LIFE SCIENCES SNAPSHOT

A Quarterly Report on Financing Trends

NOVEL APPROACHES FOR TREATING NEURODEGENERATIVE DISEASES Q2 2024

orrick

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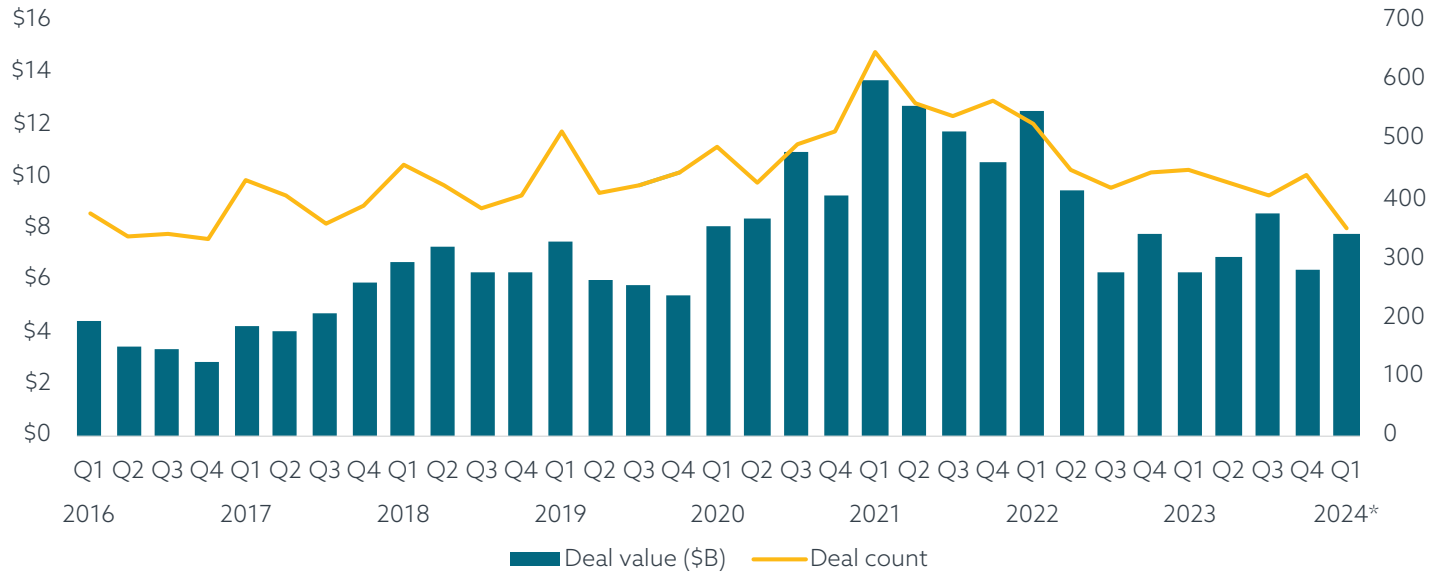
Key Takeaways

Life sciences VC deal activity by quarter



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*As of March 31, 2024

This report series examines quarterly trends in life sciences venture investment. Key findings for Q1 2024 include:

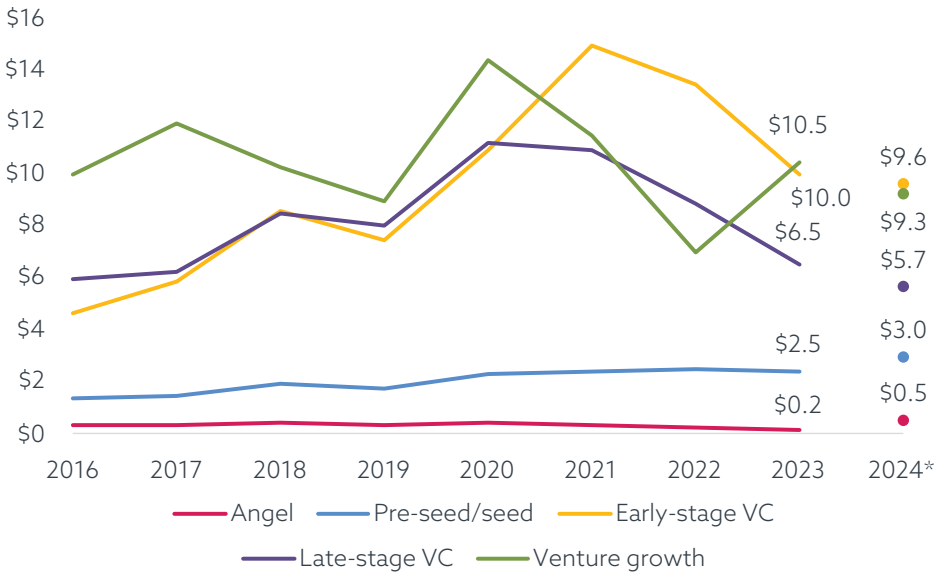
- Life sciences VC deal value in Q1 totaled $7.8 billion, which represents a 22.1% increase in value from Q4 2023. A total of 349 life sciences deals were completed in Q1, a 20.7% decrease in deal count from Q4 2023. Q1 marked the slowest quarter for life sciences deal count since Q3 2017, but larger deal sizes buoyed cumulative value for the industry.
- Valuations showed resilience early in the year, rising across all company stages in Q1. Valuations in the late-stage VC category rose 42.4%, making up for the 11.0% decline seen in 2023, while valuations in the early-stage VC category grew 12.5% after having plateaued in 2023.
- Larger deals exhibited more durability in Q1, with deals over $100 million representing a larger portion of total deal value and count compared to 2023.
- Exit activity is still muted, but each of the past three quarters saw more than $6.0 billion close, which represents a tepid upswing from 2022 and early 2023. There were 10 IPOs in Q1, accounting for $1.8 billion, compared with just 31 IPOs in all of 2023.

Market Analysis

Life sciences VC dealmaking started off the year on a higher note than in 2023, with $7.8 billion in deal value closing in Q1 2024, representing a 22.1% increase from the previous quarter and a 23.9% higher value than the same period in 2023. There were 30 deals of over $100 million each in the first quarter, with a strong presence of drug discovery and oncology verticals among them. Advancements in mRNA applications and antibody drug conjugates (ADCs) are among the catalysts for future cancer breakthroughs and are driving continued investment. The broader industry continues to see a concentration of capital invested into fewer deals, as evidenced by a 20.7% quarter-over-quarter decline in deal count, and the fact that Q1 marked the lowest quarterly deal count since Q3 2017.

Due to the lower deal count, companies that can successfully close rounds are often securing larger check sizes. Median deal values for the angel, pre-seed/seed, and late-stage VC categories saw double-digit increases in Q1. The gap in median deal values for the early- and late-stage VC categories has nearly disappeared after three years during which the median early-stage check size was larger than the late-stage check size. Early-stage VC deal values remain somewhat elevated compared with pre-2020 levels, due in part to the more selective population of companies successfully raising. Late-stage VC deals have expanded their share of life sciences activity for several years since the pandemic, and since 2022 have represented at least one-third of the total VC deal count. Relatedly, larger deals exhibited more durability in Q1, with deals over $100 million representing a larger portion of total deal value and count compared

Median life sciences VC deal value ($M) by stage



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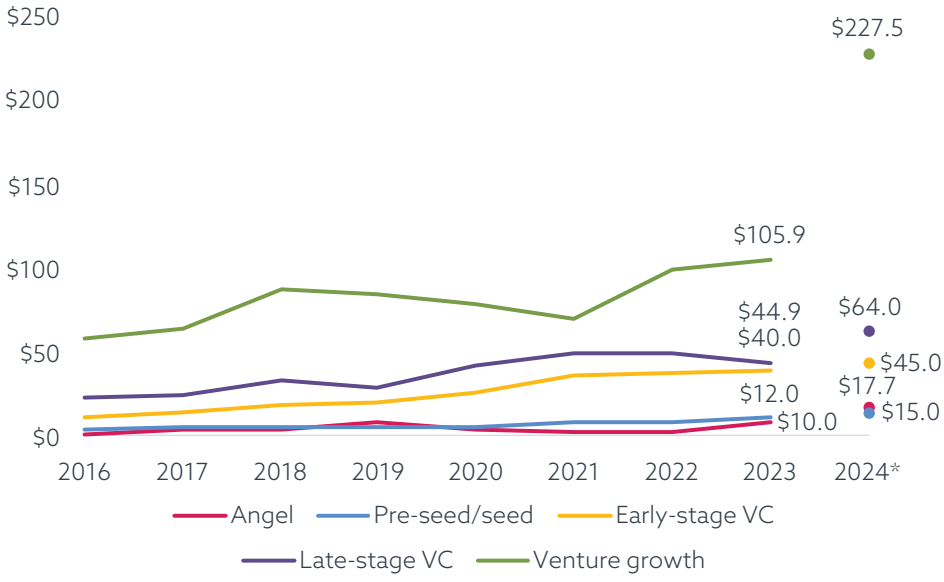
Median life sciences VC pre-money valuation ($M) by stage



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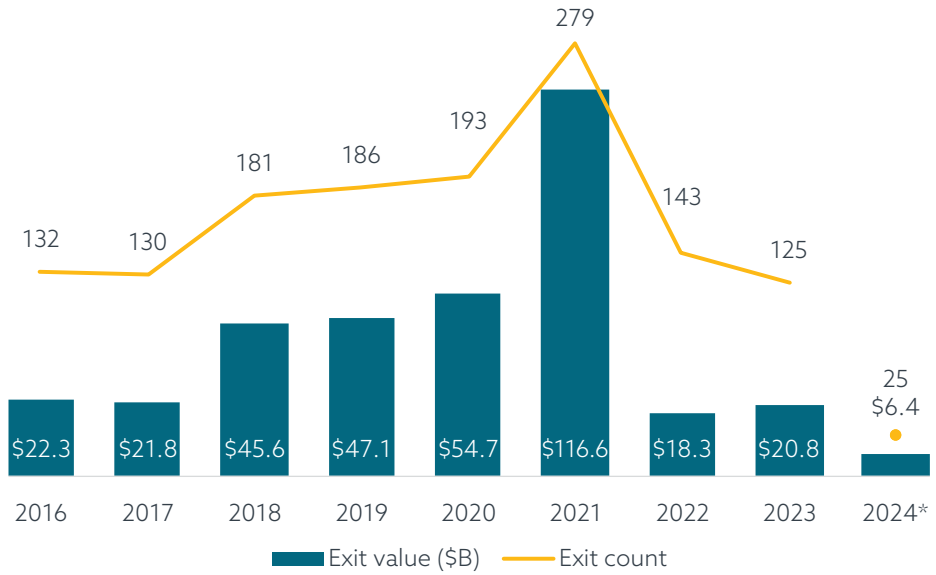
Market Analysis

with 2023. Valuations rose across all company stages in Q1, which demonstrates resilience and is largely in line with deal value trends. Valuations in the late-stage VC category rose 42.4%, which makes up for the 11.0% decline in 2023, while valuations in the early-stage VC category grew 12% after remaining flat in 2023.

Overall dealmaking trends indicate a growing pipeline of M&A targets in the form of startups successfully securing financing, and public markets have seen some warmer receptions for new listings. However, a full recovery in exit activity has not yet materialized, with Q1 2024 marking the lowest quarterly count of life sciences exits since Q1 2013. The past three quarters each saw more than $6 billion close, demonstrating higher and more consistent levels of cumulative exit value than in 2022 and 2023. 10 IPOs closed in Q1, compared with just 31 in all of 2023. The largest listings early in the year included CG Oncology, Fractyl Health, and Kyverna Therapeutics, representing a variety of drug targets. 11 acquisitions closed in Q1 for a total of $1.8 billion. Most of that value was derived from GSK's $1.4 billion purchase of Aiolos Bio, a clinical-stage company targeting respiratory and inflammatory diseases. Companies that went public during the pandemic continue to feel pricing pressure, while private companies face additional challenges in the near term. This is evidenced by several large layoff announcements in Q1, which may set the stage for a higher volume of acquisitions later this year. Interest rate movements remain in limbo, with fewer investors operating on the assumption that rates will come down this year, but overall, more positive dealmaking sentiment materialized in the first quarter.

Life sciences VC exit activity



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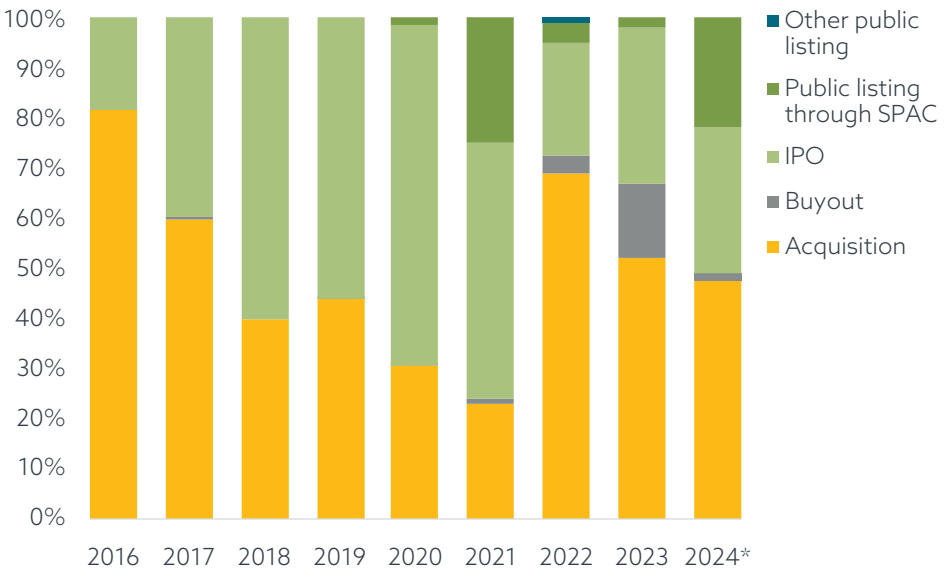
Share of life sciences VC exit value by type



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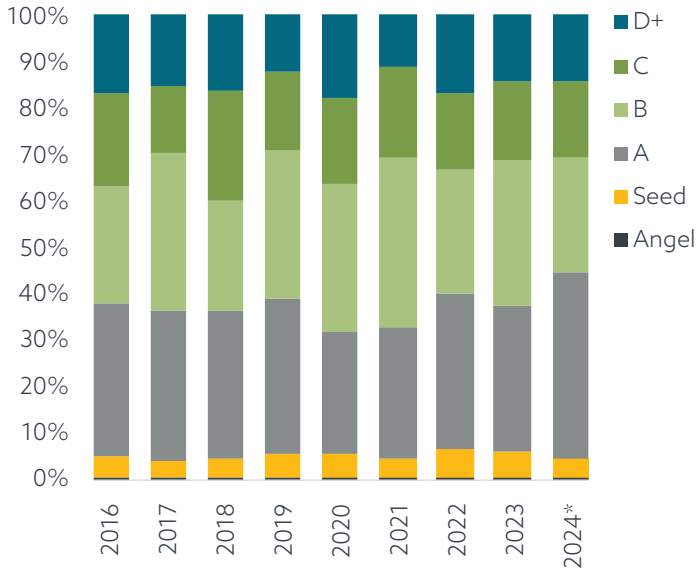
Share of life sciences VC deal value by series



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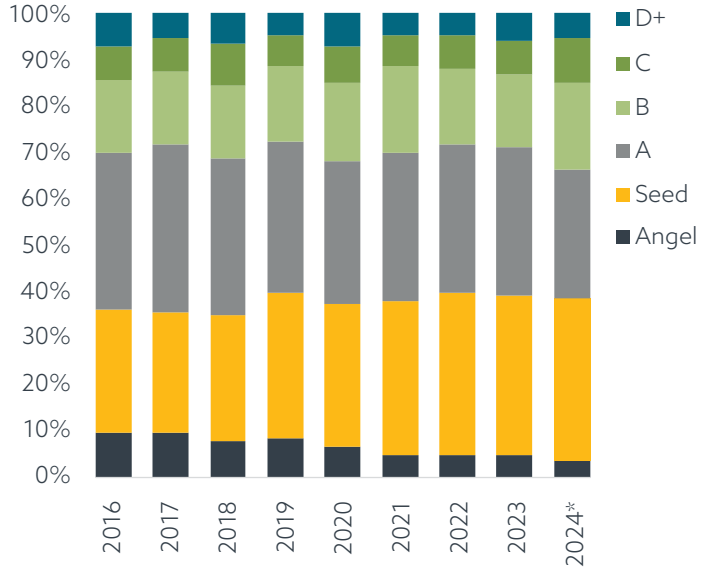
Share of life sciences VC deal count by series



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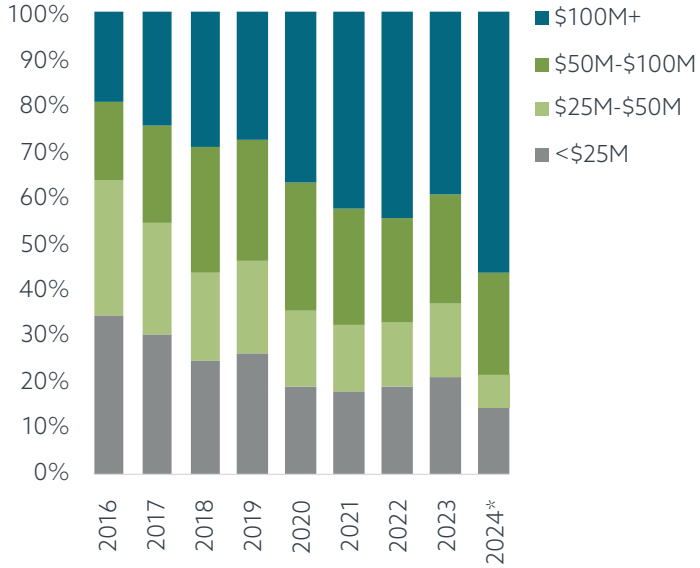
Share of life sciences VC deal value by size range



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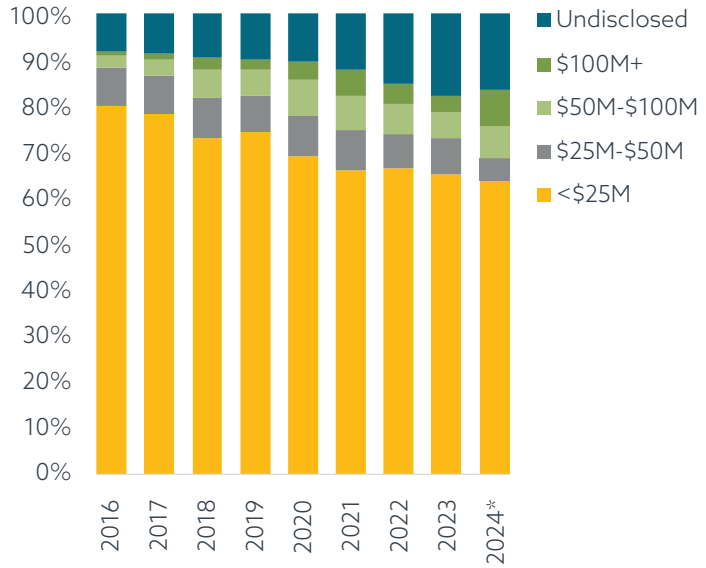
Share of life sciences VC deal count by size range



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Roundtable

INTRODUCTION

Neurological disorders are one of the leading causes of death worldwide. Millions of Americans are diagnosed with neurocognitive disorders each year, and the most prevalent neurological diseases cost the U.S. economy nearly $800 billion annually. In 2024, an estimated 6.9 million Americans aged 65 and older are living with Alzheimer's disease. The necessity for innovation to address these crucial barriers in brain health appears to be a catalyst for increased funding and support. In this issue, we speak to some of the key innovators in this exciting space.

Panel

Contributors

Katrine Bosley
Founding CEO, DaCapo Brainscience

DaCapo's mission is to develop the first disease-modifying therapies for neurodegenerative diseases.

Brian Magierski
Founder, 21 Impact Labs

21 Impact Labs envisions a world where exercising brain healthy habits becomes second nature. By igniting your brain's infinite potential, our Xponetiq app and solutions help to make exercising brain healthy habits a daily norm for millions, to achieve enhanced clarity of mind, peak performance, and emotional wellbeing. The Xponetiq app is based on evidence-based strategies through licensed content, IP and partnerships with leading scientists and institutions in the field of brain function and health. Our Xponetiq app will be available in Q4 2024.

Brittany Cassin
CEO and Co-Founder, DigiCARE Realized

DigiCARE Realized is an emerging AI-technology firm commercializing evidence-based solutions to modernize care for complex brain disease in early detection and care management. Its initial focus is Alzheimer's disease and related dementias (ADRD).

Dr. Dean Ornish
Founder and CEO, Ornish Lifestyle Medicine and Clinical Professor of Medicine at the University of California, San Francisco.

The Ornish Lifestyle Medicine Program is designed to demonstrate that lifestyle modifications can do more than merely prevent disease and other chronic ailments, they can potentially reverse them.

Facilitators

Thora Johnson
Partner and Co-Chair of Life Sciences Group, Orrick

Neel Lilani
Global Head of Tech Clients, Orrick

Neel Lilani: Why is this a pivotal moment in treating and understanding neurodegenerative disorders? Has the percentage of the population diagnosed with these disorders grown on a proportionate basis because of better testing/ understanding? Have today's lifestyle choices had an impact?

Dr. Dean Ornish: All of the above. The technology is getting better. The population is aging, and people are making fewer healthier choices on average. Many people, even though the technologies for diagnosing Alzheimer's disease can pick up Alzheimer's (or, at least, the likelihood of getting it) up to 10 years before it becomes clinically apparent, say "why would I want to know if I'm likely to get something so devastating if I can't do anything about it? It's just going to make me crazy."

This is why I think our research, which shows that these same lifestyle changes found to reverse heart disease and other conditions may often improve cognition and function in people that have early-stage Alzheimer's disease, are important not only for people who have early-stage Alzheimer's disease, but perhaps even more so for preventing it. It's an ounce of prevention, a pound of cure. You don't probably have to make very intensive changes to prevent Alzheimer's. You certainly don't for preventing heart disease and other similar conditions, and they share a lot of the same underlying biological mechanisms. That is why what's good for your heart is good for your brain, and so on.

We tend to think that advances in medicine have to be something high-tech and expensive. Billions of dollars have been spent developing drugs for Alzheimer's disease in the last 20 years; only two are approved.

More recently, Lecanemab was approved, but it only slows down the rate of progression, at best. It slows down the rate at which you get worse by about 27%. It's $26,500 a person and has other associated infusion costs. Up to 20% of people have significant side effects, like bleeding into your brain and brain swelling. It doesn't work very well in women, even though twice as many women as men get Alzheimer's. But people are so desperate for some sense of hope that this is scheduled to be a $2-$5 billion drug for Medicare alone in the coming year.

People often have a hard time believing that these simple lifestyle changes can be so powerful. They think it must be a new drug, or a new device, or a new surgical intervention. I think our work is to show how powerful these very simple and low-tech, low-cost interventions can be.

Katrine Bosley: It is important to understand, though, that if you're diagnosed with a serious disease, lifestyle may not do it. These are real diseases that need real medicines and therapies, and from a technology standpoint, I think there's a couple of things important about where we are in this moment in time.

Brittany, I'd be interested in your view on this, since you had an interesting point about diagnosis: that all of the work people have done to develop real treatments for Alzheimer's, but also Parkinson's, and ALS, Huntington's, all of these, feed into our understanding. This includes how do you measure endpoints? What are measures are imaging or biochemical measures? Those are not the same as an endpoint where a patient feels improvement, but they can be profoundly important in the development of a drug. For example, there are now a lot of effective therapies now for multiple sclerosis. If you're diagnosed with MS today, you have a lot of different treatment options; 25 years ago, not true at all.

One of the biggest enabling factors in the creation of those treatments was the advent of using frequent MRIs of the brain to look at the progression of MS and judge its development. It's not an endpoint where a patient necessarily feels better because their MRI looks better, but it is an endpoint that helps with making good decisions during drug development. With these other neurodegenerative diseases, I think we're starting to see some of those kinds of biomarkers. For example, neurofilament light chain is probably the top one. Again, this is not the same as improving that a patient's clinical status, but if it helps us make good drug decisions early on, we're then able to try many different treatment options. We must go down that path like what's been seen in cancer, where we have a "precision medicine" approach. We need these sorts of tools to crack open our ability to understand the disease as it's going along. Brittany, sounds like you've seen that through other programs you have worked on.

Brittany Cassin: We're at a pivotal moment because we now have optimism where we didn't before. We have the data that shows the importance of taking action today in our brain health because these are life course diseases. The fact that we now have an FDA-approved treatment, even with modest clinical efficacy, is an important treatment advancement.

We now put emphasis on understanding the different biomarkers to define diseases, such as Alzheimer's disease or Lewy body dementia. This creates focus on different molecules therapeutically, or different behavioral or preventative interventions.

Brian Magierski: What we've seen in our research is a desire to learn more about brain health and what these lifestyle interventions are. "What can I do about it? What can I trust? What shouldn't I trust? What works? What doesn't work?" There is some confusion, but there is eagerness, especially among the population with biomarkers, where they say, "I don't want what I have seen happen in my family to happen me and to my kids and grandkids, so I'm interested and willing to be invested in this."

We are at a point of technology development with AI machine learning, big data, the ability to aggregate data, miniaturization, wearables – we're about to have so many sources of data coming to us. We're going to have so much more engagement because people want to be engaged individually, down to the consumer level, in their brain health. I think one of the things that we are trying to enable is the connection of the data sources and engaging people in this movement. Now, you have the population at large saying, "yes, I want to do something about it," and "yes, I want to share and be part of helping researchers start during some of these conditions that are far along that are going to need molecules and therapeutics to solve." You are empowering those researchers with so much more than just money now: you're empowering them with an engaged population and lots of data and analytics that can help accelerate things or yield new insights.

It's a broad pivotal moment. It's not just the aging population and the Alzheimer's epidemic; it's also the mental health crisis that is leading to neurodegeneration in cases, too. I think there is a great opportunity right now to engage the public and get them participating and empowering everybody along the chain, from digital apps to therapeutics.

Thora Johnson: What other new sources of data are we seeing besides connected apps, and are you seeing any work done on training data for AI?

Brian Magierski: We're early in this journey right now. AI is trained on the cognitive brain health index assessments that onboard you into the app and give you your brain health index. So, that's a starting point, which is a corpus of cognitive neuroscience assessments and feedback. We will connect wearables into the device as we see more come along. We've got more and more sources that will be personal health data to therapeutic devices and different levels of data privacy and rights to share. We're also looking at various ways to incentivize our users so that if they do decide to turn on certain data sharing toggles, they can get rewards that carry value with them, because the data is generating value that can pass back that value to the users that are sharing it.

Katrine Bosley: The data point is interesting because over the last decade or more, in several different areas, people have been building these data sets with a little bit of a "if we build it, they will come" mindset. I will point to three sources that I think are particularly important. One is governments, the UK and others; two is academic groups; and then the third is patient groups. There's a few different patient groups who have taken the initiative to build these sets. These data sets are all different in size and working with different kinds of data.

As one example, The Michael J. Fox Foundation has helped create the PPMI, which is the Parkinson's Progression Marker Initiative. This is a data set that's extremely high quality and properly consented. Very important, I think that's one of the things that all these different groups have really thought about that upfront. They are high quality, they are consented at the front end. However, they are also small.

We tend to talk about big data when we talk about machine learning, but these are small data sets, and they're going to be small for a while. One of the cutting edges of machine learning is to be able to use small data sets because data insufficiency is a challenge not only in our field. There are completely different fields that have a data insufficiency problem, and they are never going to have large data sets. It is a lot about the data curation, not just about the algorithms, to be able to extract signal from noise. You then have to prospectively dig into that biology, but I do think one of the exciting aspects of this moment is, in the last decade or more, these well curated, properly consented, high quality data sets have been created, though they are small.

Brittany Cassin: We have access to a lot of healthcare data, including digital biomarkers, to help us with predictable health conditions and/or adverse situations. For example, along with AI/ML techniques we are processing digital biomarkers found in patient health records to identify early all forms of unrecognized dementia. Right now, diagnosis is delayed two to five years. We know that with all the treatments and advancements in clinical trials right now, we've got to intervene early. So, how can we use AI to help provide that indicator to get someone on a cognitive care pathway, to perhaps to an intervention, whether it's a treatment, clinical trial, or lifestyle modification?

However, it is important to highlight there is a gap in the data when it comes to data representation in communities of color. We don't really do a great job of necessarily reaching these communities, be it for treatments or be it for the interventions that work for them. I think it's important for us to be intentional about how can we leverage big data and, Katrine, I love what you said about the small data. We know Lecanemab is not performing the same in females as opposed to men, so how can we start using the data to give us some more insight earlier. Health care data, such as digital biomarkers, start creating the opportunity for personalized medicine. This becomes another area to be intentional in collecting that data for a comprehensive population data set.

Brian Magierski: We also often find an unawareness to be an issue; people are not aware that pathology is developing, you know, 10, 20, 30 years before symptoms set in, and so we can do that with getting to the consumers through the app and the education. We can educate people about this, why it matters to actually understand this sooner than

later, match it with some of those detections that really are detections and understand what data we need to be gathering to be able to detect earlier and earlier. And get people motivated and contributing, so we can empower people. We are also looking at ways to get broader access people with both the education and participation, so we can start pulling those data sets from diverse pools and not just people that can afford to pay for something.

Brittany Cassin: That's a key point. I think now we start to see the definitions of affordability and accessibility. And, honestly, preferences and other social determinants of health. We have to acknowledge that not everyone wants an app, we need options to support empowerment because 'one size does not fit all." It's a really exciting time in terms of how we are defining breakthroughs and finding solutions that fit the different context for care so people do feel that what they are investing in impacts their own care or impacts the care of their loved ones.

Neel Lilani: How are patient voices and experiences being integrated into the research and development process? What innovations are being made to improve the quality of life for patients and their caregivers?

Katrine Bosley: As we think about developing new therapies, what are we measuring as the end point? What's meaningful to patients? Things like wearables and apps let you measure aspects of what is really going on in that patient's daily life. There are a lot of people working on new kinds of end points that are more sensitive and that can detect a change that really is impacting somebody's life.

Some of these diseases have a real physical component — obviously with Parkinson's, one thinks about the tremor as an important part of the disease — as well as a cognitive component. Obviously it would be great to stop or reverse all of these aspects of disease, but if you are only able to impact some, that might be incredibly meaningful to that person. And as these diseases get further along when they do progress, what's meaningful for caregivers? I will use one specific example in Alzheimer's: sleep disruption. Sounds simple, but sleep disruption is often the straw that breaks the camel's back where you can't care for that individual at home anymore. It also, obviously, is a contributor to the cognitive decline.

If you can keep a person at home a year or two, or even three years longer, they also do better cognitively. It is not just about costs, it's about emotion and family and every dimension of that. Sometimes the things that could really have the biggest impact for the patient and/or for the caregivers are not classical or clinical. And I do think people are getting a lot more creative about that, partly because there are some interesting technologies like wearables. I give credit to the patient groups here for being the voice of advocacy for what's meaningful to the patient, what's meaningful to the caregiver.

Brittany Cassin: And with us being able to start to identify mild cognitive impairment, the faces of these individuals are younger and who their care partners are. You have people that are in their 50s getting diagnosed, and some of them may still be working, our previous notions of what the experience looks like is shifting.

Dr. Dean Ornish: Dennis Burkitt, who discovered Burkitt's Lymphoma, once said that not everything that counts can be counted and not everything that's meaningful is medical. As scientists, we like to measure things, but it's a little like the story about the guy who loses his wallet in the dark alley but looks for it under the streetlight because he can see better there.

In our upcoming Alzheimer's paper, we used the same measures of cognition and function that are used in many FDA drug trials. It's a randomized controlled trial published in one of the leading peer-reviewed journals. We found that an intensive lifestyle medicine program significantly improved overall cognition and function in those with early dementia due to Alzheimer's disease. Using one of the four measures of cognition and function, 71% of patients in the intervention group showed improvement or were unchanged, whereas 68% of patients in the usual-care control group worsened and none improved. For more information, www.pmri.org.

Katrine Bosley: With the advent of personal genetic testing for some of these diseases, there are different risk alleles that people uncover they do or don't have. I think that also changes somewhat how people think about these diseases. One of the challenges with that in particular is that having a risk allele does not tell you whether or not you're going to get the disease in question. On a population basis, it's meaningful, but for you — it doesn't tell you anything, really, besides maybe to improve your lifestyle. You might get the disease and you might not. If you do, the risk allele won't necessarily tell you if your trajectory is going to be more or less severe. There are some rare genetic variants where it is more determinative, and most of the risk alleles aren't like that. How do you think about your life with a risk factor? We all have our family histories and whatever medical history might be impacting us in some way, but it feels a little different when you can name a gene. I think people begin to think about "How do I live my life?" and other personal choices. But a risk variant is not the same thing as a diagnosis.

Dr. Dean Ornish: I'm glad we can agree on that, because I've found that risk is really about fear, and fear is not a sustainable motivator. But what is sustainable is joy, and pleasure, and love and feeling good. When someone's been diagnosed

with a heart attack or they've had a stent or a bypass, they'll do pretty much anything that their doctor or nurse says for maybe a month or two, and then they stop doing it because we all know we're going to die. The mortality rate is 100%. It's one per person, so efforts to try to motivate people to make sustainable lifestyle changes based on fear don't really work. But when they start to make changes in lifestyle and they start to feel better, they say okay, that's a whole different equation. It is not about doing something today to prevent something really bad from happening years down the road. But they can often think better. They like eating cheeseburgers, but they like being able to not have chest pain even more.

Brian Magierski: Our app and program build on these points exactly. The strategies that we're going to start delivering are things that give people more focus and help them achieve bigger goals on a daily basis that are important to them, which leads to positive outcomes. They make themselves more productive and their stress levels are going down through some of these strategies. They're being told they can go take a five-minute break, do nothing and kind of reset. These habits are not only brain healthy and neuroprotective, but they're making you more productive, more fulfilled on a daily basis, and your stress and anxiety is going down. But these are also brain-healthy habits, and what do they do? They lead to you have less times on a daily or weekly basis where you get angry about something. You're not shouting at someone or honking the horn in a traffic jam at the person who cuts you off. And those are all signs of deterioration in brain health. But if you practice these strategies, you're getting these positive motivators, which make you feel good about your life, and the people that you're interacting with feel good being with you. Fear is just a temporary motivator.

Katrine Bosley: I think it's critical, though, that if you get diagnosed with Parkinson's, or Alzheimer's, or ALS, or Huntington's — we need treatments that get at the biology that's active at that point of diagnosis. Whatever we can do to optimize our health up till then is good, but when you get that diagnosis, what are you going to do? There's likely been pathology accumulating silently up until that point – many studies have shown this. But what is the biology that's active in driving the disease process at that moment of diagnosis? I think particularly in Alzheimer's, where there's been so much focus on a-beta for such a long time. Clearly, a-beta is involved, but it's a complicated heterogeneous disease. There must be many other relevant mechanisms. I do feel like there's a lot more creativity in pathways and targets that people are going after now. I think similarly about Parkinson's, and I mention those two particularly because, obviously, they're the big ones. Not to diminish the challenge of some of the less common diseases. But I do think there is a lot of creativity about targets that can be relevant at that point of diagnosis. Can we have more of a precision medicine approach? Can we define those subsets of patients that need different treatments? There's a lot of people taking that approach. That is, to me, a point of optimism. There's still a long path ahead to get to real medicines, but I think there is a lot of real creativity.

Thora Johnson: Where do you see the commercial opportunities in treatment and management of Alzheimer's and other neurodegenerative disorders?

Brittany Cassin: There needs to be more focus on how we innovate the diagnostic pathway. We have data indicating that it takes two to five years to get to an accurate diagnosis or if the incidence only represent 50 percent of those living with a form of dementia, we still have an opportunity to innovate through evidence-based solutions.

Additionally, I think being able to continue to focus on treatments that get to the sub types of dementia is so valuable. I'm really excited by what focus on inflammation could mean and I think that kind of goes to the spirit of what we're talking about. All these systems are connected, but we haven't necessarily reduced the fragmentation. These become cool commercial opportunities, along with the opportunities to make sure that we are being intentional about closing gaps in care and reaching out to all communities.