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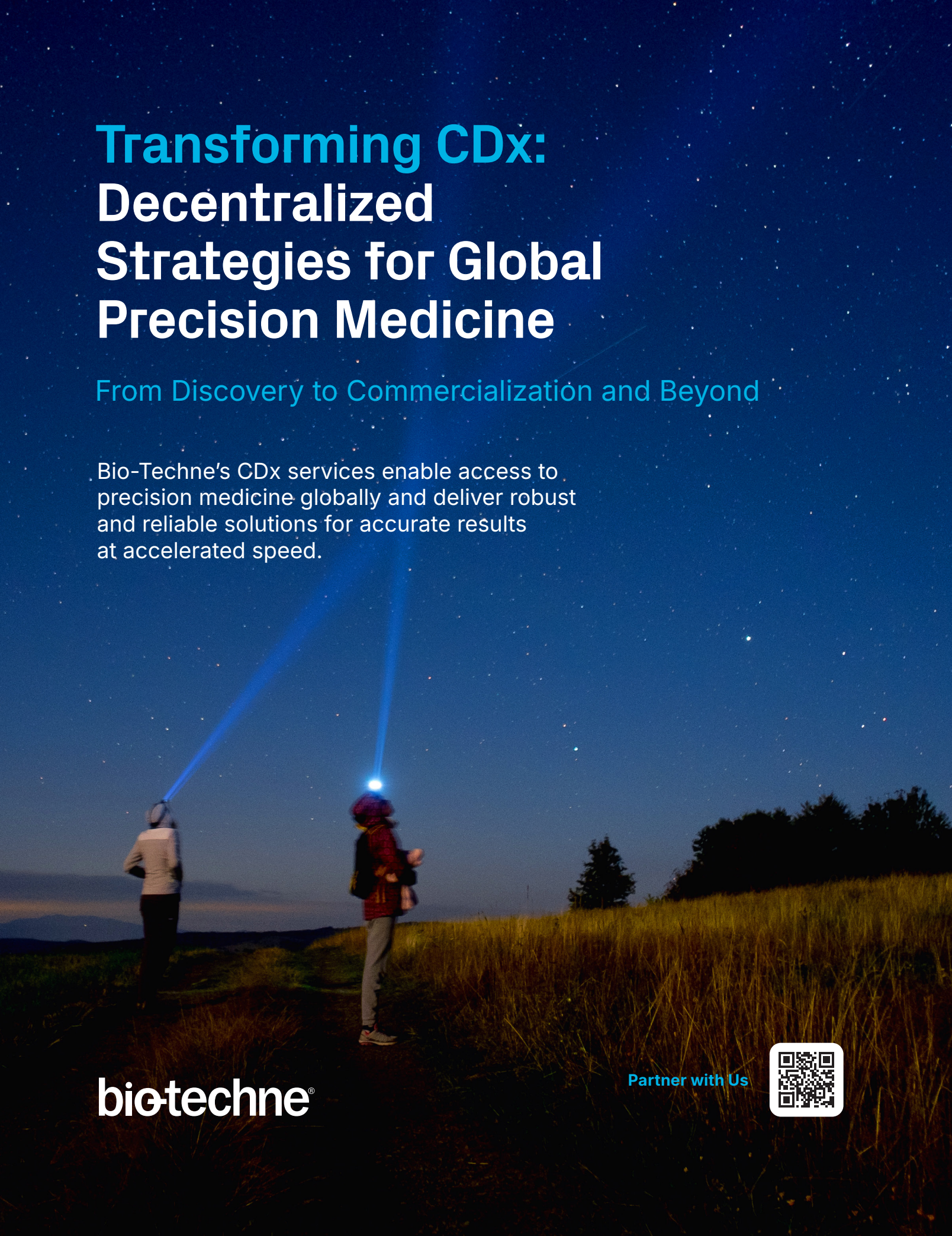

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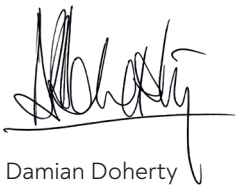
Editor's Note

"Diversity doesn't look like anyone. It looks like everyone."
—Karen Draper

In a world that seems at times more divided than ever, where tolerance, understanding, and acceptance can feel like virtues long since abandoned in pursuit of self interest in commercial and political spheres, healthcare can often be an outlier for demonstrating the best of humanity, a compassion for the person behind the patient. The Hippocratic oath, medicine's foundational tenet, should however be entrenched in all of healthcare's constituent parts. Primum non nocere means not simply doing what's best for the patient at the point of care, but should also uphold the values of inclusivity, equitability, and accessibility. By not including significant swathes of the human population in research, we are in fact doing untold harm to those we are excluding.

Research in medicine has to be representative, longstanding inequalities perpetuated by years of neglect, discrimination, and inertia has created an elite, myopically driven system and one that has simply failed to grasp what diversity at its core means and how it can contribute to medicine. None more so than when we look to the African continent—often seen as the cradle of all human populations, and home to substantial genetic diversity. Despite its foundational role in human evolution, the African genome is still largely underrepresented in genetic studies today. This paucity limits our knowledge of human evolution and clearly hinders the development of valuable data sets that can translate to tailoring precision therapeutics to patients of African ancestry.

There is, however, a vanguard of scientists around the globe challenging the status quo—creating more inclusive research programs, mitigating the disparities that prevent access to healthcare, and engendering trust amongst underrepresented communities in order to boost diverse clinical trial participation. This is a moral challenge and one that centers around protecting often the most vulnerable in society; we need to do more to actively engage with communities that have been left behind, this is about justice, fairness, and beneficence. We are all accountable in making sure we create a more equitable biomedical landscape—the Belmont Report was written in 1978, and after nearly 50 years, its aforementioned founding principles relating to the ethical conduct of research involving humans holds true today. Perhaps there should be a clarion call to rethink a revised framework, future proofed for a new era in biomedical research that reflects not only the needs of communities today, but also the ongoing evolution of research practices to come.



Damian Doherty
Editor in Chief

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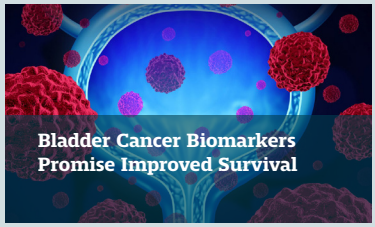

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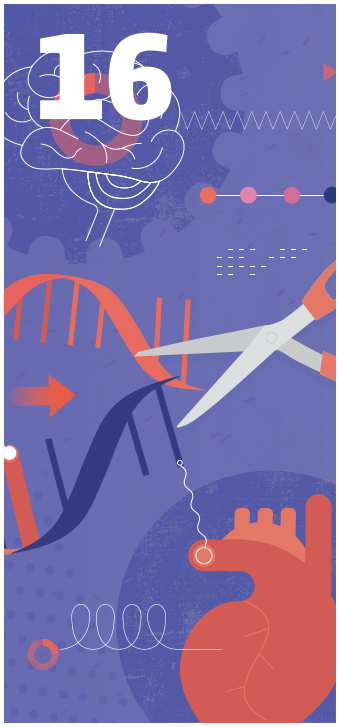

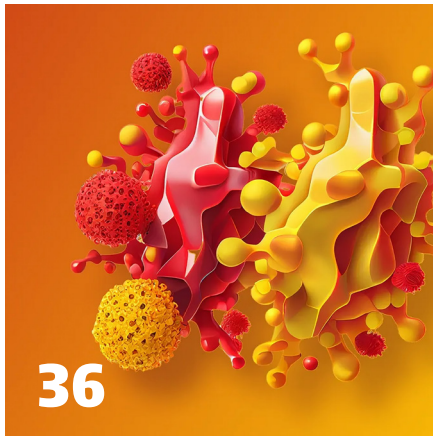

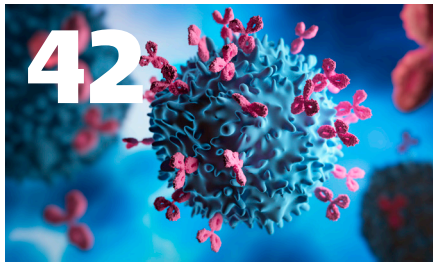

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Building a Precision Medicine Ecosystem in Africa

by Helen Albert Senior Editor

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African populations are not well represented in genomic research, despite the enormous amount of genetic variation present in African populations. This gap makes it harder to develop fair and effective precision medicine programs that work for everyone.

Lack of funding and infrastructure in the region has made it hard to establish local programs in Africa in the past, but things are changing. Genomics and the early stages of precision medicine are now being set up in a number of countries on the continent.

The idea of precision medicine, or tailoring treatment to a patient's individual characteristics, is not a new one. The so-called "Father of Western Medicine," Hippocrates, who practiced medicine over 2,000 years ago, wrote about the importance of tailoring a patient's treatment based on factors like age, physique, and constitution.

However, tailoring therapy requires as much information as possible. The completion of the Human Genome Project and rapid improvements in genetic technology over the last 20 years have made it increasingly possible to make precision medicine a reality.

Resource-rich developed countries such as the U.S. and U.K. have benefitted the most from advances in precision medicine. For example, while it is yet to be applied in all areas of medicine, it is now common for patients in these regions to undergo genetic diagnostic testing to assess cancer types and progression risks, and receive appropriately tailored treatments as a result.

Shahida Moosa, MBChB, PhD
Professor of Medical Genetics
Stellenbosch University
and Head of Medical Genetics
Tygerberg Hospital, Cape Town

Human genomic databases and research are the backbone of modern precision medicine. To build a polygenic risk score that can predict risk for a specific disease, researchers first need to carry out large-scale genome wide association studies (GWAS). To date, the majority of these studies have been carried out almost exclusively on people of European ancestry.

A website built by researchers at the University of Oxford, the GWAS Diversity Monitor, has been tracking the diversity of participants in published GWAS studies in real time since 2005. The percentage of African or African American/Afro-Caribbean people included in this kind of research remains depressingly low at 0.19% and 0.46%, respectively, compared with 94.53% people of European ancestry (as measured on Nov 2, 2024).

"If we continue this way, we are not going to get to a point

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of having precision medicine in Africa," emphasized Segun Fatumo, PhD, a professor at Queen Mary University of London who focuses on genomic diversity research. He is from Nigeria and also holds a position as the head of NCD Genomics at the Medical Research Council/ Uganda Virus Research Institute. "We are still far, far behind in terms of precision medicine. We need to improve our representation of African genomics first."

Segun Fatumo, PhD
Professor
Queen Mary University of London

Fatumo went on to add that it is important for genomic research to be carried out on as large a scale as possible in different populations in African countries, as opposed to just in people of African ancestry who live in Western countries.

"You cannot just focus on the Africans in diaspora, because they don't fully represent the diversity in Africa. In Africa there are more than 3,000 ethnic groups, and they speak more than 2,100 languages. The African ancestry individuals in the U.K. and the U.S. represent a very tiny proportion of what you see in the African population, so you cannot just take those individuals in diaspora and say, 'This is Africa.'"

Although there is a long way to go before many people in Africa can truly have access to precision medicine, there are signs that things are moving in the right direction. This is particularly evident in countries like South Africa, which has built up substantial genomic and genetic resources over the last two decades.

"Genomics is where we need to focus. Embedding it within public health, with governmental and regional governmental support, is the way for us to be able to provide these services not only to our own South African population, but to our neighbors and to the region," said Shahida Moosa, MBChB, PhD, a professor of medical genetics at Stellenbosch University and head of medical genetics at Tygerberg Hospital in Cape Town, South Africa.

Early foundations for precision medicine in Africa

The Uganda General Population Cohort (GPC) was set up in 1989 as a joint project between the Medical Research Council in the U.K. and the Uganda Virus Research Institute to study HIV prevalence, incidence, and factors affecting viral spread. It includes around 22,000 people from 25 villages in southwestern Uganda.

The GPC has had in-depth community engagement and consultation built into the program from the start. In 2011, during round 22 of the study, a new group of participants was recruited from the original cohort to take part in a spin-off project called the Uganda Genome Resource, led by Fatumo. This group includes 6,500 participants with genotype data, and around 2,000 who have had their genomes sequenced.

A cardiometabolic GWAS was carried out using the Uganda Genome Resource cohort data, as well as other African and European genomic data for comparison purposes. Published in *Cell* in 2019, the paper showed significant differences between the African and European samples in terms of genetic variation. Many new genetic variants linked to blood, lipid, and glycemic traits were found in the African samples, including 9.5 million genetic variants only found in the Ugandan samples.

"We are currently expanding the Ugandan genome resource," said Fatumo. "The phenotyping and the study we did previously was focusing on cardiometabolic traits, but now we are expanding much more than that and looking at psychiatric traits like depression and PTSD."

The African Society of Human Genetics was founded in 2003 and has been a key player in driving the development of human genetics and genomics in the region. In a meeting in 2007, members agreed to start an African genome project, which became Human Heredity and Health in Africa (H3Africa). The goal was to "empower African researchers to be competitive in genomic sciences, establish and nurture effective collaborations among African researchers on the African continent, and generate unique data that could be used to improve both African and global health."

H3Africa was funded over a ten-year period between 2011 and 2021 and received funding from the National Institutes of Health (NIH), the Wellcome Trust, and the African Academy of Sciences (AAS). The project achieved many things, like raising the profile of African genomics and improving training in the region, but its key achievements were the establishment of three African biorepositories in Nigeria, Uganda, and South Africa, and the creation of H3ABioNet, a pan-African bioinformatics network across 17 countries (16 in Africa). Overall, 51 projects led by African scientists resulted in the genotyping of 50,000 human samples during the project and whole-genome sequencing of samples from 426 people from 50 ethnolinguistic groups.

Ananyo Choudhury, PhD
Reader and Senior Researcher
University of the Witwatersrand
Johannesburg

"I think H3Africa has been perhaps the best example of how to really bring genomics to the continent," said Ananyo Choudhury, PhD, a reader and senior researcher at the University of the Witwatersrand in Johannesburg. "For the last ten years, I have gotten a lot of resources and training from H3Africa and have been very involved in that project."

Oncology has been a poster child for precision medicine in the West, but targeted therapies can only be effectively used when healthcare providers have enough clinical and genetic data about their patients.

Yvonne Joko Walburga, MD, PhD, a clinician and researcher from Cameroon, is currently a research associate at the University of Cambridge who studies cancer epidemiology in the U.K. and Africa.

Yvonne Joko Walburga, MD, PhD,
Research Associate
University of Cambridge

She has worked with the African Cancer Registry Network, which was founded in 2012 and includes 34 registries in countries across the continent. The network was set up to improve knowledge of patients with cancer in Africa and to promote research and access to better treatments and diagnostics. The registries record data such as the date of diagnosis, place of residence, profession, exact tumor type, and sometimes, stage at diagnosis of cancer patients attending hospitals in the region. The registries do not currently include genetic data.

"It's a great network because it brings together the different registries. It helps us increase the quality of the data and help it to be used for international studies and comparisons," said Joko Walburga.

"It also does a lot of training and capacity building for the staff, so it's not just about data which is being taken away and published in big papers, but it's also about ensuring capacity building across Africa."

Expanding knowledge and investing in infrastructure

While the H3Africa project has ended, its legacy continues. Many new projects have been founded to continue or expand on the work it started.

A key barrier to rolling out genomic and precision medicine in the African region is a lack of infrastructure, access to relevant data, and expertise. For example, a lack of suitable labs, equipment, and people qualified to analyze the data.

A dearth of genetic testing or sequencing facilities means that African researchers or clinicians are often faced with higher costs than their counterparts in the West, mostly due to the need to ship samples to a suitable facility in a different country.

"We don't have enough sequencers or skilled people. We don't have logistics chains to organize this even if we get enough money," explained Choudhury.

"If you go to an African service provider and say, 'We need 500 sequences in six months,' they will say, 'Oh, we can't do it.' So that's the problem. I think there are a select few places here that can do anything at scale and others are really not equipped to do those things."

One way to build capacity and knowledge in genomics is through the initiation of sequencing projects in the region. For example, a large-scale genome project is underway in South Africa.

"On a day-to-day basis, if I do a clinical test like a clinical exome or a clinical genome, it's very difficult for me to interpret those results because I have to compare them to a reference sequence, and the reference is not based on the population that we're serving here," explained Moosa.

"A positive step in that direction is the South African 110,000 Genomes Project. I think they're going to start with a pilot project of 10,000, and then it's going to be 100,000 after that from different populations around the country."

Earlier work carried out by Fatumo and colleagues using data from the Uganda Genome Resource shows just how varied genetic diversity is in Africa. For example, a genetic risk score linked to lipid levels performed significantly better in a South African Zulu cohort versus a Ugandan one. This finding, among others, illustrates the need for more diverse data on genetic variation in African populations.

The Assessing Genomic Diversity in Africa study is seeking to change this by sequencing genomes from around 1,100 people from African groups and countries which have historically had limited or no access to genetic resources or projects.

Choudhury is working on this ongoing project along with other African colleagues such as Ezekiel Adebiyi, PhD, a professor at Covenant University in Nigeria and at the German Center of Cancer Research in Heidelberg.

"Our aim was to include under-studied geographic regions as well as ethnolinguistic divisions," explained Adebiyi.

"This project was very difficult to implement, because for four of these countries this was their first major genomic project, but we managed to do it," added Choudhury. "It's not a big dataset, but it's really diverse, because it's filling 11 different blocks in the African map."

Moosa is helping to build genetics knowledge in two ways. First, by improving medical training and second, by compiling a rare disease genetic database to help diagnose children and adults with these conditions in her clinics.

"Most people here have never done genetics in their undergrad medical training. That's something that I changed when I came back to South Africa five years ago and I joined Tygerberg Hospital and the University. We completely revamped the undergrad genetics and genomics curriculum," she explained.

Moosa works to help children and adults with rare diseases achieve a diagnosis and treatment. As with patients in Western medical systems, the diagnostic odyssey can be long and arduous. "I started the Undiagnosed Disease Program, which is the first in the region, just under four years ago. We started with exome sequencing. And within the first year, the diagnostic rate was around 50%, which was phenomenal because most of those individuals were getting diagnoses and being the first in Africa with that diagnosis." The cohort Moosa is building is still small, but having a local database to draw on seems to be effective in many cases, despite its size.

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Access to sequencing facilities in Africa is getting better, particularly in richer countries such as South Africa, but analyzing genomic sequences and big datasets needed to implement precision medicine remains difficult.

Daudi Jjingo, PhD
Senior Researcher
Makerere University, Uganda

This is something Adebiyi and fellow bioinformatician Daudi Jjingo, PhD, a senior researcher at Makerere University in Uganda, have been working to improve for the last few years with two H3Africa spinout projects: Nurturing Genomics and Bioinformatics Research Capacity in Africa (BRECA) and the West African Sustainable Leadership and Innovation Training in Bioinformatics Research (WASLITBRe). These are just two of several similar projects designed to increase bioinformatics capacity across Africa.

"Our emphasis for the first three to four years was actually training students at a graduate level. That means having them trained, not just for a week or a single day workshop, but having them trained in depth, so that they can be able to really competently handle this," explained Jjingo.

"We're still very much doing work on that, but now that most of these trainees are beginning to come of age in terms of their skills and exposure, we are now beginning to try and bring these tools and skills to bear on abiding problems in our ecosystem."

Breaking down barriers

Building up infrastructure and a good knowledge base are essential tools to enable genomic and precision medicine, but other challenges to broader rollout exist in Africa.

A key problem in Africa, both in academia and medicine, is the "brain drain" phenomenon. "In the last five years, all the registrars that we've trained have moved either into private practice or moved overseas," said Moosa. "And by overseas, I mean Canada, Australia, or similar. They've been trained as the new generation of geneticists and it's a real loss for our country and for the region."

Joko Walburga believes thought needs to be put into how to retain good people or encourage them to come back to their home countries. "When it comes to training and capacity building, it's always about making it easier for researchers trained elsewhere to go back home. You can get all the training, but sometimes you really want to give back. You really want to be able to do what you're doing in the West back home, but you may not have the right infrastructure in place."

Moosa acknowledges that South African hospitals and research institutes are better equipped than those in many other countries in the region, but says there is still much more that needs to be done to bring precision medicine to Africa.

"We have many more resources available to us, we've got the machines that are necessary to bring precision medicine into the mainstream, into public health. We are training the people necessary to do the human work that goes into it, but there hasn't been that much buy in from our really key stakeholders. I'm talking about the national government. I'm talking about the Department of Health," she emphasized.

> "In sub-Saharan Africa, we have a lot of patients who are diagnosed young, but who will never get tested, who will never receive a BRCA1/2 test, who don't know if they are triple negative."

Choudhury agreed: "So many of our local governments don't want to bother about this. They have many other challenges, and this is not on their priority list."

Simply getting access to necessary genetic testing and a healthcare professional who can explain the results can be very difficult. "When I compare us and our situation in South Africa to other parts of sub-Saharan Africa, you won't find genetic services until you reach the Democratic Republic of Congo, and there it's done mainly on a research basis," said Moosa.

"There's no genetic counseling other than in South Africa. There's a new program in Ghana, and I think they've just graduated their first cohort of genetic counselors. But you won't find genetic counselors anywhere else."

This can be a big problem for patients with cancer in countries like Cameroon, where even if targeted therapies are available, the lack of genetic testing opportunities means that therapies cannot be matched with the right patients.

"Let me take the example of ovarian cancer, which has such poor survival rates even in the most developed countries. In the last ten years, PARP inhibitor drugs have been developed, like olaparib and niraparib. They're more effective in patients who either have a *BRCA1/2* pathogenic variant or who carry some kind of homologous repair deficiency gene," explained Joko Walburga.

"In sub-Saharan Africa, we have a lot of patients who are diagnosed young, but who will never get tested, who will never receive a *BRCA1/2* test, who don't know if they are triple negative. You're not tailoring their treatment to their cancer type, as a result of which there could be a lot of waste of resources as well, because you could give treatment which doesn't necessarily benefit the patient."

The formation of a more active biotech and pharma industry

in Africa could help improve infrastructure and bring precision medicine to the region on a more advanced and larger scale. "There needs to be some industry that's kind of taking the innovations and packaging them into products, which could be helpful in keeping the skills we produce," said Choudhury.

Inevitably, the more active companies in a region, the easier it is for new startups to join them because existing companies build infrastructure and attract investors. Being the first, or one of the first, in an area can be difficult.

54Gene was one such company, founded in Nigeria in 2019, and was aiming to create a diverse African biobank, improve drug efficacy for African people, boost translational genomics research, and develop new medicinal products. Sadly, despite a great initial fundraise of $45 million and a good premise, the company shut down in 2023.

Melissa Gymrek, PhD
Associate Professor
UC San Diego

It is unclear exactly why the company folded, but financial troubles, leadership changes, and legal issues were all cited as possible reasons in the media. "I hope they will be able to recover and be able to get back to continue what they were doing in Nigeria," said Adebiyi.

There is a small biotech sector in South Africa and a few companies beginning to make a name for themselves in other countries, for example, Yemaachi Biotech is based in Ghana and trying to revolutionize how cancer is treated in Africa. But ultimately, more financial, government, and regulatory support is needed for more startups to be launched and to succeed in the region.

New directions

The African continent may not yet have widely accessible and affordable precision medicine, but there is no doubt that the region is a hotbed of research and new genomic projects that will drive precision medicine forward.

The success of H3Africa has sparked interest in African genomics and a wave of new African projects, biobanks, and companies have either started or are in the process of launching. For example, a new initiative to build a network of Genomic Centers of Excellence (GenCoE) across Africa aims to improve the continent's ability to address rare and emerging diseases through the application of cutting-edge science.

Adebiyi is a contributor to this project. "GenCoE is already working with also a new initiative, namely the Partnership for Accelerating Genomics research in Africa, and in their first pilot project, the collaboration will fund the sequencing of up to 25,000 genomes."

Working with Jjingo and U.S.-based collaborator Melissa Gymrek, PhD, an associate professor at UC San Diego, Adebiyi and colleagues are currently using data from H3Africa and AWI-Gen to look for tandem repeat mutations in African populations.

"Most expansion disorder loci were discovered in European populations, and so they're actually more common in European populations," noted Gymrek. "Part of our goal was to find repeats that are specifically expanded in African populations now that we have this other data to look at. Even though we don't yet have the disease phenotypes to tie them to, we actually did find multiple regions of the genome that are very commonly expanded in African individuals, but almost never expanded in European or other non-African populations."

Fatumo is expanding on earlier projects through the newly set up KidneyGenAfrica Research Partnership Program. "It's a partnership to deliver research and training excellence in genomics of kidney disease in Africa," he explained.

Persuading local government and regulatory authorities to spend time and money on developing precision medicine in Africa can be a challenge.

Adebiyi believes one strategy is to show governments that precision medicine can help save money. "The governments are interested in cost saving. We need to tell them that precision medicine will strengthen the public health system, and the scarce resources available will be used to directly benefit the population."

Moosa advocates for adopting a model like the one used to roll out precision medicine in Thailand, as they are a similar size country with an equivalent economy. "They've moved centuries beyond us already in the last five years, because they've incorporated this into public health and because they have serious buy in and support from their government," she emphasized.

She also cautioned that it is important to fix problems locally and not rely on international help. "We can't always depend on the NIH or the European Union or somebody else to help us. This needs to be something that is also led and co-led by local governments."

Costs for patients also need to be affordable or limited. "There's a push for universal health care. It's not all bleak," said Joko Walburga. "There are some countries like Kenya, like Nigeria, which are pushing for universal health care, meaning that patients with cancers would benefit from access to better treatment."

There are still challenges that need to be overcome, but genomic resource and capacity building is increasing in many countries across the region, bringing hope that patients will gradually have access to more genomic and precision medicine services over the next few years. ■

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.

The Importance of Increasing Diversity in Clinical Trials

by Larissa Warneck-Silvestrin

Before reaching the market, new drugs are tested in people who voluntarily participate in clinical trials. However, for a new medicine to work in as many people as possible, these drugs should be tested in a patient population that is as diverse as possible.

"I think about diversity through the lens of diversity, equity, inclusion, and accessibility," explained Karriem Watson, DHSc, chief engagement officer of the *All of Us* Research Program at the National Institutes of Health (NIH).

"In broad terms, it emphasizes that people differ in many ways—such as race, ethnicity, gender, gender identity, sexual orientation, age, national origin, religion or spirituality, disability status, and socioeconomic background, including income, education, marital status, and even veteran status. Diversity also encompasses language, physical appearance, and diversity of thought. Where we live—rural versus urban areas—and our access to healthcare are also part of how we can understand diversity."

Karriem Watson, DHSC
Chief Engagement Officer
All of Us Research Program
NIH

Historically, however, clinical trials greatly lacked diversity of any definition and new medicines were tested primarily in white, middle-class male participants. This led to a growing problem, wherein drugs proven effective for white men often did not provide the same benefits to patients from diverse racial and ethnic backgrounds, to those assigned female at birth, or to other underrepresented groups.

Staci Hargraves
VP Innovative Health, Engagement, and Advocacy
Johnson & Johnson

"People from all backgrounds need medicine, and that means that for a new medicine to truly impact the people it is intended for, a diverse group of people need to be part of research studies," explained Staci Hargraves, vice president of innovative health, engagement, and advocacy at Johnson & Johnson.

"Pharmacogenetic research has shown that there are significant differences among racial and ethnic groups in the metabolism, effectiveness, and side-effect profiles of many drugs. These differences can lead to varying drug outcomes and patient reactions."

Watson added: "Diversity in clinical trials is not only about the ancestral and biological characteristics of people. A clinical trial design may not be diverse because it doesn't include the

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> "Diversity action plans have changed so that they require enrollment goals for clinical studies to be broken down by race, ethnicity, sex, and age to reflect the diversity of the target patient population."

lived experiences people can have. A drug may have to be taken in the morning—what about people who work shift jobs? Including the diversity of lived experiences in clinical trials can allow us to better understand how interventions can work both from a biological as well as from a social perspective."

Efforts to increase diversity

In 1993, the United States Congress passed the NIH Revitalization Act[1], which aimed to increase the enrollment of "women and minorities" in clinical trials. Although the NIH Revitalization Act focused only on NIH-funded research, it was a first step toward increasing diversity in clinical trials and helped spread awareness to other trial organizers.

Since then, several regulatory documents and published guidelines have aimed to address this issue—and included several definitions of diversity—to help clinical trial sponsors increase diversity in clinical trials. For instance, most recently in June 2024, the FDA issued the draft guidance "Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies." [2]

Hargraves elaborated on this latest update: "Diversity action plans have changed so that they require enrollment goals for clinical studies to be broken down by race, ethnicity, sex, and age to reflect the diversity of the target patient population. Previous guidance recommended considering sex and age only, so this broader definition and requirement of inclusionary information is a notable shift."

The data shows that efforts to enroll people who are assigned female at birth have been successful and participation in clinical trials has increased. However, despite continuous efforts, people of underrepresented backgrounds are still in the minority in most clinical trials.

The FDA's most recent annual Drug Trials Snapshots summary report[3] shows that the FDA approved 55 novel therapies in 2023, supported by pivotal studies involving around 44,000 participants worldwide. The report revealed that the percentage of female participants in clinical trials ranged from 41 to 67%, with a median of 48%. But for most of the approved drugs except three (Loqtorzi, Augtyro, Xacduo), white people comprised over 50% of the trial population, reflecting a continuous lack of ethnic and racial diversity in clinical studies.

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So why are the majority of clinical trial participants white? Why is there still a lack of participation from underrepresented groups?

Addressing diversity challenges

"There are many factors that impact the perceptions certain communities have around clinical trials [...]," Hargraves explained. "Lack of enrollment in clinical trials may be attributed to mistrust resulting from malpractice and maltreatment of certain communities throughout history. Other factors that impact diversity in clinical trials can also be the difficulty to reach certain underserved populations because of logistical factors like travel, accommodations, lack of access to childcare, or not being able to take time away from work."

Clinical trial sponsors—pharmaceutical companies and contract research organizations—as well as various other organizations are working to increase diversity in clinical trials.

"We know that without tailoring medical care to all who need it, people will be left behind," said Hargraves. "We see creating inclusive clinical trials as a critical first step. Reaching and recruiting participants from a variety of demographics is crucial to ensuring research is representative of the incredibly diverse communities served. We have several initiatives in place to increase clinical trial awareness and gain the trust of underrepresented and underserved communities."

One example is the Johnson & Johnson Diversity, Equity and Inclusion in Clinical Trials team which collaborates with therapeutic area teams across the company to "embed diversity, equity, and inclusion into every stage of the clinical trial process." The team also partners directly with patient advocacy organizations and works with communities to learn from patients of all backgrounds and increase diversity in clinical trials.

Xoli Belgrave
Senior Director and Head of Clinical Trial Diversity and Inclusion
Parexel

For Xoli Belgrave, senior director and head of clinical trial diversity and inclusion at Parexel, ensuring diversity in clinical trials begins by understanding the incidence and prevalence of an indication, by looking at the product's pharmacokinetic–pharmacodynamic profile, and analyzing the history of other clinical trials for that indication.

"Unlike thirty years ago, we now recognize the importance of including diverse patient populations in clinical trials," Belgrave said. "The work begins with making data-driven decisions and forming a container of the patient population. Based on what we learn from that, we can get a sense of where these patients are, geographically. Once we have the geography, our site selection should take us to a range of patients, ensuring that we include sites in urban, suburban, and rural settings, people of high and low socioeconomic status, patients with different abilities, homogenous racial communities, and multiracial communities."

> "We also see the program participants as partners, and that means we have a model ensuring that our participants are involved in multiple levels of our governance, for example, helping to design our surveys or ensuring that our studies are responsive to the participants' desires and needs."

Organizations fighting for diversity

For clinical trial sponsors, increasing awareness and building trust within communities is essential to reach people from underrepresented groups. However, "We can't do that on our own," Belgrave emphasized.

"We need to partner with the communities themselves whether that is in the form of advocacy groups or community groups. Partnership is the way to go in this space because no organization can fix this on its own. We have to work with others and put aside our competitive differences for the sake of the patients. Let's collaborate and try to make clinical trial access as easy as possible for patients."

Examples of organizations that work to broaden awareness and clinical trial access for patients of underrepresented groups are the Lazarex Cancer Foundation, LUNGevity, and the NIH *All of Us* research program.

The Lazarex Cancer Foundation, for instance, helps people from underserved communities access cancer clinical trials by covering travel costs, assisting with trial navigation, and engaging with communities to reduce healthcare disparities and improve patient outcomes.

As part of the NIH, the *All of Us* Research Program aims to accelerate medical research and breakthroughs by collecting diverse health data so that everyone, especially those historically underrepresented in biomedical research, can benefit from precise, personalized medicine that considers the varied health needs of different communities.

"One of our core missions and values is to make research accessible to all," Watson explained. "We also see the program participants as partners, and that means we have a model ensuring that our participants are involved in multiple levels

of our governance, for example, helping to design our surveys or ensuring that our studies are responsive to the participants' desires and needs."

Some argue[4] that the U.S. healthcare system favors people with higher socioeconomic status, making it more difficult for people with lower socioeconomic status to receive medical care and, by extension, learn about new medicines in clinical trials. The non-profit organization LUNGevity helps lung cancer patients access clinical trials but also supports patients in accessing organizations like Family Reach, which works to remove financial barriers so patients can receive their treatments.

Financial barriers remain key drivers of enrollment-related inequities in clinical trials. The financial status of an individual can influence whether they can afford to travel to a trial, cover the costs for food and childcare, or even take days off from work.

People with low socioeconomic status are disproportionately affected by this and can often not access the high-quality care and novel treatment options—especially if they have not responded to standard-of-care treatments—that clinical trials offer. In fact, research has shown[5] that patients with yearly household incomes of less than $50,000 were 27% less likely to take part in cancer clinical trials.

Receiving financial reimbursement for trial-related expenses could increase diversity in clinical trials. Unfortunately, clinical trial sponsors still face legal hurdles in providing financial reimbursement. Recently, efforts have been made[6] to simplify patient reimbursement for clinical trial participation. For example, the NIH "Allowable Costs Related to Participant Inclusion Activities" resource from November 2023 and two proposed bills, "The Clinical Trial Modernization Act" and "Harley Jacobson Clinical Trial Participation Income Exemption Act".

Using technology to reach people

"There is more acknowledgment of certain barriers that exist within our healthcare system," said Watson. "I want to encourage all clinical trial sponsors to consider two things: One is to eliminate the term 'hard-to-reach' populations and rather talk about 'under-engaged' populations. Two is to consider that these under-engaged communities can be in rural areas that may have limited access to technology. It is on us and our partners—everyone who is doing research—to think about access to technology and how patients will get to clinical trials in rural areas. Be intentional and address the barriers that prevent certain populations from participating in clinical trials."

Many clinical trial sponsors are already using technology, including artificial intelligence (AI), to increase patient diversity in clinical trials. Johnson & Johnson, for example, uses AI in the planning and execution of its clinical trials and is using its AI-driven platform across approximately 50 clinical trials to increase diversity.

"Our AI platform enables us to combine real-world data to better identify where patients that meet our clinical trial criteria are geographically located," explained Hargraves. "This informs our clinical site footprint and helps us identify new locations where there is a high probability of enrolling diverse patients. Through this approach in 2023 we saw that the average enrollment of Black patients in five Johnson & Johnson multiple myeloma trials was more than twice the historical industry standard."

Belgrave added words of caution: "Technology is a friend and a foe. AI and technology have their place, but we mustn't forget the people who are analog, we mustn't forget about the human element. I believe a hybrid approach is the most helpful in terms of people participating in research. We can use technology to aid people in more rural locations—have tele-visits or use sensors to measure someone's blood sugar, for example—but we need to shape the treatment around the patient without compromising them."

Hope for the future

The most important thing to increase diversity in clinical trials is to stay intentional, Watson emphasized. "We need to ensure that there's resources for community engagement because we know that it's an effective approach to ensure diversity in clinical trials," said Watson.

"We need resources for training and education of a clinical research workforce that truly reflects the populations that carry the greatest burden of disease, that has an understanding of the lived experience in underrepresented communities. Creating a diverse workforce will allow us to engage those populations historically underrepresented in clinical trials."

"Ideally," added Belgrave, "we won't need people in the industry to talk about diversity in clinical trials in the future because it would be business as usual. We'd work ourselves out of a job. But in reality, I expect that politics and economics will influence the amount of investment we can make to ensure that clinical research involves diverse patient populations. We need to work to keep the voices of all patients in the room. We need to remember that, at the end of the day, the patients are why we do clinical research, and if we can keep the patients' voices in the room, there will be a conscience that will keep us doing this work for as long as necessary." ■

Read more:

1. History of Women's Participation in Clinical Research, NIH Inclusion Outreach Toolkit: How to Engage, Recruit, and Retain Women in Clinical Research, National Institutes of Health.
2. Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies Guidance for Industry, Draft Guidance, U.S. Department of Health and Human Services, FDA.
3. Drug Trials Snapshots, Summary Report 2023, FDA Center for Drug Evaluation and Research.
4. Needed: a clearer explanation of why diversity in clinical trials is important, Arthur L. Caplan, *STAT*, June 2022.
5. Patient Income Level and Cancer Clinical Trial Participation, Joseph M. Unger, PhD; Julie R. Gralow, MD; Kathy S. Albain, MD; et al, *JAMA Oncology*, January 2016.
6. Could Financial Reimbursement Increase Clinical Trial Inclusivity?, Courtney P. Williams, DrPH; Mark E. Fleury, PhD; and S. M. Qasim Hussaini, *ASCO Daily News*, June 2024.

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Getting CRISPR to the Clinic

Although this gene-editing technology promises impressive improvements in healthcare, various obstacles must be addressed before large numbers of patients can benefit

by Mike May

In November 2023, the U.K. Medicines and Healthcare Products Regulatory Agency (MHRA) approved the first CRISPR-based therapy. This endonuclease—targeted to the gene of interest by clustered regularly interspaced short palindromic repeats (CRISPR)—and CRISPR-associated protein 9 (CRISPR-Cas9) method can be used in treatments by editing a patient's disease-causing DNA. Specifically, MHRA approved Vertex Pharmaceuticals' Casgevy (exagamglogene autotemcel) to treat sickle cell disease and transfusion-dependent ß-thalassemia. A few months later, the U.S. Food and Drug Administration (FDA) approved this treatment for the same diseases. These approvals, though, only marked the beginning of how CRISPR will impact treatments and patients.

Eric Kmiec, PhD
Executive Director and Chief Scientific Officer
Gene Editing Institute
ChristianaCare

As of mid-October 2024, clinicaltrials.gov listed nearly 60 studies involving CRISPR-Cas9. As Eric Kmiec, PhD, executive director and chief scientific officer at the Gene Editing Institute at Delaware-based ChristianaCare, said, "CRISPR has been a part of many of the novel treatments for cancer already, specifically as a tool to reengineer the antibody or the T-cell for cell therapy or immunotherapy."

As explained here, CRISPR is being vastly improved as a treatment for cancer and offers promise in treating other gene-based diseases.

Precision placement

Although a day at the beach can be relaxing, it's also dangerous. The danger comes more from the sun than from sharks circling offshore. In fact, most melanomas arise from exposure to the sun's ultraviolet light.

As in any treatment, getting a melanoma drug to its target forms the foundation of efficacy and safety. Nonetheless, meeting that objective is not always easy. "Systemic delivery of any sort of biomolecular drug induces severe side effects and ignites drug resistance, and it always will," Kmiec explained. "We focus on directly delivering CRISPR to tumors to disable genes involved in the development of cancer-drug resistance." In this way, Kmiec emphasized, he and his colleagues can "attack the problem of extensive side effects and the development of drug resistance at its genetic core."

Despite just getting started with this approach, Kmiec's team is seeing what he calls "outstanding results in animal models." Taking a direct-delivery approach of getting immunotherapies to melanoma tumors is key. "If you don't do that, you're just simply adding greater drugs with more side effects to patients who eventually fail, because they're simply so unhealthy from the treatment [that] they quit the research trial," he said. "We think the combination of our genetic approach coupled to pharmaceuticals is a winning formula, especially when you can deliver it directly to the tumor."

In particular, Kmiec's team is targeting mutations in the *BRAF* gene, which appear in about 50% of people who have melanoma. Of those with melanoma and a *BRAF* mutation, 90% have a mutation called *BRAF* V600E. Although effective *BRAF* inhibitors are available for patients with a *BRAF* V600E mutation, most melanomas become resistant to these drugs, often through the development of a mutation in the *NRAS* gene. So, Kmiec's team created a CRISPR-based method that restores sensitivity to inhibitors in cells with mutations.

DrAfter123 / Getty Images

"By disabling genes that the tumor uses to fight off standard care, including pharmaceuticals, we can reduce the amount needed for effective cancer care," Kmiec says. "*BRAF* inhibitors are classic examples of effective drugs that eventually become ineffective because of a unique genetic mutation."

The scientists also developed methods that reduce off-target effects of the CRISPR-based treatment. For instance, Kmiec's group used a proprietary, in-house algorithm to identify a unique site within the *NRAS* gene that produces low off-target effects.

"The work has been surprisingly effective, and what's most important is that we've identified two Cas proteins that can be designed to act only on the tumor cells and leave healthy cells unchanged and unedited," Kmiec noted. "The effect is the restoration of sensitivity to *BRAF* inhibitors, and the tumor cells selectively die while the healthy cells thrive, which we think is a good step forward."

Mutations and the brain

Although many therapeutic applications of CRISPR target cancers, this technology can be used in other areas of healthcare. One of those areas might turn out to be brain-related disorders.

"One of the most striking findings in autism, as well as in other neurodevelopmental disorders, is that mutations in many genes can lead to the disorders," said Joseph Buxbaum, PhD, director of the Seaver Autism Center for Research and Treatment at the Icahn School of Medicine at Mount Sinai. "CRISPR provides a rapid means of disrupting, downregulating, or upregulating specific genes to understand their function in a high-throughput manner." CRISPR can therefore be used to explore how mutations, and the impact of other genes on overlapping and converging pathways, are linked to the pathobiology of neurodevelopmental disorders.

Joseph Buxbaum, PhD,
Director
Seaver Autism Center for Research and Treatment
Icahn School of Medicine at Mount Sinai

Studying such mutation-based effects in the brain requires tools that improve the analysis of information. One tool that Buxbaum and his colleagues use is Perturb-seq, which combines CRISPR-based gene perturbations with single-cell sequencing of RNA. "This is a very useful tool for high-throughput studies because you can carry out studies where—in a large mixture of cells—each cell receives a specific guide RNA against a specific gene of interest," Buxbaum explained. "And that specific cell will have that specific gene perturbed." Then, barcoding can be used to examine the RNA sequence and determine which guide RNA was taken up by a given cell.

"In other words, you can know which gene was disrupted and the impact of that disruption on gene expression in that cell," Buxbaum said. "What this means is that one can take a library of guide RNAs against many genes and work out conditions where each cell takes on only a single guide RNA—on average—and then look at the consequences of disrupting each of those many genes on a cell-by-cell basis."

As an example, studies by the Autism Sequencing Consortium, which Buxbaum co-directs, have identified over 200 genes strongly implicated in the risk of autism. About half of those

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Seaver Autism Center for Research and Treatment

At the Seaver Autism Center for Research and Treatment at the Icahn School of Medicine at Mount Sinai, New York, director Joseph Buxbaum and his colleagues, including graduate student Lauren Dierd shown here, use CRISPR-based methods to study the impact of mutations on neurodevelopmental disorders, such as autism spectrum disorder. Eventually, CRISPR-based treatments might be developed for various neurodevelopmental disorders.

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genes regulate the expression of other genes. Buxbaum and his colleagues picked 70 of these regulatory genes and made a library of guide RNAs to independently impact each gene in different cells, and then applied Perturb-seq. "At the end, we had sufficient data from disruption of 60 genes, and by sequencing single cells that had a perturbation in one of those 60 genes, we can begin to understand the impact of perturbing that autism gene on neurodevelopment," Buxbaum said.

> "Ultimately these mutations may be correctable using CRISPR editing, which we are still far away from, but modulating the expression of genes is perhaps a nearer goal."

Buxbaum and his colleagues explore neurodevelopment with induced pluripotent stem cells (iPSCs) to track their development in two- and three-dimensional models of the brain, such as organoids. This produces a complicated analytical challenge because the perturbations could completely change brain function. "Imagine, for example, if a perturbation may change the ratio of excitatory to inhibitory neurons in the brain, or may alter the timing of the development of an excitatory or inhibitory neuron," Buxbaum said. "Separating these kinds of clear developmental impacts is an emerging challenge."

As one way of analyzing such complex information, scientists could use structural topic modeling (STM), which "treats cells as 'books' and the expression of distinct genes in that cell as 'words,'" Buxbaum explained. For example, if you had a computer algorithm that could count the number of specific words in two books, then "you could develop a metric that tells you how similar the two books are in terms of topics," Buxbaum said. "If both books have many words associated with geopolitics, for example, they would be more similar by this metric than a book that had many words about geopolitics and another book that has many words about maintaining a healthy garden."

Led by Xuran Wang, PhD, an assistant professor at the Seaver Autism Center, Buxbaum and his colleagues apply STM to neurodevelopmental disorders. "Some of the genes in the cell will be more highly expressed when the cell is becoming an excitatory neuron, versus an inhibitory neuron," he said. "Other genes will be more highly expressed when a cell is differentiated and reaching terminal differentiation as a mature neuron." Even more possibilities exist, making analysis complicated. "By using the gene expression from Perturb-seq as words, and assigning 'topics' to each cell, we can begin to

find convergence of different genes and see how they might impact aspects of neurodevelopment," Buxbaum said. "And importantly, we do this in an unbiased way, allowing the words to speak for the cells, in the sense that we allow different biological processes—for example, cell fate and developmental trajectory—to vary naturally, and we don't constrain things, which is done in most of the current approaches."

Using such methods, Buxbaum and his colleagues identified converging pathways in genes related to autism spectrum disorder, but many of these genes are yet to show any convergent mechanisms. "This means, first, that we need to expand our models and analyses to better capture brain development, but also highlights the critical importance of precision medicine in autism," Buxbaum said.

> "Very talented people are coming up with different views on how to make CRISPR affordable, but I don't think there is a single magic bullet."

Jon Rueda, PhD
Postdoctoral Fellow
University of Basque Country

One day, precision medicine for neurodevelopmental disorders could include CRISPR-based treatments. "The same technology that allows us to manipulate gene expression in preclinical studies allows us to manipulate genes in vivo," Buxbaum said. "Ultimately these mutations may be correctable using CRISPR editing, which we are still far away from, but modulating the expression of genes is perhaps a nearer goal."

Buxbaum is already thinking about how CRISPR-based treatments might work. For example, if a disorder arose from a loss-of-function mutation in a gene, CRISPR might be used to upregulate the expression of the healthy, second copy of that gene. In that way, "we would get more RNA and protein, which is likely to ameliorate the impact of the mutations," he said.

Is economic equity possible?

Although treatments based on CRISPR promise to offer extensive benefits to patients, many of them won't be able to afford it. For example, Casgevy costs about $2 million.

"Although the treatment is priceless for the patient who is cured, the cost of Casgevy is astronomical from a lay perspective," said Jon Rueda, PhD, a postdoctoral fellow at the University of Basque Country in Leioa, Spain, and lead author of a 2024 article about CRISPR pricing in *The CRISPR Journal*. "This price was not surprising, though, because we have—sadly—gotten used to multi-million dollar prices for gene therapies in recent years."

When asked why Casgevy is so expensive, Rueda emphasized that it cannot be simply explained. That said, he provided an overview. "To summarize it very hastily, the cost mainly reflects the following: Casgevy is a therapy that cures patients while saving health systems and insurers the cost of lifelong treatment, and pharmaceutical companies want to recoup the investment in the development of this particular therapy and previous unsuccessful therapies." In addition, he pointed out that the price of Casgevy depends on other potentially costly factors like highly skilled labor, vector production, and safety and efficacy controls.

For now, Casgevy can only help some patients regardless of the price. First of all, it's only approved for specific groups of people even within those who have sickle cell disease or ß-thalassemia. Even if this treatment gets approved for more diseases, only some people will get it. "The high cost greatly limits the potential users," Rueda said. "It is clear that this cost can be a significant financial barrier, even in high-income countries."

That leaves a crucial question for today and tomorrow's CRISPR-based therapies: Can they be made more affordable? "Very talented people are coming up with different views on how to make CRISPR affordable, but I don't think there is a single magic bullet," Rueda said.

In fact, CRISPR-based treatments are not alone in high cost. "The prevailing research ecosystem is prioritizing the private profit-making of start-ups, which often build on previous basic science research funded by public money," Rueda explained. "I believe that the development of gene therapies for people with rare diseases should be a public goal and that it should also go beyond the patent wars."

In today's biopharmaceutical market, the process of making foundational changes is very complicated, but worth pursuing. "Setting a price that divides the threshold between the affordable and the unaffordable would be subject to multiple problems," Rueda stated. "But most people would find it very far from their common sense for an affordable therapy to have a multi-million dollar price tag." ■

Mike May 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.*

Breaking New Ground in Immunology & Inflammation

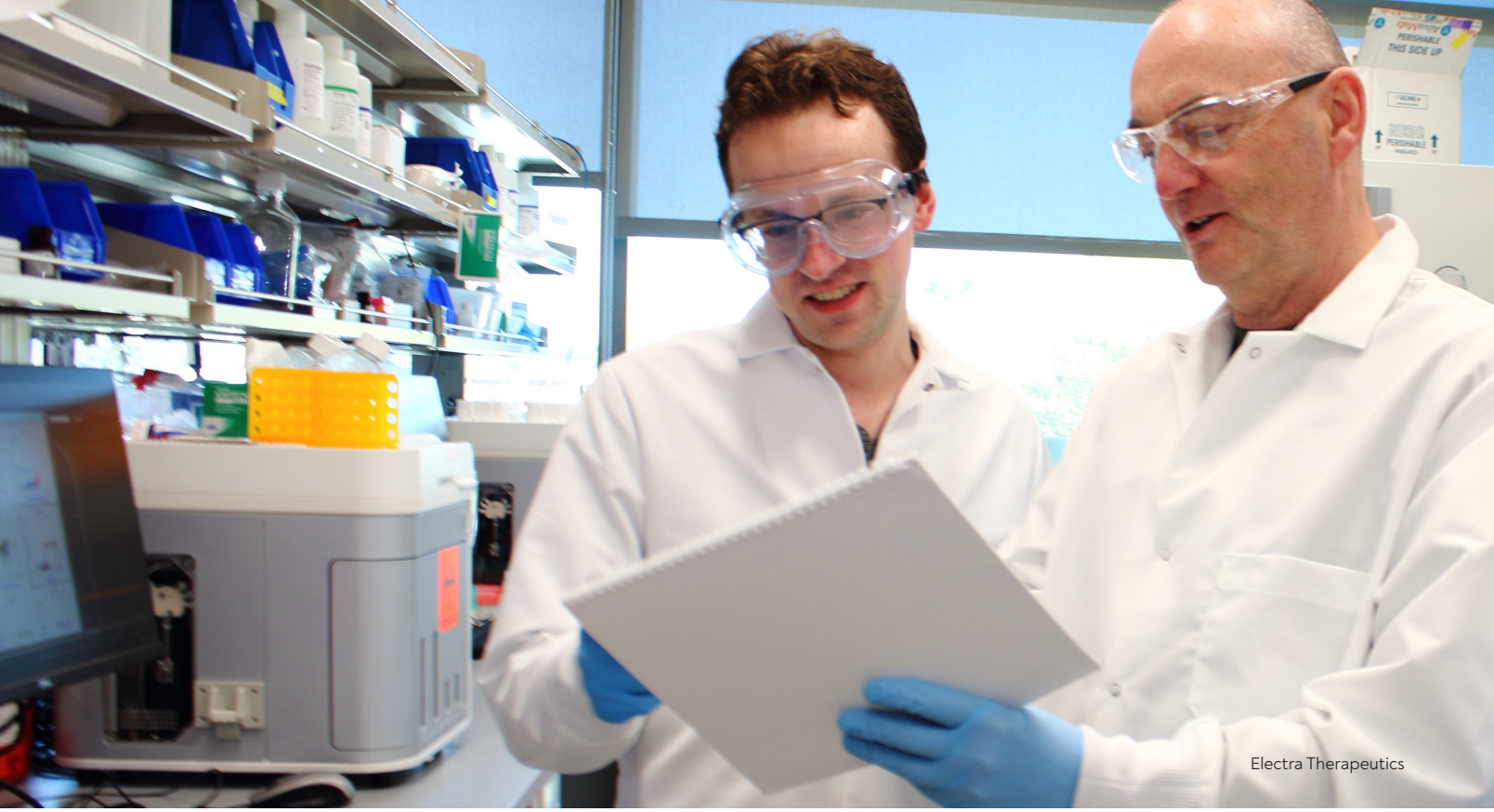
Kathy Dong, PharmD, is the president and CEO of Electra Therapeutics, a clinical stage biotechnology company developing antibody therapies against novel targets for immunological diseases and cancer. The company's lead drug candidate, ELA026, is a first-in-class monoclonal antibody that represents the new generation of drugs for immunology and inflammation—now referred to as I&I drugs—that selectively target disease-causing pathways of the immune system with precision. Discovered by Electra, ELA026 targets signal regulatory proteins (SIRP) on the surface of myeloid cells and T lymphocytes, and selectively depletes pathological immune cells. ELA026 is in clinical development for secondary hemophagocytic lymphohistiocytosis (sHLH), a rare, life-threatening hyperinflammatory disease for which there is no approved treatment.

Dong recently spoke with Damian Doherty, editor-in-chief of *Inside Precision Medicine*, to discuss this rare inflammatory disease, the encouraging clinical trial results for ELA026, and her dedication to developing first-in-class drugs that address complex and difficult-to-treat diseases.

Q: What motivated you to tackle such a complex, challenging disease as sHLH?

Dong: We were driven by the strong scientific rationale and the high unmet medical need. Our team doesn't shy away from tackling hard challenges and making bold decisions to drive an innovative drug forward to benefit patients.

At Electra, we applied a pioneering approach to target SIRP on certain immune cells as a novel approach for treating immunological diseases and cancer. When our first SIRP-targeted drug candidate, ELA026, emerged and showed the



Electra Therapeutics

ability to selectively deplete the principle immune cells that drive the pathogenesis of sHLH, we selected it as the lead indication. Despite sHLH being a complex condition with no approved treatment and no established path for drug development, we were motivated by the strong scientific basis and significant unmet need for an effective therapy.

I've always had a passion for working on first-in-class treatments that can have a meaningful impact on diseases, particularly those that are challenging to tackle or may be overlooked. The experience at Electra builds on my earlier career. I spent nine years at Gilead Sciences, where I was involved in the launch of transformative treatments for hepatitis B and C, including Viread, SOVALDI, and HARVONI. These drugs changed the standard of care for millions of patients worldwide and enabled us to focus on enhancing diagnosis and linkage to care so that as many patients as possible can achieve clinical benefits. At True North Therapeutics, I was part of a stellar team that pioneered drug development targeting classical complement biology, and discovered a portfolio of antibodies that has now progressed to an approved first-in-class drug for a rare hematological condition as well as clinical proof-of-concept in other diseases.

Like many who work in drug development, I find it so rewarding to work as part of a team, bringing together a shared passion and complementary skills to achieve groundbreaking results.

Q: Can you please describe secondary hemophagocytic lymphohistiocytosis?

Dong: Secondary hemophagocytic lymphohistiocytosis (sHLH) is a rare and life-threatening hyperinflammatory condition. It occurs when the body's immune system becomes excessively activated and is unable to regulate its response, leading to severe inflammation. The pathophysiology of sHLH is initially triggered by a strong antigenic stimulus such as cancer, infection, or autoimmune disease. Awareness of sHLH has been on the rise over the past two decades and particularly during the last few years, driven by COVID-19 and immunotherapy being possible triggers for sHLH. This has resulted in significant increases in the clinical detection of sHLH.

> "The pathophysiology of sHLH is initially triggered by a strong antigenic stimulus such as cancer, infection, or autoimmune disease."

Clinically, patients with sHLH present with symptoms such as persistent fever, low blood cell counts, enlargement of the spleen and liver, and issues with blood clotting. These symptoms are signs of an overwhelming immune reaction, often referred to as a cytokine storm, which can rapidly lead to multiple organ failure and death if not effectively treated.

Secondary HLH has a high mortality rate, particularly within the first few months after diagnosis. Cancer patients with malignancy-associated HLH, or mHLH, tend to have the poorest outcomes.

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Q: What types of treatment are currently available for sHLH?

Dong: Unfortunately, there is no currently approved treatment for sHLH, and existing therapies that are used off-label, including chemotherapy and anti-cytokine therapies, have shown limited effectiveness, underscoring the urgent need for new, safer, and more effective treatments to improve survival for these patients. The severity of this condition, along with the lack of effective therapies, provided a strong rationale for developing a new treatment option to improve outcomes for sHLH patients.

> "I believe we are successfully building the case for ELA026, with a strong scientific basis and compelling clinical proof-of-concept serving as the foundation."

Q: Tell me about ELA026 and recent clinical trial results.

Dong: We believe ELA026 has the potential to transform the treatment landscape for sHLH patients. During this year, promising results from our initial clinical study in sHLH were selected for oral presentation at the most prominent medical meetings in our field, including the European Hematology Association and the American Society of Hematology.

ELA026 is a monoclonal antibody designed to target immune cells that contribute to the cytokine storm in sHLH. It binds to specific receptors (SIRPα, SIRPβ1, and SIRPγ) on myeloid and T cells, and promotes the removal of these pathologically activated cells through cell killing mechanisms. This targeted approach allows for a rapid onset of action, which is crucial in treating the acute nature of sHLH.

At these medical forums, it has been gratifying to share our early data with the clinical and research community. In patients with mHLH who have the poorest prognosis, frontline treatment with ELA026 achieved a 100% response rate by week four, compared to a historical response rate of approximately 40–50% with standard therapies. Additionally, 100% of these patients were discharged from the hospital and about 90% achieved 60-day survival. This improvement in early survival is clinically significant, given the high mortality rate observed in the early stages of sHLH.

In addition, ELA026 has shown effects on key biomarkers of inflammation, such as CRP, ferritin, and sCD25, while demonstrating a favorable safety profile for this patient population. These findings suggest that ELA026 could provide rapid suppression of hyperinflammation and deliver meaningful clinical benefits, representing a critical advancement in treatment options for this severely ill patient population. It is particularly striking that ELA026 achieved such positive initial results in the most challenging segment of patients with mHLH.

Q: How have you been able to build the case for your first-in-class drug candidate?

Dong: Advancing any new drug idea entails both the scientific promise and the practical pathway to market—and for a first-in-class drug candidate, even more rigor and resolve are required. Confidence in a novel drug opportunity is bolstered by showcasing early-stage clinical validation, offering tangible evidence that supports the drug's potential. Equally important is outlining a clear strategy for addressing unmet needs and how the new drug will fit into the existing market landscape or change it.

I believe we are successfully building the case for ELA026, with a strong scientific basis and compelling clinical proof-of-concept serving as the foundation. Through our clinical program, we are demonstrating meaningful benefits, including improved survival, as a frontline treatment in the patient population with the highest unmet need. I believe these elements will naturally lead to a transformative impact for patients and a compelling value proposition that will result in a successful drug candidate.

Like many drug hunters, we continue to strengthen our case every day as we interrogate scientific queries and act with urgency to achieve progress toward bringing a first-in-class drug to help patients address their disease in a new way.

Q: Looking to the future, what are you most excited about?

Dong: There is tremendous momentum at Electra, and the entire team is excited about the progress of ELA026 in sHLH as well as the potential of our pipeline. The early clinical data for ELA026 in sHLH is highly encouraging and underscores the potential to offer meaningful benefits to patients. As we continue to advance ELA026 through the development process, we are optimistic about its role in transforming outcomes for sHLH patients and potentially becoming an example of a first-in-class treatment in the rapidly emerging landscape of next-generation I&I drugs. Furthermore, validation of the novel SIRP-targeted biology and the unique approach that we set out to explore five years ago enables the expansion of our pipeline into numerous other opportunities. ■

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

A New Era of Healthcare: Patient Monitoring Meets Precision Medicine

Ravjeet Sandher, Client Executive

The genesis of alarms in patient monitoring

The technological breakthroughs of the 1940s paved the way for digital patient monitors in the 1950s. These monitors, initially basic, evolved in the 1970s to multimodality devices that could assess multiple parameters, such as blood pressure and electrocardiogram. The late 1970s and 1980s saw the introduction of algorithms, enabling alarms to become a staple in patient monitoring. However, the variance in these alarms hasn't changed much over time across different vendors and patient populations. This uniformity raises concerns as the same alarm settings apply to both a healthy 35-year-old and an 85-year-old with multiple health issues. A one-size-fits-all approach doesn't cater to the specific needs of diverse patient groups, who could benefit from customized default settings or alarm limits.

The risks of poorly managed patient alarms prompted The Joint Commission to publish National Patient Safety Goal (NPSG) 6.01.01, aimed at improving the safety of clinical alarm systems (*The Joint Commission, 2021*).[1]

The importance of alarms in the patient care environment

As technology rapidly advanced, the realm of clinical alarms remained stagnant. Despite the evolution of artificial intelligence (AI) in healthcare, alarm systems have not seen substantial improvements. In both pediatric and adult acute care, regardless of manufacturer, the same alarm settings are observed. For example, oxygen saturation (SpO2) is often set at 90%. However, healthy individuals typically maintain an SpO2 of 99% or higher, while patients with chronic conditions may never reach 90%. This presents challenges in patient care: healthy individuals could suffer if alarms are triggered at 89%, while chronically ill patients might constantly trip alarms, leading to alarm fatigue, which can result in missed or delayed responses.

Adjusting these parameters often requires manual input from healthcare professionals, typically requiring a physician's order. This reliance on manual changes introduces the possibility of human error. More often, alarms are simply silenced, introducing another risk to patient care.

Changing the paradigm in alarms

Asking "what if" often leads to innovative approaches. Initially, complex discussions between experts in modeling and simulation sparked new ideas, evolving into opportunities for bringing precision medicine into patient monitoring. Concepts around digital twin technologies, where a virtual replica of the patient is created, have allowed for studying parameter changes against real-world outcomes. AI and machine learning further refine these outcomes to enhance precision.

What sets this approach apart is the use of real-world data from patient monitoring systems, electronic medical records, and secondary devices like infusion pumps and ventilators. This digital twin continuously receives and processes patient data, updating its parameters and improving precision.

The future of monitoring and precision medicine

Science fiction's vision of the future is now becoming a reality. Patients entering acute care can be connected to monitors that generate a digital twin, with its parameters constantly refined throughout the patient's stay. This system can integrate with alarm technologies to send actionable alerts when necessary. In this setup, AI becomes a safeguard against human error, enabling patients to be shifted between care paradigms as needed.

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This approach not only aligns with but exceeds the standards set by NPSG 6.01.01, offering a promising future for clinical alarm systems. The ultimate goal is to provide every patient with access to precision medicine that improves outcomes and assists clinicians in delivering optimal care.

The future of precision medicine is now

There is an ethical responsibility to bring precision medicine to patient monitoring across all modalities. The healthcare industry has unlocked new possibilities in patient care, and it is crucial to ensure that every patient benefits from technologies that enhance outcomes and support clinical decision-making.

Reference

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5 THE TOP 5 PLAYERS SHINING A LIGHT ON DIAGNOSTIC IMAGING

by Jonathan Smith

As the population ages, growing health challenges are increasing the demand for diagnostic imaging technology. Here are the five top companies primed to meet this demand.

When healthcare professionals need to see inside a patient's body, they can either use invasive probes or they can deploy less invasive diagnostic imaging techniques. In the latter scenario, the patient is beamed with radiation, ultrasound, or strong magnetic fields to produce high-resolution images of their tissues and cells.

In the case of cancer, capturing the complexity of tumors is a major challenge for precision medicine. The rise of medical imaging techniques such as radiomics and artificial intelligence (AI)-based tools is a promising development to help deal with this complexity more quickly than traditional methods, boosting patient care.

The global market for diagnostic imaging equipment is projected to grow from $47.65 billion in 2024 to $59.25 billion by 2029, with an annual growth rate of 4.45%. The growth is being driven by the increasing demand for medical imaging devices like magnetic resonance imaging (MRI), computed tomography (CT), and ultrasound scanners. There is also an increasing awareness of portable imaging devices that can be used at the point of care.

The main providers in diagnostic imaging consist of tech giants in the U.S., Europe, and Japan. Check below for a list of the top five market players based on their role in the market and market capitalization.

Canon

Founded: 1937 | **Headquarters:** Tokyo, Japan
Market cap: $45 billion

Canon began with a focus on camera technology but has expanded its reach in the last few decades to encompass multiple sectors like commercial printing, network cameras, and medical and industrial equipment.

Canon's Medical Group supplies diagnostic imaging equipment such as CT, MRI, X-ray, and ultrasound machines. It is developing a new type of CT scanning called photon counting CT, which is designed to scan patients with less exposure to radiation than with traditional CT. The company is also increasing its automation and in-house production muscle.

Canon's medical business unit saw a record 7.9% growth in 2023 to 553.8 billion yen ($3.6 billion), driven by increasing overseas demand for CT and MRI scanners amid the disruption of the COVID-19 pandemic, high inflation, and geopolitical uncertainty.

In 2016, Canon bought Toshiba's medical business Toshiba Medical for $5.9 billion, eventually renaming it Canon Medical Systems. The move, which was partially made before getting clearance from the European Commission, invoked a €28 million ($30 million) fine for Canon.

Canon is set on international expansion, particularly in the large U.S. market. In 2023, the company set up a marketing business called Canon Healthcare USA. It also acquired Resonac's Minaris Medical, which offers in vitro diagnostic reagents and automated analytical instruments, for $29 million in 2023.

Canon is now in the process of establishing local bases in India, Saudi Arabia, and other emerging markets.

Fujifilm

Founded: 1934 | **Headquarters:** Tokyo, Japan
Market cap: $30 billion

Like Canon, Fujifilm began with a focus on selling equipment for photography. The firm launched its first X-ray film product in 1936 and has since expanded into multiple branches of medical imaging.

Its diagnostic imaging offerings include equipment for X-ray imaging, endoscopy, ultrasound, and in vitro diagnostics.

Fujifilm also works in medical IT such as image processing and is developing AI-based tools to support diagnostic imaging professionals.

Fujifilm acquired Hitachi's diagnostic imaging business in 2019 for around $1.2 billion, with assets including R&D, manufacturing, sales, and maintenance of diagnostic imaging systems as well as electronic health records. The aim of the acquisition was to make its own offerings more comprehensive, enhance imaging with its own AI tools and obtain new sales channels.

The revenue from Fujifilm's healthcare division increased to 975.1 billion yen ($6.4 billion) in 2023, 5% higher than in 2022. The revenue was driven by steady sales of devices like endoscopes, CT, and MRI, with endoscope sales especially rising in the U.S., Europe, Japan, and China.

In addition to diagnostics, the company is active in other parts of healthcare like cosmetics, supplements, and biopharmaceuticals.

GE HealthCare Technologies

Founded: 2023 (as a spinoff from GE)
Headquarters: Chicago, Illinois | **Market cap:** $42 billion

GE Healthcare originated as a business owned by parent company General Electric (GE), which was founded in 1982 with a focus on selling machinery across industries such as appliances, transport, and healthcare. After years of declining profits and stock prices, GE split into three companies, with GE Healthcare taking on its diagnostic imaging division.

GE Healthcare sells a wide range of diagnostic imaging equipment ranging across ultrasound, CT, MRI, and X-ray scanners. The company also boasts one of the highest counts of AI-enabled medical devices approved by the U.S. Food and Drug Administration, with 58 in its roster as of October 2023.

GE Healthcare saw a revenue of $19.6 billion in 2023, with its imaging business taking the lion's share of the winnings in the last quarter of 2023. This represents a 7% increase in total revenue year-over-year. This year, the company anticipates an additional 4% growth in its revenue year-over-year.

GE Healthcare acquired the AI and medical imaging player MIM Software earlier this year to boost the former's digital solutions, particularly in precision care such as theranostics in oncology. The firm also recently teamed up with University Medicine Essen to establish a theranostics center of excellence in Germany outfitted with radiopharmaceutical production and imaging equipment.

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4 PHILIPS

Philips

Founded: 1891 | **Headquarters:** Amsterdam, Netherlands
Market cap: $30 billion

Philips was established in Eindhoven, Netherlands, by Frederik Philips and his son, Gerard. The company initially specialized in the production of light bulbs before ballooning into other markets like appliances, data storage, and healthcare.

Philips sells imaging equipment such as CT scanners and MRI machines, including MRI scanners that require a fraction of the increasingly scarce element helium compared with traditional machines.

Philips' Diagnosis and Treatment segment saw €8.8 billion ($9.6 billion) in sales last year, an 11% increase compared with 2022's €8.3 billion ($9 billion). This was driven by high growth in the company's image-guided therapy and precision diagnosis offerings.

Philips has been actively acquiring diagnostic imaging assets in the past few years, with examples including the takeover of the healthcare information systems business Carestream Health in 2019 and the purchase of French cardiac diagnostics firm Cardiologs. Philips delved further into the world of AI with the acquisition of DiA Imaging Analysis for almost $100 million in 2023. DiA specializes in harnessing AI to read and interpret ultrasound images more efficiently than traditional methods.

The company carved out its medical imaging equipment supplier AGITO Medical in a sale to the private equity firm Duke Street earlier this year.

5 SIEMENS Healthineers

Siemens Healthineers

Founded: 2017 | **Headquarters:** Erlangen, Germany
Market cap: $64 billion

Siemens Healthineers started off as part of its parent company Siemens, which was established in Berlin in 1847. Siemens began as a provider of machinery like trains, factory equipment, and communications and soon expanded to healthcare. Siemens spun off its medical technology division to afford more flexibility and continues to keep a 75% stake in the spinoff.

Among Siemens Healthineers' main products is equipment to handle CT scanning, angiography, X-ray, and ultrasound machines. The company also produces IT systems deploying AI to help small teams navigate complex healthcare and increase automation.

Siemens Healthineers launched an initial public offering in 2018 and merged with its long-term collaboration partner, the imaging and cancer care provider Varian Medical Systems, in 2021.

In 2023, Siemens Healthineers bagged almost €21.68 billion ($23.54 billion) in revenue, which was 0.2% less than the €21.71 billion ($23.57 billion) it earned in 2022. Its imaging segment was the biggest earner with €11.84 billion ($12.85 billion), representing 9% growth compared with the previous year.

Earlier this year, Siemens Healthineers bought Novartis' radiopharmaceutical business for more than $223 million, including the diagnostic arm of radiopharmaceutical titan Advanced Accelerator Applications. The move also helped Siemens Healthineers expand its expertise in PET and radiopharmaceuticals in Europe. ■

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

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"Ideal Laser Illumination: Light Engines for MERFISH, STORM, PALM, and PAINT"

New light microscopy techniques with esoteric names such as MERFISH, STORM, ORCA, OPS, and SIM are rapidly emerging. Each one has its own technical refinements and application niche. It is perhaps surprising then that just two multiline laser illuminators, Lumencor's ZIVA and CELESTA Light Engines, can fulfill the lighting requirements of all of these demanding techniques.

Dr. Bogdan Bintu at the University of California San Diego is well-placed to make this assessment, both from his current research in applying MERFISH to study neurogenesis in aged mammalian brains (*Figure 1*) and his previous experience in Dr. Xiaowei Zhuang's laboratory at Harvard University.

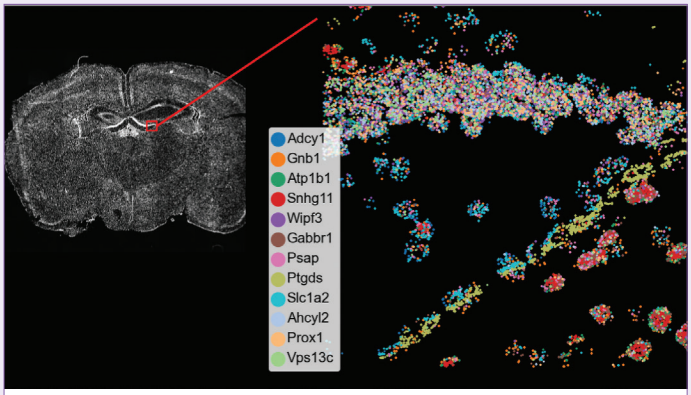


Figure 1. MERFISH imaging of 12 RNA transcripts in mouse brain tissue.

Light microscopy requires an illuminator. For modern "alphabet soup" microscopy designed to provide high-resolution spatial mapping of multiple RNA, DNA, or proteins over large fields of view, that source is an array of lasers with discrete outputs. The temporal and spatial coordination of the laser outputs is critical to the end results. ZIVA and CELESTA Light Engines generate light of various wavelengths which remain spatially and temporally consistent. They offer a compact, integrated, turnkey box, providing the robust, stable, and maintenance-free illumination necessary to foster routine data acquisition that can proliferate to many end users.

STORM (stochastic optical reconstruction microscopy), invented in Xiaowei Zhuang's Harvard University laboratory, is a super-resolution microscopy technique enabling resolution of objects below the diffraction limit of 200 nm. High irradiance illumination drives stochastic activation of fluorescent molecules to spatially distinguish them from their transiently dark neighbors. Bintu and colleagues implement STORM imaging using a CELESTA Light Engine for fields of view of up to 100 µm x 100 µm. Although the nuances of super-resolution microscopy may not be self-evident, the new insights offered to investigators certainly are (*Figure 2*).

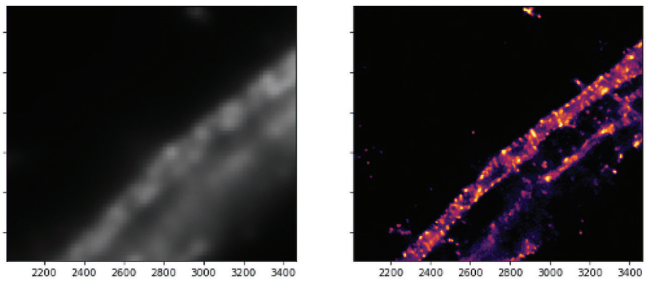
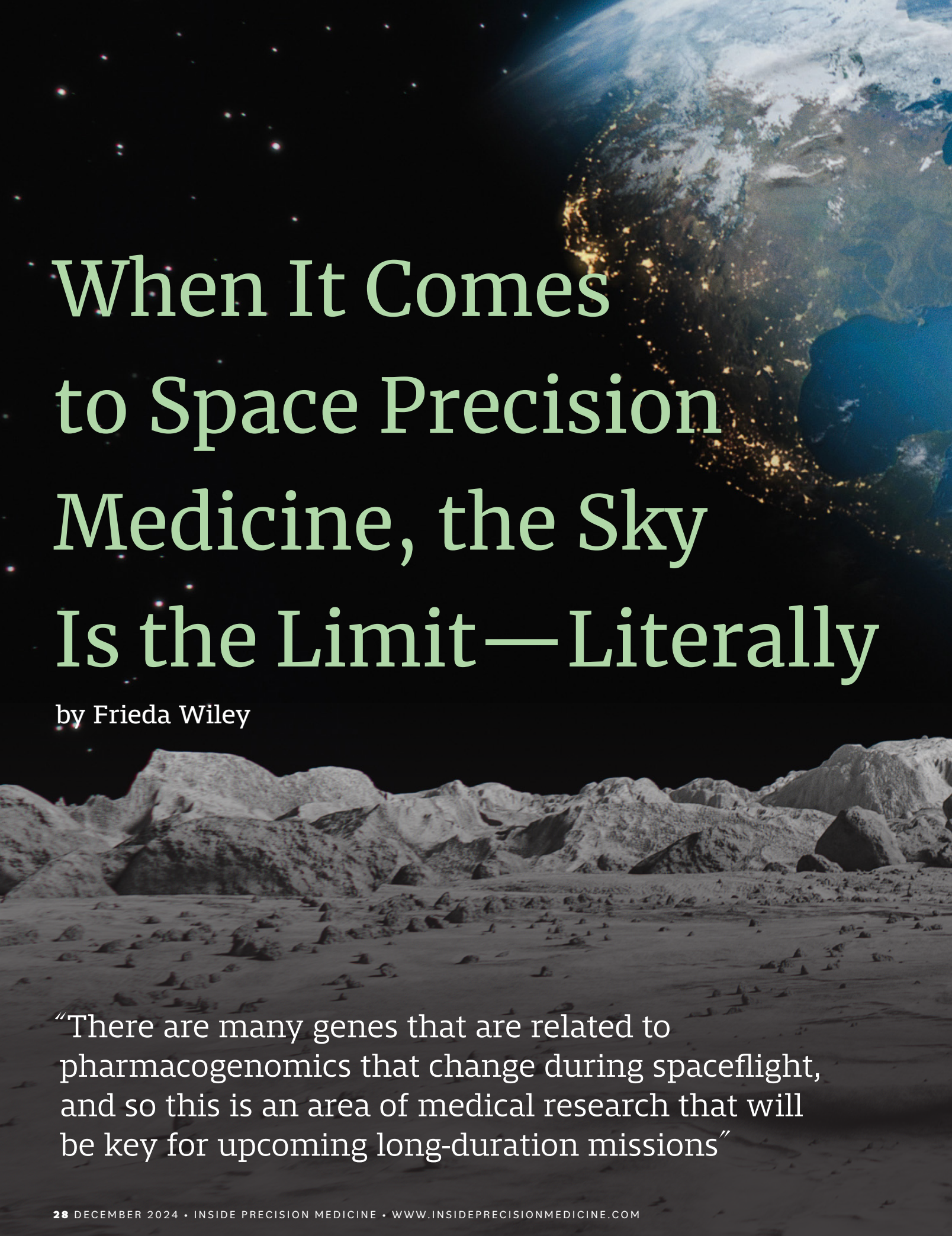


Figure 2. Actin, spectrin, and associated molecules form a membrane-associated periodic skeleton (MPS) that plays an important role in the regulation of neuronal function and dysfunction. Diffraction-limited (left) and STORM (right) images (50 µm x 50 µm) of axonal MPS illustrate why this is so.

Like STORM, MERFISH also originated in Zhuang's laboratory. MERFISH (multiplexed error-robust fluorescence in situ hybridization) is a massively multiplexed single-molecule imaging technique. It is capable of measuring the copy number and spatial distribution of hundreds to thousands of target RNA transcripts in single cells [2]. In turn, single-cell transcriptomic characterization allows in situ identification and spatial mapping of cells in complex tissues (*Figure 1*). MERFISH requires high-intensity, spatially uniform light matched to typical sCMOS camera sensor dimensions. CELESTA Light Engine can provide 1,000–10,000 mW/mm2 at the sample plane. 477 nm, 637 nm, and 748 nm lasers identify DNA probes hybridized to RNA transcripts; 405 nm and 545 nm outputs illuminate DAPI-stained nuclei.

Only with bright, stable illumination which embodies spatial and temporal robustness can the capabilities and impact of the newest light microscopy techniques be realized. Pushing past traditional imaging hardware limitations and offering the highly multiplexed mapping capabilities required for spatial resolution techniques demands bright, well-behaved light. Turnkey Light Engines are a critical component in pushing past historical diffraction limitations to enable such groundbreaking imaging.



When It Comes to Space Precision Medicine, the Sky Is the Limit—Literally

by Frieda Wiley

"There are many genes that are related to pharmacogenomics that change during spaceflight, and so this is an area of medical research that will be key for upcoming long-duration missions"

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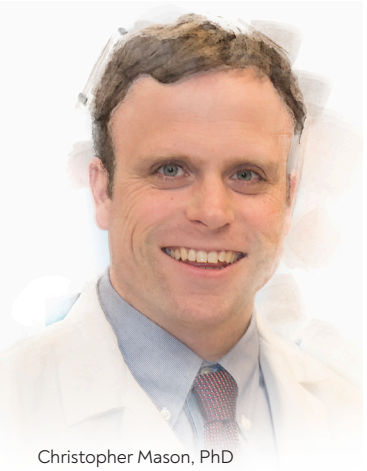
Man's fascination with space predates the first space shuttle launch or human footprints on the moon. Yet, sustaining human life in space requires creating a conducive environment and equipping the body with vital resources—such as pharmaceutical drugs—to help withstand the consequences of unique extraterrestrial stressors not experienced on Earth.

The specific spaceflight properties human visitors encounter demand special strategies to resist environmental side effects and treat emergent situations and chronic illnesses. Treatment modalities used on Earth do not always extrapolate to the universe. Spaceflight alters drug integrity and how the human body reacts to it—even in the case of precision medicine. Based on a growing body of data, some experts believe that pharmacogenomics-guided spaceflight is the foundation of precision medicine, a feature that they believe will enable long-term human habitation on the Moon.



Christopher Mason, PhD
Professor
Weill Cornell Medicine in New York

"There are many genes that are related to pharmacogenomics that change during spaceflight, and so this is an area of medical research that will be key for up-coming long-duration missions," said Christopher Mason, PhD, a professor of genomics and computational biomedicine at Weill Cornell Medicine in New York.

Mason's research is important as advancements in aerospace pharmacogenomics have largely stalled today, plagued by hurdles to space-flown pharmaceutical data such as limited access, data privacy concerns, interoperability, and reproducibility. The aerospace community has responded by enhancing interdisciplinary collaboration to produce a digital network of databases maintained by space industry stakeholders. Mason and his colleagues have contributed to these efforts by compiling data from publicly available repositories. His team's efforts have also helped support their own research interests.

Microgravity places the body under unique stress, causing health challenges

Before uncovering how spaceflight impacts pharmacogenomics, one must first understand how the body responds to spaceflight. The unique stressors the human body encounters in space cause it to respond in some unusual ways. These characteristics make medicine, pharmacogenetics, and even cancer behave differently in the extraterrestrial setting.

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Perhaps the most commonly known extraterrestrial side effect is a lower gravitational pull called microgravity. Microgravity describes the extent to which acceleration affects an object in outer space. Because space exerts a significantly lower gravitational pull compared to Earth, microgravity is commonly called "zero gravity" (0g). However, at $1x10^{-6}$g, the colloquial phrase is slightly misleading, according to the NASA website.

As for specific effects, previous research conducted in models both in space and on Earth has shown that microgravity alters proliferation, migration, adhesion, survival, and apoptosis in human cells. The altered gravitational environment also affects the cytoskeleton structure, focal adhesion, the extracellular matrix, and growth factors.

Theodore Maximillian Nelson
recent computer science graduate
Cornell University

On a larger scale, some long-term health issues associated with extended space travel manifest as immune system dysregulation and impaired wound healing. More notably, astronauts who spend months in space wrestle with muscle atrophy, bone loss, and potential cardiovascular problems. To counter these problems, astronauts exercise for up to two hours a day to help strengthen the heart and bones; they also take medications such as alendronate to counter bone density, commonly prescribed to treat Earth-dwelling men with osteoporosis and postmenopausal women who either have osteoporosis or are at risk for it.

How does spaceflight alter pharmacogenetics?

"The most critical genes for spaceflight-guided pharmacogenetics are likely those which most impact processing of drugs for inflammation and immune function as well as those that regulate sleep, since they are very common," said Mason.

Examples might include genes that metabolize the sleep-fighting drug modafinil, sleep-inducing zolpidem, and muscle relaxant scopolamine—all drugs commonly used during space assignments.

It is also worth noting that spaceflight upregulates *GCLC* and *GGTI*, which are genes that stimulate glutathione activity. Known as the "master antioxidant," glutathione plays several important roles in the liver, like activating various drugs. However, in this case, its upregulation suggests an increased response to oxidative stress.

For these reasons, exploring genetic mutations in the liver's drug-metabolizing CYP450 enzymes is a natural progression. Not only is drug-related inhibition or induction of CYP450 enzymes responsible for most drug–drug interactions, but inhibiting or inducing of one of these enzymes with one drug can simultaneously inhibit the activity of another drug processed by the same enzyme. In addition, while a previous study has shown that spaceflight-induced proteomic activity downregulates CYP450 activity by 50%, no existing studies have evaluated whether pharmaceutical drugs contribute to decreased CYP450 activity.

Of the 218 unique drugs logged in their database, Mason and colleagues have identified 190 interactions with 772 distinct genes, accounting for a total of 2,318 interactions.

"Searching for mutations in drug metabolizer genes active in the liver is a first step towards personalized pharmacogenetics in space," said Theodore Maximillian Nelson, recent computer science graduate of Cornell University and lead author of the study with Mason and his colleagues.

They concentrated on spaceflight-induced shifts, which helped them identify a new method of identifying the most impactful changes in absorption, distribution, metabolism, and elimination parameters. Pharmacogenetic activity can influence these properties.

Once ingested, spaceflight alters pharmacokinetic activity in the following ways. Delayed gastric emptying and altered microbial community structure accelerate drug degradation. Meanwhile, several factors decrease drug absorption. These include faster intestinal transit, shift-induced hypoperfusion of the gastrointestinal tract, as well as expression of gastrointestinal transporters and enzymes. Through their investigation, Nelson, Mason, and colleagues found that a certain group of solute transporter genes, namely *SLC19A1, SLC23A,* and *SLC2A2,* contribute to gastrointestinal cancer.

Other genes seemed to remain stable.

"*CYP1B1, CYP2D6, CYP3A43* were differentially expressed within the selected spaceflight study, suggesting that the remaining CYP450 are less affected," Nelson said. "Nevertheless, while we do not have available human hepatic transcriptomic data, instead we analyze human cardiomyocyte transcriptomic data."

Based on this information, Nelson described their findings as "rather preliminary."

Spaceflight alters post-absorption drug metabolism of both orally ingested and injected drugs in many ways. The characteristics vary as much as the individual responses.

For example, spaceflight shifts fluid dynamics. This environment drives fluid toward the head, which increases urination and natriuresis, or sodium excretion through the kidneys, while hindering lymph flow and lymphatic drainage. Astronauts may find themselves less thirsty than usual despite losing more fluid through their lungs and skin in space than on Earth.

Space-bound individuals will also experience a redistribution of fluid from plasma to extracellular volume and subsequently, from extracellular volume to intracellular volume. In addition,

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unlike on Earth, microgravity decreases volume and drug distribution while increasing plasma concentration. Additional extraterrestrial changes that affect drug behavior are altered binding expression, plasma concentration, and hepatic blood flow.

Space laboratory research could give rise to a new class of cancer therapeutics

Although not directly correlated with pharmacogenomics, another group of researchers at biotechnology startup MicroQuin have uncovered an element of microgravity that could very well lead to breakthrough cancer treatment. The Cambridge, Massachusetts–based firm made an important discovery while growing 3D prostate and breast cancer cell cultures at the International Space Station (ISS) National Laboratory orbing 250 miles above Earth.

MicroQuin found that targeting a specific protein called TMBIM6 that regulates the intracellular environment and defines cell structure can kill cancer cells. MicroQuin researchers developed a small molecule therapeutic that binds to TMBIM6, disrupting the intracellular environment in the process. When the small molecule complexes with TMBIM6 and prevents it from functioning, cancer cells die. In addition, not only is this novel treatment only activated in cancer cells, but researchers found it to work in all kinds of cancer, with potential uses in traumatic brain injury, neurodegenerative diseases, and viral infection.

"Discoveries in space aren't just achievements on a space station," said Amelia Smith, ISS National Lab science communications manager in a recent press release. "They are breakthroughs that could lead to a world where families like mine are filled with hope instead of fear in the face of cancer and other devastating diseases."

MicroQuin could not be reached for comment.

Can artificial intelligence help predict drug responses in space?

Despite having compiled the largest catalog of spaceflight medicine within the current scientific literature, Nelson and his colleagues' database, combined with pre-existing repositories, is not large enough to train a predictive artificial intelligence (AI) model for drug response at present. However, two other databases have amassed volumes nearly large enough to clear the AI threshold. Space Omics and Medical Atlas (SOMA) is a collaborative project uniting the efforts of more than 25 institutions around the world and collating integrated data and sample repositories for cellular, multi-omic, and clinical research profiles. Nelson and Mason compared their findings to these databases.

"We did not find evidence of astronaut-specific pharmacogenetic profiles being utilized to predict responses, which is becoming more common on Earth in drug prescription," Nelson said.

Current research highlights the need for greater investigation into other "omics"

Spaceflight-induced immunosuppression has prompted scientists to investigate potential pharmacological treatments, including novel drug therapies. These explorations have increased the risk of polypharmacy but have borne no relationship to genotype profiles. Interestingly enough, the breadth of impact spans beyond drug-metabolizing genes to encompass any known space-induced, drug-gene interactions. In addition, various factors such as epigenetic markers, genotype, transcriptomic upregulation or downregulation, post-translational tagging, and post-transcriptional modification may be involved.

Nelson and his colleagues believe that space genes serve as the primary drivers of individualized transcriptomic responses. The extraterrestrial frontier can expand research to advance research and medicine, especially in the case of proteins.

"For protein crystallization, these space flight studies can allow for the formation and study of proteins in a manner which could not be possible on earth," Nelson said. "There are research and development case examples where drug manufacturing has been performed in space with greater efficacy because the microgravity environment is more permissive to the formation of complex 3D structure for processes such as biofilm formation and protein crystallization.

"A comprehensive investigation of spaceflight-related pharmacogenetics with pharmacokinetics and biological settings could elucidate novel mechanisms of action for drugs."

Nelson, Mason, and colleagues cite double reporting as a study limitation. They also noted that labeling their current research as "pharmacogenomics" may be somewhat of a misnomer, as their research focused heavily on transcriptomics. However, Mason and Nelson envision spaceflight pharmacogenomics as amassing a breadth that incorporates every viable mechanism affecting drug behavior that could one day be quantified through high-throughput analysis. ■

Frieda Wiley, PharmD, is an award-winning medical writer, best-selling author, speaker, and pharmacist who has written for *O, The Oprah Magazine*, the National Institutes of Health, *American History*, Pfizer, Merck, AstraZeneca, and many more notable organizations.

Fallout: A New Era in Post-Opioid Pain Therapeutics

Efforts to reform pain research and therapeutic development involve the necessary reassessment of preclinical models and clinical frameworks

by Jonathan D. Grinstein North American Editor

Penalty. Torment. Hardship. Suffering. Punishment. These definitions of poine and poena—the Greek and Latin words for pain—describe our complex relationship with pain, speaking to something beyond the physical discomfort, a phenomenon experienced in both body and mind. Pain is not a simple, unidirectional, linear process whereby a physical stimulus activates a nociceptor, triggering the propagation of a signal along a nerve to the brain to become salient. It is more akin to an ouroboric Gordian knot made of mental and physical fibers.

Kara Margolis, MD
Director
NYU Pain Research Center
Associate Professor
New York Dentistry and NYU Langone

We all feel pain. In the U.S., pain annually affects 100 million Americans, amounting to half a trillion dollars in terms of economic burden. Still, the opiod epidemic rages on, a major cause for mortality among young adults—one in five in their 20s and 30s—and tamper-proof opioids that reduce addiction and risk continue to be developed as painkillers. Only ziconotide, developed into a therapeutic called Prialt by Elan Pharmaceuticals and approved by the FDA to treat pain in 2004, but due to side effects, is rarely used. Without question, the need for new non-addictive pain treatments is as critical now as ever.

> "There are many factors that make pain highly diverse and complex, such as comorbidities like addiction and mood disorders."

Mind over Matter

During her pediatric residency at Albert Einstein College of Medicine's Montefiore Medical Center, Kara Margolis, MD, treated patients who changed her career path. "Healthy kids would come in, and then suddenly they'd be blind or couldn't walk," Margolis told *Inside Precision Medicine*. Although the children did not show any signs of neurological damage, they were clearly experiencing symptoms of motor or sensory loss. But Margolis noticed a common thread—all of the children seemed to be living in challenging and stressful situations. It was as if they were experiencing such intense emotional pain that the children suddenly experienced symptoms typically caused by having a bundle of neurons severed or a chunk of brain removed.

Although Margolis did not end up studying this baffling condition, it did point her in the direction of studying the

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interaction between psychiatric conditions and pain. Margolis, who is the director of the New York University (NYU) Pain Research Center, believes that it is critical to capture not only the biological factors contributing to pain but also the psychological and social ones as they seem to be essential to the most up-to-date model for human pain, the neuromatrix (or the brain pain matrix). In this model, patterns of nerve impulses across several interacting networks in the brain (i.e., sensory, cognitive, and affective) create the multidimensional experience of pain not only through the physical stimulation of pain receptors but also via environmental and internal non-nociceptive stimuli.

Rajesh Khanna, PhD
Professor and Director
Pain and Addiction Therapeutics Collaboratory
University of Florida

Part of the Margolis lab at NYU focuses on gut signaling in mood disorders and abdominal pain-related disorders of gut-brain interaction (DGBIs), which affect as many as 20% of children and adolescents in the United states. The symptoms DGBI patients experience do not primarily result from gastrointestinal damage but from challenges associated with processing pain signals between the gut and the brain. “There are many factors that make pain highly diverse and complex, such as comorbidities like addiction and mood disorders,” Margolis said. “Understanding the shared mechanisms between pain and these other comorbidities could not only lead to novel targets but potentially targets that can treat multiple disorders at the same time.”

Of mice and men

Rajesh Khanna, PhD, a professor and director of the Pain and Addiction Therapeutics Collaboratory at the University of Florida, has been studying voltage-gated sodium channels (NaVs) as targets for non-opioid therapeutics. For decades, his darling has been Nav1.7, a nociceptor preferentially expressed in the cell bodies of neurons located within the dorsal root ganglion of the spinal cord. These receptors are critical for sensing pain and relaying the signal to the brain. NaV1.7 makes sense as a therapeutic target because patients with mutations in *SCN9*, the gene encoding the channel, display many pain-related phenotypes and conditions. For example, loss-of-function results in pain insensitivity whereas gain-of-function confers pain hypersensitivity.

A major issue limiting pain research is the poor translatability of existing preclinical models. “We have solved chronic pain in rodents a thousand times over—we and everybody else who works on it,” Khanna told *Inside Precision Medicine*. “But it doesn’t translate because humans have this feeling, the emotional aspect of pain, the affective dimension. How do you assess that in an animal? It’s been done, but it’s very difficult.”

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Even when the emotional dimension of pain is taken out of the equation, Khanna thinks the cellular and molecular complexity in the biology of pain relative to other diseases, such as cancer, is extraordinarily challenging. Khanna explained, "There's so much about pain that has to be connected: the circuits, the cells, and the proteins. And it's not all neurons, but also astrocytes, glia, and immune cells; there's so much of a cross-talk that it becomes overwhelming to think about. It's complicated. It's not just [like cancer] where you can say, 'Let me eliminate this thing and everything goes away.'"

Linda Porter, PhD
Director
NIH's Office of Pain Policy and Planning

Moving from preclinical to clinical, however, is like jumping from the frying pan into the fryer. One of the reasons for this, according to Margolis, is the dearth of pain biomarkers. "There's no consistent reliable biomarkers for pain, so without those, it's challenging to accurately, objectively, recruit for clinical studies and also to determine drug efficacy or other outcomes," Margolis said. "How do you characterize and how do you personalize medicine when you have no biomarkers?"

The power to HEAL

In 2018, with Congressional support, the National Institutes of Health (NIH) initiated the Helping to End Addiction Long-term Initiative, or HEAL Initiative, as a comprehensive research endeavor aimed at expediting scientific solutions for opioid use disorder, overdose, and pain management. According to Linda Porter, PhD, a director at the NIH's Office of Pain Policy and Planning, an initiative like HEAL was critical to rejigging their entire approach to the study and treatment of pain. While lots of pain research had been done at the NIH—for example, the National Cancer Institute did a lot of research on cancer pain, chemotherapy-induced pain, and post-cancer survivor pain—there had not been a centralized effort behind what Porter calls the "neurological disease of pain."

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In its first five years, the HEAL Initiative has put financial eggs into lots of baskets, like the Program to Reveal and Evaluate Cells-to-Gene Information that Specify Intricacies, Origins, and the Nature of Human Pain (PRECISION Human Pain) network that focuses on research efforts to identify and describe mechanisms underlying pain experiences in humans instead of animal models. The HEAL Initiative has also funded a clinical screening program for small molecules and biologics for pain therapeutic development. "The compounds, or the potential drugs, that have come through the pipeline so far are not really ready for the large effectiveness trials because it's only been five years," said Porter. "But what we're hoping in the next five years of HEAL is that some of those could maybe move into larger trials. So we've got a number of approvals from the FDA of products to move forward."

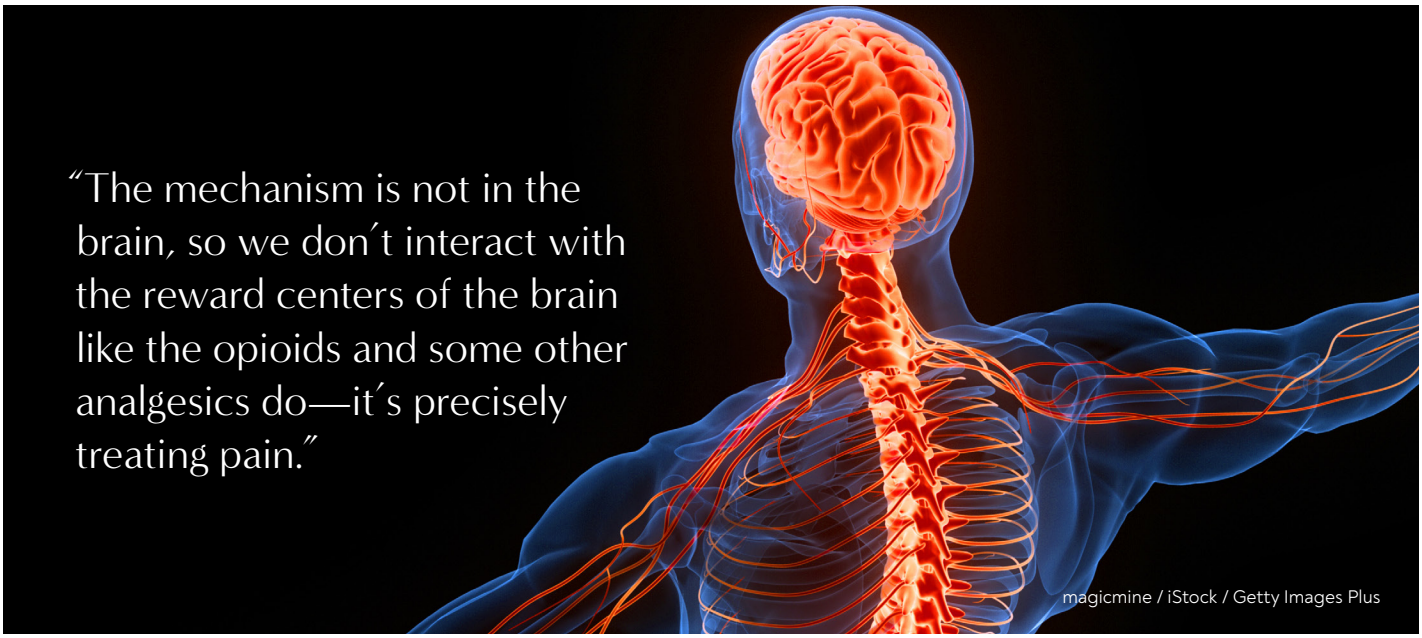
Paul Negulescu
Senior Vice President and disease area executive (pain)
Vertex

Another key area for the HEAL Initiative is to get at the heart of the many issues that have plagued the clinical study of pain treatments, whether therapeutics or devices. The HEAL initiative has built clinical trial networks that would take in trials at the early efficacy or proof of concept stage and also run effectiveness and implementation trials. "We also built large programs to provide a pipeline from start to finish of how we could find validated tests and then move into the implementation component of new therapeutics," said Porter. "The game has really changed as far as how we were able to evaluate interventions."

Khanna believes that initiatives like HEAL are critical to this new push to find non-addictive pain medications, in part because he does not think that Big Pharma wants to go on a wild goose chase to find and validate new targets. "This is a great service that the NIH is supporting in terms of either validating, de-risking, or eliminating potential new targets for pain. I see this as a way to fill the void left by [Big Pharma]. They want a blockbuster, but I believe they have been burned by so much investment that has not really paid off."

A temporary reprieve

Paul Negulescu, senior vice president and disease area executive (pain) at Vertex, is leading an effort that stands to prove Khanna wrong by targeting a different sodium voltage-gated channel, NaV1.8, which is a nociceptor found in many of the same cells that carry NaV1.7. To do so, Vertex developed a pain-in-a-dish approach to model NaV1.8, or any other voltage-gated channel, with two key aspects. The first is studying the channel in isolation with very fine control and high-resolution



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measurements of channel dynamics. Vertex developed specific technology for expressing a single voltage-gated channel in HEK cells, enabling measurements of action potentials elicited by the channel. "We can vary the frequency and the intensity of the stimulus, and we can really see how the drug interacts in real time over repeated cycles," Negulescu told *Inside Precision Medicine*. The second is to take the chemical entities identified as having the ideal properties for controlling a NaV and add them to a population of neurons from a human dorsal root ganglion (DRG). Studying the candidate molecules in this more complex context of a population of pain-sensing neurons is important because the firing of a neuron involves an orchestration of several voltage-gated channels, which work like a "bucket brigade," as Negulescu likes to call it. DRGs are a heterogeneous place, made of neurons with nociceptors specific to heat, cold, pressure, chemical insults, and more. This setting allows the team at Vertex to study the flavor of pain signals their candidate molecules modulate. "Short of having a whole human dorsal root ganglion all the way to the fingertips and the spinal cord, this is as far as we've gotten at modeling pain in a dish, and it's translated pretty well so far in terms of both the efficacy and the lack of effect on other sensory systems that are not pain sensors," said Negulescu.

"If possible, we'd like to be as efficacious as an opioid, to relieve the pain at the level of morphine. Whether we can do that, we don't know. Ideally, people in the future may not have to take an opioid at all. But we're far away from that today."

Formerly known as VX-548, suzetrigine targets sodium voltage-gated channel Nav1.8 to inhibit pain-signaling pathways in the peripheral nervous system, which, theoretically, should not pose a risk of addiction. "The mechanism is not in the brain, so we don't interact with the reward centers of the brain like the opioids and some other analgesics do—it's precisely treating pain," Negulescu said. So far, that theoretical derisking of addiction has proven true, and suzetrigine has made the most clinical headway in treating irritated lumbosacral radiculopathy. This condition, where the nerve roots in the lower back are compressed, affects 3–5% of Americans throughout their lifetime, translating to several millions of patients. The Nav1.8 inhibitor has completed two Phase III clinical trials. A Phase II study of lumbosacral radiculopathy has been granted FDA Fast Track and Breakthrough Therapy designations and is under priority review with a target action date of January 30, 2025.

Negulescu said that this clinical work on suzetrigine, which could also treat peripheral neuropathic pain such as painful diabetic peripheral neuropathy, has served as a proof of concept for Vertex's approach to developing pain therapeutics. "It's a simple vision to precisely treat pain without risk of addiction, and we have a fairly straightforward strategy, which is to fully exploit the idea of selective sodium channel inhibition as the way to achieve that," said Negulescu. "If possible, we'd like to be as efficacious as an opioid, to relieve the pain at the level of morphine. Whether we can do that, we don't know. Ideally, people in the future may not have to take an opioid at all. But we're far away from that today." ■

Jonathan D. Grinstein, 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. Before *IPM*, Jonathan wrote 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.

entrePRECISIONeur

Improving Precision Oncology

by Helen Albert Senior Editor

Cancer is one of the first areas where precision medicine was applied in a clinical setting. Today, particularly in developed countries such as the U.S. and U.K., it is becoming increasingly common to undergo precision diagnostic testing and subsequent targeted therapy depending on the tumor mutations and type of cancer.

It is widely acknowledged that targeted therapy guided by suitable diagnostics has a beneficial impact on patient outcomes and can more than double survival times, depending on the cancer and treatment in question.

While there have been large steps forward in cancer therapy, there is much left to be achieved and a pressing need for new and innovative startups to address unmet needs in the field. For example, Zahra Jawad, PhD, founder and CEO of Cambridge-based biotech Creasallis, noticed an unmet need to improve the efficacy of antibody therapies used for treating different cancers and to reduce side effects from these drugs.

In contrast, London-based techbio company Concr, led by CEO Irina Babina, PhD, is taking a computer-led approach and developing analytical tools to predict the effectiveness of potential cancer therapies both at the drug-development stage and in patients in the clinic.

Both CEOs spoke to *Inside Precision Medicine* senior editor Helen Albert about their journeys and what they are trying to achieve in their respective companies.

In conversation with Zahra Jawad, CEO and founder of Creasallis

Q: Did you always want to be a scientist?

Definitely! I have always wanted to be a scientist ever since I was 11 years old and started doing science at school. It was my science teacher who really inspired me. He thought I was good at science, and he would always encourage me to do more projects on the side through the summer holidays. I only ever wanted to do science, so that means I essentially ignored every other subject! I got to A levels, and my studies were still too broad. I still wanted to be more specialist. It was only during my final year at university that I felt like I was finally doing stuff I really want to. And then my PhD at the University of Cambridge was even better, because I was finally doing what I really wanted to do.

I was interested in proteins and how you can engineer them from an early age, for example, by changing their structures by just one or two amino acids. It was a totally fascinating subject for me. The more I could engineer them myself, the happier I became in my education. I just love the magic of the lab. I mean, it still fills my heart with joy every day that I see a gel!

Q: How did you decide to move to industry from academia?

My first job in industry was at a biotech called Domantis, which was acquired by GSK in 2006. I always thought I was going to be an academic, a researcher or a lecturer, that's what I was aiming for. I finished two postdocs, and then I applied for loads of postdocs and fellowships, and then I saw this one job in industry, and I just thought, 'Okay, I'll apply for that as well, because I'm at a crossroads. I'm going to apply for everything.'

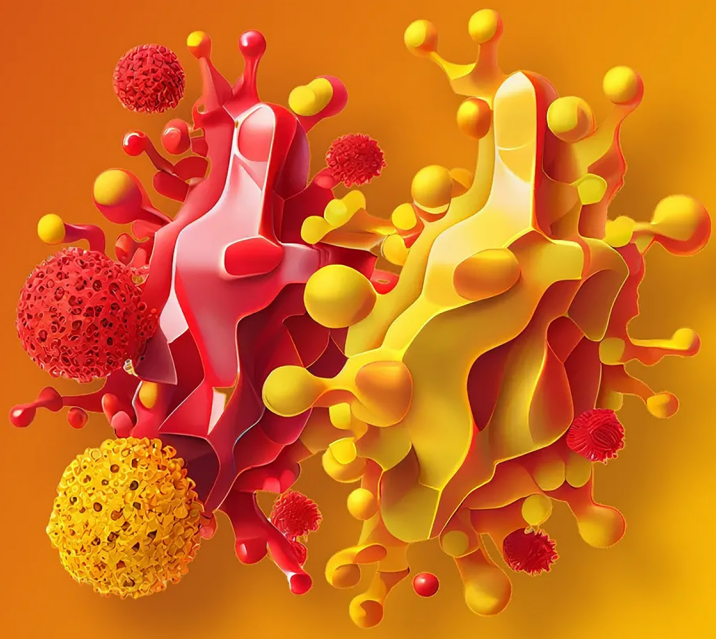
The only job I got was the one in industry. I thought it was going to be a boring, monotonous job. I remember when I applied, the hiring manager said to me, "You won't regret this." And he was right, because I loved it.

I like the industry way of working together to achieve your aim. When you're a postdoc, you're doing your own cloning, your own expression, your own testing of your project. It takes you years to get some data, whereas in industry, it's set up in such a streamlined way that we're getting data back in weeks. I like the sort of camaraderie that you get in industry, which I think you don't get in academia, and developing things that are actually really useful to humanity.

Q: Why did you decide to launch Creasallis?

I was head of an innovation group at one of the other companies that I'd worked for, and I had a young woman in my group who developed a stage four lymphoma. One day, I think she was on her fourth cycle of treatment, I said to her, "Look, can I come to the hospital with you?" I took the day off work, and I went with her. She was taking an antibody treatment as well as chemotherapy.

"I like the sort of camaraderie that you get in industry, which I think you don't get in academia, and developing things that are actually really useful to humanity."



creasallis

I spent the whole day in the hospital seeing how bad it was and how the drugs we were designing were actually getting to the patients. She told me, "It's the antibody that's really bad, not the chemotherapy. It's what gives me the side effects." When I looked around there were other people taking these therapies as well and it was the same thing, when the antibody infusion came in the patients got really sleepy, really nauseous, and that's what was most toxic, which surprised me.

"The founder's journey is a tough one. It's a huge amount of responsibility, especially when you start hiring people. It can be quite a lonely journey as well, because nobody quite understands the passion that you have, and nobody's on that same level as you in the organization."

I was always told "We're close to curing cancer, we're almost there" and that was when I realized we're not even close. When I looked into it more, I realized that the actual antibody doesn't get into the tumor very well. It always just accumulates around the blood vessels.

We knew quite early on from Domantis that making antibodies smaller does make them penetrate organs really well. But because they're so small, they also filter from the kidney really quickly. So, we can't just make things smaller, we've got to keep them in the serum and get them to bypass the kidney.

Proteases cause havoc in cancer. They start overexpressing in the tumor, and the cells are able to escape into the blood vessels and they metastasize. We were designing antibodies to block them, and I thought, "What if we use the proteases to break antibodies into smaller parts?" Then you would get a size improvement, but only inside the tumor. It wouldn't happen anywhere else because these are only expressed in the tumor.

Q: What was founding the company like?

I spent three years going through a cycle of thinking about this idea and not telling anybody about it. Then I was headhunted for a company called bit.bio, which has nothing to do with antibody engineering, as head of research project management. I got a project management framework set up but missed the science after a year.

I was getting more and more anxious, and I felt like I was in the wrong role. A friend said to me, "Well, Babraham's got this startup competition, and you should apply. If you get a place, they'll give you £10,000, and it might just be useful to get some feedback on your idea. See what they think, and maybe they'll help you figure out what investors you need to talk to."

I filled out the application form. It said at the bottom I needed a Companies House number, so I paid £15 and set up a company. Then I won a place, I was so surprised! They taught me how to start a company. I had absolutely no idea, I didn't have a bank account, I didn't know how to pitch, they taught me everything from scratch.

I was very open with bit.bio, and I told them, "Look, I've applied for this, and I need to satisfy my scientific curiosity." They were super supportive. We left on really good terms in the end. I got offered some seed investment and I quit my job the next day to start Creasallis properly in 2022.

Q: How have things gone since then?

The founder's journey is a tough one. It's a huge amount of responsibility, especially when you start hiring people. It can be quite a lonely journey as well, because nobody quite understands the passion that you have, and nobody's on that same

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level as you in the organization. It does help to connect with other founders.

I think that the biggest learning for me is that it can be so easy to just throw yourself into the company that you forget about yourself. Forget to eat well, forget to exercise. You kind of neglect yourself and it's best not to do that. We're now five people, still based at the Babraham Research Campus near Cambridge. I've tried to purposefully keep the team as lean as possible. I'm a big believer in getting high-quality people that can just get things done. I've kept the team purposefully very small. I'm still in the lab, even though I'm the CEO. It's a really important part of my happiness and my productivity. I don't do the major stuff anymore, but I do maxi preps and other non-critical stuff. I want to be in there every day.

Since we started, we managed to prove that we can re-engineer antibodies with protease, and they cut inside tumors and improve how much they penetrate into tumors, all in a mouse model, which has been fabulous.

We incorporate these tumor-specific protease sites into the antibody, so that they're fine in the serum when they inject it in, but as soon as the antibody goes into the tumor, there are these proteases inside it that chop it up into smaller parts. It's those smaller parts that are now able to diffuse inside the tumor. It really is a very simple modification of the antibody itself, rather than making a complex sort of drug or a formulation, or a delivery mechanism.

We're now gearing the team up to apply this to our first indication, our first asset. We're at this point scrambling to plan what that's going to look like and what that data package is going to look like for the next two years.

Q: Do you think you will pick a pre-existing antibody treatment to modify or design a brand-new therapy?

I'm more inclined to the former rather than the latter. I do think there's been a lot of great antibodies that have shown such promise in the pre-clinical stages and then failed in clinical trials because they were too toxic for the patient.

I think there's an opportunity there to repurpose drug candidates, rather than coming up with our own novel drugs. To try and improve those ones that were doing so well preclinically. We are interested in going into the antibody drug conjugate (ADC) space as well, because they are also very toxic. We're not planning to come up with brand new antibodies with brand new targets. That's not what the focus of the company is. We're more looking at improving things that have failed in the clinic, to try to get them through the clinical stages again.

There's so many people looking for that magic cancer target that's going to be as good as the anti PD-1 drugs like Keytruda [pembrolizumab] and it's been a struggle. Every company I've worked at has a target discovery group where they're also looking for better targets, and it's been a struggle for everyone to find those targets.

I think we do need to start getting creative about what we already have and improving them. Keytruda only benefits 20–30% of patients. That's the overall response rate. There's still 80% of people that cannot tolerate Keytruda.

Q: What are your future plans?

The part of the antibody we are engineering typically hasn't been engineered before, so at the moment we are swimming in our own lane. I don't have plans to exit the company anytime soon. My plan is to build as high a value company as I possibly can and see where the environment and the people on our journey want to take us.

Moving forward, there's going to be so many more people that come on board, who all will help us build something. I'm not here for short-term gain, I am really here to bring creative solutions to solve these antibody discovery bottlenecks that we have. For example, the blood brain barrier is still a big problem. Getting antibodies into the brain is a challenge. In so many disease areas we see limitations with the current drugs that we have. There's so much scope for improvement and that's the philosophy of what I'm trying to build.

In conversation with Irina Babina, CEO of Concr

Q: How did you end up where you are today?

I trained as a geneticist and spent about 12 years in academia developing targeted therapeutics against oncogenic mutations in breast and gastric cancer. I trained at the College of Surgeons in Ireland, and then did postdocs at the Institute of Cancer Research and the Royal Marsden Hospital, and then I went into funding management.

I decided to move from doing science to funding science, and that's why I went into government funding. I helped to deliver about £120 million in government funding via the U.K.'s National Institute for Health and Care Research into research programs at the Imperial NHS Trust and Imperial College.

That was fascinating, because you got to see really cool ideas come to life, and being able to actually support it was great. During that time, I did an executive MBA and ended up in venture capital consulting.

I consulted for Concr at the start and then I got more and more involved. The company was founded in 2018, but it didn't really get going until 2021. I realized it was a really great company that I wanted to be a part of. Then I went full time, and I eventually succeeded the CEO in January this year.

Q: What made you want to move from academia into investment?

I saw how much good science died. We're always told as academics that industry is the dark side, but ultimately, we all want to make drugs or help target drugs to the right patients and nobody has the scale and the expertise and the cash to be able to do that in academia. You have to collaborate with industry or other organizations. So I thought, okay, what makes good science go around is not the science itself, it's the funding behind it. In order to influence that, I needed to go and work in funding. I started with government funding, because that was the opportunity at the time. Then I went into private funding.

> "I must say, the team has been really supportive. All the founders are still with the company, and we have been working really closely together."

Q: What has it been like being a CEO for the first time?

I must say, the team has been really supportive. All the founders are still with the company, and we have been working really closely together. The transition was also very smooth and was happening slowly for quite a while. But it's certainly one thing when you invest and another when you are actually in the trenches, building the venture from the ground up! They are definitely different things, and I'm humbled by the experience.

Q: Do you think your experience on the investment side has helped you to be a better CEO?

Not necessarily a better CEO, but it really helped me assess how to deliver a message. I'm continuously working on this, because we're talking about astrophysics, medicine, and biology, but being able to talk about science in business terms really helps. So I think I definitely benefited from the experience.

Q: What attracted you to working at Concr?

What really attracted me to Concr, which is headquartered in London, is that I don't like waste. That's one of the reasons that I moved out of academia into funding. What Concr has done is adopted a technology that already existed in a different field but applied it to biology.

In biology, the data is really fragmented. It's all over the place and each one of these data parcels and datasets carries information about responses to a therapeutic. What Concr was founded to do is predict an individualized response to cancer treatment. To be able to predict this, you need to model a person's biology, because we're all fundamentally different at a molecular level and you need to be able to model interactions between so many different things and take into account learnings from so many datasets. So, it's not just about real-world data or big data. You need to be able to connect it all and apply it in a particular setting.

The company founders realized that we need to be able to deal with a lot of uncertainty, because we don't understand enough about biology. We need to be able to interpret it, but we don't understand enough about it. This was the very problem cosmologists faced when they were studying the distribution of dark matter to discover black holes. They can't observe them directly, but they can observe the effect of that invisible thing on the surrounding environment.

For cancer, it's exactly the same. You can't observe it directly, but you can measure different things about it and infer properties about it. So that's why Concr adopted methodologies from astrophysics and adapted them to cancer biology. To me, that was really appealing, because it's not just convergence of science, but is also saving so much time. Rather than developing conventional machine learning algorithms that have a lot of limitations, you leapfrog that development process.

Q: What is Concr trying to achieve?

We are a predictive analytics provider. We create tools to predict the efficacy of cancer drugs, now in a preclinical setting, using preclinical models in patients in the clinical trial space, but we're aiming to eventually penetrate the clinic as well.

We are positioned as a platform. We have a predictive engine based on machine learning, but using a Bayesian approach, as opposed to conventional foundation models. Hence the uncertainty distribution element, so that predictive engine is packaged in a software piece called FarrSight named after William Farr, a statistician. This is to enable a biologist to interact with their data and the results of our predictions. Because biologists don't just take things at face value. They like to drill into the data, understand the data.

It's a little bit like a comparison between a paper map and GPS. If you want to get from A to B, through a dense forest, and you have a paper map you follow the map and that's great. You will get from A to B because it's been done before. But, if you encounter, let's say, a fallen tree, you might have to go back and reassess and see where you need to go next. With a Bayesian approach, it happens almost in real time. You start off, you will assess the data that surrounds you right now and you will follow the most likely scenario at every step of the way. That's where the unknown bit comes in. You're taking into account the data that's available to you at a given moment. That's why it makes our approach quite efficient in that you don't have to retrain the model every time and we don't require large data sets to work with.

The uniqueness is that as a biologist, you can interact with a really sophisticated system, ask it questions, and then infer

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kind of results yourself. At this point in time, there is an element of collaboration between us and the partner or the client, because they know everything about their drugs. There is a lot of interaction and tailoring going on there, but it is a hybrid model in that it's not a purely tech read out. It is a prediction that's made, delivered via a software platform, but it's also put in a context by our clinical and scientific experts. So you get a service, and a SaaS, and AI as a service all in one.

Q: How can your technology help cancer drug developers?

We use the minimal amount of research data that the client provides us with to make predictions. To give you an example, they have an emerging small molecule that they've tested in ten cell lines. They will give us that data, and we will make a prediction based on the structure of the drug and the little data that they give us about future efficacy in all available cell lines, or the cell models that we have access to, in order to identify what the biology behind response across all cancers is. We would then make a prediction of what would be the best indications for this particular therapeutic.

In a way, at every step of the development pathway, we're predicting what the most likely scenario will be for the next step. So instead of the company carrying out all of the experiments, they're kind of guided through that process.

As soon as there is a therapeutic, or a structure of the therapeutic, we can already start making predictions. The minimum data required is the structure of the drug. At the moment, it is small molecules and ADCs only, we don't do immunotherapy just yet.

The biggest gap at the moment is moving from pre-clinical testing into patients. This is, of course, what everybody struggles with. But at least we can make a prediction with broad confidence intervals. As soon as there is any clinical data, those intervals shrink, and then we'll be able to make predictions about how to identify responder populations and the biology of response, or the biology of resistance.

Q: How do you hope to reach patients in the clinic in the future?

What we want to do is be able to predict an individualized response to all available treatments in order for patients to be put on the best first-line treatment for their disease.

What happens at the moment is all based on average response rates. Everybody gets the same. Only about 30% of cancer patients respond to first-line therapy and what we want to do is really challenge that. This is no mean feat, especially for a small company.

As an individual patient, do you want to know what's good for you, or what's good for an average population? To be able to not just match patients to treatments based on clinical characteristics, but to be able to model their individual biology to make that decision more accurately—that will transform cancer care.

We currently have a prospective clinical trial running at the Royal Marsden Hospital, funded by Innovate UK, but we will need a lot more of that evidence before we can get into the clinic, and that is okay. The path to the ultimate goal is long, heavily regulated, and expensive, but at least we can already see that regulators are jumping on board. One example would be the FDA-led Project FrontRunner. That's a project where they want pharmaceutical companies to test their cancer drugs in earlier lines of therapy.

> "I do think that these solutions, including our own, apply in other fields. I think we will become a lot smarter in the way we develop therapeutics, or in how we identify patients."

Q: Where do you see this field going in the next five to ten years?

I do think that these solutions, including our own, apply in other fields. I think we will become a lot smarter in the way we develop therapeutics, or in how we identify patients. Our technology can also be used to review large datasets of failed assets to repurpose them for other uses, for example.

The rare disease space is an interesting one. More data doesn't necessarily mean more informative outputs or more insights. With linear machine learning models, you will hit a plateau of predictability. So actually, you need diverse data. Rare diseases, especially rare cancers, are a wealth of biological information that we don't use. The focus of pharma and biotech is the "big four" cancer types [breast, lung, prostate, and colorectal cancers]. But that other group is so informative in terms of biology of response that we have to use it.

With Concr's technology, we can make predictions on a smaller dataset. This is where I think using this kind of technology will really add value. It's not just going to be analyzing loads of data quicker. It's going to really give useful insights.

Ultimately, it's about patients and about improving outcomes. There are some good drugs out there—patients just don't get them, or don't get them at the right time, and we want to help change that. ■

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

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MAKING THE GERMLINE GERMAINE

Broader cancer germline testing promises improvement in prevention and targeted treatments

by Chris Anderson

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Nearly 35 years ago, in 1990, noted geneticist Mary-Claire King was the first person to show that a germline mutation—in this case in the *BRCA1* gene—can cause a person to inherit a much higher risk of developing cancer. This first discovery in breast cancer opened the doors to the identification of many germline mutations that pass on increased risk of cancer types like ovarian, colorectal, pancreatic, prostate, endometrial, and gastric cancers, among others.

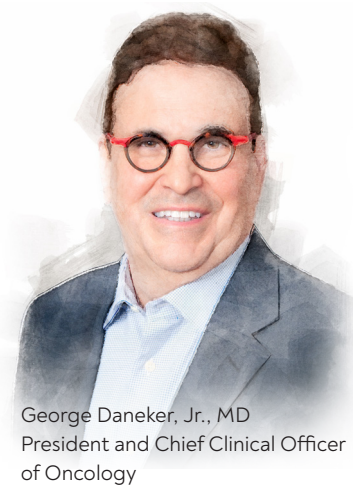
While new *BRCA1* and *BRCA2* germline variants are thought to confer roughly 20% of all hereditary cancers, other frequently mutated germline genes like *ATM, TP53, CHEK2, PALB2, APC, NF1, PMS2*, and *RB1* may play a part depending on the type of cancer.

Tuya Pal, MD
Professor of Genetic Medicine
Vanderbilt University Medical Center

But how should the increasing amounts of data on the cancer risks conferred by germline variants be used by clinicians?

"I would like people to get germline testing before they get cancer," said Tuya Pal, MD, a professor of genetic medicine at Vanderbilt University Medical Center and vice chair of the National Comprehensive Cancer Network (NCCN) Genetic/Familial High-Risk Assessment: Breast, Ovarian and Pancreatic Cancer Panel. "The purpose of these tests is to be able to detect cancer early or prevent it altogether. So, by the time someone has developed cancer, and they don't know they have a germline mutation, we're already behind the game."

That said, Pal acknowledges that treatments and known prevention strategies, if they exist at all, are scarce for most of the identified germline cancer risk variants. The notable exception is *BRCA*, for which options may include estrogen blockers such as tamoxifen. "But the only treatment, I would argue, is the double mastectomy for ***BRCA*** for prevention," she said.



George Daneker, Jr., MD
President and Chief Clinical Officer of Oncology
Myriad Genetics

Role of germline testing guidelines

The NCCN currently publishes and updates their Genetic/Familial High-Risk Assessment for a range of cancers and published their first guideline in 1999, which only included breast and ovarian cancer at the time.

The American Society for Clinical Oncology has their own set of guidelines and this year, released germline genetic testing panel guidelines to help guide clinician decision making. The guideline addresses issues such as the collection of family history to determine eligibility for testing, when multigene panel germline testing should be used, which genes are recommended for which cancers, and which patients should be referred for germline testing based on earlier somatic testing results.

"We believe these guidelines play a valuable role in advancing germline testing by addressing gaps in understanding and education among oncology practitioners about the impact of this testing on patient care," said George Daneker Jr., MD, president and chief clinical officer of oncology of the molecular diagnostics company Myriad Genetics. "Importantly, if a patient meets germline criteria, testing should be ordered regardless of genomic (somatic) results, as approximately 10% of germline pathogenic variants are missed on tumor testing."

According to Elizabeth Chao, MD, chief medical officer of hereditary genetic testing company Ambry Genetics, the company largely bases the hereditary tests they offer on NCCN guidelines. "We've seen a tremendous impact over the last five to ten years with NCCN helping the field align on who needs testing, what the benefits are of testing, and which populations benefit the most from getting germline genetic testing," she said. "I feel like that has been a big win clinically."

Further, Chao added, the guidelines have helped insurance payers better determine which germline tests to cover, for which cancer, and under what circumstances. While the payer landscape remains spotty, with different payers setting different criteria for who gets covered, published guidelines have helped make the tests more readily accessible to patients and their doctors.

The NCCN guidelines are also constantly changing, Pal said, as new information becomes available.

Cancer germline testing in the clinic

Today, germline testing for cancer-causing variants is most commonly used after a person has been diagnosed with cancer. Even then, the tests are often employed as a reflex test only after completing tumor testing for somatic mutations and if the results suggest that the disease is linked to a germline variant.

Daneker, however, thinks waiting could cause patients to miss their chance to get the most effective treatment for their form of cancer. "Once that patient does receive a cancer diagnosis, germline testing should then be paired with genomic or somatic testing to … answer whether the patient has an inherited mutation that will impact not only their management, but also their family members," Daneker said. "Having information from both somatic and germline testing can inform therapeutic options and the sequencing of therapies for that patient."

Unfortunately, germline testing rates remain alarmingly low among patients with forms of cancer potentially caused by germline mutations, as opposed to those caused by somatic mutations. Research published last year in *JAMA*, led by Allison Kurian, MD, from the Stanford School of Medicine and colleagues from research institutions across the U.S. found that germline testing rates are desperately low. The observational study of 1.3 million people diagnosed with cancer between 2013 and 2019 in Georgia and California showed that only 93,000 people, or 6.8% of those diagnosed with cancer, received germline genetic testing.

But testing rates varied widely based on the form of cancer. Of those who had germline testing, male breast cancer patients were tested at the highest rate—50%—followed by other cancers: ovarian (38.6%), female breast (26%), endometrial (6.4%), pancreatic (5.6%), and colorectal (5.6%). Prevalence of germline testing was particularly dismal for prostate cancer (1.1%) and lung cancer (0.3%).

Despite these low rates, "of all pathogenic results, 67.5% to 94.9% of variants were identified in genes for which practice guidelines recommend testing and 68.3% to 83.8% of variants were identified in genes associated with the diagnosed cancer type," the researchers wrote, highlighting the potential utility of germline testing after diagnosis—if clinicians would order the tests.

The news is not all bad, however, as the researchers noted that the testing rates represented the average over a six-year study period. They noted that testing increased steadily between 2013 and 2019. For instance, in pancreatic cancer, only 1.2% of patients had germline testing in 2013, but this number rose to more than 18% by 2019.

Increasing uptake

Although germline testing rates are rising, the tests still are not widely used. This is a significant gap in cancer care, especially considering that women with a *BRCA* mutation have an increased risk—between 45% and 85%—of developing breast cancer. Increasing the adoption of germline testing will likely take a combination of educating both clinicians and patients about its benefits.

Elizabeth Chao, MD
Chief Medical Officer
Ambry Genetics

One area of opportunity is cascade testing, which is the testing of family members of a person either diagnosed with a cancer caused by a germline mutation or whose medical history shows a risk of inherited cancer. According to Pal, the barriers to cascade testing are complex.

"Even when someone is positive in the cancer setting, it's up to them to share their information, but sometimes they're not empowered to share the information," Pal said. "It's not easy to talk to family members, and even when they do talk to family members, many don't want to do it. We see this all the time in our practice."

In other instances, treating doctors do not see cascade testing as a priority in the immediate aftermath of a cancer diagnosis, said Chao. "I've talked to a lot of oncologists who, often for very good reasons, will say things like: 'My patient just got their cancer diagnosis. We really want to focus right now on treating the current cancer.' I don't think there is much harm in starting with somatic testing and knowing that in a few months you'll move to germline testing," she said. "But germline testing can get lost sometimes in the melee of treating the cancer, and that is one of the downsides to not doing both [somatic and germline testing] up front."

Testing rates could also increase if it were easier for non-geneticists to order them. "It's not simple to order genetic testing and a lot of primary care doctors shy away from it," said Chao. "We need to change that."

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Some of this reluctance is based on the model of providing genetic counseling for people who receive germline testing for familial risk. The counseling helps those who test positive for a known variant understand the implications—an area that is not a strong suit of oncologists. Further, due to the shortage of genetic counselors, wait times for germline testing can be long.

> "We envision that germline and genomic testing will become increasingly important earlier in the treatment planning and patient journey."

But Vanderbilt, Pal noted, is beginning to break this mold.

"Many centers, including our own, have started pushing out a point-of-care model where we'll just support the oncologist to get the initial test done, and we'll deal with the results on the back end," she said. "So again, I think that really is an opportunity to increase throughput."

Pal also added that the referral process for germline testing does not need to be complicated, noting that primary care physicians routinely take family histories of their patients, but may still need to be educated on flags that would suggest a germline test.

"The family history doesn't need to be 'strong' or 'multigenerational.' You have a mother with breast cancer who died at 40? You are eligible for testing. That's how simple it can be," Pal noted, while acknowledging that the NCCN has made strides in clarifying what can often seem like complicated guidelines. She is optimistic that new clinicians are bringing a deeper understanding of genetics to their practices as school curricula are broadening their teaching of genetics.

Yet, many clinicians have developed an overreliance on somatic tumor testing to provide the information they need for a clear picture. Even if someone's tumor "does not show a germline mutation, if they qualify for germline testing based on their personal cancer history, they should get germline testing. They should not be reassured," Pal said. "I hear this from my oncology colleagues at my own institution: 'The tumor testing was normal, so I don't need to worry.' Well, no, that's actually not true, because a proportion of germline [variants] are going to be missed."

An example of this could be a *BRCA* variant-driven cancer. Chao noted that a somatic test could identify the majority of *BRCA1* and *BRCA2* mutations that would steer a clinician toward prescribing a PARP inhibitor, "but there are groups and classes of germline alterations that are very difficult to identify in somatic testing. … There are unique or rare types of variants that we target in germline testing, like Alu or mobile element insertions that typically aren't picked up on somatic testing."

Further, Chao noted, somatic testing is done on the tumor tissue itself, and because tumors are continually mutating their DNA, the germline information can get lost in this heterogeneity.

Even in a patient with breast cancer whose somatic testing has revealed a *BRCA* positive mutation and who was correctly prescribed a PARP inhibitor that eliminated the cancer, germline testing remains appropriate. "I hear this from patients again and again: 'I've already had a breast cancer diagnosis. Why does it matter to me?'" Pal said. "Well, it matters for you because if you are a *BRCA* mutation carrier, your risk for a second breast cancer is much higher than the general population. You're at risk for ovarian cancer, you're at risk for pancreatic cancer. For men, you're at risk for prostate cancer. So there are other cancers to be thinking about, even if you've already had a cancer diagnosis."

Looking to the future

One untapped area for germline testing is better understanding dual diagnoses, where the person has more than one cancer-causing variant in more than one gene. "At least 5% of our diagnoses are dual diagnoses," Chao said. "The majority of these we found are usually one positive in a high penetrance gene and one positive in a moderate penetrance gene. Some of them overlap in terms of the cancer spectrum and some of them don't. It is a challenging area and the interplay is complicated to tease out."

These findings naturally lead germline testing advocates to consider genome-wide associations studies (GWAS) to understand which genes play a role in hereditary cancer. Importantly, GWAS can help assess which combinations of known oncogenes are additive and confer even higher risk and which combinations may lower the risk despite the presence of a high-penetrance gene variant.

The way Daneker sees it, as more germline variants involved in cancer development are discovered, the increase in knowledge will sway how testing for these variants is employed in clinical care.

"We envision that germline and genomic testing will become increasingly important earlier in the treatment planning and patient journey," Daneker concluded. "The challenge of recalling multiple cancer syndromes, coupled with the recognition that patients do not know their family history, has made multigene panels attractive to many oncologists. We hope to see the expansion of gene panels, earlier testing, and targeted cancer type-specific testing to inform better treatment selection, and better risk assessment and prevention for patients and their families." ■

Read more:

1. Nadine Tung et al., Selection of Germline Genetic Testing Panels in Patients with Cancer: ASCO Guideline. *Journal of Clinical Oncology*, May 2024.
2. Allison W Kurian, Steven J Katz et al., Germline Genetic Testing After Cancer Diagnosis, *JAMA*, July 2023.

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

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References: 1. Guardant360® CDx Technical Information. Guardant Health, Inc. Redwood City, CA. February 2023. **2.** Guardant360® CDx Assay Specifications. Guardant Health, Inc. Redwood City, CA.

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