INSIDE PRECISION MEDICINE

AUGUST 2025

The Multi-Omics Revolution: Unlocking Biology's Next Frontier

Pathology’s AI Leap

Gaining on Glioma

5 Microbiome Startups Following Their Gut

PGx Education—Empowering Precision Prescribing

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. Experience the transformative power of a streamlined workflow.

Gain Deeper Insights

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

INSIDE
PRECISION
MEDICINE

Founder and Chairwoman **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, Laura Cowen, 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: paitoonpati / iStock / Getty Images Plus

Editor's Note

"It is not the years in your life but the life in your years."
—Abraham Lincoln

It's an age-old dream—not just to live longer, but to live better, for longer. To see 80, 90, even 100, not as a frail, twilight existence, but as a vibrant chapter filled with purpose, activity, and acuity. For too long, that's felt like science fiction, relegated to the wishful thinking of futurists and the lucrative promises of snake oil salesmen. But I've come to realize something fundamental has shifted. We're now standing on the precipice of a genuine revolution in human longevity and healthspan, driven by breakthroughs that are anything but fantastical. They're rooted in rigorous research and evidence, and an audacious new way of looking at our own biology.

And what's driving this seismic shift? Well, if you've been paying attention to the signals we're picking up, it's a convergence of forces that Eric Topol, MD, so eloquently lays out in his groundbreaking book, "Super Agers." He frames it perfectly: a multi-faceted assault on aging's insidious creep, encompassing everything from a turbocharged approach to lifestyle (moving beyond the obvious to the nuanced impacts of social determinants like isolation) to the astonishing power of AI, the deep dive into cellular biology, and the transformative potential of vaccines, gene editing, and Immunotherapies.

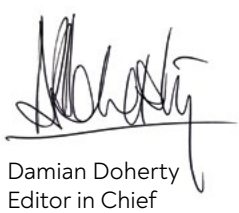
At the very heart of this new paradigm lies precision medicine. For years, it's been the rallying cry, but now, it's truly getting its teeth. We're moving away from the cookie cutter approach to therapies and prevention strategies tailored to the unique tapestry of your biology. And you can't get that level of personalization without multi-omics.

You can't truly understand the dynamic, living system by looking at just one piece of the puzzle. We need the blueprint, the live action of the proteins, the metabolic aftermath, and the epigenetic orchestration, all at once, in every single cell. It's the only logical path to genuinely decoding health and disease.

This holistic view is allowing us to spot the earliest whispers of trouble, to understand why certain individuals age more gracefully than others, and to design interventions—from targeted lifestyle shifts to revolutionary GLP-1 drugs and beyond—that are incredibly precise. These aren't just treatments for symptoms; they are interventions designed to recalibrate our fundamental biology.

Naturally, the road ahead isn't without its challenges. The glaring issues of healthcare funding, the insidious spread of misinformation, and the risk of reckless decision-making (whether political or commercial) threaten to derail even the most profound scientific advances. And the price tag of some of these innovations raises critical questions about equity and access. How do we democratize these breakthroughs so they truly extend healthspan for all, not just the privileged few? That's the moral imperative staring us in the face.

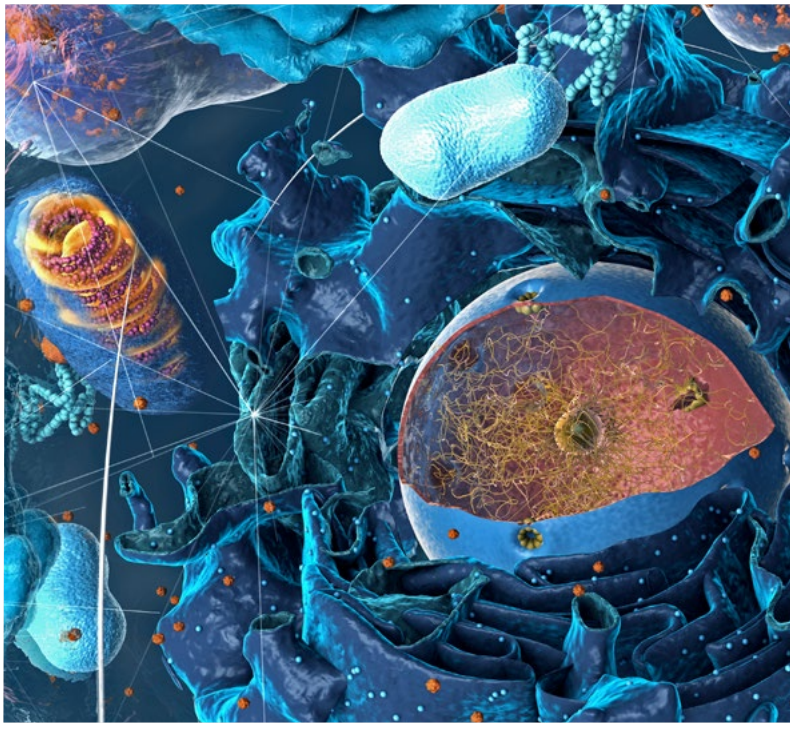
But despite these hurdles, the momentum is undeniable. We are in an era where the audacity of extending human healthspan is no longer a fringe idea but a scientifically grounded mission. The tools of precision medicine, powered by multi-omics and AI, are beginning to reveal how we can not only live longer but live better. And that, is a story worth paying attention to.



Damian Doherty
Editor in Chief

INSIDE PRECISION MEDICINE

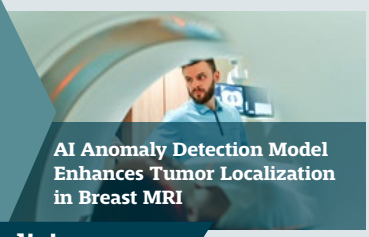
Contents



Features

View The Latest Online

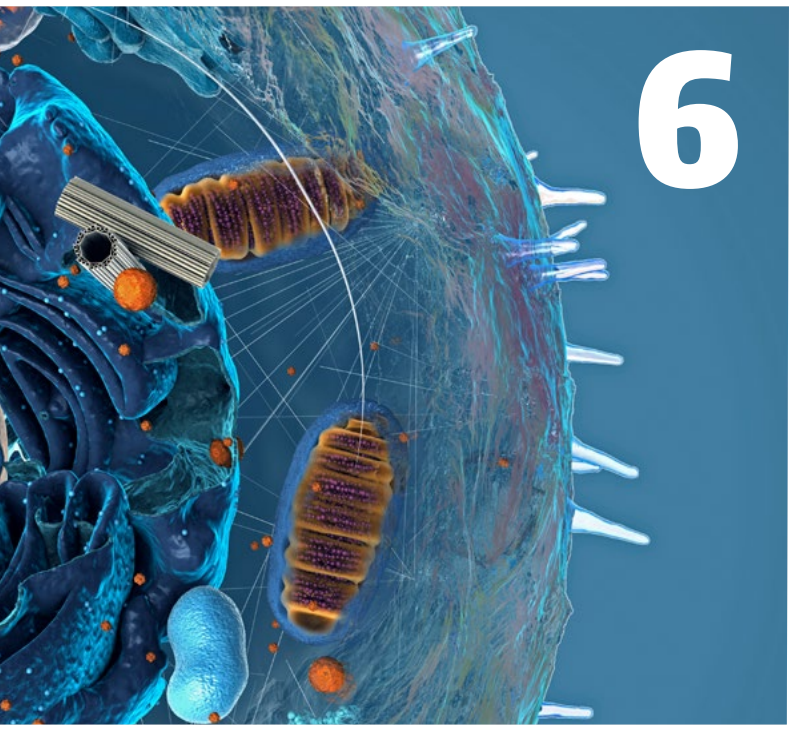
www.insideprecisionmedicine.com



AI Anomaly Detection Model Enhances Tumor Localization in Breast MRI

Take II: Off-the-Shelf CAR T Shines in Relapsed/Refractory Lymphoma Patients

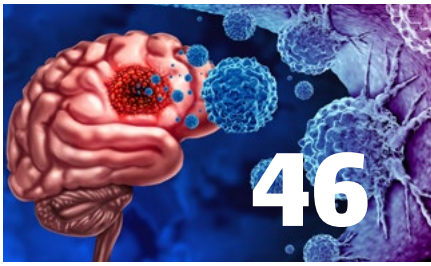
AI Could Promote Worldwide Equity in Cancer Care



6

38

42



46

Interview

Columns

50

28

Simultaneous Multi-Omics in Single Cells

From atlases and informatics to new platforms and processes, scientists can track more information than ever

by Mike May, PhD

The field of omics—genomics, transcriptomics, proteomics, and other features of molecular biology—started out slowly, but then advanced rapidly. In 1965, the late American chemist and Nobel laureate Robert Holley, PhD, then of Cornell University, sequenced a transfer RNA. Subsequently, in 1972, the late Belgian molecular biologist Walter Fiers, PhD, sequenced the first complete gene, which was from a bacteriophage. Just 31 years later, in 2003, an international team of scientists published the Human Genome Project. Today, scientists can study a collection of omics data and grab all of the information from a single cell at once—sometimes even locating specific molecules.

Vanee Pho-Conners, PhD
Vice President
Mission Bio

Still, "single-cell work is challenging on all fronts," said Vanee Pho-Conners, PhD, Mission Bio's vice president of global marketing. "Technologies have evolved, though, and with the technologies like microfluidics we've been able to achieve single-cell and combine multiple attributes."

Similarly, multi-omics relies on the combination of multiple tools and platforms, and on analyzing and merging large datasets. Some of this work is already providing vast arrays of new knowledge.

Atlases to explore

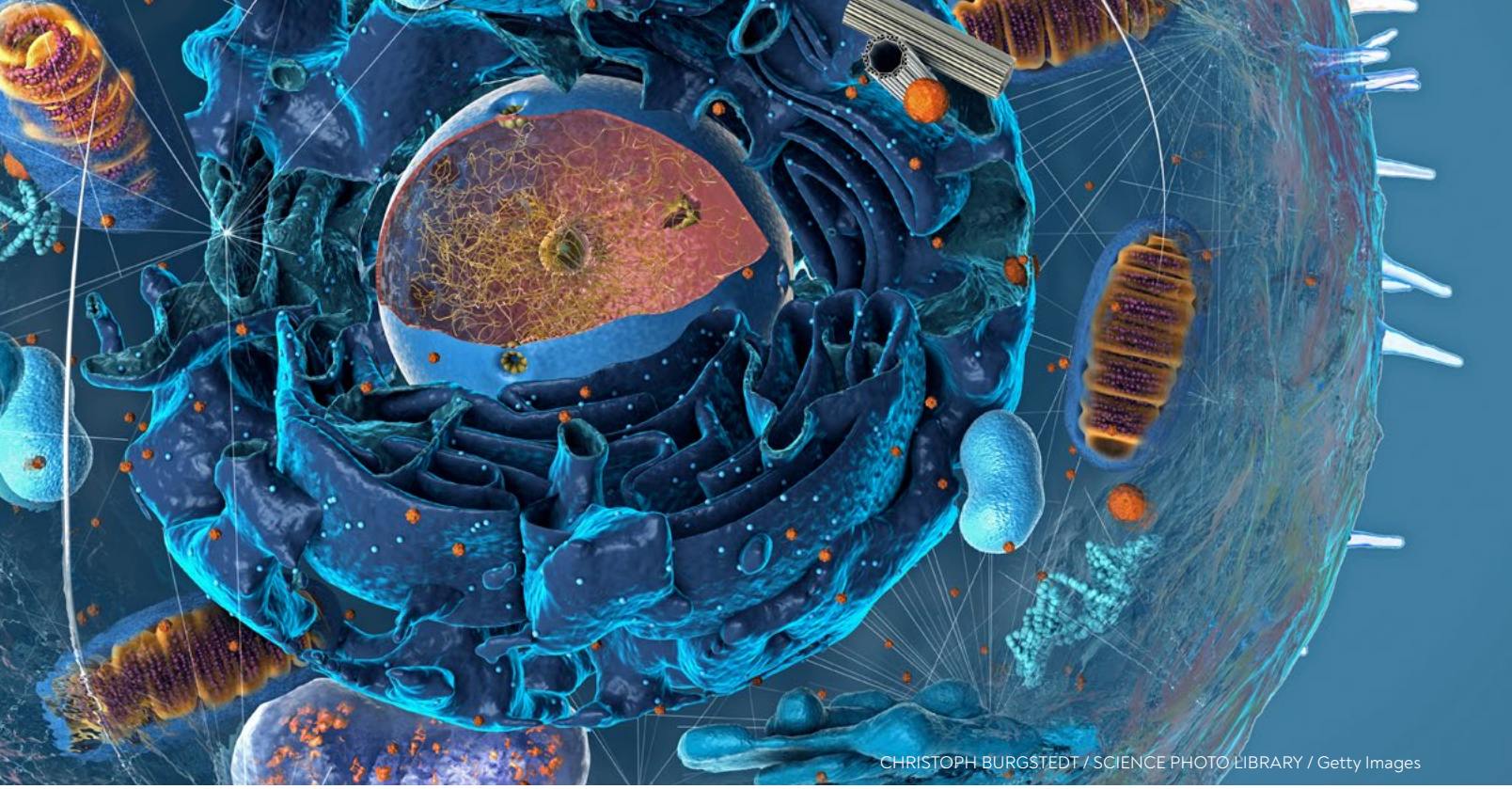
One international group of scientists built the Single Cell Atlas (SCA), which they describe as "an open access single-cell multi-omics healthy human atlas, containing 125 fetal and adult tissues from various omics, namely single-cell (sc) transcriptomics (scRNA-Sequencing), proteomics (Flow, CyTOF), epigenomics (scATAC-Sequencing), and immune repertoires." In addition, the SCA includes data from RNA sequencing, spatial transcriptomics, and genomics in specific tissues, ranging from fetal eyes, heart, and lungs to adult areas of the brain, various structures in the heart, skin that has or has not been exposed to sun, and so on.

Consider the colon-transverse tissue of an adult, for which various forms of omics data can be explored. For example, scRNA-seq can be explored for correlations between different kinds of cells—such as B, T, and muscle cells—and the genes that are expressed differently from one cell type to another.

With so much data available in the SCA, making any sense of it depends on advanced analytics tools. To help scientists analyze the information in various ways, the SCA provides 27 analysis tools, from pie charts and heat maps to dimension reduction and data integration.

The SCA, though, is just one option to explore. There's also the Human Cell Atlas (HCA), which comes from another international effort. This project aims to map "all cell types across the human lifespan, to drive major advances in healthcare and medicine worldwide." As of June 2025, the HCA was based on data from 66.3 million cells from more than 10,000 donors, which came from more than 500 projects run by scientists across over 900 labs.

These multi-omics atlases change the idea of cell types, from structure to molecular pieces and processes. Consequently,



A range of new tools and techniques help scientists explore multi-omics to learn more about the molecular mechanisms in single cells.

more cell types are being cataloged. An anatomical study of the human retina, for example, might reveal a handful of cell types, from the photoreceptive rods and cones that collect light-based data to the ganglion cells that carry information out of the retina to other parts of the brain. Using transcriptomics alone, the HCA has identified more than 120 cell types in the human retina. They even identified very rare cells, like a retinal cell that was only one of 10,000.

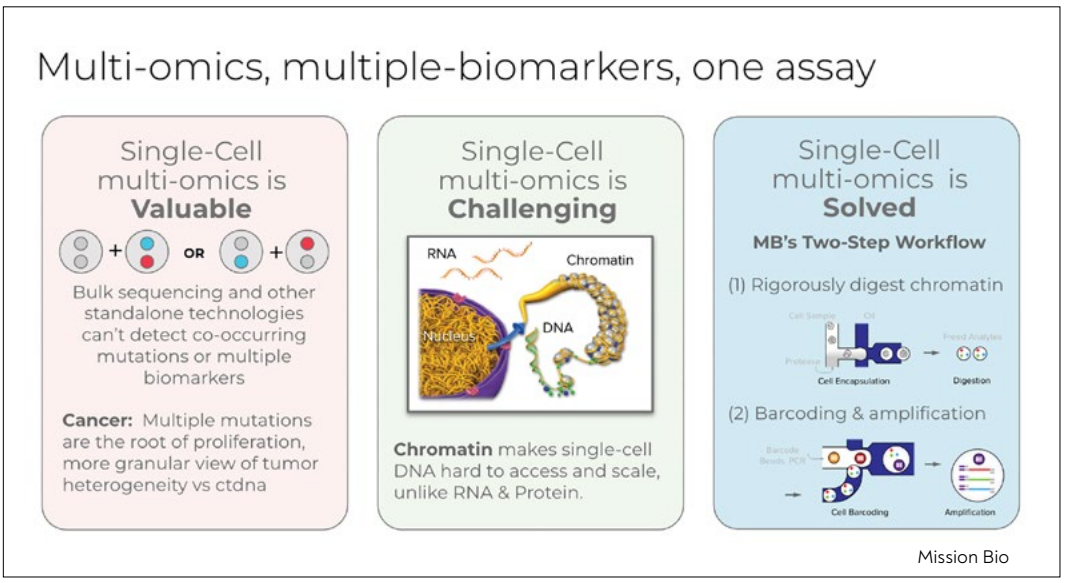
So, instead of simply looking at cells to understand what they do, scientists can use other omics like transcriptomics and proteomics to reveal some of the molecular tools used by the cells, such as genes, and how they work. Beyond that, scientists can unravel communications between cells. This information expands our understanding of basic biology, how it changes in diseases, and how those diseases could be diagnosed and treated—maybe even preventively.

Building workflows

To push multi-omics analysis even further for single cells, scientists rely on advances in tools, and new options keep arriving on the market.

As one example, MGI, a multi-omics company headquartered in Shenzhen, China, developed its DNBelab C Series for scRNA-library preparation. This series offers "three of the most in-demand library preparation kits: 3′ RNA, 5′ RNA, and ATAC," said an MGI spokesperson. "These kits utilize a unique dual-bead identification technology that accurately distinguishes droplets containing multiple beads, ensuring precise and reliable results." To separate cells, scientists can use MGI's droplet-generation systems that work with various throughputs.

After preparing a single-cell library, it can be sequenced with MGI's DNBSEQ™ high-throughput platform or



Mission Bio's Tapestri platform runs a two-step workflow that captures valuable insights beyond bulk sequencing.

(continued on page 9)

Leave staffing challenges and space issues in your wake.

Hamilton's one-touch solution streamlines aliquoting and capping, and stores samples from -20°C to +20°C using green refrigerants.

Our automated LabElite® DeCapper, Microlab VANTAGE Liquid Handling System®, and Verso® Q-Series storage system integrate seamlessly. This lets you build a plug-and-play clinical workflow that maximizes productivity while minimizing the use of valuable lab space.

hamiltoncompany.com

HAMILTON

(continued from page 7)

single-molecule sequencing platform. “This comprehensive solution offers researchers a fully integrated, multi-omics, high-throughput system with standardized automation from sample to data,” the MGI spokesperson said. At the 2025 European Society of Human Genetics conference, MGI “unveiled a fully automated single-cell workstation, that integrates MGI’s core automation technologies with complex single-cell workflows,” said the MGI spokesperson.

Unfortunately for scientists in the U.S., MGI’s single-cell products are not yet available in the country.

MGI

Today, scientists can use fully automated workstations to run complex single-cell workflows.

Raising the resolution

To track the locations of multi-omics activities in single cells, analytical tools must collect information on many data points and at high spatial resolution. MGI accomplishes that with STOmics Stereo-seq (spatial enhanced resolution omics-sequencing) technology. This method “advances single-cell technology by utilizing the DNB patterned array design to attain nanoscale spatial resolution, an extensive field of view, and comprehensive whole-transcriptome and multi-omics data profiling,” the MGI spokesperson said. “Unlike conventional scRNA-seq, which isolates cells and loses spatial information, Stereo-seq captures the whole transcriptome and identifies over 100 protein markers at single-cell resolution—while preserving the tissue’s native spatial architecture across large areas, up to 160 square centimeters.”

In addition, Stereo-seq can co-detect host and microbiome signals in the same tissue section. “This is transformative for single-cell technology because it allows researchers to not only profile individual host cells but also map microbial communities and directly study their interactions *in situ*,” said the MGI spokesperson.

Stereo-seq is also species-agnostic and able to detect messenger RNA and long-noncoding RNA. That makes this method “suitable for a wide range of organisms and research areas,” according to MGI’s spokesperson. “With an intuitive workflow and robust bioinformatics support, Stereo-seq provides a platform for exploring complex biological systems in their true spatial context.”

Barcodes and patient signatures

At Mission Bio, single-cell works starts with lysing the cells to isolate the DNA, barcoding each piece of DNA, and then encasing it in a bead. “From there, we’re able to do a readout, and a lot of our power lies in our bioinformatics, which can then measure these various barcodes,” said Pho-Conners. “Given the way we do our variant calling and bioinformatics expertise, we can measure multiple attributes within a cell.”

In cohort analysis, for example, Mission Bio can analyze multiple samples at multiple time points. This information produces “a patient signature, if you will, by looking at their genotype and which clones are expressed during a certain time point, like at diagnosis and post-treatment.” said Pho-Conners. This includes analyzing insertions and deletions of DNA, as well as other immune phenotype and therapy-relevant markers. “[With] the combination of our powerful chemistry around looking at genotype as well as proteins, as well as targeted gene expression, one could do the monitoring across any sort of time point and actually map that all-in-one.” In cancer, for example, a patient’s signature could be mapped before and after a treatment to see what changes.

“We are now partnering with some academic clinicians to do retrospective analysis showing why patients may have relapsed,” Pho-Conners said. That information might be used to improve the treatment of cancer patients in the future.

In the meantime, Mission Bio provides custom multi-omics assays that run on its Tapestri platform to provide single-cell resolution that can be used in clinical trials. For example, such an assay can be used to pick the best biomarkers to assess during a trial to determine a treatment’s safety and efficacy. These assays can also be used to better understand a treatment’s mechanism of action and use the information to select the best patients for a clinical trial.

Although Mission Bio has already supported over 100 publications that analyze retrospective data to see why cancer patients relapsed, “now our shift is really moving towards determining whether relapse will happen or not based on patients clonal architecture, and we’re excited to release some relevant proof points in collaboration with a leading cancer institute, demonstrating Tapestri’s translational insight in a few months,” said Pho-Conners.

Single-cell analysis can also improve the discovery of new treatments, which is just what Single Cell Discoveries does. “We mainly use single-cell sequencing and spatial transcriptomics for discovery workflows, understanding mechanism of action for drugs, discovering biomarkers, and understanding biodistribution of drugs,” said Dylan Mooijman, PhD, the

(continued on next page)

(continued from previous page)

company's chief technology officer. "Single-cell sequencing can also be used prior to spatial sequencing to triage samples before committing to spatial experiments."

Measuring methylation

Beyond gene sequences, post-translational modifications also matter. One of the most studied modifications is the methylation of cytosine in DNA. In Palo Alto, CA, scientists at Ultima Genomics measure methylation in various ways, including whole-genome bisulfite sequencing, reduced representation bisulfite sequencing, and enzymatic methyl sequencing using its UG 100™ Sequencing Platform. These applications are used across clinical and discovery settings.

Gilad Almogy, PhD
CEO
Ultima Genomics

"Whole-genome methylation sequencing offers a powerful window into how genes are turned on or off across the entire genome," said Gilad Almogy, PhD, founder and CEO at Ultima Genomics. "By mapping DNA methylation—the chemical tags that help regulate gene expression—at single-base resolution, this technique reveals the global regulatory state of a cell." This information can be used in many ways, from "uncovering how aging alters our epigenetic code to enabling early cancer detection through non-invasive liquid biopsies," Almogy said.

A crucial point is that whole-genome methylation sequencing provides a more complete picture than scientists get from methylation arrays, which are limited to a fixed set of probes. "In contrast, whole-genome methylation sequencing captures DNA methylation patterns across nearly every cytosine in the genome," Almogy said. "This makes it particularly powerful for exploring the methylation status of enhancers, intergenic regions, and other non-coding elements that are increasingly recognized as hotspots of regulatory activity."

As one example, Almogy mentioned his collaboration with Michael Snyder, PhD, professor at Stanford University, where they are working "to demonstrate how whole-genome sequencing can be used to map these changes in colon tissues from patients with inherited risk for colorectal cancer." This work revealed "early and cancer-specific shifts in methylation at gene promoters and regulatory regions, including enhancer elements linked to developmental genes," Almogy said. "These changes follow a complex, nonlinear pattern as normal tissue progresses to cancer, offering new insights into how colorectal cancer develops and highlighting the potential of this new sequencing technology for large-scale epigenetic studies."

Seeking automation and standardization

The number and variety of steps involved in single-cell multi-omics makes it easy to create mistakes, including slight variations between experiments. Consequently, automation should be used when possible.

"Conducting research with single-cell sequencing technology is particularly vulnerable to factors such as sample heterogeneity and operator-dependent variability due to the complexity and manual intensity of single-cell workflows," said MGI's spokesperson. "Any deviation from standardized procedures can lead to substantial data variability—fluctuations significant enough to affect the interpretation of scientific results."

Although moving away from traditional methods that include manual steps can require significant investments, it is necessary to extend the range of applications, especially for clinical work.

> "Our product development has provided compelling evidence that automation consistently produces data with lower variability and higher reproducibility."

"Our product development has provided compelling evidence that automation consistently produces data with lower variability and higher reproducibility," the MGI spokesperson pointed out. "Unlike human operators, instruments perform each step with unwavering precision, unaffected by emotional state or differences in technical proficiency, and this ensures consistent, standardized execution across every run, ultimately enhancing the reliability of research outcomes."

At Single Cell Discoveries, automation is used in library preparations, which can then be used for multi-omics libraries. As Mooijman said, fully automated library preparation for 10x Genomics assays provides "consistent results, reduced hands-on time, and easier tech-transfer when training personnel."

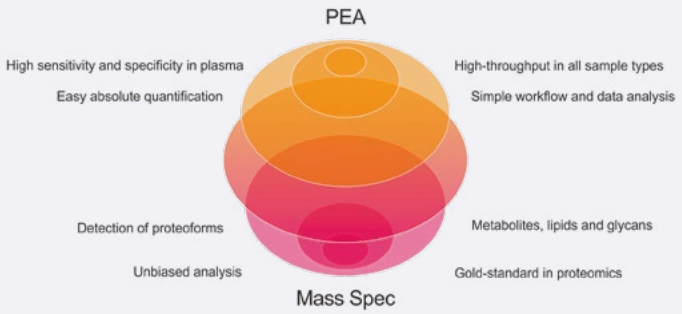
The future of multi-omics studies of single cells will surely depend on the increasing use of automation and standardized protocols. In particular, these features will be required to drive these technologies deeper into clinical applications. ■

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.*

A More Complete Plasma Proteome View for Enhanced Precision Medicine

Integrating mass spectrometry and next-generation affinity-based proteomics

Comprehensive analysis of the plasma proteome is essential for advancing precision medicine, but its vast dynamic range is a major challenge. A synergistic approach that integrates mass spectrometry (MS) with next-generation affinity-based proteomics—specifically the proximity extension assay (PEA)—offers a powerful solution. MS provides unbiased detection and detailed characterization of proteoforms and post-translational modifications, while PEA excels at high-throughput detection of low-abundance proteins. By accessing distinct and overlapping subsets of the proteome, the combined use of these technologies expands overall coverage and increases confidence in biological interpretation.



Petrera et al. (2021), demonstrated this complementarity, showing limited overlap between proteins identified by MS and PEA—with PEA capturing a greater number of low-abundance targets.

Researchers are increasingly combining the two technologies, either in parallel by analyzing samples with both methods to maximize actionable insights, or sequentially by applying each platform at different stages of the biomarker development pipeline, from discovery to validation.

Parallel use to expand proteome coverage

- In umbilical cord blood, the two platforms revealed proteomic signatures to distinguish high vs. low count of hematopoietic stem and progenitor cells, with MS favoring abundant proteins and PEA enriching for lower-abundance biomarkers (Nilsson et al. 2022).
- In SATB2-associated syndrome, untargeted MS was used to define the global proteomic landscape, while PEA provided additional insight into neurological pathways (Collu et al. 2024).
- In cardiomyopathy, combining methods doubled the identified proteins associated with left ventricular ejection fraction, highlighting their additive value (Hannemann et al. 2024).
- In a study on dietary energy restriction and aging, MS uncovered pathways related to inflammation, senescence, and protein turnover, while PEA detected additional inflammation proteins not captured by MS (Cagigas et al. 2025).

Beyond the combined use of MS and PEA to expand coverage, they are also applied sequentially to increase confidence.

Sequential use to confirm findings

PEA discovery with MS validation: Researchers can use PEA for high-throughput screening across large cohorts, followed by MS to validate and further characterize selected targets.

- In Alzheimer's disease research, PEA was employed to identify plasma proteins associated with pathology. MS was subsequently used to validate a subset of these proteins (Tokuoka et al. 2024).
- In a clinical study on acute mountain sickness, PEA enabled the discovery of altitude-responsive proteins, which were confirmed using MS in follow-up validation (Yang et al. 2022).

MS discovery with PEA validation: For unbiased discovery, researchers begin with MS to identify novel protein candidates, followed by PEA for confirmation. The high-throughput and absolute quantification capabilities of certain PEA panels may offer a smoother path to clinical translation.

- In tuberculosis research, MS was used to identify biomarker candidates that differentiate tuberculosis from other respiratory diseases. PEA confirmed a subset of these markers and enabled development of a six-protein diagnostic panel with promising performance in an independent cohort (Schiff et al. 2024).
- In a colorectal cancer study, MS enabled initial biomarker discovery, while PEA confirmed overlapping targets and uniquely identified an additional promising marker not captured by MS. Final predictive models were successfully validated using PEA in an independent cohort (Bhardwaj et al. 2019).

Toward a more complete and clinically translatable plasma proteome

PEA and MS synergize to enhance the breadth and depth of plasma proteomic profiling. This multifaceted approach, which combines parallel and sequential strategies and leverages the unique strengths of each technology, marks a paradigm shift in proteomics. These integrated proteomic workflows will be essential for tailoring treatment to patients based on proteomic and multi-omic signatures.

More Affordable Access to Single-Cell Multiomics

Advancements in single-cell prep from Illumina, along with sequencing innovations, open up opportunities

Researchers can use single-cell sequencing to study virtually any "ome" to capture critical information about specific cell types in heterogeneous tissues, rare cells, and microenvironments to study complex diseases. Still, while sequencing has dropped in cost and become more accessible, the expense and capabilities of traditional single-cell prep techniques have created barriers, limiting both access and experimental scope.

Massively scalable, single-cell multiomics

The single-cell solution from Illumina opens opportunities for scientists to explore single cell behavior. Based on particle-templated instant partition sequencing (PIPseq), Illumina Single Cell 3' RNA Prep is simple, affordable, flexible, and scalable. The approach allows large single-cell gene expression studies, while eliminating the need for complex and expensive microfluidic instrumentation, consumables, and service contracts.

The four-step microfluidics-free, emulsion-based methodology requires only simple lab tools—provided in a one-time starter kit purchase—drastically reducing initial investment costs and, thus, making the technology available to a larger number of labs.

Coupled with intuitive data analysis tools, at no additional cost, the Illumina single-cell solution provides a complete and affordable workflow, enhancing the overall cost-effectiveness of single-cell sequencing experiments that help elucidate inter-cell genetic, epigenetic, transcriptomic, and proteomic heterogeneity.

More data for less cost

"There are a lot of researchers who will now be able to actually complete projects that they've wanted to do for years and have never been able to do because it's just not in the budget," said Jamie Padilla, Research Scientist at the University of New Mexico.

Illumina Single Cell 3' RNA Prep allows researchers to prepare five times more cells for sequencing, in comparison to traditional methods, enabling larger experiments to capture more biological data along with the ability to repeat experiments. Affordable 2K and 10K capacity kits are ideally suited for both large- and small-scale experiments, such as pilot studies and grant applications. Additionally, high-throughput applications become even more cost-effective and efficient when sequencing is performed on the NovaSeq™ X enabled with the latest NovaSeq X v1.3 software release and 25B flow cell.

Increasing efficiency and reducing costs

"We have been combining samples from multiple projects and users on the same large run on the NovaSeq X Series with a 10B or 25B flow cell. This is much more affordable and acceptable to a lot of our customers here at IU," said Hongyu Gao, PhD, Associate Scientist at the Indiana University Genomics Core.

By batching sequencing runs and maximizing the capacity of each individually addressable lane, regardless of library type, cost savings are increased on the NovaSeq X series to make NGS applications, like single-cell experiments, more cost effective for labs without sacrificing quality or performance.

Now, multiomics can be performed at a lower cost than one "ome" alone. For example, sequencing both whole exomes and whole transcriptomes on the NovaSeq X Series 25B flow cell is more cost effective than running whole-exome sequencing alone on previous platforms. Plus, experiments or methods that require large amounts of data like Perturb-seq are now possible as the potential of batch effects from multiple runs is decreased.

High quality, robust chemistry innovations, along with other technological enhancements, are fueling the NovaSeq X cost drop in sequencing. In particular, two new kits for 100c and 200c reads for the 25B flow cell reduce the cost significantly (by up to 69%) to empower high-throughput and data-rich applications.

Now within reach

The new Illumina Single Cell 3' RNA Prep presents a simple, affordable, and flexible option that expands accessibility of single-cell sequencing. In combination with the latest innovations in the NovaSeq X series, available in a large pool of core laboratories, lower single-cell sequencing costs make the technology attainable for many more researchers.

illumina®

Multiomics is within reach

Enter a new era of discovery with the NovaSeq™ X Series

Harness the possibilities of multiomics with the leading-edge NovaSeq X Series. This ultimate high-throughput sequencer offers dual flow cell architecture with up to 16 lanes for extraordinary performance and maximum flexibility. The NovaSeq X Series helps you access multiomic methods to fuel a new era of discovery.

illumina.com/novaseqx-multiomics

The Expanding Frontier of Metabolomics in Precision Medicine:

Spatial, Single-Cell, Real-Time, and Beyond

by Laura Cowen

The study of metabolism is not new. Researchers have been investigating the role of small-molecule metabolites such as sugars, lipids, and amino acids within cells and tissues for decades. In the 1920s, Otto Warburg, MD, PhD discovered that cancer cells alter their metabolism to increase glucose uptake for energy generation. The Warburg effect, as it became known, underpins modern imaging methods like positron emission tomography scans, which use radiolabeled glucose analogs to detect tumors.

The term metabolomics was coined more recently. Unlike genomics or transcriptomics, which describe potential or intermediate states, metabolomics reflects the real-time biochemical activity of cells.

"We need readouts of metabolites to really understand the almost instantaneous state of the cells, organisms, and ourselves," said Theodore Alexandrov, PhD, an assistant professor at the departments of pharmacology and bioengineering at the University of California, San Diego. "That's why metabolites are so important, because they're closest to the phenotype and to the function of the cells."

This proximity affords metabolomics immense potential in identifying biomarkers for disease diagnosis, therapeutic monitoring, and drug development.

One of the earliest and most impactful clinical applications of metabolomics has been in screening newborns for inborn errors of metabolism. Introduced in the 1960s, this test now relies on tandem mass spectrometry (MS) to detect dozens of treatable metabolic conditions from a single blood spot, saving thousands of lives globally each year.

Theodore Alexandrov, PhD
Assistant Professor
University of California, San Diego

Foundations of metabolomics

At the foundation of metabolomics lies technology. Early work relied on nuclear magnetic resonance (NMR) spectroscopy, which allows for the non-destructive analysis of metabolites in biologic samples. Pioneers such as Jeremy Nicholson, PhD, now an emeritus professor of biological chemistry at Imperial College London, used NMR to study pharmaco-metabolomics, looking at pharmacodynamic responses to drugs over time. In an interview from 2013, Nicholson described how he once used NMR to measure his own response to paracetamol in urine.

NMR is still used for metabolomics today, particularly in epidemiologic studies, where large-scale reproducibility across sites is important. However, in the mid-to-late 2000s, MS became the dominant technology, largely due to advances in sensitivity, resolution, and coverage that continue to improve.

Metabolomics employs two major analytical strategies: targeted, which quantifies a limited number of predefined metabolites with high sensitivity and is suitable for clinical diagnostics; and untargeted, which aims to profile as many metabolites as possible without prior selection, enabling the


Jordan Siemens / Getty Images

discovery of novel biomarkers or metabolic pathways.

MS has taken both approaches beyond bulk analyses toward spatial mapping, single-cell resolution, and real-time monitoring.

Spatial metabolomics: Mapping metabolites in tissue

Spatial metabolomics focuses on mapping the distribution of metabolites, lipids, drugs, and other small molecules within cells. Alexandrov describes it as "finally seeing what used to be invisible." It is made possible through MS imaging (MSI) techniques such as matrix-assisted laser desorption/ionization (MALDI) and desorption electrospray ionization (DESI)-MSI.

Alexandrov's lab combines software engineering and experimental science to process and visualize spatial and single-cell metabolic data using MSI. His work on METASPACE, an open-space cloud-based platform for MSI data annotation and sharing, has enabled high-throughput and reproducible interpretation of spatial metabolomics datasets across various tissue types and experimental conditions.

Spatial metabolomics is already producing progress in areas such as oncology, neuroscience, and kidney disease and helping researchers understand drug–target and microbiome–host interactions.

For instance, a 2022 study used spatial metabolomics to identify tumor- and stroma-specific metabolic subtypes in gastric cancer to guide treatment selection. The previous year, another study used DESI-MSI to accurately distinguish tumor, normal tissue, and surgical margins in oral cancer.

"Spatial metabolomics changes pretty much everything with respect to how biology works," said Alexandrov. "You are almost obliged to include it in your studies now, because otherwise you are lagging behind."

With technological advances like including three-dimensional MSI, high-resolution MALDI-Fourier transform ion cyclotron resonance imaging, and machine learning-based image analysis, the accompanying improvements in resolution, sensitivity, and throughput will allow researchers to map molecular processes at single-cell or even subcellular scales and analyze spatial metabolomics data with greater precision.

Single-cell metabolomics: Decoding cellular heterogeneity

Single-cell metabolomics allows researchers to study the metabolic activity of individual cells, revealing crucial details about cellular heterogeneity and function that are often masked in traditional bulk analyses. This level of detail is vital for understanding complex, dynamic biological systems like cell differentiation, disease progression, and responses to environmental changes.

One approach often used in other omics disciplines is to physically isolate single cells via microfluidics, laser capture microdissection, or fluorescence-activated cell sorting. But these strategies do not work well for metabolomics because metabolites degrade during the separation processes. A much more attractive option is to measure metabolites directly from tissues using MSI.

(continued on next page)

(continued from previous page)

However, achieving single-cell resolution remains a major challenge as it depends on the diameter of the laser beam used to desorb and ionize molecules from the tissue surface. Typical MALDI laser spots (10–100 µm) often exceed the size of individual cells (~6–100 µm), leading to oversampling which masks cell-specific features.

"Although we are not there yet, spatial resolution is improving every year," said Alexandrov. His work on SpaceM, an open-source method for *in situ* single-cell metabolomics, has enabled the detection of more than 100 metabolites from more than 1,000 individual cultured cells per hour. It generates spatially resolved metabolic profiles from MALDI-MSI and links them with light microscopy-derived phenotypic data like cell shape and fluorescence. His team used the method to show that stimulating human hepatocytes with fatty acids produces two coexisting subpopulations with distinct cellular metabolic states, a finding that could help understand the function of bioactive lipids in liver disease.

Another area in which single-cell metabolomics is making an impact is the study of tumor resistance. Researchers have used single-cell MS to profile metabolic adaptations in glioblastoma and pancreatic cancer, revealing survival pathways only activated in specific cell clusters. "This is important because we want to predict drug responses in every cell of a patient. If even one subpopulation of cells resists therapy, it can cause relapse," Alexandrov remarked.

Gary Patti, PhD
Senior Director
Washington University in St. Louis

Real-time metabolomics: Toward dynamic monitoring

Real-time metabolomics focuses on tracking rapid, dynamic changes in cellular metabolism—which often occur within seconds—to understand biochemical responses during physiological or pathological events. It is challenging to obtain the real-time read outs, but several groups are developing real-time metabolomics tools to bring this capability to clinical settings.

One of the most well-known tools is the intelligent knife, or iKnife, a surgical tool that utilizes rapid evaporative ionization MS (REIMS) technology for real-time tissue analysis during surgery. The technology, developed by Zoltán Takáts, PhD, and his team at Imperial College London, combines an electrosurgical knife, which uses an electrical current to rapidly heat and cut through tissue, with REIMS, which then identifies metabolites in the vaporized tissue. It can accurately discriminate tumor tissue from healthy tissue, which is important for ensuring complete tumor removal and improving surgical outcomes.

John Gillespie
CEO
AmberGen

Another device designed for intraoperative real-time metabolomics is the MasSpec Pen, developed by Livia Eberlin's, PhD, group at the University of Texas at Austin. The handheld device delivers a microdroplet of sterile water to the tissue to extract metabolites. The droplet is then transferred via a capillary line to a high-resolution MS, where it is analyzed within seconds. Early studies showed that the MasSpec Pen could differentiate tumor tissue from normal tissue in real time with an accuracy of more than 96%.

SpiderMass, from Isabel Fournier, PhD, and her team at the University of Lille, is a real-time, minimally invasive, *in vivo* technique based on ambient ionization MS (AIMS). It uses a mid-infrared laser to excite water molecules in the tissue, creating a fine plume of ions without the need for biopsy or sample preparation. The ionized molecules are transported through a flexible transfer line to a remote mass spectrometer, where they are rapidly analyzed. One study showed that the method could diagnose glioblastoma with 90% accuracy.

While MS dominates real-time metabolomics, NMR remains a valuable tool for continuous, non-destructive metabolic monitoring. Alongside its uses in the measurement of drug responses over time, real-time NMR has been employed to monitor live cells in culture, vaccine production, and glucose and lactate turnover in live tissues and perfused organs.

Beyond metabolites: A multi-omics approach

It is becoming increasingly important to take an integrated approach to precision medicine by combining genomics, transcriptomics, proteomics, and metabolomics to gain a wider understanding of disease biology and therapeutic response.

"We're going to find cases where metabolomics provides the smoking gun that leads us to the therapy, and there's going to be cases where genomics or proteomics does it," said Gary Patti, PhD, senior director of the Center for Mass Spectrometry and Metabolic Tracing at Washington University in St. Louis. "We need an integrated view, and we should be doing all of these omics analyses together in parallel."

Obtaining this integrated view is not easy because it involves combining diverse biological data types. Yet companies like AmberGen are addressing this challenge. Their platform enables spatial imaging of proteins, RNA, metabolites, and other small molecules, all within the same tissue section and on the same instrument.

A key part of their technology is their patented technique and reagents for spatially imaging proteins and RNA in a mass spectrometer using photocleavable peptide mass tags. The technique was invented by company founder and chief

innovation officer Kenneth Rothschild, PhD, executive vice president and CSO Mark Lim, PhD, and director of MS Gargey Yagnik, PhD. It allows each molecular target to be labeled with a unique mass signature, which can be detected by MS on being exposed to ultraviolet light. "Now that we can image proteins, RNA, and small molecules together, we're no longer blind to the full biology of the tissue," said Lim.

Company CEO John Gillespie added: "Before AmberGen, people could look at the distribution of small molecule drugs and metabolites in tissue, but not the drug's protein targets. Now, we can map them together and see whether a drug is changing the metabolic signature of the intended target cells."

AmberGen's technology is being widely used by pharmaceutical companies that want to bring their drugs to market faster. "If you can see whether your drug is engaging with its target in an animal model, it saves a lot of time and money versus waiting for a clinical trial," said Gillespie.

Mark Lim, PhD
Vice President, CSO
AmberGen

The method is also pushing the boundaries of decoding biomolecular pathways. In a poster recently presented at the American Association of Cancer Research's annual meeting, Lim and colleagues showed that they could detect over 600 multi-omic biomarkers on a single lung cancer tissue microarray using untargeted lipid imaging combined with targeted protein and RNA imaging. This more complete view of tumor tissue biology is expected to lead to future mechanistic studies and ultimately, improved biomolecular signatures for precision medicine, remarked the authors.

Other companies working on multi-omics solutions include Metabolon, Panome Bio, and Sapient. Metabolon specializes in untargeted metabolomics and has developed an extensive reference library to interpret complex metabolic data across disease states, nutrition, and pharmacology. Rather than analyzing each multi-omics dataset separately and stitching them together at the end, Panome Bio takes the unique approach of processing multi-omics data using an integrated pipeline to enable a more holistic understanding of each molecular profile. Sapient, meanwhile, is integrating multi-omics data with machine learning to build one of the largest annotated human multi-omics databases, which they will use to uncover new drug targets and stratify patient populations.

In academia, researchers like Julio Saez-Rodriguez, PhD, head of research at the European Bioinformatics Institute, are developing integrative multi-omic computational frameworks that model cellular signaling and predict drug responses, further bridging the gap between omics data and clinical applications.

Impacting precision medicine

In terms of clinical applications, Alexandrov believes that metabolomics could have bigger potential for use in precision medicine than other omics. "It is the fastest and cheapest of all the omics and sample preparation is extremely simple," he said.

Furthermore, there is growing interest in carrying out high-throughput metabolomics to create large-scale metabolic atlases and databases that can be used for diagnostics and prediction. "We've entered a world where metabolomics data can be acquired at such throughput that it's entered the precision medicine arena," said Patti. "Just a handful of years ago, you would struggle to find studies that had more than a few hundred samples but now we're doing untargeted metabolomics experiments on 15,000 samples. That gives statistical power to make important discoveries."

Various research groups have demonstrated how untargeted metabolomics can reveal functional changes in tumors that are undetectable through genomics alone. These include metabolite markers that correlate with tumor aggressiveness, treatment resistance, and survival outcomes. In one study, researchers used liquid chromatography (LC)-MS to show that 2-hydroxyglutarate levels were significantly higher in head and neck squamous cell carcinoma tissue than in normal tissue, suggesting that the compound has potential has a non-invasive biomarker.

Bruker

Bruker's timsMetabo™ Mass Spectrometer

In another study, which examined 330 triple-negative breast cancer samples, researchers identified high levels of N-acetylaspartylglutamate as a metabolic signature of the basal-like immune-suppressed subtype, a group with significantly worse overall survival than others.

Moreover, Patti's work has revealed that cancer isn't just a local disease. "What has been surprising to me is how cancer affects healthy tissues. Even if the tumor is in the skin, we've seen altered metabolism in the liver, brain, and beyond." He explained that tumors hijack distant tissues and coerce them to produce metabolites that the tumors can use as fuel. "I think this is a

(continued on next page)

(continued from previous page)

really exciting area, and not only important to understanding our biology of cancer, but also as potential therapeutic targets that we can go after."

Beyond cancer, metabolic biomarkers are showing promise in cardiovascular disease, neurodegeneration, and diabetes, and are increasingly being incorporated into clinical trials for therapy monitoring.

Challenges in metabolomics: Quality control and annotation

Despite major advances, metabolomics face challenges in quality control, standardization, and metabolite annotation. Inconsistent practices across platforms and laboratories hinder reproducibility and quantitation.

"Many scientific fields are facing crises of reproducibility, and we have a duty of care to ensure metabolomics isn't one of them," said Matthew Lewis, PhD, vice president of metabolomics at Bruker Daltonics. To address this, the company has developed QSee™, a software suite that supports longitudinal quality control monitoring and instrument performance tracking, which Lewis says is essential for scalable and reproducible metabolomics.

Initiatives such as the Metabolomics Quality Assurance and Control Consortium, the National Institute of Health's Multi-Omics for Health and Disease Consortium, the Metabolomics Society, and the U.K.'s National Phenome Centre are also working to address these gaps, but more widespread adoption is needed.

Both Lewis and Patti described metabolite annotation as another bottleneck. "You collect a metabolomics dataset and see thousands of signals, but the majority can't be identified. Even today, we're only able to name a few percent," said Patti.

He suggests that there are two potential reasons for this: one is that they represent small molecules that have not been seen before and therefore cannot be identified; and the other is that the signals come from non-biologically relevant background noise such as contaminants and artifacts that have formed inside the mass spectrometer.

"I do think there are new metabolites, I don't want to miscommunicate that, but I also believe that a lot of the datasets that we struggle with identifying, at least in our lab, represent the complexities of the mass spectrometry data," Patti remarked.

Bruker's solution is trapped ion mobility spectrometry (TIMS). "It separates isomers and interferences, and generates cleaner MS/MS spectra more rapidly, with higher sensitivity, which is key for annotation," said Lewis. Their timsMetabo™ platform combines TIMS with ultra-high-resolution LC-MS and has been specifically adapted for small molecule identification.

In addition, community-driven tools like the Human Metabolome Project are providing reference spectra to support identification and classification. The resulting Human Metabolome Database now contains over 220,000 entries, including around 20,000 confirmed endogenous human metabolites, and has become an important tool for identifying metabolites, discovering biomarkers, and linking metabolic features to clinical phenotypes.

Matthew Lewis, PhD
Vice President
Bruker

Future directions

You often hear metabolomics described as the final frontier in the omics cascade. Yet upon speaking to the experts, it has become clear that metabolomics goes further. One theme that comes up repeatedly is that of exposomics—the study of environmental exposures and their biological effects over a lifetime. Metabolomics is uniquely suited to study the exposome because it can directly detect both exogenous chemicals and their metabolic effects.

As Patti noted: "Every blood sample we test contains PFAS [per- and polyfluoroalkyl substances]. We're all exposed, and we don't yet understand the long-term health effects. That's where exposomics comes in."

Large-scale projects such as EXPOsOMICS and HELIX are already using untargeted metabolomics to define exposomic signatures linked to disease.

For Lewis, the holy grail would be something that can measure the exposome in real-time. His suggestion of at-home monitoring via accessible MS may sound far-fetched, but a non-invasive device that samples urine daily to see if a person is deficient in vitamins or experiencing inflammation, for example, could benefit long-term health.

More realistically, Lewis says that democratizing the technology by making it more accessible and increasingly deployable at the point of care will be exciting future endpoints. "But bottom line, we are pushing on all fronts. We're pushing upward on scale aiming to measure billions of samples in biobanks, we're pushing downward in scope to measure metabolites at the subcellular level, and we're pushing laterally to carry out multi-omics. It's a multidimensional frontier that we're working to aggressively tackle," he said.

Artificial intelligence (AI) will also play a central role. Gillespie sees it as a critical partner to the next generation of metabolomics. "When you're collecting hundreds of biomarkers per sample, AI will help interpret and contextualize those data," he said.

Alexandrov agreed: "The impact of metabolomics will depend on how we train and apply AI models." As Lewis concluded: "The world around us is rapidly changing, there will be no final frontier. There will be new environmental challenges, new toxins, new pollutants, new food products, and the confluence of a lot of those is going to be in small molecule analysis, but I don't see finality in our future." ■

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

THE STATE OF BIOTECH
VIRTUAL SUMMIT

WEDNESDAY, SEPTEMBER 24, 2025
11:00 AM–3:30 PM ET

FREE REGISTRATION

Join *Genetic Engineering & Biotechnology News'* flagship virtual event, The State of Biotech! Discover how distinguished researchers and business leaders from the industry are reshaping biotech.

Featuring a Keynote Presentation from George Church, PhD, of Harvard Medical School

Attend on September 24th to hear additional exciting speakers including:

- **Iya Khalil, PhD** (Merck & Co.)
- The co-hosts of the popular *Biotech Hangout* podcast—**Daphne Zohar**, **Brad Loncar**, and **Chris Garabedian**
- **Rodolphe Barrangou, PhD** (NCSU); **Geulah Livshits, PhD** (Chardan); and **Amber Salzman, PhD** (Epicrispr)
- **Aiken Hackett** (BIO) and **Yvette R. Seger, PhD** (FASEB)


GEORGE CHURCH, PHD


IYA KHALIL, PHD


DAPHNE ZOHAR


BRAD LONCAR


CHRIS GARABEDIAN


RODOLPHE BARRANGOU, PHD


GEULAH LIVSHITS, PHD


AMBER SALZMAN, PHD

Learn more and discover the full agenda today!
Not able to attend live? No problem! Register to get the on-demand recording.

REGISTER NOW
FOR THIS **FREE** EVENT

Hosted by
GEN Genetic Engineering & Biotechnology News

Sponsored by
cytiva

gorodenkoff / Stock / Getty Images Plus

From Microscopes to Computers: Reaching an Inflection Point in Digital Pathology

by Clara Rodríguez Fernández

Digital pathology is changing the ways in which pathologists work, driving a shift away from traditional diagnostic workflows that rely on glass slides and microscopes. However, change can be challenging in a field with over 100 years of history. Despite the benefits of digitization, most pathology practices have remained analog due to significant cost and technological barriers.

This could soon change as the past two decades have seen a significant increase in the image quality and resolution, enabled by whole slide imaging (WSI) scanners, and accompanying decreases in the costs of obtaining, storing, and managing digital slide data. Together with rapid progress in artificial intelligence (AI), these advances could unlock new applications, make diagnostic workflows more efficient, and address a worldwide pathologist shortage that is compounded by rising workload volumes and complexity.

"We are reaching an inflection point where we are going to see much broader adoption of digital pathology over the next couple of years," said Andrew P. Norgan, MD, PhD, chief medical officer at Mayo Clinic Digital Pathology and consultant at the department of laboratory medicine and pathology at Mayo Clinic.

> "Digital pathology really comes to power when it is combined with AI and new developments in precision medicine."

The Mayo Clinic has been an early adopter of digital pathology. Over the past few years, the non-profit medical group has undertaken the task of scanning its extensive archive of pathology slides, as well as slides from current patients, with the help of automated robotic scanning, leveraging more than 20 million digital slide images to date.

"We made the decision to digitize our practice because we fundamentally believe this is the way to advance medicine broadly for complex diseases," said Norgan. "Pathology slides are a rich source of information that has previously been unable to be accessed digitally and combined with all the other patient data we store."

One of the major benefits that the implementation of digital pathology has brought to the Mayo Clinic is logistics and workflow improvements, especially when it comes to sharing information remotely. This allows pathologists to quickly access expertise across the hospital network. "It has really revolutionized what used to take days," said Norgan. "No more sending slides back and forth. We now do that instantaneously, and patients are getting expert answers a lot faster than we were previously able to provide them."

Katharina Von Loga, MD, PhD
Head of Pathology
Owkin

But the best may yet be to come. Rapid advances in AI technology are enabling new diagnostic capabilities that were previously unthinkable. Through partnerships with Google, Microsoft, and NVIDIA, the Mayo Clinic has undertaken the development of AI models that can accelerate medical discoveries and further improve the efficiency of pathology practices. In collaboration with Aignostics, the organization recently built an AI foundation model to analyze histopathology slides using data from 1.2 million digitized slides provided by the Mayo Clinic and Charité – Universitätsmedizin Berlin, Europe's largest university hospital.

Trained on vast datasets, foundation models can serve as the building blocks for more specialized applications down the line. Norgan emphasized their potential to break the log jam that currently exists in digital pathology, allowing AI to increasingly bring value to the pathology practice and ultimately, to patients.

AI drives innovation

With AI breaking new ground in digital pathology, a number of companies have been developing algorithms that serve digital pathology applications. One of them is Owkin, a French-American enterprise that has been working with big pharma partners like Merck and AstraZeneca to develop AI-powered digital pathology tests.

"Digital pathology really comes to power when it is combined with AI and new developments in precision medicine," said Katharina Von Loga, MD, PhD, head of pathology at Owkin. She sees huge potential in digital pathology applications that focus on the prediction of patient outcomes, where AI can go far beyond the human eye.

For instance, Owkin has developed and validated an AI diagnostic for breast cancer patients that can assess an individual's risk of relapse within five years by analyzing WSI and clinical data, helping doctors choose the best course of action. Another AI model pre-screens digitized slides of colorectal cancer samples for microsatellite instability, a genomic biomarker that is predictive of immunotherapy response in solid tumors.

Von Loga expects AI technology to soon enable breakthroughs in patient selection for next-generation precision treatments. Increasingly, detecting whether a biomarker is present or

(continued on next page)

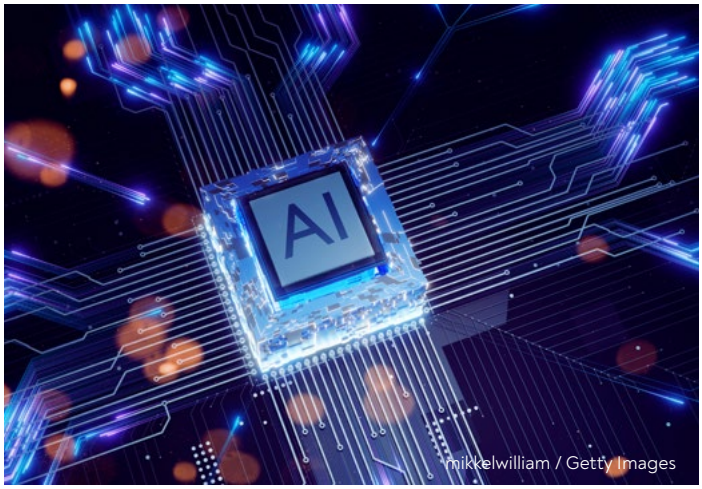
(continued from previous page)

absent in a sample is no longer enough to make optimal treatment decisions. That is the case, for instance, of immune checkpoint inhibitor therapies targeting the programmed death ligand (PD-L1), for which it has been established that not all patients with PD-L1 tumor expression will respond to the treatment.

Chad Richards
President
Quest Diagnostics

A much deeper level of biomarker analysis will be required going forward, including but not limited to expression levels, heterogeneity, and spatial distribution across a tissue sample. Here is where AI can step in to make better outcome predictions that bring together all information available, from histopathology to molecular diagnostic techniques and electronic patient records.

Furthermore, the capacity of AI to sort through large amounts of data will prove invaluable as the amount of tests and drugs available to patients continue to increase, pushing physicians to keep up with constant changes in the standard of care. "We are getting much more detailed in our reporting for all the different biomarkers and drugs available," said Von Loga. "That would be impossible to do in a timely fashion with a standard workflow for a patient who may have multiple drugs available for their condition."



mikkelwilliam / Getty Images

Quest Diagnostics, a provider of diagnostic information services, has been scaling its efforts in the digital pathology space through an ongoing collaboration with PathAI. "Beyond assisting the pathologist in looking at and identifying problem areas on the slide, there are a lot of AI tools that can help the pathologist become more efficient and work more quickly," said Chad Richards, president of pathology and medical services at Quest Diagnostics.

> "Being sensitive to those differences and developing tools that are helpful rather than a hindrance is key to success in digital pathology."

In this context, AI tools can assist with routine tasks that take valuable time away from pathologists. For instance, one of the AI tools developed by PathAI can automatically detect issues with a slide image and can flag the sample to be re-scanned or re-cut before a pathologist looks at it. Another tool for oncologists can identify which cases are most likely to be malignant, prioritizing them to ensure the pathologist looks at them first and orders any additional tests within the same day.

In addition to productivity gains, AI can help pathologists be more objective in their analysis, especially when it comes to borderline cases where a certain biomarker is near the threshold required to benefit from a given therapy. "If you showed a borderline case to ten pathologists, you will probably get half of them on one side and half of them on the other," said Richards. "AI can do that much more accurately and much faster."

Challenges to implementation

Across the board, the number one challenge facing the adoption of digital pathology remains the costs of digitization. Slide scanners are expensive, and the cloud storage, image management systems, and AI tools all carry additional costs. To make matters worse, there are currently no direct reimbursement programs in place for the digitization of a pathology practice, meaning that the return on investment has to be realized through improvements in efficiency and diagnostic accuracy.

There is still room for improvement in scanning technology, which cannot yet cover every use case within a pathology practice. The available technology may also present some interoperability issues, meaning customization efforts are often required to successfully implement digital pathology, driving costs further.

For tool developers, the challenges go beyond purely technological development. Any digital pathology tools need to be seamlessly integrated in an organization's workflows and be as simple and straightforward as possible for users. "Every hospital has their own equipment and protocols, and we need to make sure that these systems work equally well in all of them," said Von Loga.

Even within the same organization, different medical specialties can have very different needs. A dermatologist and an oncologist, for instance, may work very differently based on the number of cases they take on every day and the speed with which they need to establish a diagnosis. “Being sensitive to those differences and developing tools that are helpful rather than a hindrance is key to success in digital pathology,” said Richards. “If the tool does not integrate well in the daily workflow of the pathologist, it will only slow them down.”

Navigating regulations also remains an obstacle. “The biggest hurdle for tool makers is working with regulators,” said Richards. He explained that one of the challenges of working with AI is that the algorithms continue to change and improve as they look at more and more cases. This can clash with current FDA requirements for medical devices, which have to go through the whole approval process every time anything is changed. “That is something we still have to work out with the regulatory bodies.”

James Rogers, JD
CEO
Mayo Clinic

When it comes to implementing new tools and workflows within an organization, change management has to be considered throughout the whole process to ensure success. “Change is hard for everyone, and it takes time to get comfortable with a new way of doing things after years of doing them a certain way,” said Richards.

On the bright side, giving pathologists enough time to adapt to new tools can allow them to fully come on board with digital pathology. “Some of the pathologists who used to be diehard microscope people are now the most digitally oriented, because they have seen the intangible benefits of digitization,” said Norgan.

Ultimately, these challenges are not that different from what other fields, like radiology, have experienced through digitization in recent years. James Rogers, chief executive officer of digital pathology and senior administrator for generative AI at Mayo Clinic, is confident that all these challenges can be overcome, and that as technological costs decrease and the value generated by AI integration continues to increase, more and more pathology practices will start investing in digitization.

Preparing for a digital future

Experts have already noticed a shift in the digital pathology market, signaling the growing maturity of the field. “We see some of the bigger players, such as Roche Diagnostics and Leica Biosystems, starting to really ramp up their efforts in digital pathology, whereas three or four years ago the space was dominated by small startup companies,” said Richards.

With more players entering the market, there will be more choices available to cover a wider variety of use cases and address the unique needs of each organization. In the coming years, the number of approvals for drugs with AI companion diagnostics will grow, said Von Loga, and those who do not undergo digitization will not be able to diagnose and administer these treatments without relying on external services.

FatCamera / Getty Images

As organizations compete for an ever-scarcer talent pool, Rogers believes that digital pathology capabilities will also become a valuable recruitment tool. Digitization can be particularly attractive to prospective candidates because it offers pathologists more flexibility, allowing them to work remotely without being tied to the physical location of their laboratory.

Finally, “Digital pathology is opening up an avenue of research that has not been available before,” said Rogers. He sees immense potential in layering information from digital pathology together with omics data and electronic health records to build a detailed picture of each patient’s case, enabling breakthroughs on both the diagnostic and therapeutic fronts.

“We can now use AI in a way that is unprecedented,” said Rogers. “As more and more of these larger data sets become available, we will find solutions we had no idea had been sitting in front of our face. Now all that data is being unlocked, the best minds in the world can be put to work against today’s problems. This is a once in a lifetime opportunity to truly transform medicine.” ■

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.

The Dawn of Personalized DNA Vaccines

Luigi Aurisicchio, PhD, is the CEO of Neomatrix Biotech, a company developing neoantigen cancer vaccines. Their platform brings together expertise in cancer biology and immuno-oncology with several advanced technologies. These include the identification of tumor-specific neoantigens, the design and production of fully synthetic, personalized DNA vaccines, and a delivery system that enhances the immune response and works synergistically with immune checkpoint inhibitors.

Aurisicchio spoke with Damian Doherty, editor in chief of *Inside Precision Medicine*, to discuss the promise and potential of neoantigen cancer vaccines and breaking new ground with the use of synthetic DNA to enable the production of personalized vaccines within weeks of a tumor biopsy.

Q: What drove your interest in the potential of cancer vaccines?

Aurisicchio: I'm a molecular biologist and immunologist by training. Early in my career, I focused on identifying transcription factors involved in thyroid cancer differentiation. I then transitioned into industry, spending 15 years at Merck developing gene therapies and cancer vaccines. In 2009, I founded Takis to continue advancing immunotherapy approaches. Building on that experience, I launched Neomatrix in 2020 with a mission to develop personalized neoantigen vaccines, tailored to each patient's tumor and delivered back to the patient within just six weeks of biopsy. Our initial focus is to combine these vaccines with immune checkpoint inhibitors (ICIs).

Luigi Aurisicchio, PhD

Q: What is the scientific rationale behind combining neoantigen vaccines and ICIs?

Aurisicchio: Checkpoint inhibitors activate the immune system in terms of recognizing tumor-associated antigens. Within a set of tumor-associated antigens, neoantigens are those molecules that are expressed on the cancer cells and not on normal

Luigi Aurisicchio, PhD, presenting at the World Vaccine Congress 2024 in Washington, DC.

cells. If you now combine ICIs with a vaccine that stimulates the immune system to target those neoantigens, you have a synergistic effect, and there is clear scientific evidence showing this. The ICI may act, together with the immune system, in a general way by reducing the tumor mass, and potentiation with a neoantigen-based cancer vaccine may help amplify this effect.

Q: Are there certain types of cancer that would benefit from a combination of immune checkpoint inhibitors and these neoantigen vaccines?

Aurisicchio: Technically speaking, every type of tumor may benefit from this combination. The real difference is the number of mutations that are accumulated in the tumor. There are some tumors that contain more mutations, such as melanoma and lung cancer. Other cancers are much less mutated, and so you have to look for the neoantigens using molecular analysis. Hence, our approach is agnostic in that we can combine an ICI and the vaccine to treat every type of tumor.

What is clear also in the literature is that, provided you identify quality neoantigens, even if there are very few, you can achieve a therapeutic effect. So, the algorithm we use to identify the neoantigens is key. These are then presented to the immune system via our DNA vaccines.

Q: What is unique about your approach to producing neoantigen DNA vaccines?

Aurisicchio: Our approach stands out in the cancer vaccine field because most companies rely on mRNA or viral vector platforms, which have limitations. Viral vectors are costly to manufacture and can't be used repeatedly due to the risk of triggering neutralizing antibodies, which are problematic in cancer, where long-term treatment is often required. mRNA vaccines are faster to produce and more flexible, but they rely on lipid nanoparticles for delivery, which some patients can't tolerate. Other companies in the cancer vaccine field use plasmid DNA, but that requires complex bacterial production and extensive purification, leading to long timelines, which can extend to several months.

In contrast, our method uses enzymatically produced synthetic DNA, designed for speed, repeat dosing, and scalability. This is the first approach of its kind, and we believe it gives us a key advantage, particularly when treating these patients as fast as possible is imperative to clinical outcome. The synthetic DNA vaccine, personalized to each patient's specific neoantigen profile, can be ready in a matter of weeks following biopsy of the patient's tumor.

Q: Your approach uses synthetic DNA to produce the neoantigen vaccines. What advantages does this offer?

Aurisicchio: We partner with 4basebio, a company that produces synthetic DNA using a cell-free process. Unlike traditional plasmid-based approaches, which rely on bacterial fermentation processes, there's no need to create a master cell bank or use large bioreactors, allowing the delivery of GMP (Good Manufacturing Practice)-grade material in the compressed timeframe we need for a therapeutic advantage for patients. Another major advantage is the stability. Synthetic

(continued on next page)

(continued from previous page)

DNA is stable at room temperature and is compatible with lyophilization, requiring no complex formulation. In contrast, mRNA vaccines must be kept in a cold chain, which complicates storage and distribution, especially at a commercial scale. Finally, the process facilitates small batch sizes at GMP-grade, which is ideal when each batch is personalized to individual patients.

We like the 4basebio technology and believe it is the way to go for our vaccination technology. We are collaborating closely as we advance our programs in a brand-new field. So far, nobody has injected a human with a synthetic DNA vaccine. It's not only a new experience for our companies, but also for regulatory agencies, and we are speaking with the European Medicines Agency. It's exciting to be pioneering this kind of experience together.

Q: Why is the speed enabled by the use of synthetic DNA such an advantage?

Aurisicchio: Speed is critical in cancer treatment. Once a patient is diagnosed, you need to act fast. Waiting even a few months can significantly impact outcomes. That's why our ability to deliver a personalized vaccine within six weeks from the tumor biopsy is such a key advantage. Our partnership with 4basebio and the use of DNA electroporation technology are two key aspects that enable us to achieve that timeline reliably.

While the underlying mechanism of our approach is similar to other platforms in terms of introducing genetic material so the patient's own cells produce tumor-specific antigens, our approach differs in that the synthetic neoantigen DNA vaccine is delivered directly into muscle tissue via electroporation. This triggers local antigen production and recruits T cells and antigen-presenting cells both at the injection site and nearby lymph nodes. DNA also has prolonged expression kinetics compared to mRNA, helping to sustain and strengthen the immune response after a single administration.

Q: What is your process for identifying neoantigens?

Aurisicchio: This is one of the most critical steps in creating a personalized cancer vaccine. It starts with the patient's tumor biopsy, which must contain at least 30% cancer cells. That's not always guaranteed, especially in cancers like lung cancer, where biopsies often contain a mix of inflammatory cells, fibroblasts, and endothelial cells that aren't useful for vaccine design.

Once we have high-quality DNA and RNA from the biopsy, we perform next-generation sequencing and compare the tumor tissue to normal tissue to identify mutations that generate neoantigens. Our proprietary algorithm then goes through several key filters. First, it predicts whether a mutation can generate a peptide that is likely to trigger an immune response, essentially, whether it's truly immunogenic. Then, it checks whether that neoantigen resembles viral or bacterial epitopes; if so, the immune system is more likely to recognize it as foreign and respond robustly.

Another essential step is our dissimilarity filter. We want to avoid targeting peptides that resemble proteins in the human proteome, which could risk triggering autoimmunity. Finally, our algorithm determines how best to assemble the selected neoantigens into a synthetic DNA construct, or "minigene," optimizing the order and format of epitopes to elicit the strongest possible immune response.

Q: Why have you started with lung cancer as your first indication?

Aurisicchio: As I mentioned, lung cancer is one of the most mutated tumor types together with melanoma. Melanoma is a crowded area. Many ICIs have been validated in melanoma due to the number of mutations and because it is an immuno-reactive type of tumor. In lung cancer, there is still a very high medical need, and it is very highly mutated, so there are windows of opportunity there.

Q: What are your clinical development plans?

Aurisicchio: As of today, we've completed all the toxicology studies and what is needed for the preparation of an IMPD (Investigational Medicinal Product Dossier), which is the comprehensive dossier submitted to regulatory authorities for approval of clinical trials. We expect to begin a clinical trial with [a] synthetic DNA vaccine against lung cancer in the second half of 2025.

An important area we're also actively exploring is the use of circulating tumor DNA (ctDNA) as a biomarker for long-term patient monitoring and early detection of recurrence. There are two key reasons for this. First, ctDNA levels correlate closely with tumor burden, even when a patient appears clinically cancer-free. Detecting ctDNA could allow us to intervene earlier, before the tumor becomes visible again. It's a powerful tool for proactive care. Second, ctDNA could serve as a dynamic source of information for designing follow-up vaccines. Cancer evolves over time, especially under selective pressure from treatments like chemotherapy, checkpoint inhibitors, or even the initial personalized vaccine. As a result, new neoantigens may emerge. By analyzing ctDNA in real time, we aim to identify these new targets and produce updated, patient-specific vaccines tailored to the evolving tumor. This represents the future of personalized cancer immunotherapy—one that is adaptive, responsive, and truly individualized.

Ultimately, our vision is that this could be the future for therapies for every cancer patient. ■

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

PIPETBOY GENIUS

Aliquot faster, aspirate safer, pipet smarter.

The most revolutionary serological pipet controller

Brings color into your lab!

INTEGRA
integra-biosciences.com

The Slow and Winding Path to Pharmacogenomic Test Adoption

by Helen Albert Senior Editor

A cornerstone of precision medicine, pharmacogenomic testing allows drug treatment for a disease to be tailored to a person's genetic makeup. Despite a large amount of research having been carried out in this area from the 1990s onward, only a few of the findings have reached the clinic in the form of tests.

High costs, unreliable data, and a lack of physician education have been cited as reasons for this slow adoption, but recent developments like improvements in data and guidelines, reductions in test costs, and government support for pharmacogenomics suggest that the this technology will be increasingly adopted in the U.S. and elsewhere in the near future.

Drug-metabolizing enzymes evolved to help humans and other animals metabolize poisonous substances consumed by accident (e.g., toxins in plants) or, more recently, deliberately (e.g., consumption of alcohol or other drugs).

At least 448 genes encoding drug-metabolizing enzymes are believed to exist in humans. The most famous group of these enzymes is the cytochrome P450 family, which consists of approximately 57 related genes. A small number of enzymes from this group metabolize most clinical drugs on the market.

Mutations in the genes encoding drug-metabolizing enzymes are responsible for a large amount of the variations in drug responses seen between individuals. Sometimes the variation in response can be minimal and harmless, but it can also be life threatening or cause significant disability if left undiagnosed.

John McDermott, MBChB, PhD
Clinical Geneticist and Researcher
University of Manchester

For example, it's been known since 1993 that as many as one in 500 people carry mutations in their mitochondrial DNA, which predisposes them to permanent hearing loss if they take aminoglycoside antibiotics like gentamicin. Surprisingly, despite these findings having been known about for 30 years, they are not a routine part of newborn testing for most children.

Dina Mariani / iStock / Getty Images Plus

"In some clinical settings, we do test for that. For example, when a child is diagnosed with cystic fibrosis," explained John McDermott, MBChB, PhD, a clinical geneticist and researcher at the University of Manchester who focuses on pharmacogenomics.

"But the challenge is that most prescriptions of antibiotics don't work like that. You don't know years in advance [if] they're going to need antibiotics."

Even in the field of oncology, the poster child for pharmacogenomics and precision medicine, the number of pharmacogenomic tests for cancer medications that are widely reimbursed and routinely carried out across the U.S. is relatively small and focused on variants with a large evidence base such as *DPYD* genotyping to reduce fluoropyrimidine toxicity.

Despite the slow adoption of pharmacogenomics, many factors are coming together to improve the situation and allow these potentially lifesaving tests to reach more people.

"I think that not only is testing more available, but physicians are specifically looking at pharmacogenomics now to help their patients. Here in the U.S., more insurance companies are also providing some reimbursement for these tests," said Kelly Caudle, PharmD, PhD, an associate member of the St. Jude Children's Research Hospital faculty and director of the Clinical Pharmacogenomics Implementation Consortium (CPIC).

Pamala Jacobson, PharmD
Pharmacist and Professor
University of Minnesota

However, she acknowledges that there remain barriers to uptake. "I still think we have got a lot of work to do on really educating physicians not only on the benefit of ordering a pharmacogenomic test, but also on how to utilize it. I think there's still a big gap there."

Implementation challenges

Despite an ever-increasing amount of data supporting the use of pharmacogenetic testing, it is still not as widely used as it could be. There are a number of reasons for this, but one key factor is a lack of physician education on this topic.

"Many people who are healthcare professionals haven't been educated in the field," said Pamala Jacobson, PharmD, a pharmacist and professor at the University of Minnesota who leads the Pharmacogenomics Extension for Community Healthcare Outcomes (PGx ECHO) educational program.

"We have done a tremendous job educating our students. Many young healthcare professionals have already been educated in the field of pharmacogenomics. But the reality is that the people in practice are still the older individuals, the more experienced and seasoned practitioners. They didn't get this when they were in school."

Aimiel Casillan
Genetic Counselor
Valley Children's Healthcare

Even genetic counselors do not cover pharmacogenomics in depth during training. Aimiel Casillan is a genetic counselor based at Valley Children's Healthcare in Madera, California, who has a research interest in pharmacogenomics.

"I did have probably a handful of sessions regarding pharmacogenomics, but it's not the focus of our genetic counseling training program," she explained. "I did have to take some extra training to better understand how to read pharmacogenomic reports, understand the implementation from a practical perspective."

Although there is a good research base on pharmacogenomics and disease-related variants, some areas of medicine lack consistent and reliable data and clinics do not have easy access to standardized tests. This can make the process even more

(continued on next page)

(continued from previous page)

difficult to navigate for healthcare providers who may not be experts in genetics.

"There's a lot a lot of issues with standardization in our area," said Caudle. "Not only regarding what variants you are testing, but also how we're reporting this out. We take a patient's genotype; we translate it to a phenotype. If we're not standardizing how we interpret that, then the patient is not getting the right recommendation."

Cassie Hajek, MD
Medical Director
Helix

Testing has historically also been too slow to be of real value to clinicians and other healthcare providers. "When you're sitting in front of your patient in your clinic, you don't want to wait seven days to know if I should or should not apply this, or if I should pick a different medication. You want to be able to treat them at that moment," said Cassie Hajek, MD, medical director at Helix, a population genomics and precision health company developing pharmacogenomic tests.

Cost is of course a big factor, both in terms of test price and whether insurance companies or governmental health systems in countries like the U.K. will pay for the tests. "I think our private insurers don't exactly see the value, quite yet, of pharmacogenomics, and that tends to be the sticking point as far as being able to connect our patients to this resource is concerned," said Casillan.

In 2022, McDermott and colleagues worked on a pilot program to institute newborn testing for mitochondrial variants linked to aminoglycoside-induced hearing loss in the U.K., called Pharmacogenetics to Avoid Loss of Hearing (PALOH).

He explained that the National Institute of Health and Care Excellence, which evaluates the value of a treatment or test for use by the National Health Service in the U.K., did an early value assessment of their study, but they ultimately concluded that more data was needed for a full endorsement.

McDermott and colleagues are now doing a longer and larger study to back up the initial data they collected, but the delay in broad implementation is understandably frustrating. "After you've done a program like PALOH, you've done a really nice implementation pilot, you've shown that actually this is something that could be used, getting that into routine care is really, really hard."

As patient records are becoming increasingly electronic, making results accessible to both patients and healthcare providers should theoretically be easier, but this is not always the case. This is a notable problem in the U.S., where the use of many different electronic health record systems make continuity of care problematic.

> "I think the pharmacogenomic guidelines have helped a lot, partly because of the genotype to phenotype translation and then the recommendation. Now you know what you should do if you have this genetic test available."

"It should be something that's right there at the center of that electronic health record," said Caudle. But "the electronic health record itself may not have the capability of even providing a pharmacogenomic result or genomic result in general, because it's just not set up to do that."

Breaking down barriers

Pharmacogenomic testing is not yet as widespread as it could be, but many motivated people, projects, and organizations are working hard to improve access.

Jacobson is leading the PGx ECHO project, which aims to boost confidence and competence in using pharmacogenomics to improve patient care. The project involves an online presentation for healthcare professionals once a month, which is free to join.

TEK IMAGE / SCIENCE PHOTO LIBRARY / Getty Images

"What's unique about ECHO is that it's case-based learning. So, you don't listen to somebody give a didactic lecture, but the education comes from the case," she explained.

"Somebody will come to us and say, I have a case, and I want advice on whether or not I should get pharmacogenomic testing for this person. Can I present it at your ECHO? Or we say, 'Can you please present the case you just had so we can train other people about what you learned?'"

CPIC was established in the U.S. in 2009 as a shared project between the Pharmacogenomics Knowledge Base and the Pharmacogenomics Global Research Network. It serves as an excellent education tool for everyone in the field of pharmacogenomics. The organization includes both experts and volunteers and has produced 28 clinical practice guidelines for more than 30 genes and 150 drugs.

"We have a full working group of about 10 to 15 people that actually work on that genotype to phenotype translation. And then we have a guideline author group," explained Caudle.

"I think the pharmacogenomic guidelines have helped a lot, partly because of the genotype to phenotype translation and then the recommendation. Now you know what you should do if you have this genetic test available."

In addition to working on the PALOH trial, McDermott and colleagues have been working on the Pharmacogenetics Roll Out – Gauging Response to Service (PROGRESS) program. This project helps primary care physicians (general practitioners) in the U.K. to integrate pharmacogenomic testing into their workflows in an efficient and easy-to-use manner.

It is still ongoing, but the team recently analyzed data from the first 500 patients included in the study, which was presented at the recent European Society of Human Genetics congress in Milan. "We were able to deliver pharmacogenomic results back for all of those patients," said McDermott.

"Over 95% of patients carry what we call a non-wild type pharmacogenetic variant. If you look at patients where they've got a relevant variant and they're exposed to that medicine, that's around 50% of participants, and in around one in eight people there would have been a recommendation that they should have a change to their prescription," he explained.

McDermott says that the physicians taking part in the project have been following the prescribing guidance given to them during the study but notes that the simple and easy-to-use online set up of the project has probably boosted uptake. "Our view is that if you make the tool easy enough to use, people will use it," he said.

In recent years, the cost of genetic testing has dropped and there are now many tests either on the market or being developed that aim to get quick results to patients and healthcare providers.

For example, both McDermott and Casillan have been developing quick tests for babies carrying risk alleles for aminoglycoside-induced deafness.

"When a newborn is being admitted into the neonatal intensive care unit and then has sepsis, an infection that needs to be treated right away with antibiotics, a doctor or neonatologist can't wait for a week to two weeks for results to make decisions about treatment," said Casillan.

"Usually, they have to be able to make that decision right away, so the intent of this technology is to limit that time to 20 to 45 minutes."


Westend61 / Getty Images

Helix has also been developing fast and efficient tests that can be performed within a short time and provided to healthcare systems at a reasonable price. Some are single gene tests, such as a test for the *APOE4* allele in patients with Alzheimer's disease who want to start treatment with Leqembi or Kisunla, both of which can cause significant side effects in individuals with two copies of the *APOE4* allele. Others can be gene panels for genetic variants that impact drug metabolism in a specific area like mental health, where certain genetic variants can predispose people to worse side effects from psychiatric medicines.

"Part of the reason for a panel is that it's a little more efficient," explained Hajek. "So, for example, in mental health, just going gene by gene would be pretty inefficient and probably fairly costly. Putting it in one test tackles both of those needs. It also puts everything in one place so that what we include on there is the information not just about the metabolizer status, but also the guideline recommendation."

Less than half of pharmacogenomic tests are reimbursed by health insurance companies in the U.S., but this is improving. Earlier this year, Florida passed legislation that mandates Medicaid coverage for biomarker testing, including pharmacogenomic tests, when supported by scientific and medical evidence. Similar legislation is now being considered by other states. Since the end of last year, the U.S. Department of Veterans Affairs (VA) has also supported pharmacogenomic testing for various indications for veterans.

(continued on next page)

(continued from previous page)

"There's definitely a cost-benefit to doing these tests, which is why I think the insurance companies are slowly starting to pay for them," said Caudle.

Due to the genetic nature of pharmacogenomic results, it is important that these findings are not lost in the medical system and are highlighted in the electronic health record. "Those results are valid for the rest of your life," emphasized Caudle. "Yes, we may discover new variants, so maybe a retest at some point in your life is a good idea, but what we discovered originally is still valid from the age of zero all the way up until the patient dies."

The lack of a true centralized and interconnected electronic health record system in the U.S., or even in countries like the U.K., can make this difficult, but steps are being made in the right direction.

> "When that patient goes to their general practitioner, there will be a prescribing moment. … And if there's pharmacogenomic guidance to be issued, it's pushed out and it flags inside of the electronic healthcare record."

"Our electronic health record system is immediately able to produce a best practice advisory, where if there's something contraindicated for an individual based on their pharmacogenomic status or their results, there's going to be a red flag for a provider who tries to prescribe a medication … all informed by CPIC guidelines," said Casillan.

McDermott and colleagues in the U.K. have been creating their own easy to use online tools to help with projects like PROGRESS.

"What we're doing is we've created a cloud-based resource where we store that data centrally," he explained.

"When that patient goes to their general practitioner, there will be a prescribing moment. … And if there's pharmacogenomic guidance to be issued, it's pushed out and it flags inside of the electronic healthcare record."

Is pharmacogenomic testing getting close to mainstream?

The pace of adoption of pharmacogenomic testing in the U.S. and elsewhere has been undeniably slow over the last few decades, but is it about to speed up?

"This year, I think it's going to change," says Hajek. "We have systems asking us for it, and they wanted to swap it in. … I think we're just going to start to just see it, I won't venture to say as standard of care, but more standardly in care. That will come as the evidence base grows."

Governmental legislation mandating biomarker testing, as well as uptake by large organizations like the VA, will definitely help promote pharmacogenomic adoption. Proposals like the Right Drug Dose Now Act, put forward by U.S. Representatives Dan Crenshaw and Eric Swalwell earlier this year, will also help uptake if passed.

Kelly Caudle, PharmD, PhD
Associate Member
St. Jude Children's Research Hospital

"I think there's been a lot of movement," said Caudle. "It's been slow. We always want things done tomorrow. That's just the world we live in. But I think it's been a good, slow growth, a real gradual growth where we get to learn as we move forward."

The reduction in price and increase in speed of testing will undoubtedly benefit uptake, with more providers being able to afford testing and insurance companies more likely to approve reimbursement.

Rapid digitization and an increase in the use of artificial intelligence (AI), for example, to clarify or flag test results for prescribing clinicians, will likely hasten the uptake of pharmacogenomic testing by making the whole process quicker and easier to navigate.

"Tuning into that and being able to allow the technology to integrate with the electronic health record system is something I'm looking forward to," said Casillan.

"I really think that AI is going to change things," said Jacobson. "There's some people developing artificial intelligence programs for pharmacogenomics, and those, to me, are exciting. … You could have an AI agent to help you make your clinical decision."

McDermott adds that it is important to remember that pharmacogenomic tests are just biomarkers and that integrating them with other medical information is key.

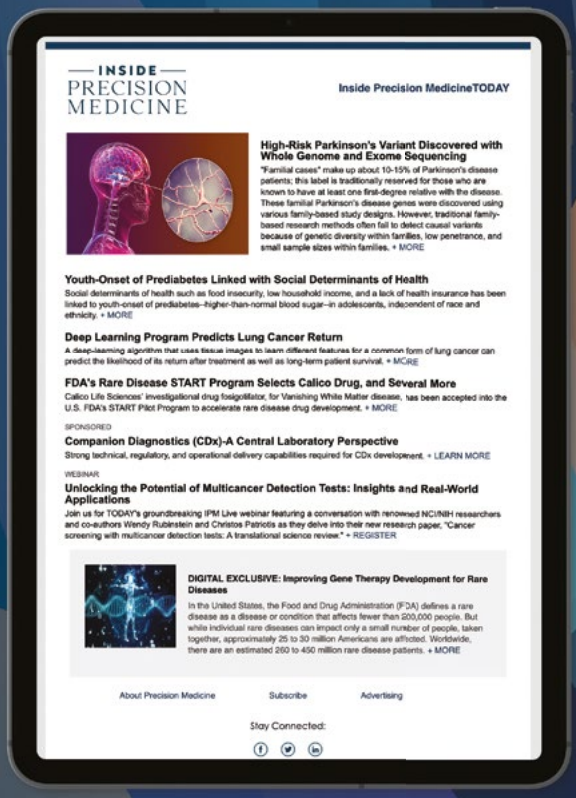
"I think where we need to move to in the field is thinking about how we can use not just pharmacogenomic data, but explicitly and specifically integrate it with other data."

He adds that it's important to consider what both patients and healthcare providers want in the pharmacogenomics space. "We see that there is an overwhelming demand from patients for this type of intervention," he said. ■

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.

Navigate the Evolving Landscape with *Inside Precision Medicine* eNewsletters

FREE SUBSCRIPTION



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

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

Subscribe Today and Gain Access to:

INSIDE PRECISION MEDICINE TODAY

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

INSIDE PRECISION ONCOLOGY

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

SPECIAL EDITIONS

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

PRODUCT INSIDER

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

Be the owner of your inbox.

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

SUBSCRIBE NOW

INSIDE PRECISION MEDICINE

Alena Butusava / iStock / Getty Images Plus

5 THE TOP FIVE EMERGING MICROBIOME STARTUPS FOLLOWING THEIR GUT

by Jonathan Smith, PhD

Fecal microbiota transplantation (FMT) has gained traction in the last few decades and microbiome-based therapeutics are getting ever more precise. These five private companies are harnessing the gut to treat inflammation, infections, and even cancer.

As sequencing technologies get faster and cheaper, researchers are increasingly shedding light on the complexity of the human microbiome.

Disruptions to the gut flora are linked to many diseases, with one classic example being *Clostridioides difficile* infections, where the pathogens exploit imbalances in the gut. As bacteria become increasingly resistant to antibiotics, FMTs have the potential to "reset" the microbiome and prevent *C. difficile* infections more effectively than traditional methods.

Unfortunately, FMT has drawbacks, like a poorly standardized manufacturing process and the risk of giving a recipient an infection. For this reason, newer therapies such as Ferring's Rebyota and Vowst by Nestlé Health Science and Seres Therapeutics have been approved by the U.S. Food and Drug Administration (FDA) with a more consistent and standardized manufacturing approach.

This rapid evolution is spurring strategic deals in the microbiome space and growth of the global market for microbiome therapeutics, which was worth an estimated $94.9 million in 2022 and is expected to grow by 35% per year to more than $1 billion by 2030.

While some startups in the field face challenges, with examples like Finch Therapeutics and Federation Bio, others are raring to develop more targeted and tailored microbiome-based therapies in immunology and even cancer.

Read on to see our take on the most promising private companies in the microbiome field, with a focus on those that have raised major funding rounds in the last few years.

1 EnteroBiotix®

EnteroBiotix

Founded: 2017 | **Headquarters:** Glasgow, Scotland

EnteroBiotix was set up by a medical doctor with the aim of harnessing the gut microbiome while retaining more diversity in the gut microbes than previous approaches.

In particular, the company is developing pharmaceutical-grade oral capsules containing gut bacteria derived from healthy donors as more refined alternatives to FMTs.

EnteroBiotix's lead candidate, EBX-102-02, showed promise in a Phase IIa trial for irritable bowel syndrome with constipation in March this year, with improvements in symptom severity, bowel habits, and abdominal pain appearing as early as week one. The company expects to follow up with a Phase IIb study later in 2025.

EnteroBiotix is also developing other Phase II-stage programs of EBX-102 for the treatment of liver cirrhosis, with promising safety and translational biomarker data released last year. Another program, run in collaboration with Imperial College London, is designed to reduce complications and improve survival in patients undergoing allogeneic bone marrow transplantation.

To date, EnteroBiotix has raised over £47 million ($64 million) from leading investors like Thairm Bio, Kineticos Life Sciences, the Scottish National Investment Bank, and Scottish Enterprise. The funding includes a £15.5 million ($21.2 million) Series A round in 2021 and a £27 million ($37 million) Series B round in 2024.

2 Enterome

Enterome

Founded: 2012 | **Headquarters:** Paris, France

Founded by biotech veterans and serial entrepreneurs, Enterome is using machine learning to mine huge databases of proteins from the human gut microbiome and develop what it dubs OncoMimics™ immunotherapies. These consist of combinations of microbiome-derived bacterial peptides that mimic antigens associated with tumors, training the immune cells to better hunt down a patient's cancer cells.

Enterome has raised an impressive €135 million ($158 million) in private equity and loans, including a $52.6 million round in 2020 and a $19 million round this year. The firm will use the latest cash to bankroll a Phase I/II clinical trial of its lead program EO2463 for the treatment of indolent non-Hodgkin lymphoma and prepare for a Phase III registrational trial.

EO2463 has so far shown a 78% complete response rate in relapsed/refractory follicular lymphoma patients when combined with standard of care including the drugs lenalidomide and/or rituximab.

Other clinical-stage pipeline programs include EO2401 for recurrent glioblastoma and adrenal tumors, and a third candidate for the treatment of metastatic colorectal cancer.

Enterome has had close ties with Nestlé's subsidiary Nestlé Health Science, with the partners teaming up to develop microbiome-based diagnostics in 2017 and immunology treatments in 2022.

3 KANVAS

Kanvas Biosciences

Founded: 2020 | **Headquarters:** Princeton, NJ

Kanvas Biosciences was co-founded by a team comprising a microbial imaging expert and an infectious disease specialist, who aimed to turn their microbiome and imaging know-how into treatments for conditions including cancer.

The company harnesses technology such as spatial biology, high-resolution imaging, and microbial genomics to precisely map host–microbiome interactions and tease out microbial strains with the best therapeutic potential. After selecting strains of interest, Kanvas uses culturing technology to produce up to 148 strains at an industrial scale.

The first preclinical-stage candidate in Kanvas' pipeline, KAN-001, is in preparation for entering clinical trials and addresses a common issue with a class of cancer drugs called checkpoint inhibitors: not all patients benefit from these treatments. KAN-001 is designed to restore balance to the gut microbiome and rebalance the immune system, which could improve the response rate of checkpoint inhibitors.

Kanvas is also working on a candidate called KAN-004 to ease colitis, which is a major side effect of immune checkpoint inhibitors, with the goal of improving patient outcomes in this setting.

Management has raised $29.5 million as of 2024, including a $12.5 million round in July 2024 and a $12 million pre-Series A round, both led by DCVC and Lions Capital. The latest funds will support the push to clinical trials this year.

(continued on next page)

4 microbiotica

Microbiotica

Founded: 2016 | **Headquarters:** Cambridge, U.K.

Microbiotica was spun out of the Wellcome Sanger Institute, with its co-founders including academics who researched techniques in anaerobic culturing and banking of the human gut microbiota.

The startup characterizes which bacterial strains are linked with positive outcomes in clinical trials with the help of bioinformatics techniques like machine learning. It then researches how the strains benefit patients and designs live biotherapeutics (LBPs) for specific patient populations.

Microbiotica was initially focused on treating *C. difficile* infections before shifting focus to immunology and oncology. Its lead candidate, MB097, an oral capsule containing nine commensal gut strains, is in a Phase Ib trial to test if it can boost response rates in melanoma patients to the checkpoint inhibitor Keytruda.

Microbiotica's second candidate, MB310, is in Phase Ib clinical development as a monotherapy for the treatment of inflammatory bowel disease. Data from both candidates are expected in 2025, and the milestones are expected to spur its growth this year.

Microbiotica has raised over £62 million ($85 million) in equity financing so far, including a £50 million ($68 million) Series B round in 2022 co-led by Tencent and Flerie Invest, and support from the Crohn's & Colitis Foundation.

5 VEDANTA BIOSCIENCES

Vedanta Biosciences

Founded: 2017 | **Headquarters:** Cambridge, MA

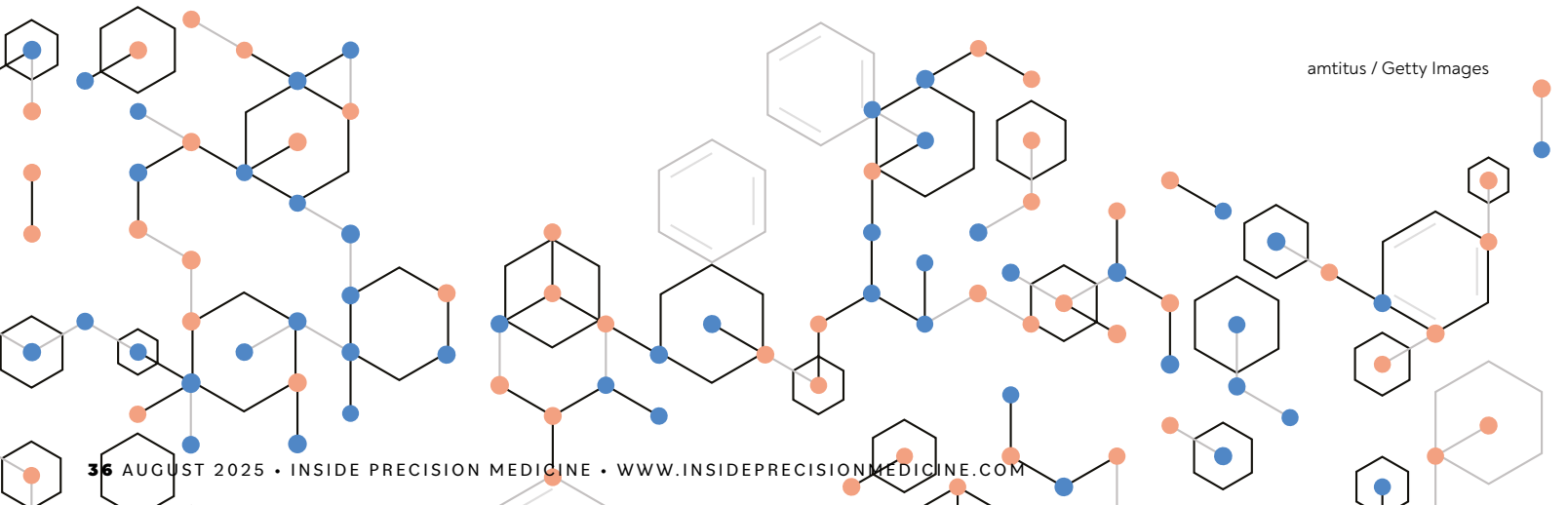
Vedanta Biosciences is a highly funded addition to this list, bagging a $106.5 million Series E round in 2023 with backers including co-founder PureTech Health, AXA IM Alts, the AMR Action Fund, the Bill & Melinda Gates Foundation, and Seventure Partners.

The company's academic founders applied their backgrounds in research on the immune system and its interactions with the microbiome. This expertise, along with a large gut bacterial strain library and manufacturing muscle, is helping the company develop therapies for recurrent *C. difficile* infections and immunology conditions based on specific bacterial consortia.

Its lead candidate, VE303, is composed of strains selected to suppress *C. difficile* through competition for nutrients and production of key metabolites to reduce gut inflammation. VE303 is currently being evaluated in a Phase III trial, with plans to apply for market approval from the FDA.

Another candidate called VE202 is in development for the treatment of inflammatory bowel disease with the aim of modulating immune responses. A preclinical candidate is also in development for the prevention of gram-negative antimicrobial-resistant infections, with backing from CARB-X. ■

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*.



amtitus / Getty Images

TARGA Imager: Accelerating Mechanistic Profiling Beyond Cell Painting

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

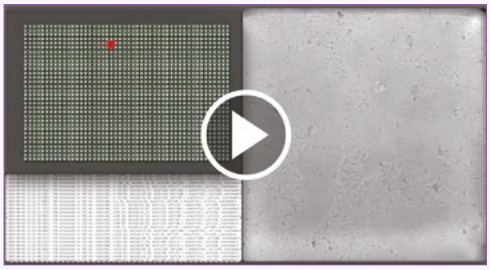


Figure 1. TARGA imaging 1,536-well plate in under two minutes.

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

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

Figure 2. TARGA Imager

References

S. Gustafsdottir and colleagues. Multiplex cytological profiling assay to measure diverse cellular states. PLoS ONE. 2013. 8:e80999.

M. Bray and colleagues. Cell painting, a high-content image-based assay for morphological profiling using multiplexed fluorescent dyes. Nat Protoc. 2016. 11: 1757-1774.

B. Cimini and colleagues. Optimizing the cell painting assay for image-based profiling. Nat Protoc. 2023. 18(7): 1981-2013.

J. Cross-Zamirski and colleagues. Label-free prediction of cell painting from brightfield images. Scientific Reports. 2022. 12: 10001.

C. Baker and colleagues. How phenomic foundation models are empowering the brightfield comeback. www.recursion.com/news/how-phenomic-foundation-models-are-empowering-the-brightfield-comeback

My Personal Genomics Journey in 23andMe's Resurrection Era

This three-part series examines the current paths for sequencing, analyzing, and utilizing an individual's genome to guide healthcare decisions

Jonathan D. Grinstein, PhD North American Editor

piyaset / iStock / Getty Images Plus

On January 27, 2011, a video called *Making Medicine Personal* aired with three customer testimonials that all shared a successful experience at the hands of personalized genomics.

In the first, an older white man explains how he gave his doctor his genomic testing results, which led to a diagnosis that would save his life. In the second, a middle-aged white woman shares how, over 15 years, doctors failed to properly diagnose her, but all that changed when she signed up for personal genomic testing, which pinned down the diagnosis. In the third, an older white man compares his prostate exam results supplied by his doctor with his genomic testing profile and is able to conclude that he probably has prostate cancer.

That was a commercial from 23andMe **(Box 1)**. This raises the question: *How has there not been a personal genomics revolution in healthcare in the past 14 years, and where are we now?*

In this three-part series, I will dive into the realm of personal genomics, which is experiencing a transformative resurgence. In Part 1, I interview the CEOs of an array of genetic testing companies to get a sense of the role of DNA sequencing in personalized healthcare, primarily focusing on the differences between direct-to-consumer (DTC), provider-mediated, and clinician-initiated models. In Part 2, I share my experiences with using a handful of these personalized genomics tests, all whole genome sequencing (WGS) and one microarray, from both the DTC and clinician-initiated sides. Finally, in Part 3, I offer thoughts on the direction of genomics in healthcare and medical research.

Kian Sadeghi
CEO and co-founder
Nucleus Genomics

We're all adults here

Kian Sadeghi has a captivating, Bill Gates-esque story of a young college dropout and technology whiz turned founder. His motivation stems from a family tragedy—his cousin died in her sleep due to what was belatedly discovered to be a rare genetic cardiac disorder. The mission to save people like his cousin is why Sadeghi says he founded the personal genomics company Nucleus Genomics.

According to Sadeghi, there has historically been a false dichotomy between clinical genetics and consumer-initiated genetics companies like 23andMe. He believes that this confusion is the result of decisions made by initial DTC genomics companies that were limited by the cost of sequencing a genome, which, in turn, dramatically limited the interpretability of the data.

"If you go back to 2006, when the cost of reading a whole genome was $10 million a sample, you can't sequence a person's genome commercially," Sadeghi told *Inside Precision Medicine*. "So, you have a choice: microarrays, gene panels, or sequencing small slivers of DNA. . . . The consumer companies

went with microarray technology, while the clinical companies went with gene panels. But if you use microarray technology like 23andMe, you can't identify the most consequential hereditary disease markers."

Today, New York-based Nucleus Genomics is selling consumer-initiated, provider-mediated kits that are not currently covered by insurance (but are HSA/FSA eligible) for a few hundred dollars, a figure Sadeghi believes will drop further still. The clinical-grade Nucleus DNA Health Test, which goes for $499, performs whole-genome sequencing at 30x coverage to screen for more than 24 common diseases, around 900 rare diseases, and, as a bonus, traits. It also includes Nucleus Family, a carrier screening analysis that analyzes hundreds more genes than even the largest panels today. That's a major jump from the microarray days of 23andMe and Ancestry not many years ago.

James Lu, MD, PhD
CEO and co-founder
Helix

The goal at Nucleus, Sadeghi said, is to empower consumers in healthcare, aligning with a broader societal movement toward greater personal agency. This approach, Sadeghi believes, could redefine the doctor-patient dynamic, shifting from what he calls a paternalistic model to a partnership aimed at proactive, preventative care. "By starting with the consumer, you implicitly give them agency and treat them like adults," Sadeghi said.

Sadeghi criticized the current system, where insurance often only supports genetic testing after a disease is diagnosed. "The largest insurer might cover a genetic test for cancer only after a woman gets breast cancer—that's crazy," said Sadeghi. Noting the inefficiency of waiting for insurers to adopt cutting-edge technology and predicting that genome sequencing will soon become so affordable that it will bypass traditional healthcare systems entirely, he said, "The cost of genome sequencing is dropping so rapidly that it will shortly be ubiquitous and inexpensive, requiring no insurance coverage at all."

From DTC to healthcare systems

When James Lu, MD, PhD, founded Helix a decade ago, he started with the DTC genomics model. But over time, he shifted the company to focus on population genomics rooted in a desire to drive meaningful healthcare outcomes. Reflecting on his experience, Lu highlights two key challenges with the DTC model.

First, Lu believes that the transactional nature of DTC genomics creates problematic incentives. Companies often market report volume, which requires a consistent need for more content. "When your incentive model is to have more reports, you will constantly ask, 'What is the minimum scientific requirement to create a new report?'" Lu explained. If you need to increase the number of reports, you inevitably have to include more marginal studies to be competitive. For Lu, a physician and scientist, this approach conflicts with the goal of delivering valid and useful genomic insights.

The second issue has to do with turning genomics insights into actions, which requires navigating a complex healthcare system. "If I tell you something about the risk of X, Y, Z … I actually have to go to work in the healthcare system to get them to do the things I need done," Lu noted. Without systemic support, individuals face barriers to accessing care, leading to missed opportunities for intervention. For instance, when women receive *BRCA* mutation results but lack system-level follow-through, "70% of those patients will get lost in follow-up within a year," said Lu.

Helix's pivot to population genomics focuses on integrating genomic insights into healthcare workflows to ensure actionable outcomes. "When we work with the health system, we spend only a little bit of time talking about genomics and most of our time talking about workflow," Lu stated. This task involves coordinating referral pathways, genetic counseling, access to additional screening, and follow-ups—essential

(continued on next page)

Box 1: The Life of 23andMe

In 2015, 23andMe, once the darling of DTC genetic testing, made a major turn with a business decision to pursue drug discovery themselves, under the direction of former Genentech executive Richard Scheller. Founded in 2006, the company revolutionized personal genomics by offering affordable genetic insights to millions, but as consumer interest plateaued, 23andMe began leveraging its massive genetic database to enter the biopharma arena, even after the FDA made a decision that led the company to stop offering health-related reports to new customers after November 22, 2013. Partnering with industry giant GlaxoSmithKline in 2018 marked a bold step into drug discovery, aiming to translate its massive database of human genetic data into novel therapeutics. The decision was a gamble on the promise of precision medicine but also a shift away from its DTC roots.

Yet, this pivot has faced formidable challenges, reminiscent of the Icelandic genomics pioneer deCODE genetics. In the early 2000s, deCODE sought to capitalize on its national genetic database for drug development but eventually faltered under the weight of scientific, financial, and market complexities. For 23andMe, the risk lies in replicating deCODE's trajectory—a visionary company caught between lofty scientific goals and the harsh realities of drug pipelines. While 23andMe's integration of consumer genomics with biopharma is innovative, the company filed for Chapter 11 bankruptcy in March 2025. In the June 2025 bankruptcy auction, founder Anne Wojcicki and her new nonprofit, TTAM Research Institute, reacquired 23andMe for $305 million.

(continued from previous page)

components for timely and effective care. He emphasized that "95% of that is not genetics. This care is fundamental, consisting of a patient's initial consultation, ongoing monitoring, and subsequent treatment.

To this end, for screening purposes, Helix mostly focuses on CDC-defined Tier 1 genomic applications—those with the most evidence to support their early detection and intervention for public health impact: hereditary breast and ovarian cancer, Lynch syndrome, and familial hypercholesterolemia. Helix has teamed up with several health systems to create programs offering free whole-exome sequencing for 100,000+ individuals, such as Tapestry with Mayo Clinic, In Our DNA SC with the Medical University of South Carolina, and The Healthy Nevada Project with Renown IHI.

Giordano Bottà, PhD
CEO and co-founder
Allelica

Less is more

On the scale of DTC evangelist to non-believer, Giordano Bottà, PhD, Allelica CEO and co-founder, is basically an anti-theist. "Most DTC tests do not have clinical value," Bottà told *Inside Precision Medicine*. "They often provide information on traits such as IQ, that don't have real medical impact and their predictive performance is very poor, harming the field by creating confusion. It's extremely difficult for individuals to understand what level of testing they're getting and whether it's actually useful for them."

Instead, Bottà's mission with Allelica is to fully capitalize on the use of polygenic risk scores (PRS) for actionable clinical care to prevent common diseases with significant genetic components **(Box 2)**. Allelica is not unique in using PRS, but Bottà is keen on targeting only a few major health challenges. Whereas Nucleus Genomics reports on over 900 disease risks—as of June 2025, only 91 were classified as actionable by the American College of Medical Genetics and Genomics—Bottà has focused Allelica on just a few common diseases, such as coronary artery disease, breast cancer, prostate cancer, type 2 diabetes, and Alzheimer's disease, by helping physicians identify patients at high risk, often invisible to traditional risk models.

"Up to 30% of heart attacks occur in people without traditional risk factors," Bottà explains, emphasizing the gap in current care. PRS, validated across diverse ancestries, allows reclassification of patients in borderline or intermediate risk categories into actionable groups. "We identify increased risks that are clinically actionable, like a two- or three-fold increase comparable to familial hypercholesterolemia," he noted.

> "Managing high-risk patients requires empathy and a personalized approach that cannot be replaced by handing information directly to consumers."

Emphasizing precision over mass-market approaches, Bottà contrasts Allelica's physician-led model with DTC testing, which he says lacks both scientific rigor and clinical relevance. Bottà said, "Consumer tests often overgeneralize risks, such as presenting a 2% lifetime risk as 'high,' which confuses users and undermines the field." Bottà, critical of DTC's inability to incorporate nuanced clinical decision-making, said, "Managing high-risk patients requires empathy and a personalized approach that cannot be replaced by handing information directly to consumers."

Allelica focuses on integrating PRS into existing clinical workflows to enhance prevention. For example, in cardiovascular care, PRS can intervene earlier than traditional tools like calcium scores by identifying plaque formation risks before disease progression. This, Bottà highlights, is real and immediate "precision medicine

Box 2: What are polygenic risk scores?

Polygenic risk scores (PRS) are reshaping the future of precision medicine by providing a deeper understanding of genetic susceptibility to common, complex diseases. Unlike single-gene mutations that drive conditions like *BRCA*-related cancers, PRS aggregates small genetic variations across the genome to calculate an individual's inherited risk for diseases such as heart disease, type 2 diabetes, and certain cancers. The promise of PRS lies in its ability to stratify risk within populations, highlighting individuals who might benefit from tailored prevention strategies or earlier interventions. For example, someone identified with a high polygenic risk for coronary artery disease could adopt intensive lifestyle changes or receive more frequent cardiovascular screenings, potentially averting a heart attack. Similarly, PRS for type 2 diabetes can guide at-risk individuals toward proactive weight management and dietary adjustments before the onset of disease. While still emerging as a clinical tool, PRS represents a paradigm shift—bridging the gap between population-level genetics and individualized care. As research expands and methodologies improve, PRS can be integrated into routine healthcare, offering a nuanced approach to disease prevention and redefining what it means to practice personalized medicine.

in action," where patient thresholds like LDL cholesterol are adjusted based on genetic predispositions.

Can anyone use a personal genomic test?

MyOme CEO Premal Shah, PhD, is outspoken about the shortcomings of many genetic testing companies, particularly those touting extensive gene counts in their reports. "I see reports all the time where people claim 800–1,000 genes," Shah said. "But we prioritize quality over quantity. We constantly reevaluate our gene reports. For example, we recently updated from an 81-gene to a 151-gene report after careful analysis by our clinical team. If a gene cannot be properly communicated to a patient for actionability, we won't include it. That's the rigor we take."

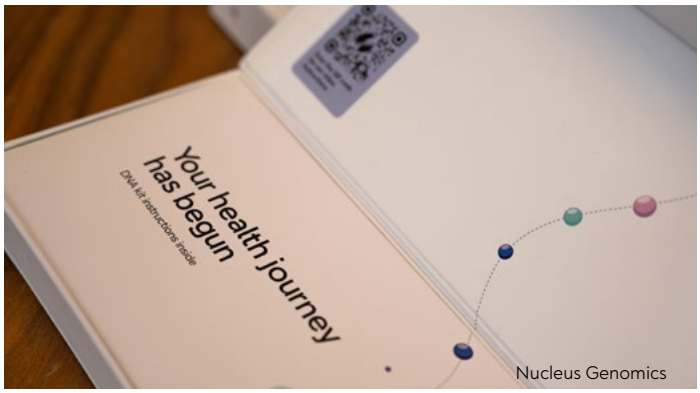
But perhaps the biggest question for Shah, regardless of whether the business model is DTC, goes back to the 23andMe commercial I mentioned at the beginning—they were three white people. For MyOme to be a success, Shah believes that everyone has to be able to benefit from the tests, including himself. "As an Indian male with inherent cardiac risk, I know how much this matters—to me, my family, and others I care about," he shares. This ethos underpins MyOme's mission to deliver meaningful, preventative insights tailored to diverse populations.

> "Most clinical models, like Framingham or the current iteration called the ASCVD calculator, were developed on predominantly Caucasian cohorts."

Shah criticizes the widespread use of unvalidated PRS models, often adapted from online repositories without proper consideration of ethnic and ancestry differences. "Most clinical models, like Framingham or the current iteration called the ASCVD calculator, were developed on predominantly Caucasian cohorts," Shah noted. "Similarly, PRS scores developed and validated in predominantly white cohorts will not provide accurate risk for non-Caucasian individuals. Being high-risk as a non-Caucasian may not accurately reflect your risk and clinical actions taken could do harm and [the] same can be applied to those deemed low risk that don't act. Additionally, companies claiming to adjust for ancestry often do so inaccurately."

Premal Shah, PhD
CEO
MyOme

MyOme employs proprietary ethnic decomposition technology to analyze genetic variants at an individual level, ensuring precision across mixed-ancestry individuals. "This technology allows us to rebuild models relevant to specific diseases while accounting for admixture," Shah explained. "We don't rely on self-reported ancestry, which is often inaccurate, and we validate all algorithms on independent cohorts before publishing our results."



Nucleus Genomics Kit

Shah contrasts MyOme's rigor with the practices of many competitors. "Some companies download public data, tweak it slightly, slap a logo on it, and call it a report," he said. "That's malpractice in my opinion." By prioritizing scientific integrity, MyOme aims to transform genetic testing into a tool for actionable, equitable healthcare outcomes. Shah said, "If we're not delivering insights that lead to meaningful actions for everyone, what's the point?"

Is there clinical use of DTC genomic screening?

The caption for the Making Medicine Personal commercial highlights a specific part of the video: *Because I had given my doctor the information from 23andMe, he got to a diagnosis much faster. I do say 23andMe saved my life.*

While this may have happened, many of the clinicians I spoke to say that if a patient arrives with data in hand or their genome stored on a hard drive, they are unlikely to look at it, let alone make a diagnosis or treatment decision based on the DTC test, even if the results come from a CLIA-certified, CAP-accredited, clinician-ordered test. To be fair to DTC companies, many have been providing direct connections to genetic counselors, ensuring that customers are not completely overlooked and have some guidance for what to do next, which may include repeating a similar test in a clinical setting.

There are still questions that linger in my mind around clinical validation, ethics, and patient privacy, however to learn more about these tests, I decided to participate in the process of having my genome sequenced and received a few kits from various genomic screening companies. The second installment of this series covers everything you need to know about these testing kits, from collecting DNA to analyzing results to deciding what to do next. ■

Jonathan D. Grinstein, PhD, North American editor for *Inside Precision Medicine*, investigates the most recent research and developments in a wide range of human healthcare topics and emerging trends, such as next-generation diagnostics, cell and gene therapy, genome engineering, and AI/ML for drug discovery for publications like *Scientific American* and *Genetic Engineering and Biotechnology News* (*GEN*). Jonathan earned his PhD in biomedical science from the University of California, San Diego, and a BA in neural science from New York University.

IN CONVERSATION *with*

Josh Mandel-Brehm

Chief Executive Officer, CAMP4 Therapeutics

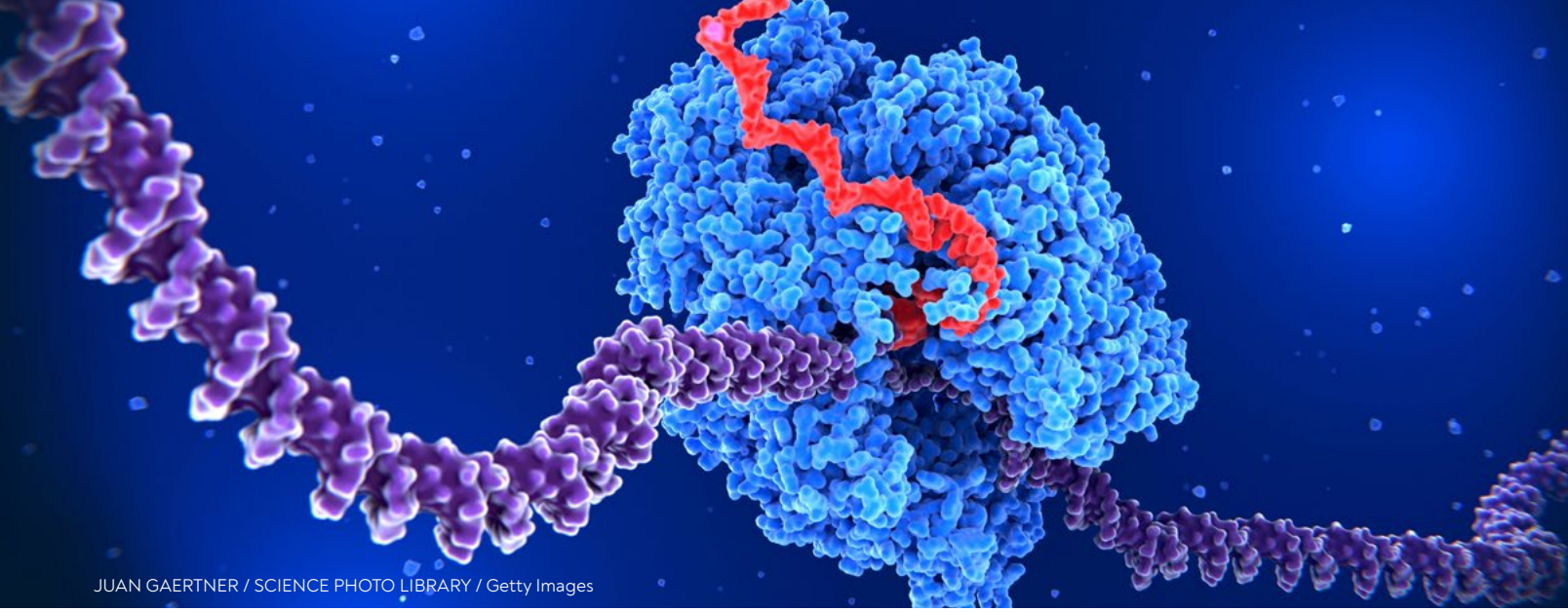
Genetic alterations that result in insufficient protein levels are a factor in numerous human diseases. Increasing messenger RNA (mRNA) to boost the production of healthy proteins holds potential therapeutic benefits for a wide array of conditions. CAMP4 Therapeutics is exploring this area by focusing on a previously unexploited form of RNA that regulates gene expression, known as regRNA.

The company has developed a platform to map regRNAs with the aim of precisely controlling gene amplification. This approach allows for the systematic development of antisense drug candidates designed to target specific regRNAs. Damian Doherty, editor in chief of *Inside Precision Medicine*, sat down with Josh Mandel-Brehm to discuss the potential of this innovative therapeutic strategy.

Josh Mandel-Brehm

Q: CAMP4's RAP Platform™ targets regulatory RNAs to upregulate gene expression. Could you elaborate on the novelty of this approach compared to traditional gene therapy or gene editing, particularly in terms of precision and potential for tunable protein level restoration across different tissues?

We developed our RAP Platform to systematically map regulatory RNAs (regRNAs) across human tissues and design antisense oligonucleotide (ASO) candidates to increase gene expression and restore healthy protein levels. Our approach stems from breakthrough research from our scientific co-founder, Rick Young, PhD, a professor of biology and core member of the Whitehead Institute at the Massachusetts Institute of Technology. Rick and his team discovered regRNAs, a novel class of RNAs that fine tunes the expression of every



JUAN GAERTNER / SCIENCE PHOTO LIBRARY / Getty Images

single gene in the human genome. Using our proprietary RAP Platform, CAMP4 can pinpoint the regRNA controlling a desired protein-coding gene and using ASOs, we can target and block specific regRNAs to increase the expression of the given gene. This approach has the potential to address the root cause of more than 1,200 haploinsufficient or partial loss-of-function diseases where upregulating gene expression may have a meaningful clinical benefit.

While gene therapies and editing aim to replace or permanently alter DNA, ASOs do not make any permanent changes to the genome. This enables tunable and programmable control of gene expression, which is especially important in diseases where overexpression can pose risks. Additionally, we can build on the significant work done to improve the durability of ASO activity and the already growing tissue-specific targeting strategies.

By combining new biological insights into gene regulation with a clinically validated modality, we have an incredible opportunity to rapidly advance therapeutics that target the root cause of a broad range of genetic disorders.

Q: Your lead program, CMP-CPS-001 for urea cycle disorders, has shown promising Phase I safety data. What specific preclinical evidence gives you confidence that targeting this specific regRNA will translate to clinically significant improvements in ureagenesis and reduced ammonia levels in patients?

Urea cycle disorders (UCDs) are a group of rare, genetic metabolic and potentially fatal conditions caused by mutations in enzymes or transporters involved in the urea cycle—the body's primary pathway for converting toxic ammonia into urea. When the cycle is disrupted, ammonia accumulates to dangerous levels, leading to symptoms ranging from lethargy and vomiting to life-threatening brain dysfunction, coma, and death. Our lead candidate, CMP-CPS-001, targets the regRNA controlling CPS1, which is a key enzyme within this pathway. Additionally, our research has found that increasing CPS1 expression can drive increased activity in other enzymes within this pathway, allowing us to potentially address more than 90% of patients with late onset UCDs.

In multiple models, we've demonstrated that CMP-CPS-001 can significantly upregulate CPS1 mRNA and protein levels in the liver, resulting in increased enzymatic activity in the urea cycle. More importantly, we were able to demonstrate that in non-human primates, administration of CMP-CPS-001 resulted in a significant increase in ureagenesis activity. Preliminary safety data from our Phase I clinical study of CMP-CPS-001 in healthy volunteers further reinforced the tolerability of our approach, and with the mechanistic clarity we've established preclinically, we're optimistic about the potential to deliver the first disease-modifying treatment option for patients living with UCDs. We look forward to sharing pharmacokinetic and biomarker data from this Phase I study later this year.

Q: Beyond UCDs and SYNGAP1-related disorders, CAMP4 highlights a broader potential for its platform in metabolic and central nervous system (CNS) diseases, with expansion into muscle, heart, and the immune system. What are some of the key criteria you use to select new disease targets and how do you prioritize them within these diverse therapeutic areas?

At CAMP4, our approach to target selection is guided by biological rationale and strategic scalability. We're building a pipeline that leverages the full potential of our RAP Platform by focusing on well-characterized, genetically defined diseases where upregulating gene expression can deliver a clear therapeutic benefit, particularly in areas with high unmet need.

We use several key criteria to evaluate and prioritize new targets:

- Transcriptional control via regRNAs: We first assess whether there's a clear regulatory RNA element that modulates gene expression because that's central to our platform's mechanism.
- Therapeutic window and dose-responsiveness: We prioritize genes where even a modest increase in protein levels is predicted to drive meaningful clinical outcomes.

(continued on next page)

(continued from previous page)

- Tissue accessibility and ASO delivery: Liver and CNS are our current focus since these tissues have well-established delivery mechanisms, but we're actively expanding into additional tissues via partnerships where ASO pharmacology is viable, including muscle and immune cells.
- Clinical and regulatory path clarity: Beyond the technical aspects, we are focused on selecting indications where there is a clear unmet need and a potential fast path to proof of concept and approval, using either surrogate biomarkers, and/or by leveraging accelerated regulatory pathways given the significant unmet need.

Q: CAMP4 has established collaborations, including the recent one with BioMarin. What is your strategic approach to partnerships? Are you primarily looking to leverage their expertise in specific disease areas or delivery mechanisms, and how do you envision these collaborations accelerating your pipeline?

Partnerships are a core part of our strategy to maximize the reach and impact of the RAP Platform by enhancing the speed, scale, and success of translating our science into transformative therapies for patients. We look to collaborate where there's strong scientific alignment and an opportunity to accelerate the development of RNA-based therapeutics in areas that complement our internal focus. Our ongoing collaboration with BioMarin is a great example. The BioMarin team brings deep expertise in rare genetic disease R&D and clinical development, augmented by their expertise with genetic medicines and related modalities, where our platform is already showing promise. This partnership allows us to extend the reach of our regRNA-targeting approach to new targets more efficiently, while benefiting from BioMarin's experience in developing disease-modifying therapies.

More broadly, we view partnerships as an opportunity to:

- Access complementary capabilities, such as novel delivery technologies or deep domain knowledge in specific therapeutic areas.
- Accelerate validation of our platform technology in diverse tissues.
- Advance additional programs and expand the impact of our pipeline beyond what we can deliver alone.

Q: With the recent IPO, CAMP4 has secured significant funding. How will these resources be strategically allocated between advancing current clinical programs, expanding the RAP Platform's capabilities (e.g., enhanced artificial intelligence/machine learning integration for target identification), and exploring new disease areas to maximize long-term value creation?

That's a very important question. Since debuting in the public markets last fall, we are focused on demonstrating clear proof of biology and clinical value for our UCD and SYNGAP1-related disorders programs. At ASGCT this year, we presented preclinical data from our SYNGAP1 program showing that administration of CMP-SYNGAP-01 in non-human primates led to a significant increase in SYNGAP protein levels that we believe will be therapeutically relevant. Building on these encouraging results, we're now preparing to initiate GLP (Good Laboratory Practice) toxicology studies as we advance toward the clinic.

We also are continuing to make strategic investments into tools to further enhance the power of our RAP Platform to identify additional clinically relevant targets where significant unmet needs remain, such as genetic CNS disorders, while maximizing value for our shareholders.

Q: Many genetic diseases involve complex regulatory networks. How does CAMP4's understanding of these networks, as captured by the RAP Platform, allow you to address diseases where multiple genes or pathways might be implicated, and could this lead to the development of combination therapies or multi-targeting RNA actuators in the future?

CAMP4's RAP Platform was purpose-built to decode the layered regulatory architecture that controls gene expression and precisely target regRNAs. In diseases with well-defined monogenic drivers, such as SYNGAP1-related disorders where mutations in the *SYNGAP1* gene result in a ~50% decrease in SYNGAP protein levels, this gives us a powerful foundation to select indications where a modest, tunable increase in a single gene's expression can be clinically meaningful. For more complex biology, such as in the urea cycle, the RAP Platform enables us to understand regulatory feedback loops, where boosting expression not only addresses the primary enzymatic deficiency but also reinforces upstream metabolic control. This level of network-aware targeting enhances both precision and potential efficacy.

In the future it would certainly be possible to deliver multiple candidates simultaneously; however, we're focused on monogenic disorders where there is a clear path to proof of concept. While designing a single multi-targeting candidate could be conceptually possible, our ASOs are designed for high specificity, typically binding to a single regRNA. That said, in certain loci, a single regRNA could conceivably influence multiple nearby genes, offering future opportunities for broader modulation where biology supports it. Ultimately, our indication selection strategy is grounded in rigorous preclinical validation and a focus on diseases where upregulating a single gene can have outsized therapeutic impact. As pioneers in the field of gene upregulation, we're excited about the potential of targeting regRNAs as a truly innovative therapeutic strategy. ■

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

THE STATE OF
PRECISION MEDICINE

WATCH NOW ON DEMAND | **REGISTRATION IS FREE**

Join *Inside Precision Medicine* as they explore the prevailing barriers and uncover potential avenues to ubiquitously implement precision healthcare

Effecting change in healthcare, especially through precision medicine, requires facing significant obstacles. From integrating vast amounts of genetic and clinical data into usable insights, to dealing with data privacy and security concerns, and addressing the high cost of advanced testing and precision therapeutics, issues in precision healthcare must be addressed directly. During the event which originally aired on March 5th, we unpack these challenges and discuss actionable solutions for widespread adoption of precision medicine.

Highlights of the summit include:

- Exploring the transformative potential of AI in diagnostics, clinical trials, imaging, and genomic data analysis
- VC perspectives on investment trends in 2025 within the precision medicine ecosystem
- Barriers to precision medicine in cancer care in community-based oncology practices
- Multiomics and the promise for precision medicine
- Real-world evidence and how to optimize real-world clinical care
- Registration is entirely free!

FEATURED SPEAKERS INCLUDE

Mara Aspinall
Illumina Ventures

Tam Nguyen, PhD
St. Vincent's Hospital Melbourne

Diana Azzam, PhD
First Ascent Biomedical
Florida International University

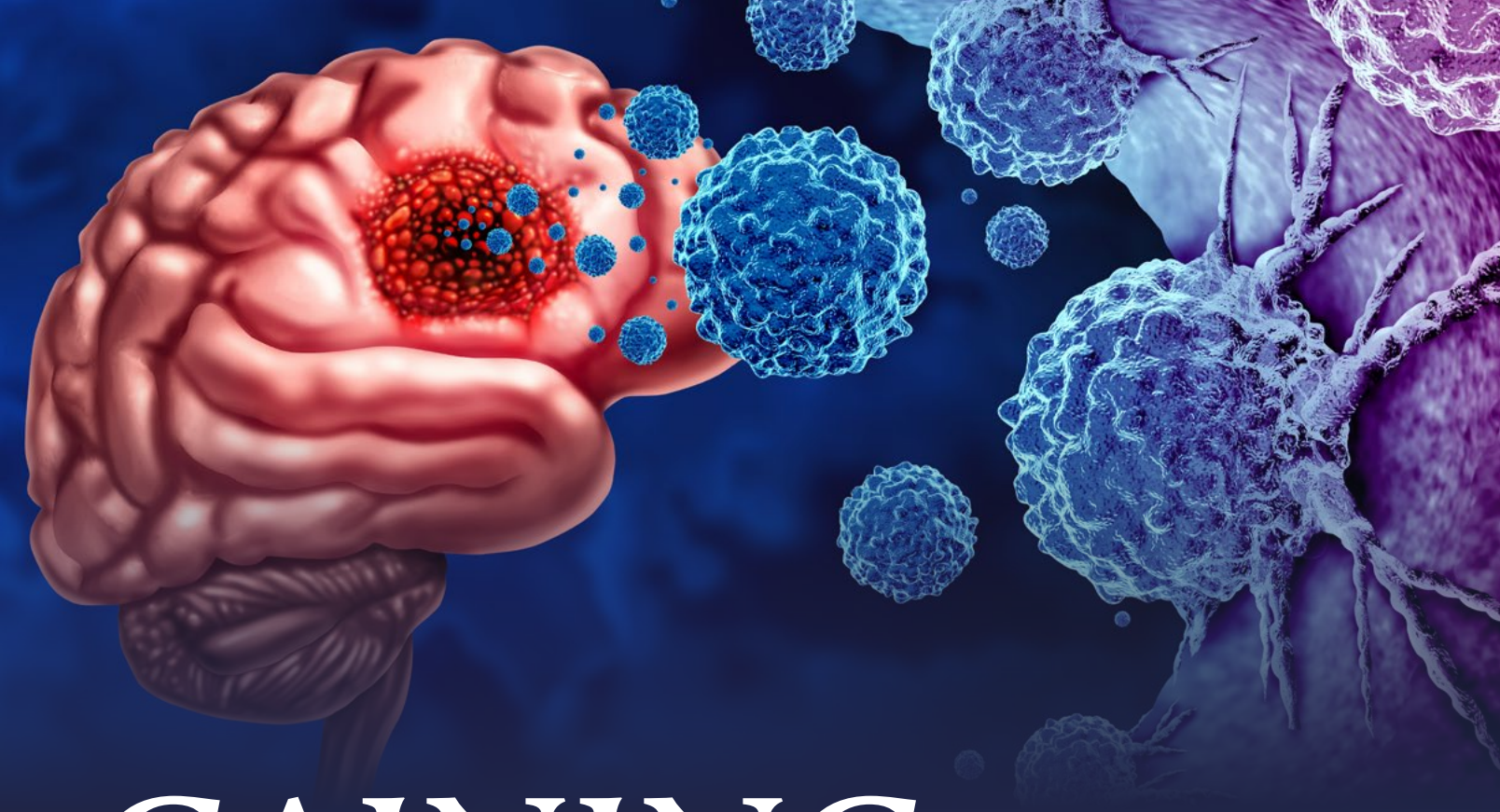
Nigam Shah, PhD
Stanford Health Care

Päivi Östling, PhD
SciLifeLab

SCAN HERE TO WATCH ON DEMAND

HOSTED BY
INSIDE PRECISION MEDICINE

SPONSORED BY
illumina® PROSCIA®



GAINING ON GLIOMA

New insights into glioma genomics and artificial intelligence tools are reshaping how we diagnose and treat brain cancer's most aggressive form

by Chris Anderson

wildpixel / iStock / Getty Images Plus

Gliomas are the most common primary brain tumor. Among all forms of glioma, glioblastoma is both the most aggressive and the most common, representing as many as 55% percent of all gliomas according to data from the National Institutes of Health.

The challenges to treating glioblastoma are many, which is part of why it so deadly. Glioma is often diagnosed at later stages of the disease. In addition, glioblastoma could be considered two diseases: one comprising a solid tumor that most often forms in the frontal or temporal lobes and the other an infiltrating element that coexists with normal brain cells. Treatment that involves surgically removing the tumor, therefore, cannot address the second element.

Currently an incurable cancer, most treatments focus on controlling the tumor to preserve a patient's quality of life for as long as possible. The prevailing treatment regimen, often referred to as the Stupp protocol, has remained virtually unchanged for nearly 20 years and involves tumor resection followed by radiation therapy and chemotherapy with temozolomide. Progress to improve treatments

has been slow due to factors like invasiveness, tumor heterogeneity, immunosuppressive characteristics of the tumor microenvironment, and a variety of resistance mechanisms to both chemo- and radiotherapy.

The frustration that accompanies the slow progress is palpable among researchers. "If ten years from now, I have to sit at a tumor board and hear 'temozolomide and radiation,' I'll know I wasted my life," said glioblastoma researcher Matija Snuderl, MD, a professor of pathology and director of molecular pathology and diagnostics at the NYU Langone Medical Center.

Matija Snuderl, MD
Professor and Director
NYU Langone Medical Center

Recent research efforts leveraging improvements in sequencing technology, combined with machine learning and artificial intelligence (AI), are now accelerating advances in the development of new therapeutic modalities like immunotherapy, as well as in diagnostic approaches that can more accurately characterize disease subtypes. These advances perhaps foretell a future of targeted therapies for glioblastoma.

For instance, based on research at Snuderl's NYU lab, and clinical validation completed in 2019 used a combined machine learning and genome-wide profiling approach to develop a DNA methylation-based system identifying epigenetic signatures to classify CNS and other tumors. Using this approach researchers have been able to accurately classify more than 180 different subtypes of CNS tumors including more than 10 distinct molecular entities that were previously lumped into a single GBM diagnosis.

"It has really changed the paradigm," Snuderl said. "Because when I was a pathology fellow, all our diagnosis of glioma largely was based on hematoxylin and eosin slides, which is a technology from the 19th century. That's all we had. Now we know that all these tumors that look alike are actually composed of multiple biologically, clinically, molecularly distinct entities. It's the first time we have a better chance of finding new therapies."

Insights from extrachromosomal DNA

Multi-omics studies are reshaping our understanding of a variety of diseases, including cancer. Having seen the understanding of other cancers shoot ahead, glioma and glioblastoma researchers are finally along for the ride.

In one such endeavor, researchers at City of Hope and collaborating institutions have constructed a genomic framework that maps, for the first time, how extrachromosomal DNA (ecDNA) shapes the spatial and molecular landscape of gliomas. By using spatial transcriptomics, tumor-normal DNA sequencing, and bulk RNA analysis, they demonstrated how ecDNA and tumor heterogeneity co-evolve, generating subclonal tumor regions with distinct oncogenic profiles. This research provides insight into the plasticity of glioma genomes and a way to better identify therapeutic targets.

"We were seeing these ecDNAs—what used to be called double minutes—as far back as 2011," said David Craig, PhD, professor and chair of the department of integrative translational sciences at City of Hope. "They form a circular plasmid-like structure outside the chromosome, often carrying hundreds of copies of oncogenes like *EGFR*. But what's really interesting is they are not just passive carriers. They are actively changing the tumor's microenvironment at the DNA level."

Currently, the classification of gliomas relies on a spectrum of histological and molecular markers, like mutations in *IDH1/2*, *TP53*, and alterations in *EGFR, ATRX*, and chromosomal copy number states. Previous studies to characterize glioma heterogeneity have either lacked spatial resolution or did not integrate multi-omics datasets that could provide insights into the full scope of tumor evolution.

David Craig, PhD
Professor and Chair
City of Hope

The new research by Craig and colleagues focused on a less-explored area of glioma genomics—the role of ecDNA. They specifically focused on double minute chromosomes that exist outside of the traditional chromosomal framework and amplify oncogenic drivers such as *EGFR*, *MDM2,* and *MDM4*. The investigators analyzed 11 gliomas spanning glioblastomas, astrocytomas, oligodendrogliomas, and diffuse midline gliomas, along with a replication cohort of six additional high-grade glioblastomas. Using spatial transcriptomics, they tracked how ecDNA-driven oncogenes and somatic loss of heterozygosity (LOH) events influence tumor cell behavior in different regions of the tumor microenvironment.

The team found that *EGFR* amplification, often observed on ecDNA, occurred in spatially distinct clusters within glioblastomas. These *EGFR*-high regions corresponded to hypoxic tumor zones, consistent with prior reports that hypoxia contributes to therapy resistance and poor prognosis.

"Wherever we saw the progression to hypoxia, we also saw double minutes—either separate or combined amplifications of *EGFR* and *MDM2/4*," Craig said. "In one case, the tumor lost the

(continued on next page)

(continued from previous page)

entire chromosome 17, which carries *TP53*, and it had the same functional effect. That's when we realized we were looking at two major pathways converging in these aggressive regions."

Spatial transcriptomics uncovered this phenomenon in glioblastoma A1, revealing a subclone with *EGFRvIII* expression and complete LOH of chromosome 17 containing a *TP53* mutation. The spatial alignment of *EGFR* amplification and *TP53* allelic loss indicated that these genomic events may cooperate to form hyperproliferative regions, potentially setting the stage for aggressive progression or therapeutic resistance.

> "We want to get where lung cancer is. Lung cancer has EGFR inhibitors that work. We're working with the same genes in glioma and not getting the same results. That tells me we're missing something. Understanding how ecDNA drives this plasticity is key to filling that gap."

Analysis of other glioblastoma samples revealed amplification of *MDM2* and *MDM4* on ecDNA in separate tumor regions. These regulators inhibit the p53 tumor suppressor pathway, reinforcing the conclusion that ecDNA not only promotes oncogene amplification but also facilitates the inactivation of key tumor suppressors. In regions where both *EGFR* and *MDM2/4* were amplified, cells appeared less reliant on hypoxia-driven angiogenic signaling, suggesting a shift toward more autonomous and proliferative behavior.

"This is about plasticity, how tumors can adapt and carve out these micro-niches," Craig said. "The *EGFR* and *TP53* pathways together seem to condition the cells to exclude immune infiltration, creating these protected cores where cells thrive under hypoxia."

From a clinical and translational perspective, this research lays the groundwork for future studies to integrate spatial and genomic data with an eye toward developing more targeted therapies. Identifying tumor subregions that harbor both *EGFR* amplification and p53 pathway inactivation may help stratify patients for clinical studies. By mapping the distribution of ecDNA-driven oncogenes, oncologists may soon be able to identify regions of potential therapeutic resistance or recurrence.

Despite limitations that the authors noted, such as sequencing depth and resolution constraints inherent to current spatial technologies, they believe that their work provides an important model for applying integrative multi-omics to tumor biology. As these methods evolve and scale, the utility of spatially resolved tumor profiling will continue to improve for cancers like glioma. By elucidating how ecDNA and subclonal evolution shape the glioma microenvironment, researchers now have fertile ground to identify drug targets.

"We want to get where lung cancer is," Craig noted. "Lung cancer has *EGFR* inhibitors that work. We're working with the same genes in glioma and not getting the same results. That tells me we're missing something. Understanding how ecDNA drives this plasticity is key to filling that gap."

Insights from Hi-C

Recent advances in structural variant (SV) detection are redefining the molecular understanding and clinical management of gliomas, particularly glioblastoma, which is one of the most heterogeneous and therapeutically resistant forms of brain cancer. Building on his lab's groundbreaking research in DNA methylation, Snuderl and team recently applied Hi-C chromatin conformation capture to formalin-fixed, paraffin-embedded (FFPE) tissue samples to better understand how cancers and gliomas develop. The team showed that Hi-C that could detect complex structural variants (SVs) at the DNA level, including rearrangements involving non-coding regulatory regions. This allowed the NYU researchers to identify tumor drivers that were previously not detectable via RNA next-generation sequencing (NGS) or other standard clinical panels.

The three-dimensional (3D) perspective provided by Hi-C can be combined with methylation and transcriptomic insights to form a triumvirate of analytical methods for the identification of new biomarkers. With Hi-C, tumors once considered genomically silent can now be interrogated for hidden drivers.

In a study analyzing 71 FFPE samples across ten solid tumor types, Hi-C showed 98% concordance with established clinical tests while uncovering additional SVs in cases previously classified as negative. Among these, one subset had rearrangements involving targetable biomarkers like *NTRK* and *PD-L1*, which were not expressed as fusion transcripts but comprised regulatory hijacking events detectable through 3D genome structure analysis. In glioblastoma, where co-amplified tyrosine kinase receptors and multiple subclonal populations coexist, such events are significant.

gorodenkoff / iStock / Getty Images Plus

> "Molecular neuropathology has now outpaced probably all other fields in how well we can classify brain tumors."

"If you just target *EGFR,* you would have this whole other clone that you cannot target," said Snuderl, noting that this heterogeneity "is an inherent problem of gliomas."

Hi-C's ability to detect gene rearrangements with noncoding regions is an important advance. "These rearrangements are completely invisible to all the clinical panels," Snuderl said. The detection of ecDNA and chromothripsis through spatial analysis provides additional insight into the mechanistic drivers of therapy resistance, as also shown by the recent City of Hope research.

The heterogeneity of gliomas has made targeted therapy particularly challenging. Multiple subclones with different oncogenic alterations can exist within the same tumor, enabling clonal selection and resistance under selective pressure. Structural rearrangements involving non-coding DNA, metabolic divergence between pediatric and adult gliomas, and epigenetic plasticity further complicate treatment. "Considering glioblastoma one disease is the same as if you said that leukemia is one disease," Snuderl said, while admitting that for years he was jealous of the tools that could be used to diagnose and classify different forms of leukemias and lung cancers. "I wished that one day we would be there, and now we are there. Molecular neuropathology has now outpaced probably all other fields in how well we can classify brain tumors.

"We sub-classified this disease to molecular minutiae in every possible way. I'm not saying we know exactly the significance of each of those subtypes, but we know that they are different."

Snuderl is now hopeful that Hi-C can experience a relatively quick transition as a diagnostic tool. It requires fewer tissue slides than RNA NGS, is compatible with existing NGS infrastructure, and employs a standardized, single-pot chemistry workflow that can be automated, all of which should aid in future development. Additionally, Hi-C can be performed on FFPE samples up to 15 years old, expanding access to archival material that is critical to identifying biomarkers and drug targets.

"The idea was always to build it here (at NYU Langone) and then distribute it," Snuderl said, which aligns with his broader vision of democratizing access to precision diagnostics by translating them into routine clinical care.

Sequential imaging to detect recurrence

Not all recent advances in glioma characterization have come from molecular analysis. A new study led by researchers at Mass General Brigham's Artificial Intelligence in Medicine (AIM) Program leveraged deep learning models to analyze sequential magnetic resonance imaging (MRI) scans and showed that they could significantly improve the prediction of glioma recurrence in pediatric patients.

Using nearly 4,000 post-treatment MRI scans from 715 pediatric patients across three institutions, the research team built a self-supervised temporal deep learning tool that analyzed changes in brain scans over time. Unlike traditional AI models, which evaluate single imaging timepoints, their method taught the algorithm to recognize the chronological sequence of scans before training it to predict recurrence. "We hypothesized that AI could be trained to also analyze serial scans, but that this would require novel techniques," said Benjamin Kann, MD, an assistant professor of radiation oncology at Harvard Medical School and part of the AIM Program. "Simply feeding a traditional AI tool multiple scans leads to poor performance, so we devised a strategy using a self-supervised learning technique called temporal learning."

Benjamin Kann, MD
Assistant Professor
Harvard Medical School

This approach substantially improved the accuracy of predicting disease recurrence, achieving 75–89% accuracy for identifying recurrence within one year of completing treatment. This was significantly better than the current rate of 50% accuracy achieved using single images. Improvements plateaued after incorporating four to six sequential scans, suggesting a practical threshold for future clinical use. The model's design also mimics clinician reasoning by focusing on comparative changes over time, which could support greater trust in its outputs. "When we as radiologists or clinicians interpret scans in surveillance, we always compare the current scan to prior scans," said Kann. "Our AI tool was designed in the same way."

Another significant finding was that the model performed reliably across the spectrum of glioma subtypes, despite their heterogeneity. According to Kann, "Heterogeneity actually is a good thing in developing models like these, because it allows the model to learn different signals that lead to faster, or slower, recurrence."

The study's findings offer potential avenues for risk-adapted surveillance strategies and earlier therapeutic intervention. In future clinical trials, the team hopes to evaluate whether early treatment initiation for high-risk patients identified by the model improves recurrence-free survival. If validated, the tool may support reduced scan frequency for low-risk patients, alleviating the burden of long-term imaging for children and families. ■

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*.

entrePRECISIONeur

Breaking into Precision Psychiatry

by Helen Albert Senior Editor

There is a lot of potential for precision medicine to improve the diagnosis and treatment of psychiatric disorders like depression. The complexity of these conditions, a lack of reliable biomarkers, and various other factors have made targeted therapeutic development in this area hard, but this is something that Delphine Charvin, PhD, CEO and co-founder of Elkedonia, is hoping to change.

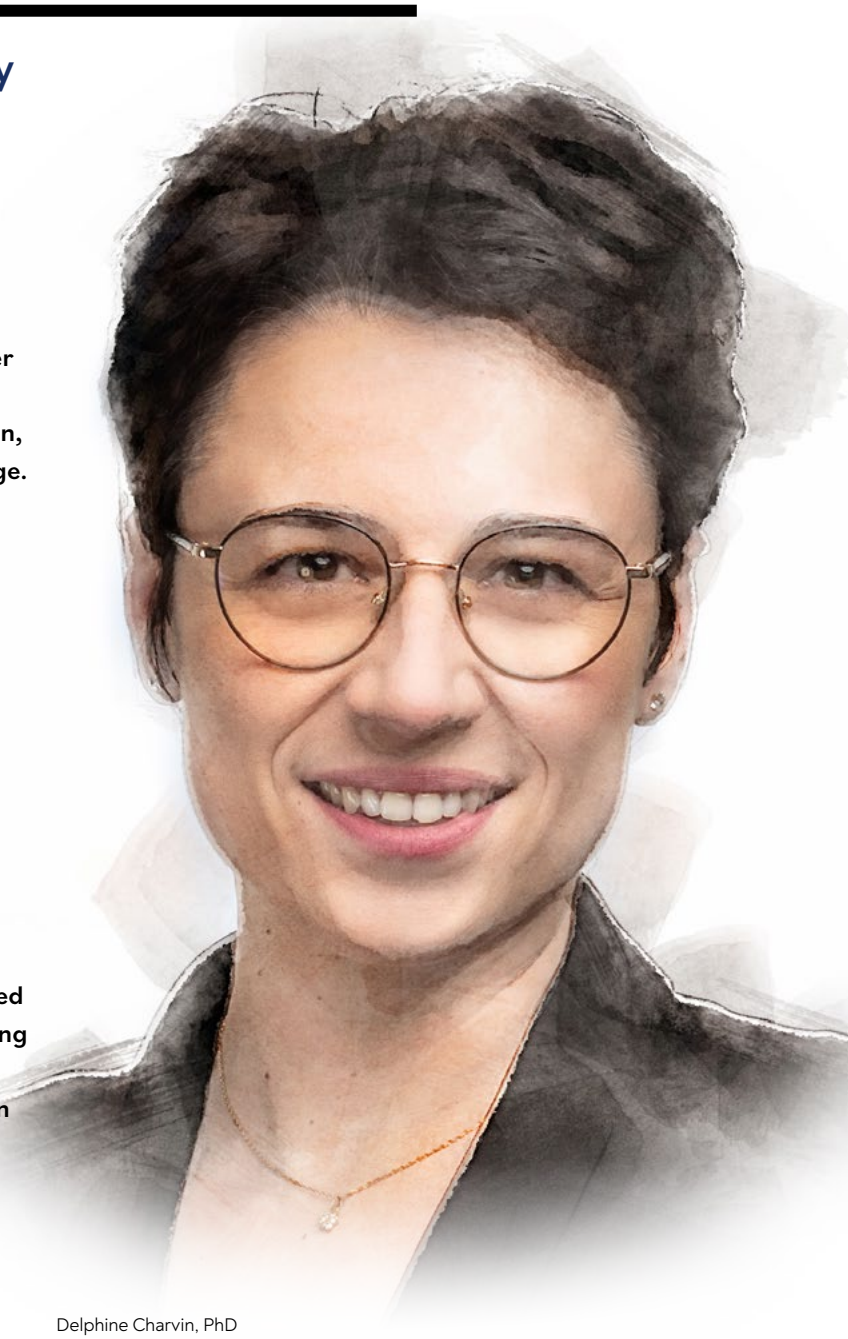
The company was launched last year by French biotech incubator Argobio Studio with Charvin as the founding CEO to develop a first-in-class, non-addictive, non-hallucinogenic antidepressant targeting the Elk1 protein. It has already raised €11.3 ($13) million in a recent oversubscribed seed funding round.

Elkedonia's premise is based on the work of scientific co-founder Jocelyne Caboche, PhD, currently director of research at the National Center for Scientific Research (CNRS) at the Sorbonne.

After completing a PhD in neuroscience in Caboche's lab and a postdoc at the École Polytechnique Fédérale de Lausanne (EPFL) in Lausanne, Switzerland, Charvin worked for Merck Serono and Addex Therapeutics before becoming a co-founder and CSO of Parkinson's disease focused Prexton Therapeutics, which was acquired by Lundbeck in 2018 for $1.1 billion.

Rather than just providing space and support for existing startups to grow, Argobio sources, builds, and launches startups by first identifying promising academic research and then assembling a good team to develop the initial research into a standalone company. Before becoming CEO at Elkedonia, Charvin helped launch other startups by working as a partner at Argobio for several years.

Charvin spoke to *Inside Precision Medicine* senior editor Helen Albert about her career and inspirations, Elkedonia, and what she hopes to achieve in the precision psychiatry space in the future.



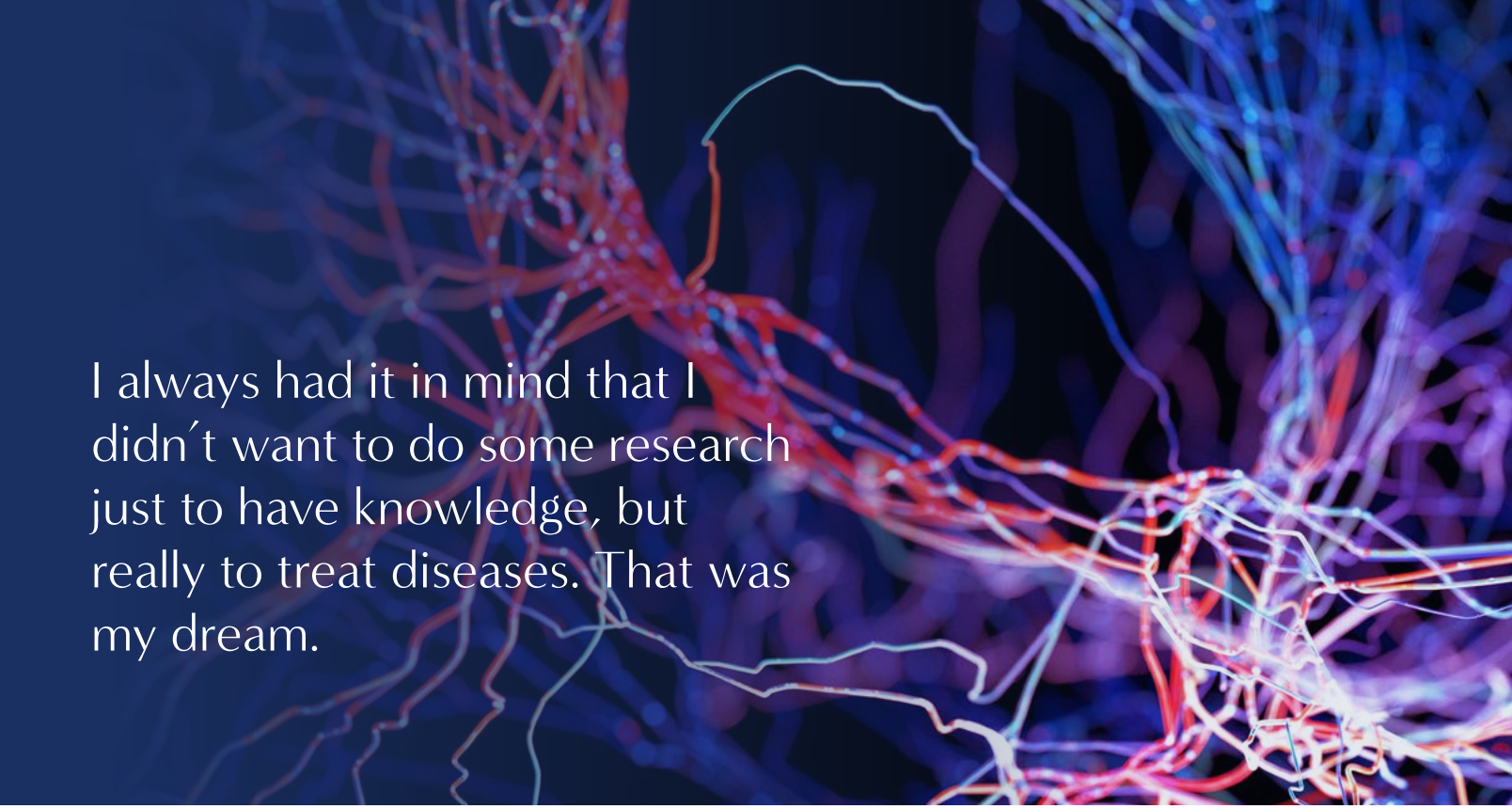
Delphine Charvin, PhD

Q: What inspired you to become a scientist?

Charvin: In France, we have a TV show every year that is called Téléthon focusing on scientists that are working to try to find new therapies for very rare diseases. I watched it when I was about 14 years old and I thought that what the scientists on the show were doing just made sense and was really purposeful. That's when I started to be interested in pursuing a career in this area, and it was always my goal to work on finding therapies for unmet needs from then.

Q: What attracted you to work in neuroscience?

Charvin: It was based on my studies. I really had a passion for neuroscience, so I decided to do a PhD in this area. I always had it in mind that I didn't want to do some research just to have knowledge, but really to treat diseases. That was my dream. I have evolved a bit on this dream, but that's how



I always had it in mind that I didn´t want to do some research just to have knowledge, but really to treat diseases. That was my dream.

Andriy Onufriyenko / Getty Images

it started. During my time in biotech and pharma companies, I understood that if you don't have a diagnostic or something to measure the effect of the treatment, then you will not have a cure. That's how I started to be very interested in precision medicine and not only in therapies, but also diagnostics and biomarkers.

Q: Did you always want to work in industry?

Charvin: I had already decided to go into the therapy side of things during my PhD, which was on better understanding the role of dopamine in Huntington's disease. My post-doc was also very applied to a condition, amyotrophic lateral sclerosis or ALS. I did my post-doc with Patrick Aebischer, MD, who is very entrepreneurial in his attitude. He has founded several companies, so he helped me understand this world better.

Q: How can precision medicine help improve outcomes for psychiatric patients?

Charvin: It's what we all want to do, but it's not easy. It's very new. In research and in congresses, we hear a lot about precision medicine for psychiatry, for neurology in general, but for psychiatry in particular. We are 30 years late when compared to oncology, but it's a good model. We don't treat cancer, we treat prostate cancer, or we treat a specific type of breast cancer or similar. This is the goal for neuropsychiatry as well. We don't want to treat depression. It's too wide. We want to treat depression associated with high inflammation, for example. And this is the precision we want to reach, but we are not there yet.

When I was working at Lundbeck there was a decision from the management team that there would be no new drug development programs without a biomarker. It was a very strong decision at that time, and it was worrying for the research team because we didn't know what biomarkers to look for. That's when I started to be very interested by these aspects because I had to be. I also have experience of bringing a drug into Phase II trials at Prexton Therapeutics and I'm sure the readout would have been different with a biomarker.

To assess treatment efficacy in psychiatry, we use clinical scales that are questionnaires. We ask the patients how they feel, and it may not be sufficient. If we can have something that we can measure that is objective, that has progression over time, that would be much easier.

Q: What is the story behind the founding of Elkedonia?

Charvin: The story behind Elkedonia is based really on the Argobio Studio model. When I joined Argobio, four years ago now, my role was to build a neurology franchise within Argobio Studio. So, the first thing I did was to go and check the literature and look for academic institutes with potential breakthrough innovations that could lead to new therapies. Elkedonia, in particular, comes from the lab where I did my PhD. It was a project from Caboche, who was my director during my PhD. I didn't work on this research, but I knew that she had this project that was very different, and I thought it was very promising for psychiatry.

I contacted Jocelyne to see if she would be interested to work with us at Argobio and assess if we thought it was something that we could develop into a drug development program. She was very happy and motivated because of our preexisting

(continued on next page)

(continued from previous page)

relationship, so there was a lot of trust among us. We did some experiments, and we realized that there is a really strong potential for something very different.

Psychiatry is not an easy field, so we wanted to test the business appetite first. We contacted a lot of venture capitalists and pharma investors to introduce the concept and the indication, and we received very positive feedback and a lot of early attention. What is particularly attractive here is that the target is very different to others in the field.

Another aspect that is very important is that we have some data from patients that show that we could just use blood samples to track target engagement for our program. This is also, I think, the big part of our attraction for pharma, in particular.

Q: What is the science behind Elkedonia?

Charvin: Our target is a transcription factor called Elk-1, which is involved in regulation of neuroplasticity. What has been shown in depression, but also in other types of neuropsychiatric disorders, is that there is abnormal neuroplasticity involved in the transition between an acute status to a chronic disorder. That's what we want to act on, the chronicity of depression. We want to restore neuroplasticity and go back to a normal acute response to stress.

> "It´s a start. I think it´s a step in the right direction, but there´s a lot to be done. For now, a lot of monitoring is done by imaging studies. But I think even in neurology, we should be able to use blood or saliva biomarkers in the future."

Q: What is unique about what you are trying to achieve?

Charvin: We are acting on neuroplasticity and our target is intracellular and not at the synapse. For now, all antidepressants act at the synapse, so very early in the screening cascades and they all have a similar profile, acting slowly with a lot of treatment resistance and some side effects.

There are some "new" medications using ketamine, which is a very old drug. What is new is that it has shown some acute efficacy. For a classical antidepressant, you have to wait between four to six weeks before seeing an effect in patients. With ketamine, in hours you can see an effect in patients. Ketamine, esketamine, psychedelics, and these

onimate / Stock / Getty Images Plus

kinds of molecules still act very early in the screening cascade and have some side effects that are not easy to handle, like producing hallucinations for some patients, or a very high risk of addiction to the drug. That's why we want to act differently, downstream in the cascade, and not trigger receptors that are involved in hallucinations or addiction.

Of course, there is a high risk because it's very early stage. We have to demonstrate all of this in patients. But if it works, it will be very different. So that's why investors are interested.

Q: Why has it been so difficult to progress therapies that are being developed for neuropsychiatry to the clinic?

Charvin: From my own experience at Prexton Therapeutics, I really think biomarkers are key. To measure the treatment efficacy, but also to identify the patients. For example, at Prexton, we were working on Parkinson's disease. We were trying to target patients with different symptoms, and it was really a wide population, with a lot of variability. For neuropsychiatry in particular, but in neurology in general, we need to better define the population that we think we can help. Maybe at Phase II, you can restrict your population. But when you go to Phase III, you have a high number of patients, high heterogeneity, and then you don't see the effect anymore. That's why Lundbeck, which specializes in neurology, made this strong decision to have no new program without a biomarker.

Q: Have recent therapeutic approvals in neurology, for example, in Alzheimer's disease and schizophrenia, helped boost the field?

Charvin: It's a start. I think it's a step in the right direction, but there's a lot to be done. For now, a lot of monitoring is done by imaging studies. But I think even in neurology, we should be able to use blood or saliva biomarkers in the future.

Q: Do you know what biomarkers you will look for at Elkedonia?

Charvin: Jocelyne and her team showed that our particular target is linked to treatment efficacy in patients with major depressive disorders. They looked at the progression of Elk-1

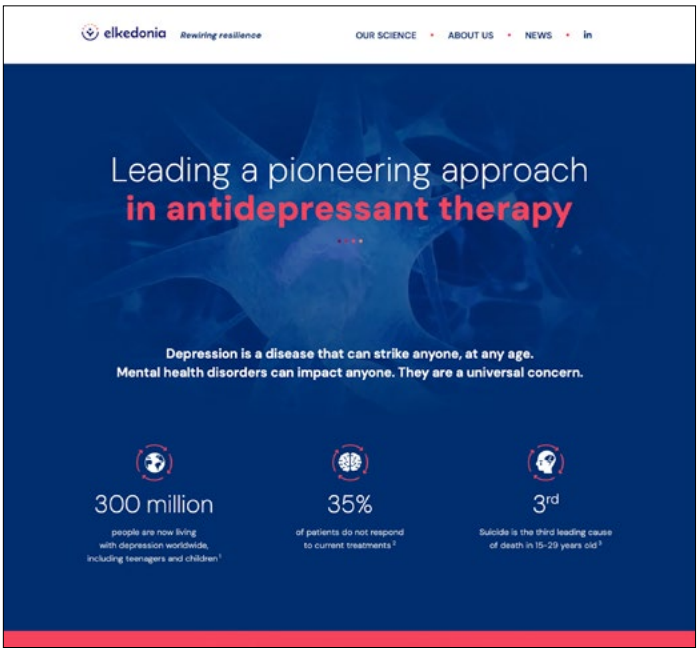
mRNA in blood before and after treatment with citalopram, which is a classical antidepressant. What they showed is that the patients who do respond to the treatment show a decrease in Elk-1 mRNA in the blood and the patients who were resistant to the treatment didn't have this decrease.

Jocelyne Caboche, PhD
Director of Research
National Center for Scientific Research (CNRS)

That is particularly interesting for us because it comes from blood, and it means that we can measure this signaling pathway from blood and there is a link with a central effect. The higher the decrease was, the greater the effect of the treatment on the clinical scale. Our hypothesis is that if we take these treatment-resistant depression patients and we decrease Elk-1 in these patients, then we should have a response to the treatment we develop.

Q: How easy has it been to fundraise for Elkedonia so far?

Charvin: We've been interacting with the VCs, pitching the project for one year, and now we are finalizing a seed round. We've been able to attract an international syndication of life science investors. Elkedonia is now leaving the incubator, but Argobio is investing in Elkedonia as part of the seed round. The company now has a headquarters in France and an affiliate in Belgium, where the biomarker part will be more developed.



Elkedonia

Q: How has transitioning into the role of CEO been for you?

Charvin: It's a big change. I was not anticipating that big a change because I was CSO of Prexton before the acquisition by

> "Some things are quite challenging. For example, I was not anticipating that closing the seed round depended on so many factors. Some of them you can't act on and you just have to wait for. This is the most difficult part for me because I like to be active."

Lundbeck and I helped the company progress from early-stage development to Phase II clinical trials. I thought I had seen everything in that role, but in fact, it's very different being a CEO.

At Elkedonia I'm both CEO and CSO at the moment because we are a very small team. It's a lot of fun. I'm very lucky to have Argobio supporting me in this transition.

Some things are quite challenging. For example, I was not anticipating that closing the seed round depended on so many factors. Some of them you can't act on and you just have to wait for. This is the most difficult part for me because I like to be active.

I'm also now leading the team, not part of the team, so I have to not worry them unnecessarily and show them everything is okay during difficult times. I have realized how lonely you can be in this position, which I didn't know before.

In Argobio, we have very experienced entrepreneurs in residence. One in particular, Yves Ribeill, PhD, has been coaching me for years. He's very present, Thierry Laugel as well. So that's why I'm very lucky, because I'm doing this transition in very good conditions, thanks to that.

Q: If you had to talk to a new founder or someone who was considering starting a company right now, what advice would you give them?

Charvin: To surround themselves with experienced people, but also to be self-confident. Sometimes, because it's the first time I'm taking this position, I've thought, "Maybe I should wait for others to take the decision?" In fact, that's wrong because I'm the one who knows the project and the vision best. I have had to learn to be more self-confident. So that's what I would suggest to other new founders as well. ■

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

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