Michael J. Fox: This is Michael J. Fox. Thanks for listening to this podcast. Learn more about the Michael J. Fox Foundation's work and how you can help speed a cure at michaeljfox.org.

Veronique Enos Kaefer: Welcome to a recap of our latest third Thursday webinar. Hear directly from expert panelists as they discuss Parkinson's research and answer your questions about living with the disease. Join us live next time by registering for an upcoming webinar at michaeljfox.org.

Welcome everyone. We are here at our November 3rd Thursday webinar about our 2025 research year-end review, Building on Breakthroughs. We'll discuss what's happening in this current moment in time in research. It is one of my favorite annual third Thursday webinars to really review the progress of the year. We'll look back on progress. We'll look forward to next steps, and we'll talk about strategies to build better treatments faster. I'm Veronique Enos Kaefer at the Michael J. Fox Foundation where I've been engaged with the Parkinson's community since our beginnings. We have a talented panel, Dr. Brian Fiske, Dr. Tanya Simuni, and Peter DiBiaso.

All right, let's meet our panel and dig into this exciting topic. Peter DiBiaso, you are a clinical development professional who supports biopharmaceutical research. You were diagnosed with Parkinson's in 2014. You quickly became engaged in research studies and advocacy. You are a devoted member of the Michael J. Fox Foundation's patient council. You deeply understand the need for research, both professionally and from the perspective of someone who's experiencing living with Parkinson's disease. Peter, what do you see as the biggest needs for the Parkinson's community and what are you optimistic about?

Peter DiBiaso: Thank you very much. I think I'd summarize it in three main areas. The first area is supporting our investigator sites. I feel it's a bit of a crisis in terms of resources. Movement disorder specialists are far and few between in terms of having equal access to everything. So, that collaboration and support of the investigative sites and the principal investigators is essential. The second is collaboration, and we've seen some great collaboration and there's so much happening on a global level, and I think being able to share and work with that is going to benefit the entire community. And then the final one is one that I'm very passionate about and that's engaging patients in the clinical trial process and making sure that we're enabling them to participate and raising the level of awareness of all.

Veronique Enos Kaefer: And we're going to talk further about patient engagement throughout the conversation. Brian Fiske, you are a PhD neuroscientist. You are chief scientist at the Michael J. Fox Foundation. You've been at the helm of helping drive research progress for Parkinson's for over two decades. You've seen so much growth in progress. Brian, in your tenure, what have you seen? What should we be encouraged by about our current understanding of Parkinson's and what are we working towards?

Brian Fiske: I mean, for me, I came in the early 2000s with the foundation. We just sort of started getting on our feet at that time. And I think the story of the foundation really tracks with, I think the story of science and Parkinson's disease. In those early days, genetics was just really getting off the ground. Our understanding of the genetic basis of diseases like Parkinson's, sort of new biological methods and techniques were really just kind of in the early days of being used. The therapeutic development that was happening for Parkinson's was sort of, I think still emerging. And then you look today and you see just I think the fruits of a lot of really great promising work. A lot of it supported by the foundation that has really just driven that biology, translated it into potential new therapies that are actually in human testing today, are actually being tested and in people with Parkinson's. And so for me that's been I think the biggest excitement and the progress and the hope that we're seeing that's moving that science really from the bench into now into these therapeutic approaches.

Veronique Enos Kaefer: Dr. Tanya Simuni, you are the director of the Parkinson's Disease and Movement Disorder Centers and Chief of Movement Disorders at the Department of Neurology at Northwestern University's Feinberg School of Medicine. You are also integral to the Michael J. Fox Foundation's Parkinson's Progression Markers Initiative or PPMI serving as site principal investigator on the executive steering committee of the PPMI study. PPMI we will talk about more throughout the conversation, but it's the Michael J. Fox Foundation's longitudinal observational multi-center natural history study that is leading to greater understanding of Parkinson's biology measures and more. Tanya, as a clinician who works with people living with Parkinson's and as a researcher, what is particularly encouraging about this moment in time for people with PD and what do we still need?

Tanya Simuni: Well, honored and delighted to participate in the webinar and really want to reinforce what Brian has just said, the role of the foundation in the advancement of therapeutic development in the disease. In regard to my clinician's role, there has been really tremendous advancement in our understanding of the disease biology, and that is the single prerequisite for the ultimate goal of developing better therapeutics and the ultimate goal of developing therapeutics to slow or stop the disease progression. We're not there yet, but we certainly are climbing the mountain to get to the peak.

Veronique Enos Kaefer: Biology is one of the topics that we will be talking about more today. Brian, we want a world free from Parkinson's. What does that mean? What will it take to get there?

Brian Fiske: Yeah, so I think we all share this vision, of course, of what that world would look like and what sort of ingredients we need to see in place. So, what actually needs to be in place for that kind of concept to actually be relevant. And really for us, it's a few things. One, of course, the therapies, the better therapies that actually can do one or both two things. Either they can slow the disease down, of course target the biology, slow the disease process down so that we can sort of reduce the progression of the disease. And also we need therapies of course that can improve the symptoms. So, give you that sort of more real time and acute sort of improvement of symptoms so that you can function daily in your life.

But that isn't enough for really that idea of a world free from Parkinson's. We also need to be able to deliver that therapy in a better way, in a more precision way or personalized way. You hear maybe the term precision medicine, a personalized medicine being used more and more frequently. It's a concept that's been around, I think for other diseases, including cancer for a number of years now. We're starting to see a movement towards this idea of more personalized medicine, I think now in neurological disorders like Parkinson's disease. But we need more of that in place. We need the right tools and the screening tools and the other types of diagnostic tools in place for that to really, I think, be in practice.

And we also have to appreciate that Parkinson's, the things that can lead and contribute to Parkinson's aren't just intrinsic things, genetics and the biology within us, but there probably are external environmental factors, lifestyle factors and environmental exposures that we sort of live. We're living organisms walking around this environment. So, we need a better understand some of those external factors too, and to the degree we can see if we can mitigate and reduce some of those. So, we need all of that together, all that sort of ecosystem of ingredients in place really to, I think truly live in a world that is free from Parkinson's.

Veronique Enos Kaefer: So, how far are we along with this? How are we doing?

Brian Fiske: I mean, we're actually making some pretty good advances. So, I mean certainly on the treatment side, we've got over the last 20, 25 years, we've seen a lot of advances in symptom improvement therapies, particularly, especially for the symptoms, more core movement symptoms that people struggle with Parkinson's. So, we continue to see innovation and optimization there. New ways of, for example, delivering the levodopa, the dopamine therapy, new ways of targeting that. And people tend to think maybe that's just the same old drug. Why aren't we improving? Why aren't we getting better than that? But it's actually are making some significant advances. We're getting better at extending the lifetime that you can use the dopamine therapies later in the disease course addressing some of the complications that come with later disease course. So, we're seeing a lot of, I think, advances there in the improved symptom category, what we think about Parkinson's disease treatments.

We'd like to see probably a little bit more work around some of the non-movement problems. I think there's still a lot more to happen there around developing better therapies for some of the non-movement issues. And of course, we don't have yet the therapies that will slow the disease process down itself. So, that obviously remains a big gap on the personalized medicine side. This is kind of exciting. I mean, I would say if you asked me a couple of years ago, I probably would say, oh, it's years and years away. But we really are seeing some real movement now. I think in the field that, and certainly Tanya had mentioned that talk about this too, about getting to that potential world of personalized medicine. We're actually taking a little bit of a page, we're watching very closely right now, the Alzheimer's field where they actually have some initial early therapies that have been approved that seem to maybe possibly slow some of the disease progression for Alzheimer's disease.

And they actually also have some of the screening tools in place now. So, Alzheimer's is actually in a really interesting moment where they're having to have these real world conversations about how do you move those tools into clinical care settings and actually start offering people the ability to get screened and potentially then offer these therapies. So, we're kind of watching that very closely, Parkinson's isn't quite there yet. We're at a point where you actually can see that future now much more realistically than I think you could a few years ago. So, we're getting definitely closer to that concept of personalized medicine. And then environment, I mean, we've known for decades about the role environment may play in diseases like Parkinson's. It's hard to identify the factors, and so we're still working quite a bit on trying to reduce some of those environmental factors, but there's a lot more awareness around environmental aspects of Parkinson's.

Veronique Enos Kaefer: So, Brian, one more quick question and then we're going to pull in our other panelists. So, the foundation's mission is to develop a cure through strategically funded research agenda, and we're always working on getting better treatments for people living with Parkinson's right now. All of this that you've discussed, set it up for us. How is the foundation thinking about it and approaching it? Is there a framework that we can consider?

Brian Fiske: Yeah, yeah, I mean this really is that the current sort of approach in the strategic agenda that the foundation has in place. We've had a strategic agenda from day one, and this is sort of the evolved version of that in the world that we're living in today. And it's really focused on four important objectives that we have as a foundation in the work that we're trying to support to get to these objectives. One, we want to sort of build again that path to getting to a clear disease diagnosis. And really that is built around the biology. We need to move away from just pure clinical symptom diagnostic frameworks. You have some slow movement and motor issues, you maybe have Parkinson's. We really want to move that down to the biology. We want to be able to have much more biology informed disease diagnosis. We want to take that biology and we want to translate it as I could say, translate it into the language of therapeutic development so we can get to then better treatment pipelines.

So, we want to really support work that can help move that biology into therapeutic development stages. And then we want to really speed that process up, especially in the clinical trial space where things can get really bogged down. These trials are big, they're complicated, they're expensive, there's a lot of operational aspects to them. What can we do as an organization and to help speed that process up and really just try to move those therapeutic ideas through clinical testing more efficiently and hopefully faster. And then finally, really working with the community as a whole, really connecting and catalyzing that community. How do we bring all the different stakeholders from people living with the disease, the investigators, the clinicians, the policymakers, the industry, the FDA regulators? How do we bring those groups together, get them all sort of working on the same priority problems, rowing in the same direction, if you will, so that we can move forward and make significant progress. And that's really represents the focus of the foundation today.

Veronique Enos Kaefer: So, maybe a way to think about the strategic pillars that you just discussed is biology, therapies, clinical trials, and then the people engaged in all of this. So, Tanya, I'm not a scientist, but when I think about biological understanding for Parkinson's, it seems to me that it could open opportunities for us to define the disease, measure the disease, perhaps help with diagnosis, perhaps at some point treating it at its source and future goals, personalized treatments. How do you think about clear disease diagnosis, definitions and understanding of biology? Why is this meaningful to you and your work?

Tanya Simuni: Veronique, your interpretation of the meaningfulness of biological diagnosis is absolutely correct, right? It has to do with giving their patients clearer understanding of their disease, disease progression, and obviously therapeutic options. As of today, as Brian has alluded, we make the diagnosis based on the clinical features and when the patient asks, "How sure are you?" We say that based on all the clinical data and correlation of the clinical data with the ultimate pathology confirmation when someone passed and their brain tissue is examined, our diagnostic accuracy is somewhere between 90% can be low. What if we have the tools and we do have the tools today to increase that accuracy against the pathology getting to a hundred percent, and we finally have the tool that gives us the ability to assess the core underlying Parkinson's pathology, which is the aggregation of the protein called synuclein, that that is how the pathologist makes the confirmation of the diagnosis.

We now have the tool to do that. It is called, the tool is called biomarker of synuclein pathology. As of today it requires test of cerebrospinal fluid By the lumbar function. It is commercially available, but in 95 plus cases it is still a research tool. There is a lot of work that is going on in the field to make it more accessible to allow the testing in less invasive procedure like skin punch, hopefully getting into the blood. But again, your question is why does it matter? It matters because we can match individuals to their underlying pathology. Some people would say 10% error, that's not that bad. We can live with that, right? It's 10% error in the best characterized individuals, the error might go higher to 30 or 40%, specifically in someone with very, very early diagnosis or unclear features. And what I'm talking about the biomarker of synuclein pathology, it is essentially, but that is the beginning of the journey.

Some people arrive to that pathology through having abnormal function of the energy structures of the cells. Some people arrive to that pathology through having abnormal function of the clearance mechanism of the cells. Some arrive because they have increased inflammatory state of the cells. And if we can define reliable biomarkers of what got them to that common pathology, we can subdivide individuals. You need to participate in clinical trials, testing therapeutics, targeting that inflammatory pathway. You need to participate in the studies testing therapeutics targeting this lysosomal cell clearance mechanism pathway. And so as of today, those are therapeutic trials, but as of the future, that will be personalization of the therapies offered to the individuals in addition to our current standard of care dopamine replacement therapy. That is super powerful.

Veronique Enos Kaefer: And this sounds like a real change in where research is able to head. I suspect there are other measures that are in development too. Brian, what does this breakthrough mean for research and what else are we working on in our biological understanding of PD?

Brian Fiske: I mean, for me, I often sort of think of this framing in the sense of you want to be able to tell someone what do you have and what can you expect from it? I mean for not just Parkinson's, whenever we go to the doctor, that's kind of the answers we're looking for. And so this ability to move away from just, well, you might have this, we'll just have to wait and see. We'll try some medication and see if that works for you or not, to something that feels a little more definitive where you'd say, "Okay, we looked at your biology and matched it to your symptoms and here's where we think you sit right now and what you can possibly expect maybe over the next few years. And then hopefully, obviously we have a treatment we think we can give you to slow that down or maybe prevent you from progressing to that later outcome."

So, again, that's the fundamental goal here. So, as Tanya said, we're really focused on some certain biology that we currently have some good tools to measure right now. So, the alpha-synuclein proteins, this is the protein that we talk often about that sort of clumps in the brain and people with, or at least 95% or so, or 90% or so of people we think with Parkinson's have this sort of clumping as a contributor to their Parkinson's disease or certainly as a feature of their Parkinson's disease. But we know that's just the tip of the iceberg. So, how do you get there, as Tanya said. And so we have a lot of work that's really focusing on trying to dissect and define that biology a bunch of different levels. Genetics has been a huge resource for this. So, we've been working a lot with an international effort called the global Parkinson's Genetics Program or GP2, which is really looking globally at sort of genetics linked to Parkinson's.

And you can use genetics to help to decipher the biology and map the biology that might be affected in people living with Parkinson's. And so those kinds of efforts and then more traditional lab research that we support, global networks of labs focused on what does that biology mean? How does it actually lead to potentially degeneration in Parkinson's disease? So, really a lot of work that's just trying to bring those and bridge and connect those different biologies together, even environment. And at the end of the day, the exposures in the environment converge on biology. So, again, it all comes back down to the biology. So, I know Tanya was mentioning energy producing aspects of ourselves and how important that is and how if those break down, those might lead to Parkinson's. Well, it turns out some of the toxins out there target those energy producing aspects of our cells.

So, it could be that some exposure to some of those toxins might damage that energy producing function in our cells and then maybe lead to diseases like Parkinson's. So, how do we sort of, again, bring those together? And there's a lot of the work that we're doing to try to not only understand that biology, but also just like we can now do with the alpha-synuclein tools that we can use to measure the synuclein, can we develop measurements for some of those other biologies so they can really hopefully provide a little bit more of a personalized

map of someone's particular form of Parkinson's so that again, you can better match that to therapy.

Veronique Enos Kaefer: Peter, I have two questions. How is industry thinking about personalized medicine in consideration of this new biology that's coming out and more that we're learning? And what does it mean to you as someone living with Parkinson's to consider having treatments that are tailored to your particular Parkinson's?

Peter DiBiaso: I'll start with the second question first, then from my perspective, some of the challenges that I've faced in terms of looking at opportunities and looking at clinical studies, I think this personalized approach really makes a big difference in my ability to match the right need with the available resources. You've heard the old adage of you've met one person with Parkinson's, you've only met one person with Parkinson's. So, personalized medicine is really a way to kind of take that the next level and take advantage of the latest technology and the latest advancements in medical science. This is the Renaissance days for personalized medicine.

We've seen so many advancements, the gene therapy and all the work that goes into the personalized approach. So, from my perspective, it's great from an industry perspective, it's the future of the ongoing efforts in terms of research, it uses these biomarkers, uses the clinical staging, which we worked on last year and adopted. So, all these tools are designed to enable the Parkinson's patient to assess the landscape and to try to better understand what will be best for their needs. And their needs are very much driven by this personalized approach.

Veronique Enos Kaefer: All right, let's talk about treatments. But I'm going to say one thing. In the early days of the foundation, it felt super important that everything that we did was quickly able to translate into a treatment for someone living with Parkinson's. And that is still a huge priority for us. That is what we are trying to do. And there has been so much progress in the therapeutic development pipeline. It is so robust and healthy now that we are at a point in the fields and we're having these breakthroughs when we're able to focus on biology and we're starting to see answers is exciting to me. All right, treatments, that is the holy grail, this is what we want. There has been progress in this space. There have been five new treatments come to market just since last fall. So, within this 2025 year since 2015, so within the last decade there have been 17 new therapies that have come to market and progress within devices as well.

50% of the treatments in clinical studies are focused on symptomatic treatments. 50% are focused on disease modifying therapies or what people might think of as a cure. Last month in October, our third Thursday webinar was about treatment options for people with progressing Parkinson's, managing medications, infusion pumps and more. So, that might be something if you missed it to go back and listen to and watch, it's really good. But today, Tanya, I would love to talk about two particular advances, focused ultrasound and adaptive DBS. What are these treatments, what's new about them now and how might they help people?

Tanya Simuni: Let me start with adaptive DBS. DBS stands for deep brain stimulation. It is the surgical procedure that has been available for people with Parkinson's disease

who experience symptoms that are not well controlled with a standard oral or now subcutaneous delivery medications. And specifically the best indication for the surgical procedure are people who have uneven response to the medications, what is called on-off phenomena, meaning the medications do not evenly cover them through the day, or they experience medication induced involuntary movements that are called dyskinesia. So, those individuals who have profile of uneven response to the medications having periods of good on but inconsistent and their good on is limited by drug induced involuntary movement, dyskinesia, are considered to be the best surgical candidates. And again, deep brain stimulation term probably is familiar to most of the people living with Parkinson's disease. The procedure has been available since 1980s.

So, what is different in 2025? The technology has been about it, right? And over the years the technology allowed to go into smarter batteries, the batteries that live longer now there are available rechargeable batteries. So, people don't need to go for the placement of the battery. They can basically recharge themselves at home with their appropriate technology. Adaptive DBS takes it a step further. Again, we were talking a lot about personalized medicine approach, precision medicine approach. That is a surgical way of precision medicine approach. It basically allows the clinician who has expertise in device management to do personalized programming to achieve better control of the symptoms. There is also the ability to basically "listen" to the brain, pick up the signals from the brain that feed into that algorithm of the programming. So, it is the same approach, deep brain stimulation, the targets are the same, but advancement of the technology to have more elaborate, more sophisticated programming to meet the control of the symptoms in that particular individual.

So, that is adaptive DPS. Complex, again, technology driven. Now let's move on to the other procedure, focused ultrasound. Patients frequently refer to it as surgery without surgery because it is non-incisional procedure. But again, don't be mistaken. It is a surgical procedure when the surgeon uses the power of the ultrasound generated energy to target the area of the brain that is responsible for generating particular symptoms. Focused ultrasound was first approved for the management of the condition called essential tremor, which again is not Parkinson's disease, but subsequently was approved from management of tremor associated with Parkinson's disease. So, again, the indication was the management of tremor that is not well responsive to the medications and the surgeon would do the focused ultrasound, would map out when to go. It creates a tiny lesion that you initially can see on the MRI scan and then it disappears, but the effect persists for reasonable period of time.

And the advantage of the procedure, again, it does not require incision. It doesn't require drilling a hole in the brain. It does not require having the device implanted, programming of the device, all those other the positive things. Subsequently, the indications for the focused ultrasound were expanded to management of the other Parkinson's symptoms. But again, it is a very careful discussion. Most recently this year, the procedure was approved to be done on both sides of the brain, but in a sequential format, if someone needs that, and obviously people might ask immediately the question, so how do I choose? Which one should I like more? I'm not going to respond to that question. That is

a question to the expert who knows your symptoms and basically would present you all the options of what we call options for management of more advanced stage of the disease.

Veronique Enos Kaefer: It's encouraging to know that there's ongoing development even for approved therapies, that it keeps getting smarter and that there are new treatments coming out. Peter, as someone living with PD who kind of gets what drug development is, how do you approach it when you see that a new treatment has come to market or an improvement has been made? And what are your thoughts on the treatments that we've had in this last year and decade?

Peter DiBiaso: Well, there's been a lot of advancement in treatments and everything that we've talked about. It's with great level of optimism that I'm thankful and hopeful that some of the advances that we're seeing will materialize into true associations to find a cure. So, we're focused on that and the ability to look at that. But I think there's also a challenge as a patient, how do you judge and assess those opportunities and those new, and there's so many resources, we're getting information from all corners of the world about treatments and different things that have worked. And it's sometimes very difficult to judge what is the background behind that? What is the data behind that? Why is it available in this country and not that country? So, again, I think there's a caution in terms of looking for new treatments to really have a thorough understanding of what you're looking for.

Talk to your physician, talk to your specialist, talk to your family and really assess that. But it's not an easy decision despite the opportunities. And then there's also the challenge of, I touched on it briefly about global considerations, but a lot of times some of the new treatments aren't even available in the United States. And I live in Europe now, and I've seen access to things that haven't coordinated to the US and vice versa. So, again, I think it's real important to filter through that and try to get through the noise and going back to personalized medicine, find what works for you.

Veronique Enos Kaefer: That's really helpful. All right, our September 3rd Thursday webinar is also one that I would recommend if you haven't had a chance to listen to it. It was about disease modifying therapies. But Brian, at a high level, what's the difference between symptomatic therapies and disease modifying? Why is it important to have both in the pipeline and what stands out?

Brian Fiske: Yeah, yeah. I mean for me, I've been in part of meetings where you spend load of the entire meeting debating these concepts. So, these are not exact terms, but for me, I think it's much the way I tend to think about it, there are therapies that target the underlying biology of the disease with the goal of basically keeping you from getting worse. So, we want to sort of slow the decline, the sort of accumulation of dysfunction that might happen with a disease like Parkinson's over time. So, that being one category, we tend to maybe call those disease modifying therapies or other terms you might use for that, neuroprotective therapies.

And then there are the kinds of therapies that for me are more about, and probably the closest analogy of course being some of the dopamine therapies we have today, they're about in the short term, in the real life, daily functioning ability of your life that can acutely improve symptoms. So, they can make you move when you're frozen. They can reduce your tremor when you have a tremor, things like that, that are really the symptom of type treating therapy. So, there's fuzziness in between. You could have certainly a therapy that might slow the disease down and over time improve the symptom. But I think categorizing them in those two broad ways for me has always been a powerful framework.

Veronique Enos Kaefer: Let's move to our third section, which is about faster clinical trials. Brian, can you talk a little bit about the drug development tools that the foundation and the fields have been working on? How are we increasing our abilities to make decisions faster in clinical trials? What tools are helping us and where are we?

Brian Fiske: Yeah, so mean, and Tanya can certainly jump on this too, where clinical trials, at the end of the day, these are experiments for trying to assess whether a therapy might hold benefit for disease like Parkinson's disease. And they're not treatment trials. They really are testing theories and hypotheses. So, to be able to do that effectively, obviously you really need to first of all make sure you're testing the right people and the right hypothesis in the right people. So, being able to sort of match the right people to the particular trial question you're asking and the drug you're testing, and you need to be able to measure the impact of that drug, not just, I mean obviously like you think on the symptoms and cells, are you improving the symptoms?

Are you slowing the progression of over time of the disease process and the accumulation of symptoms? Certainly those are important key outcomes that you want to be able to measure as well. But really in the early stages especially, you really want to get answers around whether your treatment is hitting the biology that matters, that at least in your theory matters for how you think that the drug might hold benefit for a disease like Parkinson's so that you can make better judgment calls on how to interpret than the ultimate readouts of the trial. So, maybe you saw a little bit of improvement, but you're not sure, but you definitely need to know whether your drug was hitting the biology so that you can interpret the impact of that potential signal that you saw.

So, having those kinds of measurement tools that are really critical in the context of therapy development. So, it's really about finding the right people to match them to the drug and having the right measurement tools in place. For me that is really about ultimately speeding decision-making. So, maybe the trial still takes as long as the trial takes, but you want to end that trial with the ability to make a clear decision so that you're not spending multiple trials over many years before you can make that decision. The speed really comes in the information you can glean from hopefully a handful of trials versus tons of trials.

Veronique Enos Kaefer: Peter, let's talk a little bit about a patient-centered research approach. Michael J. Fox Foundation always has this as a goal to be patient-centered, to be focused on the things that people living with Parkinson's would say are their priorities. Peter,

what does patient-centered mean to you and how does that lead us to the results we want?

Peter DiBiaso: Thankfully, it's no longer a novel concept to engage patients for your drug development programs, and it's almost become kind of a standard part of the business now, which is great news. But inevitably what it is focused on is taking advantage of the feedback from caregivers, from patients and really having them understand the goals of the research and sit down with them and talk to them and share the protocol design and what are the barriers? Could this work for you? Or what are some of the challenges that you would see in participating in a study like this? And these discussions have become very rich because they're used to directly impact the real world.

We all know that there's a challenge between what might be clinically relevant and clinically perfectly set on, but that isn't always necessarily the way that it's interaction in the field. So, again, having that focus in terms of it's not a novel approach, the role of advocates, the role of patients, the roles of caregivers, it all kind of creates that community system that enables that patient centricity. I think there's definitely more that can be done, there's mid-course corrections that you can focus on. There's kind of evaluation post-program, but patients have really become a true partner in the drug development process and I think this has made both sides of that much more engaged and much more effective in terms of the goals.

Veronique Enos Kaefer: It's so encouraging. Speaking of people being involved in research, Tanya, I would love for us to talk about the Parkinson's Progression Markers initiative. So, this is a study that was started in 2010. It's been going for 15 years. It follows people with and without Parkinson's over time to learn about how the disease starts and then how it changes over time. It teaches us about the disease and that information can help doctors and scientists better diagnose, treat, and prevent brain disease. Tanya, from your view, you work so closely with PPMI. What has been the impact of PPMI over the last 15 years?

Tanya Simuni: I can confidently say, and not because I am directly involved in PPMI, but based on the data that PPMI study has been transformational, it has been transformational because it provided better tools to design studies to interpret studies. Let's start from the beginning. In order to design, Brian spoke about the tools, define people, select the right drug for the right people, choose the right measurement to assess the effect. So, PPMI launched on the journey to develop biomarkers of the disease progression specifically to enable better therapeutic development. And by recruiting people with newly diagnosed Parkinson's disease and healthy controls and comparing their metrics, clinical and specifically biologically at baseline and longitudinally, it enabled to help with the better tools. Essentially every single study that has been launched, testing disease modifying interventions, those therapists aimed to slow progression of the disease that Brian has been describing, has used PPMI data to model disease progression to assess what is the best measurement to be included in the study.

But that's not all. That's just the beginning. PPMI launched with very ambitious goal. We need to collect as much biological samples. Even in 2010, we did not

have those biomarkers. We did not have biomarker of synuclein pathology. First in literature in 2017, but the large PPMI study data publication came in 2023 that really has demonstrated that it is a reliable tool to assess presence of pathology. It took time, but it has transformed therapeutic development. Now, a number of companies are using synuclein biomarker for stratification, meaning for the enrichment of the population and the recruitment, right? FDA has issued a lot of support for synuclein biomarker, exactly for that reason. But PPMI is not going to stop there because there are plenty of research questions.

Right now this biomarker reads out as positive, negative. We essentially need that biomarker to be quantitative so that it could longitudinally assess the change. And there is a lot of work going on in that domain. So far we've been talking a lot about biomarker of synuclein pathology. We haven't spoken that much about the biomarker of dopamine loss. And that has been available for quite a number of years. That is the death SPECT scale. It is commercially available and it is used in the clinic in cases where not sure whether someone's symptoms of tremor, a little bit slowness are due to Parkinson's or Parkinson's like syndromes or something else.

In research, it is being used as a quant in PPMI, specifically as a quantitative biomarker. And in combination with the synuclein biomarker allowed us to actually introduce the biological definition of the disease, biological definition and staging of the disease. How will it accelerate therapeutics? It'll reduce the noise and reducing the noise allows us to more reliably test that hypothesis that Brian was talking. So, again, faster drug development is absolutely based on better tools and biomarkers are very important part of that toolkit, not the only one. Clinical measures ultimately are the ones that our regulators will approve the drugs on, but faster early stages of the development should be, and they going into being read out based on the biomarkers.

Brian Fiske: I mean, when we talk about this foundations research agenda, PPMI is just so foundational and fundamental to our progress in that it's helping us better understand the biological forms Parkinson's can take. So, it's helping us get the clear diagnosis that biology is the biology we want to translate into therapies. The insight that we're learning about the variability and the validation of the different measurement tools is helping us get to faster trials. And certainly the engagement with all the people who are participating in PPMI, including industry and all the other stakeholders, is really helping us connect and catalyze the community. So, I always say of all the programs we have, it's just so fundamentally foundational to our strategic agenda as well.

Tanya Simuni: PPMI is pioneering a lot, right? Peter spoke about participants are partners, right? PPMI has pioneered return of the research results to the study participants, essentially important to not for engagement, but for really enhancing that partnership, engaging the participants. They're giving a lot, they're giving their time, they're giving their effort, engaging the participants, truly making their partners in the research. That's another essential aspect of PPMI. We can continue talking about that a lot.

Veronique Enos Kaefer: Thank you all. So, PPMI is currently recruiting volunteers. You can join this study that's changing everything by clicking on the link in the resource list on the right side of your screen. Now we're going to move forward and talk about our catalyzed, passionate, smart, engaged, amazing community. It has always been our goal that we get to better treatments and cures with a combination of scientists, business strategists, and this entire Parkinson's community. Peter, when we talk about the Parkinson's community, what do we mean? How can we help? What does it mean to you to be involved?

Peter DiBiaso: Yeah, I think the Parkinson's community, it's ever-expanding, it includes obviously the patients, the caregivers, the community in and itself, family members, resources and public social services. Parkinson's really is a disease that impacts so many and from so many different sides. So, again, working together with this community and identifying the community and engaging the community is exactly what we need to do to advance our drugs and reduce the timelines and maximize the efforts that we have. Shots on goal are so important. This is the expression and that's the ability to kind of reach out and using that network is just essential. And the network is there. They're waiting. They love to be interviewed, they want to talk about it. They're not doing this for money, they're doing this for just advancing the science. And that's something that we all need to remember in terms of taking that approach, advancing the science and the patient is your partner.

Veronique Enos Kaefer: And then Brian, who else are we trying to connect? And if you could also speak to this idea that there aren't enough movement disorder specialists, what are we doing there? But first, who else are we trying to connect?

Brian Fiske: We're just saying it's really the whole community. So, I mean obviously it's the research community too. The clinician community regulators, policymakers, everybody who has really a stake in our ability to solve the issues and the barriers that we are trying to address. And ultimately, of course, get to that world free from Parkinson's disease. And so thinking about the ways that we can educate them, get them engaged, whether it's bringing them into the research, and that could be bringing people living with Parkinson's into research studies, but it's also the work we do to bring researchers into the Parkinson's field. So, through our funding programs and other ways that we can incentivize researchers or companies, there's an opportunity in Parkinson's disease. And if you're interested in being a part of it, we have resources, funding and other types of resources to get you involved and get you excited about the opportunity.

So, a lot of different ways that we can connect community in Parkinson's disease. And I think also use that opportunity to help train and educate people to be more informed members of the Parkinson's community. And so one big program we've had for a number of years is there's having really good movement disorder specialists, clinicians who can treat and diagnose people with Parkinson's, people like Tanya who really understand the disease, not just clinically and from the treatment side, but also are connected to the research side and understand the sort of emerging trends, the new signs that might be coming out. So, what can we do to help increase the number of really good trained movement disorder specialists like that? So, we have a whole program that's been going on for a number of

years now to essentially provide fellowships for people for junior new neurologists who are interested in Parkinson's or movement disorders as a specialty can now get support to actually get that training and hopefully become more informed clinicians and researchers in the future. So, a lot of different community members are trying to connect.

Veronique Enos Kaefer: Okay. Rapid fire. I have one more question for you, Tanya, and then Brian, and then we'll move to our bigger list of questions. We have tons of questions from this great audience. Tanya, your question's going to be why is it important for people to volunteer for research? Brian, yours is going to be talk a little bit about important policy moments, public policy we've had, and then we'll move to the Q&A. Tanya, why should we volunteer for research?

Tanya Simuni: Think the universal design is to eliminate Parkinson's, on the way to develop better therapists. Therapists can be developed only testing them in individuals with a disease. So, that's the answer. The other answer is that participation and research empowers people, feels them in charge, makes them connected, and that is very important.

Veronique Enos Kaefer: Brian, what's happening in public policy?

Brian Fiske: I mean, a lot. Obviously no one can deny that the last couple of years, the last year or so certainly has been challenging. Whenever there's an administration change, it can bring new opportunities and challenges. And so we've seen a lot I think over the last year. I think from our side we've continued to push from a policy standpoint and a few key areas certainly have long been a long-standing partner in trying to advocate for federal and government research funding of Parkinson's disease. So, that continues to be a big part of our message. And last year even we were able to get initiated, for example, a national plan to end Parkinson's disease was signed by President Biden at the time.

That effort is something we're continuing to push on. It's in the new administration to figure out where and how to make sure that momentum continues in that area. But even as that sort of continues to evolve, we've done a lot of additional work. So, we've actually been working at the state level to really think about ways that we can bring better resources and attention to diseases like Parkinson's at the state level. And even just recently, and this was really exciting as a native Texan, Texas actually just approved in the latest election a major, major commitment to dementia and both Alzheimer's disease and Parkinson's research and dementia research, of the tune of about 300 million a year for the next 10 years.

So, they're really going to be focusing on supporting research in Texas around brain diseases like Parkinson's. So, a huge win I think at the state levels we going to be awesome because of the federal level. This was at a state level where we're seeing this sort of commitment and we have a lot of interest in working with other states that are interested in pursuing this type of state level funding as well. So, I think some big wins. Politics is complicated working with governments, they're always a little challenging, but I think when we can have these moments

to really show why it's so important for the communities that government serves to try to address these diseases. So, I'm really excited for some of these big wins.

Veronique Enos Kaefer: Okay. We have so many questions. We're going to try and go through them quickly. Here are the first three questions so you can get yourselves ready for them. Peter, building on what Tanya said, is it hard to be involved in clinical trials? How do I do it? How do I find out what to do? Brian, your question, next question is going to be about what's happening with stem cell research. And Tanya I'm going to ask you the question is about what's happening with the genetics of Parkinson's disease. Peter, is it hard to be enrolled in clinical trials?

Peter DiBiaso: It is and it's harder than it should be probably. A lot of times it's not necessarily just getting into the study, it's the awareness. And as we talked about at the outset, these investigative sites are so overwhelmed that sometimes it's very difficult for them to kind of pause their day and raise them, well, you might be a candidate for this clinical study and then go into a series of questions and everything else. So, the hard part is do we have the resources to engage the people at the site level? So, I think there's ways to kind of streamline that communication. There's initiatives that you can do at the community level, but I think it is a challenge. And again, it also goes back to the genesis of the work that's being done and what is the goals of the program and how can we make that easier for patients and caregivers. We can't forget the role of caregivers. They're absolutely essential in getting patients engaged and recruited.

Veronique Enos Kaefer: Thank you. And I'll also say that Fox Trial Finder is a tool that will let you find what clinical trials are in your area and then you can reach out to the trial coordinator to kind of help navigate that a little bit. All right, Brian, what's happening in stem cell research? Do we think this will ever realistically be a dopamine replacement therapy? How far away are we?

Brian Fiske: Yeah, yeah. And I know we're sort of short on time. I think we had a great webinar a few months back that maybe folks can link people to that sort of talked about stem cells at a much deeper level than I have time to talk about today. But in a short sort of story version, I think we're seeing a reemergence of an approach that really started a couple of decades ago with the idea that can you replace some of the dopamine cells lost in Parkinson's disease with new cells? And so in the early days we were doing that with tissue transplantation. Was messy, the results weren't particularly great in those trials, but then stem cell technology started to improve with the idea that you can take certain types of cells called stem cells in the body and sort of using various techniques, coax them to become dopamine producing brain cells and then use those cells to actually transplant into people with Parkinson's to give them back some dopamine.

So, it's important to keep in mind that being able, at least in its current form, the way these approaches are being delivered, these really are what I would consider symptom improvement therapy. So, they're not cures for Parkinson's and we're not really fundamentally targeting the underlying biology that causes cells to die in the first place. What these are attempting to do is generate some replacement cells, put them in a part of the brain that normally responds to dopamine to see if we can kind of give you some of that dopamine back. Very often you still have to

take your levodopa pills with these approaches. So, again, it's not a cure so much as an additional symptom improvement type of approach, but it is exciting to see. I would say 20 years ago it was early days people were trying to figure out stem cell biology is very complicated.

Today though, they figured out a lot of those big hurdles and questions and now there are some 10 to 15 or so programs and we look at the sort of the landscape of approaches out there that are looking for cell replacement that are again an active human testing right now, testing these approaches, seeing if they're safe. Some of them have advanced actually to later stages. Actually there's at least one or two groups now in phase three testing for Parkinson's disease that are looking to try these cell replacement approaches. How are they compared to optimize dopamine delivery methods that have been improved in the last year or so? How will they compare to adaptive DBS approaches that Tanya mentioned earlier? Unclear. I think we'll have to see how these things evolve, but I think it'll be an interesting opportunity to see the impact that these cell replacement approaches will have. And we'll get answers I think in the near term, certainly within the next couple of years.

Veronique Enos Kaefer: All right, Tanya, what is happening in research for the genetics of Parkinson's? How can that help anyone with Parkinson's and those with a specific marker?

Tanya Simuni: Genetics definitely have a very important contribution to the mechanism of the development of the disease. About 10 to 15% of people with Parkinson's disease carry one or the other genetic variant that is known to be associated with a higher risk of Parkinson's disease. Genetically targeted therapeutics are essentially important because the world of cancer has demonstrated to us that's how it got down to successful next generation therapies. The two genes that are at the forefront of therapeutic development are GBA variant and LRRK mutation. Again, these are considered to be most common. However, it's important to understand that if you test across the Parkinson's population, about two to 3% of individuals carry LRRK variant substantially high in certain ethnic populations and about 10% carry GBA variant. So, there are studies going on targeting both GBA people who carry those variants, GBA, LRRK. But the second question is essentially important, considering that those variants are rare at the population level, will the biology that is linked to GBA or LRRK is that relevant to people who do not have those variants?

And that is an essentially important question that is being addressed and the rather these therapies first aim to be tested in gene-positive individuals, but there is already an ongoing study of the LRRK targeting therapy that is recruiting individuals finished recruitment recently who independent of them carrying the variant, counting on the fact that that biology, as has been demonstrated, is relevant to the population at large. Ultimately, speaking of personalized precision medicine, we need to identify a subset of individuals who don't carry the gene, but have either LRRK-like biology or GBA biology. That work is in progress.

Veronique Enos Kaefer: Thank you all. You have so many incredible questions. We use your questions to help inform content for future discussions and the things that we write about on our website. There's a lot of

information in there. I hope what you feel by how out of breath we are in trying to share as much as we can with you and we didn't cover it all, that there is much happening if you leave with nothing today. I hope that you feel encouraged by the scope of what's happening in Parkinson's research and that we're really in a new sort of phase for what is possible for Parkinson's disease. Thank you for being an active, engaged part of this community. We appreciate you brilliant panelists, and we're here until Parkinson's isn't. Thank you all.

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