's good reason to aim LLM at such tasks. "The administrative paperwork burden overwhelms a lot of modern healthcare processes, and LLMs have been and are a natural tool to tackle some of these," said Jonathan Chen, MD, PhD, a physician and data scientist at Stanford Medicine. "The rapid adoption of ambient scribes—faster than any health IT I've ever seen—reflects the burning need for help."

Jonathan Chen, MD, PhD
Physician Data Scientist
Stanford University

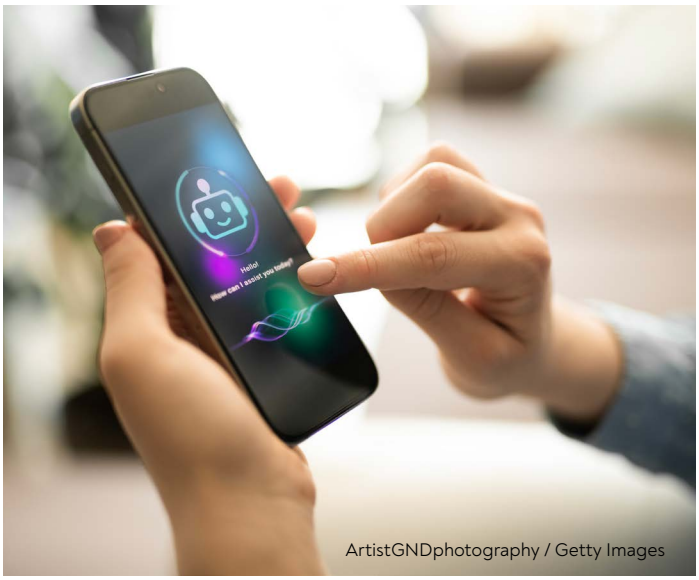
LLM-driven scribes have quickly captured the attention of healthcare, but are they helping? "With the ambient scribe and other examples of using LLMs to draft responses to patients and other documents, studies so far are often not showing much time savings," Chen said. "Some of that is learning a new process and technology, with these early physician users having to get used to optimal ways to prompt and interpret LLM responses in the context of the work they are doing."

Maybe it will just take time to turn LLM-driven scribes into time-savers. "Conceivably, the time savings will be achieved as people will naturally work out more efficient workflows," Chen said. "The other possibility is that being able to talk through a complex management problem by hashing it out with even a virtual consultant—in the form of an LLM—takes some extra time for the discussion, but you do it because it does lead to better results as found in this case."

LLMs evolving

In the best-case scenario, LLMs could play a part in many aspects of healthcare. Even before a patient visits a physician, an LLM could provide what Akalin calls "a 24/7 companion that translates symptoms into actionable next steps: likely urgency or triage, which specialist to see, and what information to bring—so visits start better prepared."

Based on a simulation of medical decisions modeled on real-world cases, Akalin and his colleagues found that an LLM did well in pre-visit assessments. For example, he pointed out that the "top-3 specialty suggestions included at least one correct specialty about 88% of the time, and triage range accuracy reached and 83% in the general-user setting."



ArtistGNDphotography / Getty Images

Patients already ask AI-based tools for answers to health questions, and these tools are heading into validation of clinical use.

For a clinician's decision-making during care, Akalin's team tested an LLM-based process that included retrieval-augmented generation (RAG), which explores medical information to assess a situation, such as diagnosing a patient. Akalin described this technique as a clinician using "an evidence-linked copilot, not an autopilot—surfacing differential diagnoses, flagging red-flags from vitals, and attaching citations via RAG."

To test the diagnostic potential of an LLM-based approach, Akalin and his colleagues asked clinicians to evaluate the AI-generated output. Here, the LLM-produced diagnosis of a patient "aligned with at least one of two clinicians about 95% of the time," Akalin said. "Even with both clinicians required to agree, alignment stayed about 70%—strong signals that LLMs fit well as team tools."

Chen and his colleagues also tested an LLM-based approach's impact on providers faced with open-ended reasoning tasks, rather than multiple-choice questions. "Multiple choice questions are preferred by computer scientists and technologists because they are easy to grade, but often don't reflect the complex realities of healthcare in practice." Chen said.

As an example, Chen asked: "What's the first-line treatment for high cholesterol?" It's a statin. That's "a relatively straightforward, closed-ended question," Chen said. "If a patient says they don't want to take their statin because they read in a magazine that it has unpleasant side effects, how should you counsel them to encourage them to take it?" That question, he said, is "a much more complex, open-ended management reasoning task."

So, Chen and his colleagues gave physicians a set of patient cases with open-ended management reasoning tasks to complete and answer. "They all had access to conventional internet resources, without LLMs or other chatbot AI systems, while half were randomized to have access to GPT-4," Chen

(continued on page 14)

Agilent

Trusted Answers

Take Your Liquid Biopsy from Translational to Transformative

It's amazing what ultra-high sensitivity can do for your translational cancer research.

Your liquid biopsy experiments have the power to redefine what's possible in cancer research. Armed with ultra-sensitive tools for ctDNA detection, cfDNA quantification, and dual DNA/methylation profiling, you can uncover insights that support your research into early cancer detection, tumor dynamics, and the discovery of novel biomarkers, even when working with the most challenging samples.

Your scientific discoveries deserve expert support, from sample integrity to delivering high-resolution sequencing data. Agilent tools for next-generation sequencing (NGS), automated workflows, and robust QC systems help your lab processes, so you can focus on advancing knowledge, publishing impactful findings, and driving translational breakthroughs.

Explore the full workflow and learn more at:

Heading to AMP 2025 in Boston?

Check out our media room to see what we're showcasing and where to find us.

For Research Use Only. Not for use in diagnostic procedures.
PR7003-142

(continued from page 12)

said. “A separate set of physicians graded the quality of their responses through expert consensus and found that those using GPT-4 often did do better.”

But what is better? “It wasn’t as much on questions like choosing the right diagnosis and medication, where doctors with the usual internet already did pretty well on,” Chen said. “It was often on the nuanced conversational questions, such as what to say to a patient when a medical error occurred, that those using GPT-4 did better.”

In part, GPT-4 spawned what Chen called “longer, more robust responses that scored better.” But that’s not all. “Even accounting for that, it’s not just that GPT-4 led to longer answers, it led to better ones,” he said.

Empowering patients

Although LLMs promise many benefits for providers, empowering patients could be even more important. “Less talked about, but what really may be the most impactful application is direct-to-consumer use of LLMs to answer and interpret medical information, if not overt advice and counseling,” Chen said. “Officially, LLMs are not qualified and should not be used for medical advice and counseling given some real risks of misinformation and harm.”

Jonathan Chen

Clinicians track enormous amounts of information on patients. Here, Jonathan Chen reviews a patient’s vital signs, and AI-based tools will soon help clinicians make treatment decisions based on similar data and even wider-ranging information.

That’s the official status of LLMs for advising patients, but what’s the reality? “When people are stuck on multi-month waiting lists to be seen by their physician or therapist, they will reach for what is available,” Chen said. “Though imperfect with a need to improve, it’s likely people are already using LLMs for such things with reasonable benefit already—kind of like how people could start to inform themselves when the internet emerged, balanced by the risks of getting the wrong information.”

Chatbots play a central role in how patients seek AI-based healthcare information. “Since ChatGPT was released, a lot of people have been really interested in using these LLM-driven or AI-driven chatbots,” said Huo. “Right now, a lot of people are doing studies to see how good these chatbots are at generating different types of advice.”

When it comes to chatbot-provided advice on health, Huo and his colleagues found 137 studies on the topic. Many studies, though, does not necessarily translate into lots of information about how well chatbots perform when patients ask for healthcare advice. Among those 137 studies, “their methodology varied significantly,” Huo said.

When asked if it’s possible to give a general idea of how good of a job a chatbot does in providing health information to patients, Huo said, “There are specific use cases right now where certain models perform better than others, and I would say that across the board they’re surprisingly good—not perfect, but surprisingly good—and they’re only going to get better.”

As Huo pointed out, “The field is moving toward the clinical setting, rather than just the pre-clinical stage, and people are starting to use these LLM-driven chatbots as clinical interventions.”

To help with that, Huo and his colleagues published guidelines for reporting on clinical tests of LLM-driven chatbots. To improve the clinical use of chatbots, “we need clear validation criteria,” Huo said. “Right now, I don’t think that it’s very clear for government or regulatory authorities to deem a version of ChatGPT as ‘safe’ for use in patient care, and it’s not clear what it would take.” So, Huo and his colleagues are starting to look at that.

In the near future, AI-based tools promise to bring even more advances to healthcare. For example, Chen envisions a time “where healthcare AI agents not only say things, but do things—for example, complete protocols, order medications, schedule appointments, coordinate follow-up and more,” he said. “These are not reliable enough for primetime yet, but just as LLMs were mostly unusable just a few years ago, it’s predictable that these agentic AI systems will be usable in the not too far future.” ■

Read more:

1. Singhal, K., Tu, T., Gottweis, J., *et al.* Toward expert-level medical question answering with large language models. *Nature Medicine*, 31 :943-950. (2025).
2. Gaber, F., Shaik, M., Allega, F., *et al.* Evaluating large language model workflows in clinical decision support for triage and referral and diagnosis. *Njp Digital Medicine*, 8, 263. (2025).
3. Goh, E., Gallo, R.J., Strong, E., *et al.* GPT-4 assistance for improvement of physician performance on patient care tasks: a randomized controlled trial. *Nature Medicine*, 31 :1233-1238. (2025).
4. Huo, B., Boyle, A., Marfo, N., *et al.* Large language models for chatbot health advice studies. *JAMA Network Open*, 8(2) : e2457879. (2025).
5. The CHART Collaborative. Reporting guideline for chatbot health advice studies: The CHART statement. *JAMA Network Open*, 8(8): :e2530220 (2025).

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


Sample prep


Automation


Sequencing


Analysis

Delivering a trusted genomic ecosystem from sample-to-report.

Visit us at Booth 719

AMP2025

ANNUAL MEETING & EXPO

Scan QR Code for more information about Illumina talks at AMP 2025.

illumina®

SEEING WHAT CAN'T BE SEEN

AI aids drug discovery by analyzing vast data troves to find patterns and insights humans can't

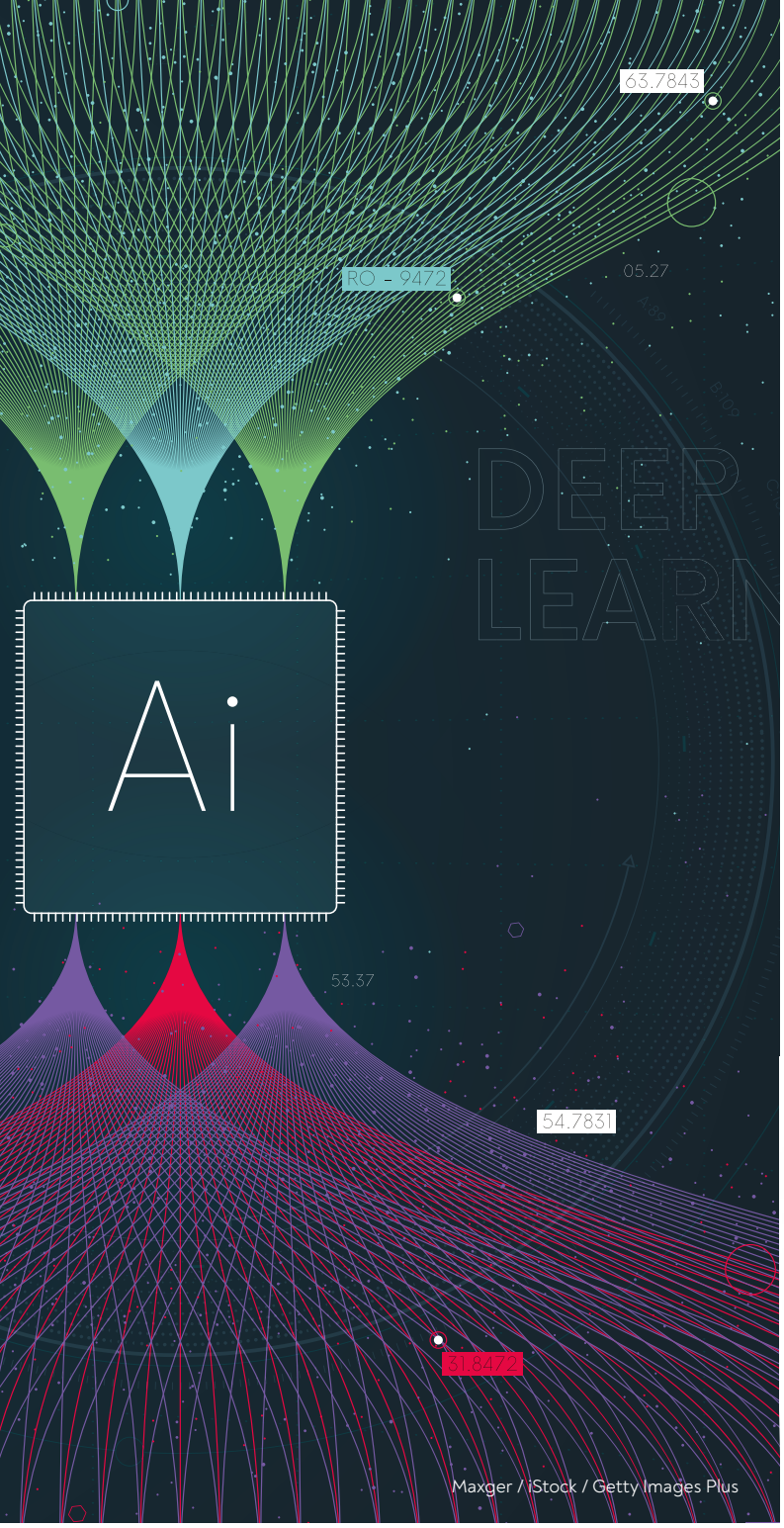
by Chris Anderson

An important question to ask within the context of today's drug discovery and development environment is: At what point does the sheer volume and complexity of data available outstrip the human ability to efficiently gather and interpret them? The reality is that the turning point likely happened some time go, but there is a silver lining. As new technology driving warp-speed increases in computational power have made Moore's Law obsolete, the same advances have enabled the emergence of a scientist's worthy aide for drug discovery and development: artificial intelligence (AI).

Today, the use of AI is ubiquitous. From large language models (LLMs) such as those driving popular tools like ChatGPT to the behind-the scenes machine learning algorithms that can readily discern cancerous tumors in digital pathology, AI's impact in the life sciences and healthcare is already being felt.

When it comes to fostering a better understanding of the complexities of human biology, applying AI to drug discovery and development may be the perfect fit. It also comes with the promise of shortening discovery and development timelines while significantly reducing the multi-billion-dollar cost of bringing a new drug to market.

AI leverages multiple technologies to make its impact: LLMs, predictive modeling, simulation, and *in silico* analysis that



Maxger / iStock / Getty Images Plus

is driving improvements from hypothesis generation, target identification, and drug design to clinical trial optimization and drug repurposing. Further, its ability to combine and interpret both traditional clinical data with real-world patient data and unstructured data is unlocking critical insights by uncovering patterns and relationships that would be virtually impossible for human researchers to uncover on their own.

"The days of 12 to 14 years and $2 billion to $3 billion (development) costs for mega blockbuster drugs—I think those days are behind us," said Mohan Uttarwar, CEO of 1Cell.ai, a precision oncology company leveraging multi omic data to improve cancer care and surveillance via the application of AI.

The question is by leveraging AI, "can we now bring that down to three to five years and $300 million to $500 million?"

As it continues to evolve, the question is no longer whether AI will play a role in drug discovery and development, but how deeply and how quickly it will reshape it.


Mohan Uttarwar
CEO
1Cell.ai

Use of real-world and multi-omic data

Leveraging AI in drug discovery and development has opened new doors of analysis using both the growing corpus of multi-omic data generated in life sciences research and real-world data like electronic health records (EHRs). But these data come with challenges.

According to Jagdeep Podichetty, PhD, senior director of predictive analytics at the Critical Path Institute (C-Path), a non-profit organization dedicated to improving and streamlining the process of drug development, "This is a secondary use of data, in the sense that it was for a different purpose. In our case, maybe a clinical trial simulation tool or identification of a biomarker," he said. "That applies to EHR (data) as well, which is mainly for billing purposes for hospitals."

But although these data might not have fit inside a traditional clinical trial, its value, Podichetty noted, is the lens it shines on the real-world setting to provide information on the variability of human diseases. This expansion to the use of secondary data is particularly important for more complex conditions like neurological diseases. "Just looking at the controlled setting of a clinical trial for complex diseases—it's not enough," he said.


Jagdeep Podichetty, PhD
Senior Director
Critical Path Institute (C-Path)

But EHR data must first be standardized before it can be applied in this way. "EHR by itself is very messy," Podichetty explained. "A single word can mean many different things. So you want to be able to map it to something more standardized." This standardization pipeline is a prerequisite for effective modeling, allowing for large-scale queries across a range of different datasets.

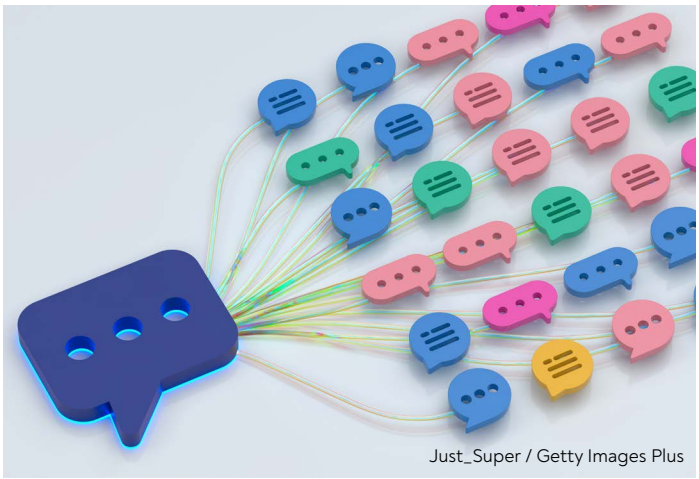
Likewise, the use of multi-omic data for drug discovery is greatly aided by AI. At 1Cell.ai, the focus is on analyzing live circulating tumor cells (CTCs) to develop insights both for the development of diagnostics and target identification for cancer treatments. As Uttarwar noted, "Cancer, as much as it is a disease, it's a data problem, and multi-omics is exponentially higher in complexity."

(continued on next page)

(continued from previous page)

The role of AI in this context is not simply to parse the data but to take disparate types of molecular data, such as whole-genome, transcriptome, and proteome data, and harmonize them into a single view that can accurately depict tumor behavior, tumor origin, and tumor heterogeneity.

Leveraging AI to dynamically curate and analyze these data can accelerate translational research. In 1Cell.ai's case this is accomplished via the collection of longitudinal data. "We are no longer relying on cell lines. With live CTCs, target identification and even target validation are huge opportunities," Uttarwar said. Additionally, live CTCs opens the opportunity for longitudinal tracking of disease development across multiple data metrics, which can then be mined by AI to identify treatment resistance, emerging mutations, and new therapeutic targets.



Just_Super / Getty Images Plus

Leveraging LLMs

As multi-omics data are increasingly integrated with clinical and real-world data, the utility of AI to interpret them continues to grow. For model-informed drug discovery, LLMs have moved to the fore due to their dynamic abilities to query data. A powerful example of using LLMs for these purposes lies in "prompt engineering," which is the strategic design of queries to guide model behavior intended to find patterns in research data that can help guide drug development. C-Path is working to optimize LLMs to assist with data curation tasks, and employing prompt engineering to replace the traditional and cumbersome methods of coding required for traditional data management.

"C-Path has explored the utility of LLMs in data curation pipelines," noted a perspective published last year in *Clinical Pharmacology & Therapeutics* with Podichetty as the senior author. "LLMs enable zero-or-few shot question answering with configurable tasks through templated prompts without the need for task-specific tuning."

In this way, LLMs can, when prompted effectively, deliver meaningful information from clinical notes or semi-structured data that in the past would require manual annotation and tuning of models.

Further, prompt engineering for LLMs is an important method for data discovery, allowing them to easily interact with structured data systems and reduce the need for specialized, highly technical database queries that can significantly slow drug development. "Large language models excel in translating natural language inquiries into queries that conform to schemas defined in a few-shot setting to retrieve structured information from graphs or tabular databases," wrote the C-Path researchers in their perspective.

But Podichetty told *Inside Precision Medicine* that there is an art to prompt engineering and that the ease of querying LLMs should not preclude planning how to best query them.

"Throwing stuff on the wall might not be a good strategy," he cautioned. "You might get information that's useless—or worse, incorrect." Instead, pharma researchers should consider taking a staged approach: using broader, more generalized LLMs for early exploratory work, then grounding what was returned with curated datasets in a vector database or retrieval-augmented generation pipeline to help ensure the reliability of information generated. This approach is an important safeguard against AI's Achilles' heel—hallucinations, which is the unfortunate ability to conjure what isn't there.

As multi-omics data—genomics, proteomics, transcriptomics, and more—are increasingly integrated with clinical and real-world data, the use of AI promises to bring multiple layers of biological and patient-level data into coherent, AI-readable formats, with an implied promise to bring human biology and disease treatment into sharper focus. "Think of it as a pie," Podichetty said. "You are only able to capture so much from a particular data type. [Each type of data] provides us with a bigger chunk of that pie." The challenge now, Podichetty noted, is not in accessing the data, but interpreting it responsibly and rigorously.

Informing clinical trials

Many clinical trials fail because they do not have the correct patient population for testing a drug. The ability of AI to detect subtle patterns from data can help drug sponsors focus recruitment efforts on the patient populations best suited for a particular trial, or to spot aspects of the trial design or study location that might be generating skewed data.

Podichetty said that data outliers that could jeopardize a trial might be something as subtle as the time of [the] day patients are being assessed. "It can be a very minute and simple thing that can be the difference from a trial failing and not failing," he noted. AI can catch these small factors and allow trial managers to correct them before the factors jeopardize the entire program.

A standout example of leveraging AI in a trial setting was enriching a patient population based on data that ran different trial scenarios as part of the Type 1 Diabetes Consortium. This use of AI identified patients who were likely to get diabetes in the next two or three years.

Using this method to analyze the patient population "you can find an intervention," Podichetty said. "So, the intervening drug

(continued on page 20)

From sample to report in 3–4 days

Introducing TruSight™ Oncology 500 v2

Now available: TruSight Oncology 500 v2

Enabling faster, scalable comprehensive genomic profiling with HRD now included

What to expect from this new assay kit

Results faster
Rapid turnaround within 3-4 days from sample to report, with a streamlined workflow, automation kits, and protocols.

Lower input
Achieves sensitive results from as little as 10 ng DNA or 20 ng RNA using innovative chemistry (30 ng DNA and 40 ng RNA recommended).

HRD Included
HRD analysis is powered by a gold-standard Genomic Instability Scoring (GIS) algorithm licensed from Myriad Genetics, now included for all sample types.

Scalability and flexibility
Supports scalable testing with 384 unique dual indexes and broad compatibility across Illumina sequencing systems.

Illumina solutions also include streamlined bioinformatics with a DRAGEN™ server and Illumina Connected Insights analysis software.

illumina®

M-GL-03713

(continued from page 18)

can gain maximum benefit by either prolonging the time to getting type 1 diabetes or [preventing] someone from getting it."

In addition, data from consenting patients allow for the creation of synthetic populations that let AI test a range of different trial scenarios *in silico*, with the aim of determining the best trial design. Similarly, synthetic populations can be used as the control arm of clinical trials, alleviating one of the more burdensome aspects of clinical development: patient recruitment. With synthetic populations, there are no physical patients in the control arm and drug companies only need to test real patients in the treatment arm of the trial.

Insilico Medicine: The poster child for AI-guided drug discovery and development

While the use of AI in various aspects of drug development is common today, and many companies developing AI and offering specific tools to aid with specific tasks, Insilico Medicine represents a company focused on informing the entire development cycle with AI, from target identification and therapy design through clinical trials.

Alex Zhavoronkov, PhD
CEO and Co-founder
Insilico Medicine

It also boasts the most advanced potential therapy in clinical development, rentosertib, for the treatment of idiopathic pulmonary fibrosis (IPF). Using their generative AI engine, the team at Insilico Medicine identified the novel target Traf2- and NCK- interacting kinase, a serine/threonine kinase whose activation plays a crucial role in cellular signaling processes that drive fibrosis development.

In June, the company announced positive results from a Phase IIa clinical trial of rentosertib for the treatment of IPF. Based on these data, the company plans to launch a Phase III trial of the drug in China and a Phase IIb trial in the U.S. later this year.

What is remarkable about the drug is that it is the farthest advanced candidate whose target and drug design were conceived entirely in silico using generative AI.

"Novel target, novel molecule is an infinitesimally lower probability success task," said Alex Zhavoronkov, PhD, CEO and co-founder of Insilico Medicine at a company celebration in 2021 for the first human dosing of rentosertib to treat IPF. What made the discovery of the target and the synthesis remarkable, he noted, was that the company didn't have a wet lab or traditional biotech drug discovery arm. "Even without having the main expertise ourselves, we trained AI to outperform humans in all of those areas and create a general-purpose engine that allows you to do all of that," Zhavoronkov said.

Insilico's Hong Kong office

Insilico

Founded in 2014, Insilico's journey was initially met with a healthy dose of skepticism. The original concept was to employ deep neural networks to test cell-drug interactions without the use of animal models. It was a 2019 paper published in *Nature Biotechnology*, which detailed the company's use of its generative tensorial reinforcement learning approach for *de novo* drug design, that established it could discover novel drug candidates—and do it quickly. In this case, it took merely 21 days to create roughly 30,000 different molecule designs with the potential to target a protein linked to fibrosis. From there, it took another 25 days to narrow down to a single molecule that showed drug-like qualities.

Now a clinical stage company, Insilico also offers its AI drug discovery services to pharma and biotech customers via its Pharma.ai division. But as Zhavoronkov has noted, the company first needed to demonstrate that it could achieve novel target discovery and create novel drug designs itself first.

Currently, the company has more than a dozen drug candidates in the pipeline at the lead optimization or more advanced stages for the treatment of diseases like cancer, inflammatory bowel disease, and obesity.

But what really sets the AI approach to drug discovery and drug design apart is the potential to slash drug development costs and timelines. Rentosertib took only four years to pass through Phase II trials and land on the cusp of Phase III. "Insilico's cost per program is only $3–5 million to reach developmental candidate, compared to the industry averages that can reach over hundreds of millions," Zhavoronkov told *Inside Precision Medicine*'s sister publication *GEN* in June. ■

Read more:

1. Clinical Pharmacology & Therapeutics
ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.3279
2. Nature Biotechnology
www.nature.com/articles/s41587-019-0224-x

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*.

BEHIND THE BREAKTHROUGHS Podcast

Hosted & Produced by: Jonathan D. Grinstein, PhD

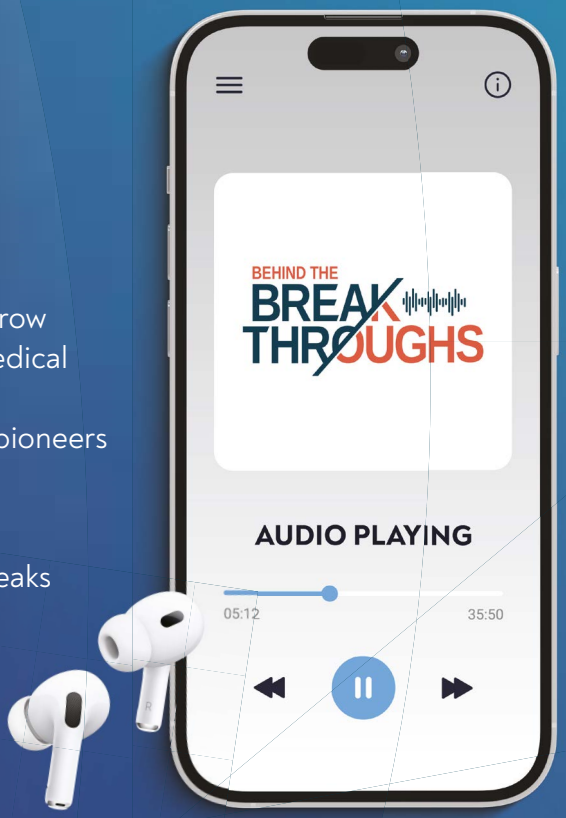
North American Editor, *Inside Precision Medicine*

New Episodes Every Other Wednesday

30–40 minutes

Step into the minds shaping the future of medicine.

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



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

NOTABLE GUESTS INCLUDE:

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

TUNE IN.
GET INSPIRED.
STAY AHEAD.

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

INSIDE PRECISION MEDICINE

fotografia / Getty Images Plus

Spotlight on Women's Reproductive Health

by Helen Albert Senior Editor

Women's health research has long been underfunded. Many reproductive health conditions that impact a significant number of women, such as endometriosis, polycystic ovary syndrome (PCOS), and uterine fibroids, have no treatments and understanding of these conditions is still limited.

While U.S. government funding remains low in this area at 10% or less of the National Institutes of Health (NIH) annual budget, there is increasing interest in the private sector. The number of startups in the region focusing on women's health has increased from around 40 in 2010 to more than 400 in 2025.

Women's reproductive health as a field has suffered many setbacks since the thalidomide scandal of the 1950s and 60s. After thousands of women were prescribed thalidomide for morning sickness around the world, over 10,000 children were born with birth defects, making it one of the most devastating adverse drug event scandals known to this generation.

This scandal and others contributed strongly to changes to the U.S. Food and Drug Administration (FDA) guidelines recommending that women of childbearing age not be included in Phase I or II trials of new drugs, even if taking contraceptive pills. Despite protests, it was not until 1993 that the law was changed to mandate the inclusion of women in clinical trials.

The exclusion of women of childbearing age from most clinical trials for decades undoubtedly set back research and development into women's reproductive health by many years compared with other fields of medicine.

Of course, reproductive health is not limited to a woman's childbearing years as the menopausal transition—affecting most women between the ages of 45 and 55—has significant adverse impacts on women's sexual, cardiovascular, musculoskeletal, neurological and mental health.

Despite the fact that millions of women are impacted by the symptoms of menopause every year, very few treatment options exist. Hormone replacement therapy (HRT) remains the main option to help women with menopausal symptoms, but its use dropped 20 years ago after trial results suggested it could be harmful.

In 2002, results from the Women's Health Initiative trials on the use of HRT for healthy postmenopausal women suggested that the treatment had more risks than benefits, increasing the risk for blood clots, strokes, and breast cancer.

These results caused consternation across the pharma and biotech industries, and in clinics across the country. Prescriptions of HRT dropped dramatically as a result. The results of the trials were later called into question and it has since been shown that many women benefit significantly from HRT, particularly if they are under the age of 60 and within 10 years on the onset of the menopause.

Fallout from both the thalidomide scandal and the Women's Health Initiative trials have had significant negative effects on the research and development of new treatments for women's reproductive health conditions. For example, investment in new treatments and in startups focused on women's health dropped substantially.

In addition to these factors, women's health research and reproductive rights have historically been marginalized due to social stigma, gender bias, and ongoing political controversies surrounding contraception and abortion.

Piraye Yurttas Beim, PhD
CEO and Co-founder
Celmatix

With so few treatments available for the many conditions affecting women's reproductive health, it is difficult to apply precision medicine principles to the problem. "In the women's health field and in the reproductive health field in particular, I would say we are where the cancer field was, maybe in the very early 2000s," said Piraye Yurttas Beim, PhD, CEO and co-founder of women's health-focused biotech Celmatix, which is based in New York.

Celmatix's first product was a genetic test called Fertilome® that analyzes DNA to identify genetic variants associated with reproductive health conditions that may affect conception or pregnancy. The company is now working on treatments for infertility, ovarian aging, and endometriosis.

"We moved from diagnostics into therapeutics because we realized that there's a bit of a chicken and egg problem. … I was so focused on diagnostics up until that point, I just assumed there was a lot of innovation on the drug side. As I started to realize there really wasn't a lot going on on that side, we realized developing therapeutics was the highest impact we could have."

Although there are many issues that need to be overcome to improve the field of women's reproductive health, it is definitely moving in an upwards trajectory. There are more companies focusing on women's health than ever before and investment in the field is also slowly increasing.

Rick Pauls
CEO and President
DiaMedica Therapeutics

DiaMedica Therapeutics is a biotech testing a treatment for preeclampsia, a serious pregnancy-specific disorder characterized by high blood pressure. It is also testing the same treatment for stroke.

"With our recent data, we are positioning our company to become a women's health company first. … We're doing it because that's what we hear from investors," said Rick Pauls, who is the president and CEO of the Minneapolis-based company. "Our stock prices increased substantially since we announced we were going into preeclampsia last year."

Reducing the diagnostic odyssey

To give patients the best possible outcomes, it is important to develop both therapeutics and diagnostics. While it is true that some diagnostics without treatments may not significantly change medical outcomes, early diagnosis can be life-changing for dangerous conditions like preeclampsia or cancer.

Although there have been extensive developments in cancer diagnostics over the last decade, some cancers remain hard to treat as they are largely diagnosed at a late stage. Ovarian cancer falls into this group.

Oriana Papin-Zoghbi, CEO and co-founder of Denver-based AOA Diagnostics, and colleagues are aiming to solve the problem of late diagnosis with their early detection test based on lipidomic technology.

Oriana Papin-Zoghbi
CEO and Co-founder
AOA Diagnostics

"Ovarian cancer is one of the most lethal cancers. It's the second most expensive cancer to treat in the U.S., second only to brain cancer, with 80% of women diagnosed at stage III and IV and a five-year survival rate of 28%," said Papin-Zoghbi.

"In 30 years, we haven't come up with a new biomarker to help solve this problem from a diagnostic perspective."

Lipids have been known to have a role in cancer since the '70s, but until recently it was difficult to reliably quantify the presence or absence of lipids in cancerous versus non-cancerous tissue.

Papin-Zoghbi and team believe they can improve outcomes for women with ovarian cancer by diagnosing it while it is still at stage I using their lipidomics-based test. It's early days, but so far, they have achieved good results in clinical testing.

"The average time to diagnosis in the U.S. is nine months," she explained. "But the window of opportunity from when ovarian

(continued on page 26)

Advancing Hereditary Cancer Care with Precision, Access, and Evidence

Bringing deeper insights, faster results, and expanded access to families at risk for hereditary cancer for streamlined precision care from diagnosis to survivorship

Reimagining hereditary cancer testing for the modern era

While guidelines for genetic testing in oncology have expanded, access to clinically meaningful results remains uneven. Many patients still face delayed diagnoses due to unclear variants, limited testing panels, or barriers to family follow-up. Natera's Empower™ hereditary cancer test is changing that. Designed to bring clarity, speed, and equity to hereditary cancer care, Natera's innovative technology and supportive access programs drive better outcomes across each patient's journey.

RNA testing, done responsibly

Criteria-driven reflex across 54 high- and moderate-penetrance genes predicted to affect splicing

Unlike conventional panels, Empower uses ±20 base pair intronic coverage—offering broader detection of variants near splice junctions. From there, Natera applies a targeted reflex RNA approach, activating RNA sequencing only when DNA analysis suggests a potential impact on splicing. This functionally relevant, criteria-based reflex model avoids unnecessary testing while enabling reclassification of a significant number of variants of unknown significance (VUS), helping clinicians move forward with confidence. And perhaps most importantly, RNA testing with Empower is performed using the original blood sample—no extra tubes and no added burden to the patient.

STAT breast cancer panel: fast results when timing matters

In time-sensitive settings, Empower supports urgent decision-making with its Breast STAT panel. This 10-gene subset—covering BRCA1/2, TP53, PALB2, and others—returns results in just 5–7 days, enabling faster risk assessment, treatment planning, and surgical decisions. This rapid turnaround empowers providers and patients to take timely action without compromising test quality.

Family testing, simplified and free for 180 days

Natera's Family Testing program removes barriers for relatives of patients with positive results. For up to 180 days, any blood relative can receive no-cost variant testing—on panels of up to the same size—helping identify at-risk individuals before cancer develops. Whether testing one relative or a dozen, the program is seamless and accessible in all U.S. states, supporting cascade testing at scale.

Closing the testing gap: The Hereditary Cancer Alert Program (HCAP)

Despite established criteria, studies show that of the over 1.36 million patients diagnosed with cancer between 2013-2019, only 6.8% had germline testing <2 years of their diagnosis.[1] Natera's Hereditary Cancer Alert Program proactively identifies eligible patients through EMR integration and lab partnerships. When combined with Empower and the Family Testing program, this initiative helps expand access across underserved populations and advance early detection—one patient, one family at a time.

Empower™ possibilities for precision care

With its integrated approach—spanning deep sequencing, intelligent reflex testing, and family outreach—Empower goes beyond traditional genetic testing. It's built for clinical clarity, patient access, and systemic impact. With Natera's commitment to innovation in molecular diagnostics, Empower is setting a new standard for hereditary cancer care..

Reference

1. Germline Genetic Testing After cancer diagnosis, Kurian et al, JAMA, Jun 5;330(1) 43-51

natera™

Learn more about Empower at
natera.com/empower

natera™ | **Empower™** Hereditary cancer test | **Signatera™** Residual disease test (MRD)

Hereditary Cancer Alert Program

Proactively identify Signatera™ patients for germline testing

Closing the gap:
Testing of at-risk patients increased by up to 2x in cancer centers

Learn more here

Choose Empower™ for customizable and accessible hereditary cancer testing:

- Pre-curated panels and easy-to-use functionality for customization options up to 192 genes
- RNA analysis for variant resolution with no additional sample or cost required
- Same-size panel Family Testing Program (FTP) at no additional cost
- Accessible and transparent pricing, pricing cap and cash pay options

The leader in molecular diagnostics

20+ years
in operation

300+
peer-reviewed publications

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

natera™

(continued from page 23)

cancer is still a localized disease [to] before it metastasizes is 4.2 months. If that woman is taking nine months to work herself through the healthcare system because there are no reliable diagnostics, it's just too late."

Maneesh Jain, PhD
CEO and Co-founder
Mirvie

Preeclampsia is another condition where early diagnosis can dramatically improve outcomes. Treatments are available that, if taken early, can help ensure safe pregnancy and improve outcomes for both mother and baby.

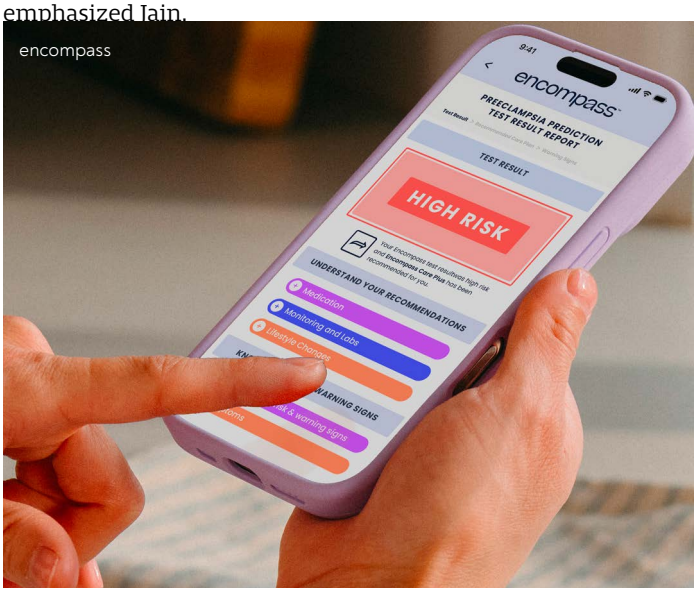
Mirvie is a San Francisco diagnostics company that has developed a platform to predict pregnancy complications such as preeclampsia and preterm birth using cell-free RNA.

"RNA is dynamic. It is changing throughout pregnancy, but it's changing in a predictable manner," said Maneesh Jain, PhD, CEO and co-founder of the company. "Just looking at the pattern of RNA, we can predict how far along you are. Tracking the development of pregnancy, we can look at deviations from that base pattern. … Whether it's preeclampsia, fetal growth restriction, preterm birth, or gestational diabetes, we've now shown that we have unique molecular signatures for each condition."

Mirvie's lead test, Encompass™, detects risk for preeclampsia at an early stage of pregnancy and was commercially launched earlier this year.

Preeclampsia can be predicted using medical history, like an earlier case of preeclampsia or preexisting high blood pressure, in about 10% of cases. However, 90% of cases of preeclampsia are hard to predict using medical history alone.

"They're apparently healthy pregnancies, but they end up developing preeclampsia and that's really the unmet need," emphasized Jain.



"What the guidelines try to do is use these very broad, moderate risk factors, so things like body mass index, race, or age, to assess risk in those pregnancies, and what we show is [that] it's completely ineffective. Predictive value is little to none because those factors are so generalized."

Using the Encompass test to assess apparently healthy pregnancies, researchers found that around 25% of those tested are actually at increased risk for placental-driven preeclampsia and can be given early treatment and monitoring.

"We know that, particularly for preventing preterm birth and more severe forms of preeclampsia, the medications are particularly effective," said Jain. "They may not stop the disease. But I think what's been widely accepted is that they're very helpful in delaying the onset of the disease, so baby has more time before delivery and that is just very helpful for everybody."

Some conditions impacting women's health, such as endometriosis, commonly take at least four years to diagnose in the U.S., which can result in an enormous physical and mental toll on those affected.

Veronika Bridgman
co-Founder
Unravel Health

It is still early days, but recent advances in diagnostics have the potential to help women with these conditions get treated faster. For example, Kephera Diagnostics announced the introduction of EndomTest™, a diagnostic blood test for endometriosis, in the U.S. earlier this year. Similarly, anti-Müllerian hormone (AMH) levels were introduced widely as a proxy measure for PCOS during the last two years.

Bringing testing to patients

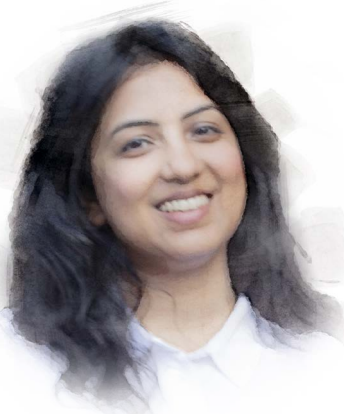
There is an increasing trend in the women's reproductive health space of bringing testing into the home. For example, several companies, like Eli Health, Everlywell, and Hertility Health, are now selling tests for hormones linked to reproductive health. The aim is to help improve access to tests that can help women understand their fertility and menstrual cycles, and whether they may be entering the menopause.

London startup Unravel Health is hoping to do something similar. "We're using a different sensor tech, which was developed to begin with, to measure many different things," said co-founder Veronika Bridgman. "The reason we want to look at many things simultaneously is so we can finally connect the dots on the interaction of women's reproductive hormones with other conditions markers, or stress markers, or medication efficacy and side effects."

Another upcoming area that can shed light on women's reproductive health is analysis of the vaginal microbiome. "It's

hugely important for women's health because it really acts as a protective barrier," said Hana Janebdar, CEO and co-founder of Juno Bio, a London-based biotech focused on direct-to-consumer vaginal microbiome testing. Several other companies such as Evvy and Bio-Me are also providing a similar service.

As highlighted in a review published by the U.K.'s Medicines and Healthcare products Regulatory Agency last month, this is a very new area of research but shows potential to help diagnose and potentially treat conditions such as infertility, miscarriage, preterm birth, gynecological cancers, and menopause-related complications.



Hana Janebdar
CEO and Co-founder
Juno Bio

Juno carried out a study of more than 1,000 women in the U.S. in 2023 to analyze vaginal microbiome profiles and collect data for potential use in diagnostic testing. "It was to observe what kind of vaginal microbiomes there are, what kind of conditions people complain about, and also it was for us to really understand, technically, what are the best ways of analyzing it," explained Janebdar.

She admits that while their test can give women a good profile of their vaginal microbiome, there are currently limited therapies available to solve any highlighted problems.

"We're trying to build a world in which women do have access to precision care, and we're doing it with the vaginal microbiome. … What's still limited is the tools that you then have access to for changing the vaginal microbiome. You do have a certain number of antibiotics that you can use and a handful of probiotics and prebiotics … but it is still rather limited when it comes to the therapies that are available."

Unravel Health Team

Despite this, Janebdar said the test has been popular with women who say it has empowered them to get better responses from their healthcare providers. "We didn't think

Juno Bio's Vaginal Microbiome test

that the test would be helpful just as a wellness test, but because 85% of women feel their symptoms are dismissed when they go to their physician, they feel like actually going in there with data is a really powerful tool."

Papin-Zoghbi says that women are looking for these kinds of tests to help them plan their own healthcare. "Women are taking a lot more control over their own health and are willing to look outside of the traditional system for the care that they don't feel like they're getting in the system," she said.

Improving treatment options for neglected conditions

While it is true that many conditions affecting women's reproductive health are lacking in effective treatments, this is starting to change.

For example, in the last month, Bayer's non-hormonal menopause drug elinzanetant, brand name Lynkuet, was approved in both the U.K. and Canada based on three positive Phase III trial results published last year. The FDA is currently reviewing extra data, but a U.S. approval is expected soon.

After switching from diagnostics to treatments, Celmatix is now working on several candidate therapies. It is developing an oral follicle-stimulating hormone (FSH), which would work in the same way as the injections a woman needs to undergo in vitro fertilization (IVF), but in a less invasive way.

"The receptor that FSH binds to is something called a GPCR. … That target is very easy to target with a small molecule," explained Yurttas Beim.

"The challenge with FSH receptor, and what killed this program for three decades … what makes this GPCR unique compared to other GPCRs targeted by oral medications is that it is very closely related to thyroid-stimulating hormone receptor. And if you have an off-target on thyroid-stimulating hormone, that is a life-threatening side effect."

Celmatix has used artificial intelligence to help with its search for a new small molecule that will avoid this potentially dangerous side effect. The program is still at an early stage, but Yurttas Beim says she is excited about the progress of the drug candidate.

(continued on next page)

(continued from previous page)

Another important and historically neglected indication that the company is developing a treatment for is endometriosis. Once endometriosis is diagnosed, there are currently limited treatment options that largely consist of drugs to control hormone levels, surgery, or pain relief medication to control the symptoms.

"Endometriosis was seen as a menstrual disorder. It was seen as a disorder of hormonal imbalances related to estrogen," said Yurttas Beim, who has the condition herself.

"We are using these big hammers. Women are having hysterectomies because of it, being put on estrogen blockers, and being put into chemical menopause to treat endometriosis. The challenge is those things are a strategy that works for many women for managing pain, but it does not help them with their infertility."

The work behind the company's endometriosis program comes from Steve Palmer, PhD, now CSO of Celmatix, who previously discovered with colleagues that Jun N-terminal kinase (JNK) inhibitors could be a good treatment for endometriosis as it can target both the pain and inflammation caused by the condition. These drugs are also being investigated as a potential treatment for cancer, which shares many cellular traits with endometriosis.

"JNK1 and JNK3 are the ones that matter for endometriosis," explained Yurttas Beim. "JNK3 is how peripheral pain in the peritoneum gets transmitted to the dorsal root ganglion, which is a part of the brain that receives that pain signal, and JNK1 is how endometriosis achieves an immune cloaking mechanism."

Importantly the company believes these drugs will not impact a woman's ability to get pregnant, although they are yet to be tested in clinical trials.

Celmatix also has an earlier stage candidate, an AMH receptor agonist to slow the depletion of ovarian reserves. "There's no way you can preserve eggs. You can preserve your fertility, but there's no way to get your ovary to function better if you have an ovarian dysfunction condition like PCOS early in life, or through perimenopause and ultimately, menopause," said Yurttas Beim.

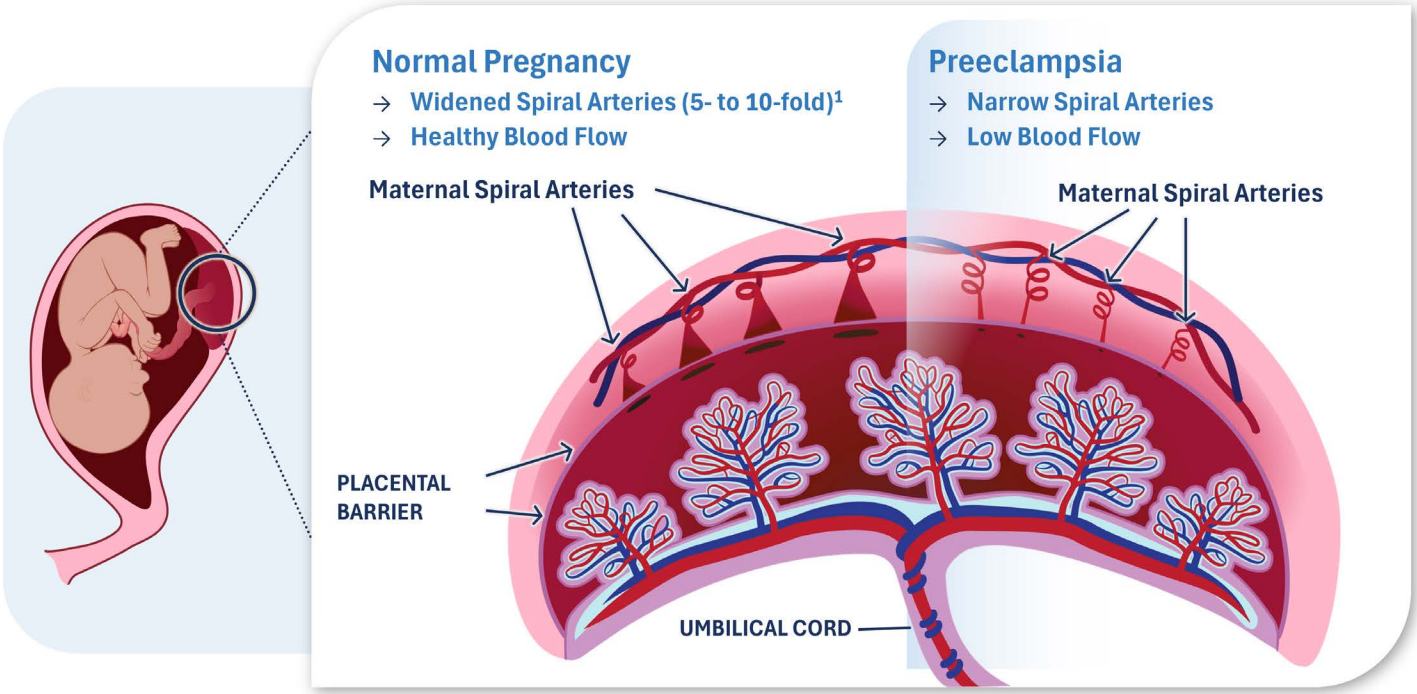
"So that was our goal. To make sure that we have tools in the pipeline being developed, to ensure that women do not have their gonadal function stop working in what is now midlife."

Developing drugs or other treatments that impact reproductive health is hard enough, but if the treatment is designed for pregnant mothers, then trials and research become exponentially more difficult due to the risks involved.

This is something that DiaMedica Therapeutics is currently navigating. The company started developing a vasodilator, DM199, also known as rinvecalinase alfa, a recombinant form of human tissue kallikrein-1 for treatment of stroke. Last year, it added preeclampsia as an indication after data suggested DM199 could be effective.

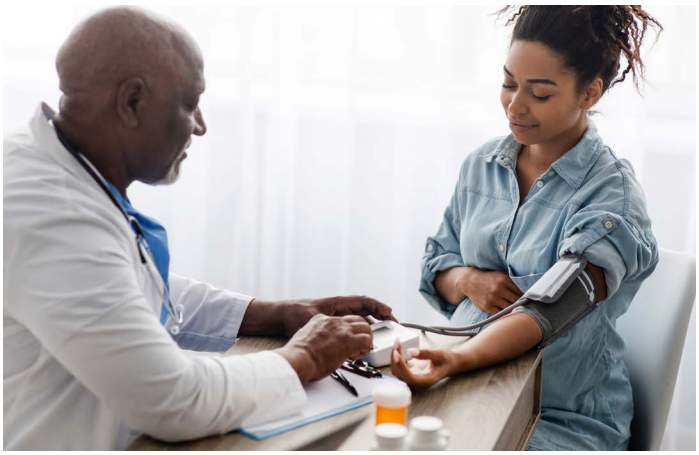
"We had to go back to the board a few times to get their blessing to do this," admitted Pauls. "There was always this concern that treating the pregnant mothers is just fraught with risk, but at the same time, that's also an opportunity. There's nothing for these mothers."

The company is now testing DM199 in Phase II clinical trials for the treatment of preeclampsia after early trials showed good results. "As soon as they're diagnosed with preeclampsia, we think we'll be able to improve endothelial health, in addition to controlling blood pressure and dilating the intrauterine arteries so there's more blood flow to the placenta."



DiaMedica

Stage I of preeclampsia Inadequate spiral artery remodeling in the first trimester



Prostock-Studio / iStock / Getty Images Plus

Preeclampsia is a life-threatening high blood pressure disorder.

Pauls also explained that their candidate therapy has the benefit of not passing through the placental barrier, which has helped get the trials to this stage as potential danger to the baby is reduced.

Initially the focus of the research is on getting the mothers to a stage of pregnancy where delivery can occur with minimal or no harm to the baby. But Pauls said that they also want to trial giving DM199 to mothers 6–8 weeks after delivery to help reduce blood pressure and potential long-term side effects from experiencing preeclampsia, which can be significant.

"The longer-term risk factors that these mothers have from having preeclampsia, especially if it's severe, are not well understood," he emphasized.

What's next for women's reproductive health?

The field of women's reproductive health is slowly moving forward, but there is still a lot to be done both on the research and the investment side of the table.

"I think currently, there's a lot of people who agree that the status quo is broken and that we really don't understand much about women's bodies in as much detail as we really should," said Bridgman. "And yet, there's a lot of debate and skepticism and anxiety around some of the stuff we're doing and new data."

Things are moving forward. For example, earlier this year, the Seckin Endometriosis Research Center for Women's Health launched at Cold Spring Harbor with $20 million in funding.

"What we're trying to catalyze is this future where we really can understand who's predisposed for endometriosis and what may make one person's endometriosis different than another," said Yurttas Beim, who is involved in the Center through her role as chairperson of the board of directors of the Endometriosis Foundation of America.

Organizations like the Global Alliance for Women's Health, a multi-stakeholder platform launched in 2024 to address systemic inequities and close the women's health gap, are also trying to improve funding, research, and political advocacy in this area.

New diagnostics for conditions like preeclampsia and endometriosis are reducing time to diagnosis significantly and new therapeutics like those being developed by Celmatix and DiaMedica are slowly moving towards approval, but there is a lot still to be done. "We've come a long way in 15 years, but not as far as we need to," said Yurttas Beim.

More data about important areas like the vaginal microbiome and its impact on health and disease is also becoming available, which will help progress the field. "When we started, you couldn't say vagina in an investor meeting. There was no women's health on the map. But since then, things have changed and we've been really happy to be part of that movement," said Janebdar.

In 2024, U.S. women's health startups secured $2.6 billion in venture capital funding, up from $1.7 billion in 2023 and around $400 million in 2015. In addition, there are now more than 400 women's health startups, a significant increase since 2015.

Overall, however, funding remains a challenge, with women's health companies receiving less than 5% of global venture capital funding. Government funding through sources like the NIH has only increased by a small amount, from around $4.4 billion in 2021 to an estimated $5 billion in 2025, which accounts for 10% or less of the overall annual NIH budget.

"Unfortunately, I would say the hardest part of this is not the science, it is getting funding to actually progress the science," said Yurttas Beim.

Papin-Zoghbi agrees but thinks this maybe a broader problem at the moment. "I think the venture capital markets are contracted, which is just pretty tough. Similarly, the government funding has contracted, but it's contracted in everything. Has women's health been hit a little harder? Perhaps, but I don't think we're as much of an outlier as maybe historically we were."

Women's health has at least finally become a category for investors in biotech and medtech, which experts in the area believe will help draw more attention to the field.

"What I'd like to see is more money going into the area and it becoming just more normal for women to seek the kind of care that they deserve, but I have to say that we are living in this time where a lot of women's health and women's rights are being taken away, and so while that is what I'd like to see, I'm not 100% convinced that we will see it unless we really fight for it," emphasized Janebdar. ■

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.

DrPixel / Getty Images Plus

5 KEY STARTUPS SHINING THE LIGHT ON RARE DISEASES

by Jonathan Smith, PhD

Growing product pipelines and government support for rare disease treatments is expected to drive the growth of the global market by 11.6% per year from $216.2 billion in 2024 to $374.4 billion by 2030.

Many rare disease treatments in the market are biologics, with one example being Sanofi's Dupixent (dupilumab), which was greenlit by the U.S. Food and Drug Administration (FDA) in June this year for the treatment of adult patients with a condition called bullous pemphigoid. However, of the more than 10,000 known rare diseases affecting 400 million people across the globe, only 5% of those conditions have an approved treatment, leaving a lot of room for more innovation.

Rare diseases are generating interest from big pharma companies, with notable examples including the $1.05 billion acquisition of France's Amolyt Pharma by the U.K.'s AstraZeneca in 2024 and Germany-based Merck KGaA's buyout of SpringWorks Therapeutics in the U.S. for $3.4 billion in April 2025.

As investors flock to promising rare disease startups, check out our list of the top five investor favorites for their potential to bring new rare disease treatments to the market.

1 Actio Biosciences

Founded: 2021 | **Headquarters:** San Diego, California

Actio Biosciences, whose name was derived from the Latin word *actio* meaning "action," aims to translate genetic insights into precision medicines.

Actio currently focuses on researching small molecule treatments for rare genetic disorders, with the long-term goal of applying its expertise to more common complex conditions.

Actio's Phase I-stage program ABS-0781 is designed to treat an incurable rare condition called Charcot-Marie-Tooth disease type 2C (CMT2C). This disease is driven by mutations in a gene called *TRPV4* that encodes an ion channel, and has symptoms like muscle weakness, vocal cord paralysis, and respiratory complications. Daily oral doses of ABS-0781 are designed to block the TRPV4 channel and restore the patient's motor functions.

Its second treatment candidate, ABS-1230, is designed to treat a rare and often fatal form of epilepsy caused by mutations to a gene called *KCNT1*, which encodes a different ion channel. By doing this, the preclinical-stage drug could clamp down on overactive ion channels and target the root cause of the disease.

Actio has raised $121 million to date, including a $55 million Series A round in 2023 and a $66 million Series B in June 2025, which was co-led by Regeneron Ventures and Deerfield Management.

Actio plans to launch the healthy volunteer portion of a Phase I clinical trial of ABS-1230 this year, with a Phase Ib study planned in 2026.

2 Aeovian Pharmaceuticals

Founded: 2012 | **Headquarters:** Berkeley, California

Originally founded as Delos Pharmaceuticals, Aeovian Pharmaceuticals was incubated at the Buck Institute for Research on Aging in the U.S. The startup is developing treatments for rare genetic and age-related diseases by focusing on a protein called mechanistic target of rapamycin complex (mTORC).

mTORC forms complexes called mTORC1 and mTORC2 to regulate a range of cellular processes. However, these regulators become imbalanced in diseases like refractory epilepsy associated with tuberous sclerosis complex (TSC), where mTORC1 becomes hyperactive and leads to seizures that are often resistant to existing therapies.

Aeovian's lead program, AV078 is in Phase I testing for the treatment of TSC refractory epilepsy, and is designed to selectively inhibit mTORC1. This makes it safer than less selective mTORC inhibitors.

Earlier-stage selective mTORC1 inhibitors in Aeovian's pipeline include AV805 for neurodegenerative diseases and AV505 for metabolic disorders, in addition to programs with a different target for the treatment of undisclosed conditions.

In March 2024, Aeovian raised $50 million in a financing led by the Saudi Arabian-U.S. non-profit organization Hevolution Foundation, with participation from venture capital investors and the German biotech Evotec.

3 Azafaros

Founded: 2018 | **Headquarters:** Leiden, Netherlands

Azafaros is researching drugs for rare metabolic disorders like lysosomal storage disorders, which comprise rare conditions that collectively affect 1 in 5,000 births.

Lysosomal storage disorders are mostly caused by mutations to proteins essential to transporting and processing sugars, proteins, and lipids, which lead to neurodegenerative symptoms and damage to organs like the liver, spleen, heart, and kidneys. While some of the conditions have specific therapies, many patients can only receive palliative care.

Azafaros' pipeline is based on research from Leiden University and Amsterdam UMC, with its lead program nizubaglustat beginning two Phase III studies for the treatment of Niemann-Pick disease type C and GM1/GM2 gangliosidoses in July 2025.

Nizubaglustat is a modified sugar molecule that can be taken orally and reach the brain to cut down on the buildup of harmful waste lipids and alleviate disease symptoms.

Azafaros bagged €25 million ($29 million) in a Series A round in 2020. This was followed by a huge Series B round worth €132 million ($155 million) in May 2025 to finance its Phase III program and expand its pipeline to different conditions. The round was co-led by Jeito Capital and Forbion Growth.

(continued on next page)

(continued from previous page)

4 glycomine

Glycomine

Founded: 2014 | **Headquarters:** San Carlos, California

Glycomine is developing therapies for rare metabolic conditions that lack treatments. Its lead candidate GLM101 is in Phase II development for the treatment of phosphomannomutase 2-congenital disorder of glycosylation (PMM2-CDG), also known as CDG-1A or CDG Type 1a.

In PMM2-CDG, a mutation in an enzyme called PMM2 impairs the production of a molecule called mannose-1-phosphate, which is essential for proper protein structure and function. This leads to a wide range of symptoms like muscle weakness, liver disease, cardiomyopathy, and coagulopathies.

GLM101, which showed promising interim results in March 2024, is designed to replace the missing mannose-1-phosphate and bypass the PMM2 mutations.

Glycomine raised $12 million and $68 million in Series A and B rounds in 2016 and 2021, respectively. It then landed an impressive $115 million in a Series C round in April 2025, which was led by CTI Life Sciences Fund, abrdn Inc, and Advent Life Sciences, with the capital used to finance the clinical testing of GLM101.

Glycomine has also collected the largest single clinical dataset of PMM2-CDG from a natural history study in 139 patients, which each patient having completed more than two years in the study as of 2023.

5 healx

Healx

Founded: 2014 | **Headquarters:** Cambridge, U.K.

Healx arose when its founders, one of them a co-inventor of Viagra, were inspired by Beacon, a patient group set up to find treatments for a rare genetic disorder called alkaptonuria faced a long and expensive drug discovery process.

Healx specializes in using generative artificial intelligence and working with patient groups to design new treatments for rare diseases more quickly and cheaply than traditional methods of drug development. Its platform, called Healnet, analyzes millions of data points in the scientific literature to generate 10–20 potential drug candidates by the end of the discovery phase.

The startup dosed the first patient in a Phase II trial of its oral lead candidate HLX-1502 in patients with a genetic condition called neurofibromatosis type 1 (NF1) in February this year. Its pipeline also includes treatments for conditions like pediatric oncology, fragile X syndrome, and Angelman syndrome.

Healx raised $10 million in a Series A round in 2018, $56 million in a Series B round in 2019, and $47 million in a Series C round in August 2024. The C round was co-led by R42 Group in the U.S. and Atomico in the U.K. and will fuel pipeline development.

In November 2024, Healx launched an agreement with Sanofi to identify new potential indications for a late stage discontinued asset that is being considered for out-licensing. Healx also partnered with SCI Ventures to discover and develop treatments for spinal cord injury in July this year. ■

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

natrot / iStock / Getty Images Plus

TARGA Imager: Revealing Development in Brain Neural Network

The technique for producing human induced Pluripotent Stem Cells (hiPSC) was first introduced in 2007 by Shinya Yamanaka, MD, PhD, and his research team, a discovery for which he was awarded the 2012 Nobel Prize in Physiology or Medicine.[1] This method is now widely used in biomedical research with applications ranging from disease modeling to personalized medicine. Scientists in the laboratory of Femke De Vrij, PhD, in the department of psychiatry at the Erasmus Medical Center (Erasmus MC), Rotterdam, utilizes hiPSCs to generate living human brain cells to uncover mechanisms of neurodevelopment and differentiation. This approach allows them to mimic brain development in a micro dish or well plate and study the biological mechanisms of psychiatric and neurodevelopmental disorders.[2]

The De Vrij group recently presented a novel method for generating three-dimensional cortical layered organoids.[3] This technique produces highly reproducible and topographically standardized structures in 384-well plates. The resulting self-organized organoids revealed a radial cortical structure with typical dimensions of 3mm × 3mm × 0.2mm. Using fluorescence-based calcium imaging, a plethora of brain cell types can be visualized within the organoids, including multiple neuronal subtypes, astrocytes, and oligodendrocyte lineage cells. The spatial organization of the organoids follows an inside-out pattern, where radially deep-layer neurons develop before shallow-layer neurons, thereby mimicking *in vivo* cortical development. Further, the organoids exhibit robust neuronal activity, indicating the formation of a functional neural network.

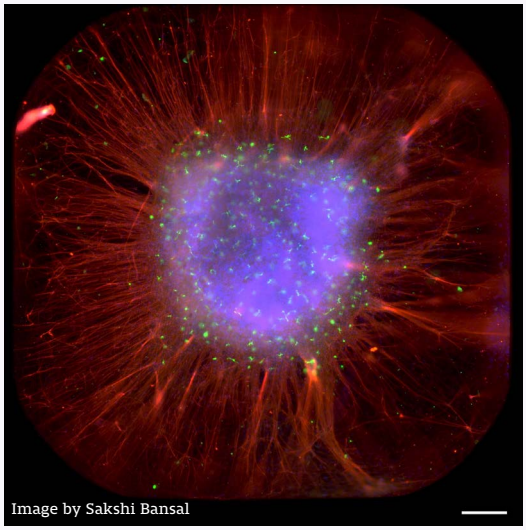


Figure 1. Full well acquired by TARGA showing radial organization of organoid. Scale bar is 0.2 mm.

Insights gained from organoid fluorescence imaging are crucial for high-throughput drug discovery and neurotoxicological screening. To facilitate rapid and consistent imaging of brain cells and organoids in the De Vrij Lab, Lumencor customized a TARGA Imager. The TARGA Imaging platform uniquely addresses a triumvirate of demanding high-performance imaging traits: fast imaging speed, large field-of-view, and sensitivity, to enable visualization and measurement of intricate and multifaceted neuronal structures.

Unlike conventional, time-consuming wide field fluorescence and confocal scanners, which acquire multiple images serially and then require tiling to piece together the entire 3 × 3 mm sq well area, TARGA images the entire large field-of-view including whole well areas instantaneously (*Figure 1*). This capability facilitates the study of dynamic properties of organoids, such as shorter-term development and disease progression. It also eliminates the need for laborious and imprecise image-stitching, ensuring consistent and undistorted visualization. TARGA reduces experimental time by an order of magnitude, compared to traditional laser scanning confocal studies, with no loss of information. Given its additional capacity to capture high speed data much faster than video rates, the TARGA Imager supports up to 1 TB of memory to provide a smooth workflow and efficient data transfer. Further, TARGA's fast multicolor illumination system enables the instantaneous imaging of distinct brain cells and sub cellular components, labeled with an array of fluorescent markers throughout the UV-VIS-nIR spectrum.

Like all Lumencor products, the TARGA Imager is part of a family of products. Should your imaging tasks demand unique spectral, spatial, and/or temporal control outside the constraints of more traditional fluorescence microscopy techniques, TARGA can be tailored to customized specifications. TARGA is pushing the boundaries of bright-field and fluorescence imaging with hardware built around the high-performance, solid-state lighting upon which Lumencor has built its reputation. How can Lumencor help to enable your best imaging experiments?

References

1. Yu, Junying, et al. Induced pluripotent stem cell lines derived from human somatic cells. *Science* 318.5858 (2007): 1917-1920.
2. Polit, Lucia Dutan, et al. Recommendations, guidelines, and best practice for the use of human induced pluripotent stem cells for neuropharmacological studies of neuropsychiatric disorders. *Neuroscience Applied* 2 (2023): 101125.
3. van der Kroeg, Mark, et al. Human adherent cortical organoids in a multiwell format. *eLife* 13 (2024).

Redefining Precision Medicine

Based in Cambridge UK, Qureight, a core imaging laboratory has been making significant progress since their inception in 2018. It has forged meaningful partnerships with pharma, biotech and contract research organisations. Their proprietary technology is accelerating lung and heart drug development using AI-powered imaging and data curation to optimize trial endpoints and patient stratification. The company also has a broader vision to explore rare and autoimmune diseases.

Damian Doherty, editor in chief of *Inside Precsion Medicine*, spoke with Simon Walsh Chief Scientific Officer at Qureight to explore the company's powerful cutting-edge AI technology and its transformative potential. From lung and heart disease to broader applications, Walsh shares how Qureight aims to revolutionize clinical insights by building a more connected view of disease, redefining the future of precision medicine through AI-driven innovation.

Simon Walsh, MBBS, PhD, CSO of Qureight

Q: Qureight has established itself as a leader in applying deep learning to clinical data for lung and heart diseases. Could you elaborate on how your deep learning technology goes beyond traditional analytics to identify novel and more sensitive biomarkers from complex datasets, such as computed tomography (CT) scans and physiological data?

Walsh: Traditional imaging analytics rely on predefined metrics such as fibrosis extent or lung volume loss. However, fibrosis quantification alone does not capture the full prognostic signal that high-resolution computed tomography (HRCT) has to offer. Our approach uses deep learning models trained on human-annotated data to extract multi-compartment imaging biomarkers that reflect prognostically meaningful changes in the pulmonary vasculature, airway tree, and lung parenchyma. These biomarkers are reproducible, scalable, and trial-ready, and they reflect biological processes that standard measures like forced vital capacity (FVC) often miss. We can also incor-

Qureight

porate measures of uncertainty, allowing us to flag areas of diagnostic ambiguity and enhance interpretability for sponsors. Beyond imaging alone, we integrate our biomarkers with other omics data, such as proteomics, to enhance risk stratification. Critically, we use these biomarkers to construct synthetic control arms in antifibrotic therapy trials, allowing more precise matching between cohorts, reducing placebo exposure, and accelerating signal detection—all while aligning with emerging regulatory frameworks.

Q: How does this accelerate the drug development process for your partners?

Walsh: Signal extraction from CT imaging is at the heart of how we optimize clinical trials. Our platform isolates and quantifies treatment effects within the specific anatomical compartments of the lung—parenchyma, airways, and vasculature—rather than relying solely on conventional metrics like FVC. This compartmental approach allows us to identify therapeutic signals that directly reflect a drug's mechanism of action. For example, in a recent Phase II idiopathic pulmonary fibrosis (IPF) trial, our biomarkers revealed a larger treatment effect size associated with pulmonary vascular volume than FVC—precisely the compartment expected to respond based on the drug's vascular mechanism. This level of mechanistic precision enables earlier go/no-go decisions, synthetic control arm design, and enhanced regulatory credibility. We also accelerate trials by enabling cohort enrichment: our biomarkers can identify patients with lightly progressive disease, who are most likely to demonstrate a therapeutic signal. By selecting the right patients and extracting the right signals from imaging, we help our partners reduce sample sizes, increase endpoint sensitivity, and compress timelines across the trial lifecycle.

Q: Your collaboration with Insilico Medicine on the IPF drug rentosertib has been a significant milestone. What specific insights did Qureight's platform provide that supported the preliminary efficacy results and future trial expansion for a drug discovered using generative AI?

Walsh: Our collaboration with Insilico Medicine focused on validating the external generalizability of their Phase II trial results for rentosertib, a novel antifibrotic discovered using generative AI. The trial was conducted exclusively in a Chinese IPF population, raising important questions about how well the findings might translate to global regulatory and clinical settings. Using our global IPF datasets, we demonstrated that the Chinese cohort showed no material differences in key enrollment criteria compared to global IPF populations. This finding supported the argument that the treatment effect observed in the Chinese trial was not specific to a unique regional phenotype and could, in principle, generalize to the broader IPF population worldwide.

Q: What does this collaboration signify about the synergy between different AI applications in the drug development pipeline?

Walsh: The Insilico collaboration illustrates the power of linking upstream and downstream AI capabilities in drug development. Generative AI can identify novel therapeutic compounds like rentosertib, but success ultimately hinges on

(continued on next page)

(continued from previous page)

proving that these candidates work in real patients. That's where Qureight comes in. Our role is to enable precision phenotyping and global applicability testing through advanced clinical and imaging biomarkers. In this case, Insilico discovered a novel IPF drug candidate; our platform validated that the trial population in China exhibited the same disease signature as IPF populations elsewhere in the world. This potentially derisks their expansion strategy and laid a scientific foundation for generalizing efficacy claims across diverse regulatory territories

Q: Beyond the use of deep learning for biomarker identification, Qureight has pioneered the use of "synthetic control arms." Can you explain the concept behind this technology, its ethical and practical advantages, and how it is revolutionizing clinical trial design, particularly for rare and severe diseases like IPF?

Walsh: A synthetic control arm is a digitally constructed comparator group, generated using historical imaging and clinical data to simulate how a patient population would behave under standard of care, or if required, treatment-naïve conditions. At Qureight, we apply a machine learning-based approach to generate these synthetic arms, combining imaging and clinical biomarkers to create high-fidelity patient matches and model projected disease trajectories. In rare and progressive diseases like IPF, this approach offers both scientific rigor and ethical sensitivity. Traditional placebo-controlled trials can be difficult to justify when promising therapies are in play, and patient recruitment is often hindered by the risk of receiving no active treatment. Our synthetic arms provide an alternative that reduces reliance on placebo groups while preserving statistical integrity and regulatory viability. This enables faster trial execution, improved enrollment rates, and supports the design of adaptive trials. It also allows for smaller, more focused studies without sacrificing robustness—an especially valuable feature in rare disease settings. We presented data at the 2025 American Thoracic Society Congress from two independent Phase II IPF studies, in which Qureight's synthetic control arms closely mirrored the behavior of real-world control groups across multiple endpoints. These results validate the methodology and mark a significant step toward regulatory-grade synthetic arms in pulmonary drug development. Ultimately, synthetic arms are not just a novel statistical strategy—they represent a step-change in trial design, accelerating the development of new therapies while upholding both ethical and scientific standards.

> "From the outset, one of the core challenges in building Qureight was forging a meaningful bridge between two fundamentally different disciplines: clinical medicine and machine learning. These worlds operate on different timescales, with different standards of validation, language, and culture."

Q: Looking at the company's trajectory since its formation in 2018, what were the foundational challenges you and the co-founders faced in building a company at the intersection of medicine and deep learning? What key milestones or moments have been most critical to the company's progress and growth to date?

Walsh: From the outset, one of the core challenges in building Qureight was forging a meaningful bridge between two fundamentally different disciplines: clinical medicine and machine learning. These worlds operate on different timescales, with different standards of validation, language, and culture. Building a shared framework required us to earn trust across multiple fronts—pharma, academia, regulators—while simultaneously delivering tools that were both scientifically credible and scalable. It was not enough to build interesting models; we had to embed them in a framework that respected the regulatory and clinical expectations of modern trials. Key milestones that stand out include the first time our imaging biomarkers were implemented in an interventional trial, and the publication of our early validation studies in high-impact journals. These gave our platform credibility in the eyes of sponsors and investigators. Raising our Series A funding round also marked a critical inflection point and proof that the commercial world saw what we saw: a future where imaging biomarkers were central to trial strategy, not peripheral. The rapid expansion of our partnerships and the emergence of our LungAI suite signaled that we had moved beyond startup experimentation into real-world deployment.

Q: Qureight is currently focused on lung and heart diseases. What new projects or disease areas are in the pipeline for expansion, and what criteria do you use to select these new therapeutic areas? How do you foresee your technology being applied to other conditions where complex data analysis is a barrier to precision medicine?

Walsh: Our current focus is on fibrotic lung disease and pulmonary vascular disorders. This reflects areas where imaging plays a central role in disease tracking but has historically lacked quantification. From here, we're expanding into heart failure—both preserved and reduced ejection fraction phenotypes—because these areas suffer from the same challenges: subjective assessment, complex multimodal data, and a need for clearer endpoints in trials. We prioritize new disease areas where

there is a strong biological rationale, unmet clinical need, and fragmented data environments that machine learning can bring into alignment. We're also actively exploring rare diseases and autoimmune conditions, especially where imaging intersects with other high-dimensional data streams. While our focus remains on supporting clinical trial design and regulatory strategy, the long-term vision is broader. There are specialist clinical centers that are increasingly data-rich but insight-poor. Our technology can close that gap. Over time, we believe structured imaging and AI-derived metrics will become core to precision medicine, not just in trials but in daily decision-making.

> "Qureight's strategy is built around a deep integration of clinical insight and technical excellence. Our core belief is that innovation in AI is only meaningful when grounded in biological relevance, medical credibility, and translational utility."

Q: In the broader context of precision medicine, how important do you believe Qureight's technology will be in enabling a more personalized approach to patient care and treatment? Are there plans to move beyond supporting clinical trials to also provide tools for clinicians in their day-to-day practice?

Walsh: In the broader context of precision medicine, Qureight's platform plays a critical role in precisely quantifying prognostic signals from HRCT—not in aggregate, but from each anatomical and functional compartment of the lung. We separate and quantify vascular, airway, and parenchymal signals, allowing us to track how different drugs act on specific biological targets. This level of precision isn't just desirable, it's essential for matching mechanism of action to measurable treatment effect. Think of it like getting a tailored suit: you wouldn't settle for a single chest measurement and hope for the best. You'd want the tailor to take multiple detailed measurements to ensure a perfect fit. Precision medicine is no different. At Qureight, we take multiple, compartment-specific measurements of the lung to build a complete and personalized understanding of disease progression and drug effect. We believe this mechanistic dissection of imaging data will be central to the future of trial design, especially in diseases like IPF and pulmonary hypertension, where traditional endpoints like FVC are crude, liable to significant measurement variability, and often uninformative in early-phase studies. Right now, our focus is on maximizing the impact of this technology in drug development, where the unmet need is acute and where precision imaging biomarkers can accelerate timelines, de-risk programs, and sharpen regulatory discussions. Clinical trials are the pressure point—and it's where we can have the biggest effect today.

Q: Given the rapid pace of innovation in AI, what is Qureight's strategy for staying at the forefront of deep learning and data analytics? How do you ensure your technology remains proprietary and cutting-edge in a competitive landscape?

Walsh: Qureight's strategy is built around a deep integration of clinical insight and technical excellence. Our core belief is that innovation in AI is only meaningful when grounded in biological relevance, medical credibility, and translational utility. To that end, we maintain an in-house team of clinical radiologists, data scientists, and machine learning engineers who collaborate closely on every model, from conception to deployment in trials. This enables us to develop task-specific, medically validated models rather than relying on generic AI tools. We invest continuously in internal R&D, with a strong publication track record that underpins our credibility and ensures that our models stand up to peer scrutiny. Our model suite is modular and scalable, allowing us to iterate quickly as new data types or endpoints become relevant. Importantly, we retain intellectual property over our analytics pipeline and design outputs with regulatory adoption in mind from the outset. Proprietary value also comes from our data partnerships. We focus on structured, high-quality, and longitudinal datasets—often drawn from real-world registries or carefully curated trial cohorts—which are essential for disease modelling. By aligning with leading academic centers and life science sponsors, we ensure our insights remain both cutting-edge and deeply embedded in the clinical research ecosystem. In a crowded space, our credibility, partnerships, and focus on trial-readiness distinguish us. ■

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

PART TWO

I Got My Genome Sequenced At Home—Now What?

The next installment of our series on personal genomics delves into the aftermath—and lingering questions—of receiving genome sequencing results

Jonathan D. Grinstein, PhD North American Editor

Kateryna Bereziuk / iStock / Getty Images Plus

As I am browsing the options of whole genome sequencing (WGS) tests I can order to my house, I start to see a trend. One website, immaculately designed (from a marketing standpoint), has large, bold solicitations: *Build generational health. Live healthier, longer. See why we're the #1 DNA test.* Just below it, there's a scrolling banner with icons of major outlets and major sports league partners endorsing their product. Another section claims their approach gets 1000x more DNA sequenced than 23andMe, leading to more insights. Then there is a table showing the price: instead of paying $3,350 for individual WGS and cancer, heart, and neurology screening, you can get them bundled for just $499.

On another website, I found a slight variation: *Discover your roots and what runs in your family so you can take action with the most accurate genetic test that decodes 100% of your DNA—and guarantees your privacy.* Similarly, there is a banner below with the icons of major outlets, many of them overlapping with the first website, in a display of syndication. There's some small print pointing to the fact it uses WGS to analyze "100% of your DNA, while typical DNA Ancestry sequences less than 1%." Finally, the price point, delivered with a big, Andy Warhol-esque 10-point star that says: *"50% Off, DNA Kits Starting at $195."*

I'm torn: on the one hand, it seems all too salesy for me; on the other, I can get my complete genome sequenced for a few hundred bucks?! Compared to the days of single nucleotide polymorphism (SNP) microarrays by 23andMe, these WGS tests evaluate astronomically more variants with predictive models for polygenic risk scores (PRS) than the handful of individual well-characterized pathogenic variants. How could this not be anything but a worthwhile thing to do if the information I

Table 1. Genomic testing technical information*

Company	Sequencing approach	Sequencing depth	Kit price	Subscription price	Variants assayed (total)	AD Markers	Sample type	Processing time	Ordering
23andMe	Microarray genotyping (Illumina GSA + ~50k custom)	N/A (array)	Total Health $499; Premium $199	Total Health $199; Premium $69	>600,000 SNPs	1 (*APOE4* variant rs429358)	Saliva	N/A	Direct-to-consumer
Nucleus Genomics	WGS (short-read)	30x	$399 (kit)	Optional $39/yr membership	Genome-wide (all callable variants; not fixed)	400 high-effect variants + PRS model	Buccal swab	29 days	Direct-to-consumer
DNA Complete	WGS (short-read)	1x, 30x, 100x	$395 (1x), $695 (30x), $2,495 (100x)	$95 (1x), $195 (30x), $495 (100x)	Genome-wide (all callable variants; not fixed)	1,929	Buccal swab	12–20 weeks	Direct-to-consumer
Allelica	PRS (microarray or low-coverage WGS inputs)	N/A (array)	Not publicly listed	N/A	3,741,053 SNPs	135,590	Saliva	22 days	Physician-ordered
MyOme	WGS (short-read, reinterpreted)	30x	Not publicly listed	N/A	Genome-wide (all callable variants)	N/A (No ACMG-approved variants)	Buccal swab	29 days	Physician-ordered
Color Health	Targeted NGS panel (30 genes) + select SNPs	100x	$299 (Free for All of Us participants)	N/A	30 genes + limited GWAS SNPs	N/A (No ACMG-approved variants)	Saliva	11 days	Direct-to-consumer

* All data is subject to change. Data shown is current as of September 9, 2025.

learn ends up saving me tens of thousands of dollars in future medical bills and/or maybe a decade or two of life? That's about as good of a return on investment as I could ever dream of. So, I dove in.

I ended up doing five tests: three direct-to-consumer (DTC) and two clinician-initiated. For the DTC tests, I ordered WGS tests from Nucleus Genomics and DNA Complete (Nebula Genomics), and a genetic test that deeply sequences a gene panel from Color Health. To balance things out, I got physician-initiated tests from Allelica and MyOme, which use an advanced SNP array akin to 23andMe and a deeply sequenced set of genes like Color Health, respectively **(Table 1)**. In the first article of this three-part series, I interviewed the CEOs of several genetic testing companies to get a sense of how the reduction in whole genome sequencing cost enables more complex DNA analysis than the SNP arrays of 23andMe and the implications for personalized medicine.

What follows is the second installment of my personal genomics series, in which I discuss what I learned about the state of personal genomics by taking these tests.

Unwrapping the results

Two categories emerged from my genome analysis. Some of the results were inconclusive—these tests came up empty. That was the case for Color Health's test, which uses 59 genes selected for their clinical actionability in accordance with the criteria set out by the American College of Medical Genetics and Genomics (ACMG) **(Box 1)**. When I digitally opened the results of this test, there was a single sentence with a big, bold font: *We did not find anything significant for your health in the genes we looked at.*

A similar story unfolded with the findings from MyOme's Personal Genome Proactive Health Report, one of the clinician-initiated tests. This report is based on 81 genes that also follow ACMG criteria and provide clinically actionable results for diseases like cancer, heart disease, metabolic disorders, and more. The MyOme result read: *No pathogenic variants were found.* So, the two tests that utilized gene panels limited to clinically actionable results returned negative results. As one genetic counselor explained to me, when it comes to genetic testing, having no findings is preferable—no news is the best news.

The other results were at the completely opposite end of the excitement spectrum, bordering on nerve-racking. What united the three tests that fall in this camp—Nucleus Genomics, DNA Complete (Nebula Genomics), and Allelica—is that they report PRS in addition to analyzing the pathogenic variants analyzed by the Color Health and MyOme tests. All three tests were negative for pathogenic variants for monogenic diseases, but the PRS results showed increased (and decreased) risk for several indications.

The Nucleus Genomics test showed five indications with increased risk. Interestingly, three of the five are tied to health

(continued on next page)

Box 1. The ACMG on PRS

When it comes to setting standards for genetic testing, the American College of Medical Genetics and Genomics (ACMG) plays a leading role, especially after the Center for Disease Control and Prevention's Office of Public Health Genomics, which supported genetic testing for the predisposition to hereditary breast and ovarian cancer syndrome, Lynch syndrome, and familial hypercholesterolemia was closed in April 2025. Susan Klugman, MD, director of the division of reproductive and medical genetics and vice chair for genetics and precision medicine at Montefiore Einstein, emphasized that ACMG's recommendations are grounded in evidence and clinical utility, especially for patients with rare or unexplained conditions. "Our evidence-based guideline recommends that exome sequencing/genome sequencing be considered a first- or second-tier test for patients with congenital anomalies, developmental delay, or intellectual disability," Klugman told *Inside Precision Medicine*. The goal is to give patients and families answers when more targeted approaches, like single-gene testing, fall short.

Susan Klugman, MD
Immediate Past President of ACMG

PRS, by contrast, remains outside ACMG's list of recommended first-line testing. While PRS has drawn attention for its potential to predict risk for common conditions such as diabetes or heart disease, Klugman stressed that the technology should not be confused with diagnostic testing. "Regarding PRS, our point is to consider outlines for dos and don'ts, first stating that PRS test results do not provide a diagnosis [and that] instead, they provide a statistical prediction of increased clinical risk, which I believe is critical for patients and clinicians to understand." That distinction has important consequences for how PRS is used in practice, especially in reproductive contexts. "At this time, ACMG feels there needs to be more research to support PRS embryo testing," Klugman said, underscoring the gap between early promise and clinical readiness.

Klugman pointed to the ethical, moral, and social questions that remain unsettled. "We need more research! Many ethical and moral issues here that are just beginning to be uncovered and addressed," she said. "Equity is a large issue here. In addition, as mentioned in the PRS statement, IVF must be performed in order to do PRS testing on embryos. IVF is not without risk and of course not available to all because of costs." For now, ACMG's stance reflects a balance between innovation and caution: sequencing-based tests with proven utility are prioritized for patients who stand to benefit most, while PRS remains a promising but unproven tool requiring more evidence and careful consideration.

(continued from previous page)

issues that have shaped my life: asthma, depression, and alcohol dependency. I have an inhaler because I was diagnosed with asthma as a kid; I take antidepressants because I was diagnosed with major depressive disorder in my twenties; and I stopped drinking alcohol five years ago because I was diagnosed with substance use disorder. The fourth was chronic pain, which I have never looked into, and the fifth was the one indication that I have been most curious and fearful about: Alzheimer's disease. Dementia has manifested in two of my grandparents in their 80s, and though they have never been diagnosed with Alzheimer's, I've always had my suspicions. But now my suspicions have gone from a hunch to being rooted in DNA analysis **(Box 2)**.

Heidi L. Rehm, PhD, FACMG
Professor of Pathology
Massachusetts General Hospital and the Broad Institute of MIT and Harvard

Did I want to know that?

A genomic medicine trailblazer with decades of experience and the hats to prove it, Heidi Rehm, PhD, professor of pathology at Harvard Medical School, chief genomics officer at Massachusetts General Hospital, and member of the Broad Institute of MIT and Harvard, strictly focuses on providing well-defined clinical variants for use in precision medicine. "The biggest challenge is that being aware of your slightly elevated risk for something does not always lead to taking different actions," Rehm told *Inside Precision Medicine*. "There are a few situations where you might act differently due to a heightened risk, but there isn't much guidance on what to do when a disease's PRS is elevated. Most PRS are not clinically useful today, which is why I don't focus heavily on it."

When it comes to genetic screening, Rehm favors testing patients with rare diseases and screening for genetic diseases that provide risk information on more highly penetrant genetic diseases and, thus, clinically actionable information. That's the same camp that both the Color Health and MyOme fall into by adhering to the ACMG gene list.

One of the many projects where Rehm is a key contributor is the National Institute of Health's ClinGen (Clinical Genome Resource), a knowledge base that defines the clinical relevance of genes and variants for use in precision medicine and research. ClinGen's main focus today is on curating gene-disease relationships and variant pathogenicity for monogenic disorders, and determining their clinical actionability. Rehm said, "We're providing people information about genetic risk that's often very high that leads them to make decisions to improve their health—for example, removing their breast tissue or ovaries based on very high risk for hereditary breast or ovarian cancer."

Given that PRS is still in very early stages of being understood for clinical utility, the abundance of DTC testing that uses PRS to report risk for complex diseases worries Rehm because it might detract from other more clinically useful genetic testing. Rehm said, "I wonder if there is a risk of undermining the effective aspects of genetics due to people's primary focus on complex traits, which often do not provide actionable predictions and may diminish the significant value of genetic testing for highly penetrant disorders."

Table 2. The DTC Report Card

Company	Web UX	Report Clarity	Clinical Utility	Overall	Award
Allelica	◑●●●●	●●●◑●	●●●◑●	●●◑●●	Best Report
Color Health	●●●●●	●●●●●	●●●●●	●●●●●	Best Overall
DNA Complete	●●●●●	●◑●●●	◑●●●●	●●●●●	Best "Under-The-Hood" Access
MyOme	●●●●●	●●●●●	●●●●●	●●●●●	Best Clinician-Initiated
Nucleus Genomics	●●●●●	●●●●●	◑●●●●	●●●◑●	Best DTC WGS

Most clinicians aren't ready

Cassie Hajek, MD, medical director at Helix, has dedicated years of research to understanding the role of PRS in diseases such as coronary artery disease (CAD) and breast cancer. She thinks it's highly unlikely for there to be uniform utility in reporting PRS to patients across the board.

Cassie Hajek, MD
Medical Director
Helix

Hajek told *Inside Precision Medicine*, "Since I've previously worked with cardiologists and breast health specialists, would I return a PRS for coronary artery disease or breast cancer? The resounding answer is yes. In those cases, we would know what to do. If you have someone with a very high PRS for CAD, you might consider starting a statin sooner or getting a calcium score to see what the coronary arteries look like. So, there are actions you can take. For breast health, we considered using it to help identify patients at high risk from the general population who might not have been identified otherwise, because it's so difficult in a clinical visit in primary care, which I did for a number of years."

Even though not everyone lives and breathes PRS like Hajek, she doesn't think the results from WGS tests are useless. Hajek has seen PRS work where pathogenic variants came up empty. "Sometimes, gathering a complete family history takes time and may require multiple visits, especially if you do not have enough dedicated time to compile the information that indicates you should be referred to a high-risk breast clinic," said Hajek. "Also, only about 50% of people who end up with breast cancer are going to have that very descriptive family history that says, 'You're at risk.' It's not a slam dunk if you don't have that family history. So, that PRS actually adds some additional value."

After showing her my results from the DTC WGS tests, Hayek proposed that I could use my results to re-evaluate my approach

Box 2. Beyond *APOE4*

In April 2017, the FDA authorized the direct-to-consumer marketing of 23andMe's Genetic Health Risk (GHR) report for late-onset Alzheimer's disease. This report assesses the single nucleotide polymorphism (SNP) rs429358, which is the ε4 variant of the *APOE* gene. The Nucleus Genomics test looked at 400 high-effect variants in genes like *APP*, *PSEN1*, and *PSEN2* and then provided a risk score using a PRS model based on 33 common genetic variants that is heavily weighted by several *APOE* variants, including rs429358. The DNA Complete report combined 1,929 variants (each of which can be investigated by the user) across 20 genes, including *APOE*, which tested for rs429358 and six other variants.

to each condition; however, there are no pathways or guidelines that incorporate those scores into care, so it's really being used in one-offs. As she was telling me all this, I could see her wheels turning, and sure enough, when the call came to a close, she expressed that she was kicking herself for not yet having done any of these DTC WGS and would likely be ordering one soon.

> "Your genome never sits still, this isn't a one-time result; it's a future-focused service that keeps unlocking new insights for the rest of your life."

Dynamic DNA data

Although our DNA remains mostly unchanged throughout our lives, our current biological knowledge of disease-causing genes and variants, as well as the models used to calculate PRS from a person's genome, is still in its infancy and subject to frequent updates. For gene lists like the one from ACMG, there are often annual updates; for some DTC platforms, there are constant model updates that can change an individual's risk scores.

Brandon Colby, MD
Founder and CEO
Sequencing.com

Brandon Colby, MD, who was born with a rare genetic disease called epidermolysis bullosa simplex, knows firsthand the impact of what is written in our DNA and believes that the era of DNA "tests" is essentially over and will be replaced with lifelong genomic intelligence. To give people the ability to learn from their genomes, Colby founded Sequencing Inc., which offers a DTC kit as well as a platform for uploading WGS data from other tests that can be reanalyzed based on monthly updates.

Colby told *Inside Precision Medicine*, "Your genome never sits still, this isn't a one-time result; it's a future-focused service that keeps unlocking new insights for the rest of your life, helping you make better decisions, live healthier, and extend your longevity. Instead of outdated reports or limited data from consumer tests, we deliver the most comprehensive dataset ever created—your entire genome. You only need to be sequenced once, and with that single, definitive dataset, our platform becomes a permanent health resource that grows in value as science advances."

I have only just gotten my data onto Sequencing.com, so I cannot speak to their updating. What I can speak to is that I get frequent emails from Nucleus Genomics with the subject line "We've updated your risk profile." In addition to the updates, the email reads, "We are always working to fine-tune our algorithms to give you the most personalized and accurate results possible. As a Nucleus member, you benefit from these advances through updated reports that better reflect your risk." (I have yet to get an update from DNA Complete.)

Was it worth it?

At the end of the day, my conclusion as to what I can do with these tests—nothing—was clear for two different reasons: the gene panel-based tests came up empty and the DTC tests both came with a disclaimer that said "this is not medical advice" or "this is not a diagnostic." That said, Alzheimer's has been on my mind since I received these results. Every slip of memory gets me a little bit more anxious than before. But there's not much I can do about it. So, was it worth it?

In my opinion, the clinician-initiated testing focused on ACMG-backed pathogenic variants is worth it regardless of who you are. Not everyone's test will come back negative and that result can be life altering. Considering my experience in genetics and genomics research, along with access to experts for analyzing my results, I found the DTC testing to be worthwhile. But not everyone has the knowledge base or access to domain experts who can go beyond what genetic counselors can share. The clinician-initiated test from Allelica, which reported both pathogenic variants and PRS, lies somewhere in the middle of those two extremes, given that there isn't clear-cut clinical guidance for some of the results.

In part III of this series, I'll focus on where personal genomics is headed, exploring the integration of omics, the role of insurance, and the resurrection of 23andMe 2.0. ■

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

Meeting in the Middle: A Collaborative Approach to Tackling Rare Diseases

by Susan Kreimer

R_Stone / iStock / Getty Images Plus

The road to an ultra-rare disease diagnosis can take a long, arduous and costly path, with scores of doctors and tests along the way. When patients finally find the culprit behind their misery, all too often, there is no effective treatment—and research moves slowly due to the limited number of patients who can enroll in clinical trials.

In Tilyn Sincere Richards's situation, the route was riddled with plenty of obstacles to identifying the cause of his developmental impairments. By age 2, Tilyn army-crawled sideways and fell frequently. However, it wasn't until other people began pointing out these strange movements that his parents realized this could be serious. They started searching for answers.

Initially, a doctor dismissed their concerns, insisting Tilyn wasn't in pain. By minimizing the complications, the doctor delayed diagnosis and treatment. "It took several more years before we were finally referred to a neurologist who ordered genetic testing," said Tilyn's mother, Miesha Thomas, a former horse dentist who lives in Moore, Oklahoma, and devotes time to advocacy for her now 6-year-old son's extremely rare genetic condition.

"Tilyn's journey has been a long road to answers," she said. "For years, I knew something wasn't right, but early in 2024, he was misdiagnosed with cerebral palsy. Just a few months later, after my own diagnosis with ankylosing spondylitis [an inflammatory type of arthritis] in May, we pushed for more answers. In July 2024, we finally received the correct diagnosis of *TUBB4A* leukodystrophy, or H-ABC." H-ABC (Hypomyelination with Atrophy of the Basal Ganglia and Cerebellum) is a rare, progressive genetic disorder caused by a single mutation in the *TUBB4A* gene. "Hearing those words was life-changing. But at the same time," she added, "it gave us the clarity we needed to move forward."

Like his mother, Tilyn was diagnosed with ankylosing spondylitis, which causes long-term pain and stiffness in the spine, often starting in the lower back and hips. He also suffers from juvenile arthritis and hip displacement. "There are so many domino effects that come with this," Thomas said. Overall, she added, "We've faced many challenges. Tilyn now uses leg braces day and night, a walker, wheelchair, bath chair, and he's undergone G tube [feeding tube] surgery following the discovery of a malrotation of his small intestine. It has been a whirlwind year of specialists, hospital visits, and constant adjustments to daily life."

H-ABC is Tilyn's greatest challenge. The ultra-rare disease, which affects roughly 200 children in the world, targets the nervous system's white matter. In particular, this genetic variant leads to hypomyelination—insufficient myelin formation—and atrophy of the basal ganglia and cerebellum. Basal ganglia help control muscle movements but also play a role in learning, solving problems, and processing emotions, while the cerebellum processes input from other areas of the brain, spinal cord, and sensory receptors to provide precise timing for smooth and coordinated movements. Damage to these areas of the brain causes motor delays, stiffness, involuntary movements, speech and swallowing difficulties, and cognitive impairment. A diagnosis of H-ABC involves brain imaging with MRI and genetic testing to identify the specific mutation. There is no

Courtesy of Miesha Thomas
Tilyn Sincere Richards

cure, but supportive care and therapies to palliate discomfort, and research into novel treatments offer hope for managing symptoms and improving quality of life.

Candidate drug designed to treat H-ABC

SynaptixBio, founded in 2021 and based in Oxford, U.K., is aiming to bring to market a therapeutic to treat H-ABC, the most severe form of *TUBB4A* leukodystrophy. It's the only company licensed to commercialize a treatment.

The company has designed an antisense oligonucleotide (ASO) specifically to treat H-ABC. "This is classified as an ultra-rare disease, so there is a very limited patient population, making design of the clinical trial a major hurdle," said Dan Williams, PhD, CEO and co-founder of SynaptixBio. "It's very difficult to say how many patients there are, but through the H-ABC charities (in the U.K. and U.S.) formed to support patients and families, we have some idea of the likely numbers involved." Every year, it's estimated that 18,000 babies are born with a leukodystrophy, of which about 1,650 are *TUBB4A*-related, according to SynaptixBio's website.

"We are totally focused right now on raising investment to support us through clinical trials of our candidate drug, which has orphan drug designation from the U.S.," said Williams, who earned his doctorate in protein translation from Dundee University in Scotland. "It also qualifies for the FDA's rare disease priority review voucher (PRV)."

Williams and his three co-founders—two of whom are also scientists—are excited that SynaptixBio has identified its lead development candidate that they expect to put through investigational new drug/clinical trial application enabling studies. "As a company, we are currently testing the molecule we have developed in the lab. Tests are *in vivo* to confirm biodistribution, pharmacokinetics, pharmacodynamics, and tolerability," Williams said, explaining that "*TUBB4A* leukodystrophy is a monogenic disease involving a mutation in the *TUBB4A* gene, resulting in a gain of function toxicity. We are targeting that mutation with gene silencing technology at the mRNA level to alleviate its toxic effects." The results within animal models, he noted, are "very good."

Hope for a devastating condition

Among the researchers seeking to improve the quality of life and lifespan of individuals living with leukodystrophies is Adeline L. Vanderver, MD, program director of the Leukodystrophy Center of Excellence at the Children's Hospital of Philadelphia (CHOP), which has entered into a research agreement with SynaptixBio.

"*TUBB4A* LD (leukodystrophy) is one of the most common hypomyelinating leukodystrophies," Vanderver said. "It can present in early infancy, childhood, or adulthood with disease of varying severity. Most people develop problems primarily with motor skills, which can be severe enough to prevent walking and swallowing."

ASOs have been designed to target a number of conditions like Duchenne muscular dystrophy and spinal muscular atrophy. ASOs are a form of "gene silencing" technology, wherein the mutated gene is stopped from making its associated toxic protein.

"The *TUBB4A* gene encodes a protein that makes microtubules, which are essential for moving proteins in the cell, particularly oligodendrocytes and neurons," Vanderver explained. "Because there are many possible proteins that can help make microtubules, removing the *TUBB4A* protein is well tolerated, and in models of the disease this has been shown to improve function. We hope that antisense technology can help us do the same in affected people and improve their neurologic function."

Among the patients who could benefit from such a discovery is Anthony Pasqualone's 6-year-old son, Luca, who received a diagnosis of H-ABC a year and a half ago at the Vanderbilt University Medical Center in Nashville, where the family lives. Since then, Luca also has seen doctors at the Children's Hospital of Atlanta, Rady Children's Hospital San Diego and Rush University Medical Center in Chicago.

Courtesy of Laura Moll

Anthony and Christine Pasqualone with sons Luca and Isaac.

Pasqualone, a creative director at an advertising agency, initially became suspicious that something was wrong when his son started "missing mile markers," such as not walking when most babies begin walking. At first, the boy's pediatrician recommended physical therapy. About nine months later, it became clear that additional testing would be the next best course of action.

"An MRI showed there was some concern over white matter and the cerebellum being smaller than usual for a child that age," Pasqualone said. "A smaller cerebellum is one of the characteristics of the disease. The MRI led them to strongly suspect it could be leukodystrophy, and genetic testing confirmed it was the *TUBB4A* variant."

Now, Luca is being seen at Rush University Medical Center, which partners with the n-Lorem Foundation, a non-profit organization that creates ASOs for patients with nano-rare diseases caused by a single gene mutation. "Being a parent of a child with a nano-rare disease can be a lonely and dark road to travel with uncertainty at every turn," Pasqualone said. "Nano-rare" refers to genetic conditions affecting only 1 to 30 patients worldwide, marked by unique, disease-causing mutations for which there are typically no existing treatments.

For parents with a child in this predicament, "the hope is [that] a drug could a) stop regression before it starts; and b) at some point help repair the *TUBB4A* gene or symptoms," he said. "It's a relief to know there are people aware and

(continued on next page)

(continued from previous page)

searching for a cure. That said, as a parent knowing your child's disease is going to get worse, you are constantly holding your breath and praying for breakthroughs to happen sooner [rather] than later.

"Even in our case with n-Lorem, although they generously provide the drug at no cost, some well-known hospitals either would not—or could not—administer it to Luca without requiring us to cover significant out-of-pocket expenses, sometimes reaching into the six figures. Several other families are currently facing the same dilemma," said Pasqualone.

Casey McPherson and daughter Rose at the annual To Cure A Rose Foundation.

He added that, "Even with the drug cost covered, families are still left to navigate the complex process of securing administration, which often falls into a gray area with insurance companies, since the treatment is considered experimental or part of a trial."

Casey McPherson is also hoping for a breakthrough. The goal: to develop a therapeutic for a very rare genetic, neurodevelopmental disease that affects his 9-year-old daughter, Rose, and other individuals. He's the CEO and co-founder of AlphaRose Therapeutics in Austin, Texas, where he lives. "We need a company that's doing this at some sort of scale," McPherson said about his precision medicine endeavor. AlphaRose's team consists of scientists, biotech professionals, and parents working to discover genetic technologies that will transform care for people with ultra-rare diseases.

Research identifies a new genetic disorder

Rose has a variant in the heterogeneous nuclear ribonucleoprotein H2 (*HNRNPH2*) gene, which causes developmental delay, intellectual disability, low muscle tone, and seizures in females. This variant was first identified by Jennifer M. Bain, MD, PhD, a Columbia University physician-scientist who specializing in pediatric neurology, and her then-colleague Wendy Chung, MD, PhD, who became chair of pediatrics at Harvard Medical School and Boston Children's Hospital. They published their findings in the *American Journal of Human Genetics* in September 2016. The goal was "to identify, understand, treat, and ultimately cure those impacted by *HNRNPH2* mutations," according to the Yellow Brick Road Project (YBRP), a charitable foundation that funds research into these mutations.

In 2016, Bain identified six girls with variants in the *HNRNPH2* gene. Each girl presented with developmental delay or intellectual disability, along with atypical muscle tone. Many of these children also suffered from seizures and conditions such as anxiety and autism spectrum disorder. In addition, Bain's team found variants in *HNRNPH2* that appeared to affect other organ systems aside from the brain. For example, the girls had abnormal growth, gastroesophageal reflux disorder, scoliosis and other skeletal conditions, heart problems, and atypical facial features.

Initially, "we thought that boys could not survive because we had not found them," Bain told *Inside Precision Medicine* in explaining why her research originally only involved girls. Later, the researchers found boys with variants in the *HNRNPH2* gene, but there are fewer boys than girls because the gene is located on the X-chromosome.

A subsequent paper, published in *Neurology Genetics* in February 2021, expanded the clinical characterization of the *HNRNPH2*-related neurodevelopmental disorder to include 33 individuals, ages 2 to 38, both females and males, with 11 different genetic variants. "I am working on the next one with 130 individuals," Bain said.

Trish Flanagan's daughter, Morgan, was 4 years old at the time of her *HNRNPH2* diagnosis in February 2016. On a very cold day in January 2017, Flanagan and the parents of three other girls arrived for an in-person "meeting of the minds" with Bain and Chung at Columbia University Irving Medical Center. Two of the families were from New York; the other two traveled from Israel and Brazil.

"Since receiving our daughter's diagnosis, it has been a series of many pieces coming together to create the path to a treatment," said Flanagan, who lives in New Rochelle, N.Y., and works full time as an early childhood educator. "We've literally built

Courtesy of Yellow Brick Road Project

John and Trish Flanagan with daughter Morgan and son Shane.

a road. The doctors and a few families began a synergistic collaboration, and the YBRP was born." She's the co-founder, director, and president of this foundation, which has connected the family members of more than 200 patients with *HNRNPH2* in 38 countries. It received non-profit status in late 2016 and began fundraising in February 2017. "This is a grass-roots effort," Flanagan said. "Everybody started knocking on doors, sending emails to try to gain some traction."

Courtesy of the Sloan family

Michele and Britt Sloan with daughter Elouise.

Targeting a specialized market

Meanwhile, McPherson said he expects the company's lead product, rosiphersen, to target a specialized market for patients with *HNRNPH2*-related neurodevelopmental conditions. Although the drug is intended for a niche population, it fits in with the overall pediatric genetic treatment market, which he believes is valued at $51 billion.

"These genetic treatments can rescue function for a lot of these diseases that we're seeing," he said, explaining that "we're fixing the underlying cause of the problems instead of treating the symptoms like many traditional small molecule programs have done in the past."

Michele Sloan, who lives in Rockville, Maryland, is also hoping to make a difference in the lives of people with an ultra-rare disease, including her 20-year-old daughter Elouise, who is afflicted by the same disease as Tilyn Sincere Richards and Luca Pasqualone. Aside from Sloan's job in real estate finance, she established the Foundation to Fight H-ABC in 2015, shortly after Elouise's diagnosis.

At first, Elouise's development appeared normal, but around age 3, she began to pull up her right arm when running. An MRI of her brain revealed hypomyelination and an undersized cerebellum and basal ganglia. "That was a telltale sign of some sort of a condition," Sloan told *Inside Precision Medicine*. However, back then—in 2008—the *TUBB4A* genetic variant hadn't been identified yet. "We had every test under the sun," she said.

Eventually, Elouise was diagnosed with H-ABC, which ultimately robbed her of the ability to stand, walk, bathe, eat, or dress herself. She can no longer speak clearly. In addition, Elouise suffers from dystonia, which causes uncontrolled muscle movement in her arms and neck.

"Watching your own child deteriorate right before your eyes is a pain no parent should ever have to experience," Sloan wrote on her LinkedIn profile. "But together, we can make a difference in the lives of families across the globe by giving children with H-ABC-related leukodystrophy a fighting chance."

When public policy impedes progress

As if the challenges of living with a rare disease weren't enough of a heartache for affected children and their parents, public policy can stand in the way of making strides in breakthrough treatments, Sloan said. "We, [and] numerous other advocates, are urging Congress to re-approve the FDA's PRV, which has been delayed since December due to other priorities."

This voucher provides tax incentives for investors in drug development and expedites review by the FDA. Cuts in research funding to the National Institutes of Health and changes in the FDA's leadership and oversight also have a detrimental effect on drug development. "All of this and general lack of attention around rare diseases, despite the collective 30 million impacted in the U.S., makes the process very challenging, causing delays and placing lives in jeopardy," Sloan said.

Even before the recent changes, in Bain's experience, federal funding for rare diseases was very challenging to obtain. She noted that pharmaceutical companies are seldom interested in developing treatments for rare conditions because the limited pool of patients makes for an unprofitable and risky venture. "The foundations are picking up the dime that the government isn't willing to do," Bain said. "And we need fierce advocates on Capitol Hill to keep pushing rare disease forward. One in 10 people in the U.S. and worldwide has a rare disease. Rare diseases collectively are very common." Overall, she added, there are more than 7,000 rare diseases.

There are also many barriers to surmount for parents trying to gain access to genetic testing for their children. "It is more and more widely available but some insurance doesn't cover the expense of the test," Flanagan noted. "Sometimes pediatricians don't recommend more than simply treating the symptoms of developmental delay through early intervention. Sometimes families don't know that a genetic diagnosis may very well illuminate other risks for their challenged child, in addition to helping them find a community and even treatments. We even made a video to underscore the importance called, *Genetic Diagnosis Matters*."

Tilyn's mother said she became more familiar with her son's genetic mutation through Sloan's foundation, which connected the family with the United Leukodystrophy Foundation. At that foundation's conference, they first heard about SynaptixBio's candidate drug. So, despite challenges that often feel overwhelming, Thomas is optimistic about the future.

"We are still new to this world, but we're learning every day," she said, while acknowledging that "our journey has been long and exhausting, marked by misdiagnosis, years of doubt, and searching for answers. But through it all, we've learned to be resilient and persistent—because Tilyn deserves nothing less. Today, with the right diagnosis in hand and the knowledge we've gained through the Foundation to Fight H-ABC and the United Leukodystrophy Foundation, we are finally looking forward with hope. The possibility of drug trials like the one being developed by SynaptixBio means families like ours can begin to see a future where there are real options, real treatments, and real hope." ■

Susan Kreimer is a freelance medical writer in New York City.

entrePRECISIONeur

In Conversation with Gameto's Dina Radenkovic Turner

by Helen Albert Senior Editor

Any woman who has frozen her eggs or undergone in vitro fertilization (IVF) to try and get pregnant knows how challenging and time consuming the process can be. This is something Gameto's CEO and co-founder Dina Radenkovic Turner, MD, is trying to change.

The company's lead candidate treatment Fertilo is currently in Phase III trials in the U.S. and already has approval in several other countries. It aims to cut the time needed for ovarian stimulation and egg collection from two weeks to a few days by using engineered ovarian support cells to mature the eggs outside the body. In addition, the company plans to develop treatments for menopause and ovarian disease.

Gameto has raised a total of $127 million in a difficult funding climate, with Fertilo being the first induced pluripotent stem cell (iPSC)-derived therapy to reach late-stage clinical development in the U.S.

Radenkovic Turner became interested in ovarian health and extending female fertility while working as a researcher at the Buck Institute for Research on Aging in California. Originally from Serbia, she studied medicine and physiology at University College London. She worked as a research clinician in the U.K. for a few years at Kings College London before moving to the U.S. She joined SALT Bio Fund as a partner in New York in 2020 while also working part-time at the Buck Institute, before going on to found Gameto in 2021.

***Inside Precision Medicine* senior editor Helen Albert spoke to Radenkovic Turner about her inspirations, goals for Gameto, and her hopes for the future of women's reproductive health.**

Dina Radenkovic Turner, MD

Q: What inspired you to get into science and medicine?

Radenkovic Turner: I think growing up, I was always very passionate about science. I was much better at science than other subjects. I went to STEM competitions in mathematics, physics, biology, and chemistry. I also come from a medical family. My father was a professor of embryology, and my aunt was a doctor too. So there was a lot of interest there. In my teens, I was trying to decide which area to go into. For me, medicine was a mix of science, but also human impact. I felt that having that short loop of seeing how your work can change people's lives and still have human interaction was the perfect combination of my passion for science and my love for interacting and working with people, and seeing that positive impact. So that's when I decided that I'd like to study medicine, I think I was about 14 years old at the time.

Q: How did you make that jump between doing medicine and founding your own biotech?

Radenkovic Turner: I was born in South Serbia and then I moved to the U.K. Where I come from, a lot of these fields like bioengineering or biotech as an industry don't really exist. If

Fertilo, Gameto's iPSC-derived product made of young ovarian support cells (OSCs) is used in a laboratory setting to mature eggs outside the body.

you do anything healthcare-related, you are either a doctor or there's not much left. I got into medical school and around the second year I took part in a competition called the F-Factor, organized by the Founders Forum by Brent Hoberman. It was like the X-Factor for STEM. I had this idea for a gestational diabetes app and how it could fix everything I've seen in my placements in the NHS. I didn't know that world existed before. Since then, I felt that that's where I really belong. Even during my medical training, I was providing scientific diligence to certain venture funds and getting into this ecosystem. I just realized that I work better in this multitasking environment where I'm still doing science and affecting patients, but also doing a breadth of things involving business and operations and corporate and legal. It was still a big decision. Sometimes I do miss patient contact, but working in biotech, we actually do interact quite a lot with patients, and we see the positive impact we make.

Q: Can you tell me a bit more about the story behind Gameto?

Radenkovic Turner: I stopped practicing clinical medicine as I moved to the U.S., but I kept my research post at the Buck Institute for Research on Aging, which gave me an angle into ovarian aging that I became really obsessed with. Working at the cutting edge and seeing a lot of companies focused on extending healthspan, I felt that if we do nothing to address female reproductive span and the health of our ovaries, we spend two-thirds of our lives in infertility and one-half of our life in worse health post menopause. It's not just what menopause means for fertility, it's what it means for systemic health. Post-menopause women have a lot more health conditions than men. We live longer, but we have longer time in morbidity.

To launch Gameto, I joined forces with Martin Varsavsky, who is also a co-founder. He's a serial entrepreneur and has built five unicorns. He is founder and chairman of one of the largest fertility clinic networks in the U.S. We decided to form a women's health biotech that would address infertility, but also have a broader women's health journey, primarily focusing on menopause and the conditions that happen afterwards.

We found very interesting science being developed in George Church's lab at the Wyss Institute at Harvard Medical School and were able to influence the science through the sponsor research agreement we did with the lab. They were already working on doing cutting-edge research on induced pluripotent stem cell technology to make different human cells and there was a team that was potentially interested in making human eggs.

We really pivoted that work on not just building ovaries in a dish. I was thinking about my own egg-freezing, and I thought, "Wait, could we make these support cells? We're already making all of these ovarian cells, and if they do this *in vivo*, could they do that *in vitro*?" Then we don't need to drug the women systemically and cause all the unwanted effects, but can potentially do it outside of the body. We were fortunate and some of the team of founding scientists decided to leave academia and join the company because they felt that they wanted to see some of this science come to life.

Q: What exactly is Fertilo and how have the trials of your therapy progressed so far?

Fertilo is an induced pluripotent stem cell-derived cell line. We call them ovarian support cells. We've engineered them so that they essentially mimic what happens in a follicle right before ovulation. A normal IVF cycle hasn't really changed since 1978; women still inject hormones twice a day for two weeks. That causes a lot of adverse effects because hormones are dirty, they have receptors in all organs. They even cross-react with other receptors. A minority of women end up with severe medical complications.

With Fertilo, we grow these follicles a little bit inside of the body so that they're still easy to extract in the same retrieval procedure, which uses an ultrasound-guided needle through the vagina to both ovaries. But we can do the final step of maturation outside of the body. We tested this in multiple animal models initially. Then we went on to test it with humans. In our first wave of studies, we looked at what happens when you put human eggs with Fertilo. We've shown that they mature and that they are genetically and

(continued on next page)

(continued from previous page)

epigenetically normal, and they resemble the eggs as they come out of the outside of the body with IVF. We've also looked at embryos, both genetically and epigenetically, and then we followed the pregnancies. We have now had over 100 couples that have gone through the procedure. We have had five babies born so far with the technology, with about 20-ish pregnancies ongoing.

It's still early days. We're in Phase III right now in the U.S. but have certain clinical pilots as post-market studies or ongoing elsewhere. For example, we have pregnancies now in Australia where we are approved. So far, the results are at parity to standard of care IVF.

Q: Are there groups of women who can benefit more from Fertilo than others?

Radenkovic Turner: There may be some populations where it may be more effective, like women with polycystic ovary syndrome (PCOS). We're going to do a study just in severe PCOS to see if it could be more effective in that population because there's some signals, but we need a conclusive study to be able to claim that. There are a lot of other patient groups who could benefit from this, like egg donors and egg-freezing patients, patients at risk of certain cancers or with previous history of certain cancers. Finally, there are these groups of patients that have failed. There are only about three regimens of IVF right now that exist. You have couples that go through all of them, and they don't get anything. It's not going to solve all of the failures, but if the issue was with your ovarian biology, perhaps it could.

Q: One of the issues with IVF is the high financial costs associated with it. How will Fertilo compare with current therapies?

Radenkovic Turner: I can't comment yet on definitive pricing as we obviously don't have it yet, but it certainly won't be more expensive. I think the hormone injections are a very expensive part. They also lead to a lot of bloodwork and ultrasounds and monitoring. So that's the other difficulty. A lot of employers are actually now covering fertility treatments in the U.S.. Not small employers, but about a half of Fortune 500 companies. But then the women don't do it because they have to use 10 days of paid time off to do this procedure and need to do ultrasound and bloodwork and so forth. There is this additional step in the laboratory, but the reduction in physician time that's needed per patient, the reduction in monitoring and in medications needed allows a safe enough margin that we do expect this treatment to hopefully promote access.

Q: I understand you participated in one of the Gameto experiments. Can you tell me a bit more about that?

Radenkovic Turner: I participated in one of our studies in New York in 2022. We were not allowed to implant, but we were looking at embryo quality. I went through the stimulation, the retrieval process, and I donated my eggs for research. We made embryos, and we looked at the embryo quality genetically and epigenetically. With that data, we were then able to proceed to implantation in the next cohort. I wanted to witness the patient journey myself and really see if this was a better product. I think the summary was, it's still not a massage. You're going for an egg retrieval. I wouldn't recommend it to people as a well-being self-care activity. But it was something that I was able to integrate into my everyday life. I went on Friday for one ultrasound, I took Clomid for the weekend until Tuesday, then on Wednesday morning I was in the clinic for the retrieval. I was able to function. It was much easier. … Normally you have restrictions for about six weeks in terms of intercourse, exercise, and other things, because once you go through full stimulation, your ovaries are enlarged because you have a lot of follicles and then they could twist. It is quite disruptive. We've been seeing egg-freezing grow enormously in the U.K. and U.S., but it's sold to women as some treatment of empowerment. But the treatment itself is the same as what women were doing when they were completely desperate to have a baby as an end-stage infertility treatment. We've just rebranded the website and the messaging, but we haven't changed the product.

Q: What other candidate therapies are you developing?

Radenkovic Turner: Our menopause program, Ameno, is incredibly exciting because we use similar cell-based technology, but the idea is to address the loss of all of the hormones and other factors that are lost by the ovary that lead to some of these acute effects. Many women experience symptoms in the first two years of menopause. Later on, the reduction of these hormones causes things like osteoporosis, heart disease, as well as vaginal dryness, painful urination, and all sorts of things that people don't want to talk about, but they cause a lot of morbidity.

Last year we won a $10 million ARPA-H grant, which was very competitive. There were 1,700 applicants from universities and companies all across the world, even though it was funded by the U.S. government. With our additional Series C that we've also closed recently, we're hoping that we can bring the first asset from that program to the clinic. It's a vaginal ring that is similar to some of these estrogen-based rings that we already have on the market. But the difference here is that it can last longer. … It contains a full cocktail of what is lost during menopause—estrogen, progesterone, androgens as well.

Beyond that, we also have a bit more of a moonshot that is an implant that is currently being tested in animals, so it's a little bit earlier. Essentially it uses the cells themselves in microbeads that would be implanted, for example in the arm. Because it's the cells themselves, they're responsive to signals from the brain and would provide real-time hormone replacement. In animals, it's so far looking good, but we don't know if it will be fully translatable from animals to humans.

In the Deovo program, that's actually stem cell-derived ovaries in a dish. We know that a big reason why there wasn't too many great companies in the space was also because we didn't have good models to understand the female reproductive system. Mice and rats that we use in the lab today don't even menstruate and primates and sheep don't go through

menopause and infertility the way we do. We induce them into menopause or infertility, but for the vast majority of women, it's not an acute event. It's a gradual decline and loss of these follicles. With our ovaries in a dish, we have published that it beats previous mouse chimeric models, and that it replicates the female reproductive system better. It allows us to test any drug before you put it into clinical trials in women of childbearing age.

Q: How has the field of women's health changed over the last few years?

Radenkovic Turner: Well, I think it's trending in the right direction overall. What I really want to see in women's health is just honestly this becoming a biopharma category. We're talking about half the population and the largest pharma companies don't even have women's health divisions. There is increased awareness and more startups. There's also more women in positions of founders or investors. The science has advanced, and we discuss it more. Every administration in the U.S. has been trying to do something. With Jill Biden, she organized the ARPA-H program, and this administration has done enormous amounts for hormone replacement therapy and menopause.

I think it's getting better, but as you go from the seed to Series A, to a couple of million funding stage, things just dry down before you become a large company with a few hundred million market cap that has several programs in either clinical trials or approved. You need to have more pharma companies in this space. We already have so much on the consumer side in women's health. We don't need more of that. But I think what I'd like to see is more validated claims that have gone into trials.

Q: What's the best way to get more investors and more money in this field in your opinion?

Radenkovic Turner: Just by good exits. Ultimately, I think everybody cares about impact and so forth, but once they have to put in their own money … they need to think that they will make money. Nobody does it because they like you. Our Series C makes it easier for somebody at an earlier stage now to raise a round, for example. Investors want to see that there's collectively enough funding to bring something to market because they will only make money if the thing makes it in the long term. If you only have money for the seed stage, but you know that nobody will fund the Phase II or Phase III, it doesn't make sense to invest.

There are obviously other reasons too. Some funds say, "We don't have a woman on the company, suggesting that should be a prerequisite or suchlike." So there's an element of that sometimes, but we're seeing more diversification. Most people just want to do a good job, and they want to have a return for investors. If you convince them that it's good science and that it's likely going to work the total addressable market, [that] makes it really easy to sell.

Q: This is your first time running a company as CEO. How have you found the experience?

Radenkovic Turner: Ultimately, you can read a lot of books, you can have great mentors, but it can't totally prepare you. The summary is always, try to do the best you can, spending the least money, as fast as you can. Over time, you get better. For example, I'm definitely much better at recruiting and I'm much, much better at saying no. Previously, I was worried about not being sure. Now I'm confident it's a no, because I know it's a no.

In terms of the company, our big challenges were, honestly, the regulatory pathway. You always start with a little bit of a risk that even if you do your best job, things may not work out. But then the risk that we've had to navigate, was "Okay, how does this get approved?" Particularly with Fertilo, because it's a cell therapy in a dish. It's unusual. Legally, it meets the definition of a device. It's not a drug product like the hormone injections, but it's living cells, so that was very hard.

We were the first induced pluripotent stem cell Phase III trial cleared by the FDA. Big pharma companies were reaching out to us and saying things like "What does the FDA think is the Phase III GMP (good manufacturing practice)?" They set the precedent with us. It took a bit longer to initiate this trial because we had to go through all of these screens on the manufacturing side. Now, obviously, that's a huge asset for us because it's massive defensibility in addition to all of the patents and biologic exclusivity. We also navigated it with different regulators across the world. That's why we have clearances in Japan, in Singapore, in India, in Australia for Fertilo and now we have a designation in Europe as well, which is a step towards approval.

Q: Is there anything you'd do differently if you could start the process again?

Radenkovic Turner: Oh, I'm sure. I mean, there's lots of things in terms of hiring paths, definitely improving efficiency in different areas. In startups, it's hard because you often cannot hire, especially in the early stages, the best expert for the field. So you have to find somebody who can become that expert with a little bit of advice from experts, so you can still afford them. You have to spot it early.

But I think that's all part of the growth. As a CEO, I always have to think about the future. I mostly worry about future problems. I mean, people always say, "Oh, are you celebrating this milestone?" and I say, "No, I'm already stressed about the next problems that have not yet started!"

I think timing is key. You have to be as fast as you possibly can. Essentially, death is always chasing us, so I always ask. "What are we doing today to escape it? What value are we creating?" ■

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

COMPANY INDEX

ADVERTISER INDEX

GO DIGITAL

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

TRY THE NEW DIGITAL EDITION

INSIDE PRECISION MEDICINE

labcorp | Oncology

Flexible solutions that meet *your lab's* workflow

Your Lab, Our Tests

FDA-authorized NGS kitted solutions

Your Tests, Our Lab

Comprehensive oncology tests across the cancer care continuum

VISIT LABCORP AT AMP

Your partners in flexible, scalable oncology testing.

BOOTH 713

Scan the QR code to meet the team