

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.

Speaker 1: 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.

Maggie Kuhl: Hello and thanks for joining us today. I'm Maggie Kuhl, vice president of patient engagement at The Michael J. Fox Foundation. It's great to be with you and with our panelists. Today we'll discuss what goes into designing a clinical trial and how recent Parkinson's research breakthroughs and strategies to improve trial design could speed treatments. All right. We've got a lot to discuss, so let's get started and meet our panelists. With me today is Dr. Tanya Simuni. She holds many titles. She is the Arthur C. Nielsen Professor of Neurology and division head for the Parkinson's Disease and Movement Disorder Center at Northwestern University in Chicago. Dr. Simuni is also the site principal investigator, the overall study co-principal investigator, and a member of the executive committee of our Parkinson's Progression Markers Initiative, PPMI study. Dr. Simuni, thank you for sharing your time with us today.

Tanya Simuni: Thank you very much for the invitation.

Maggie Kuhl: Dr. Niraj Shanbhag is also with us. Niraj you are a neurologist who has been in the drug development space in the pharma industry for many years and are currently medical director at Takeda Pharmaceuticals. Thanks for joining us.

Niraj Shanbhag: Thank you for having me.

Maggie Kuhl: And last but certainly not least, Mr. Rick Grant is PPMI study participant. Rick, you live in Bel Air, Maryland, and you were diagnosed with Parkinson's in 2018 at age 54 and you carry LRRK2 mutation. Thanks for being with us as well.

Rick Grant: Thank you. Good morning.

Maggie Kuhl: So, Rick, you're sort of the catalyst for our discussion today because you were at a workshop with Dr. Simuni that our foundation held a bit ago on how to measure memory and thinking problems, cognitive impairment in Parkinson's in trials. And you were generous enough to help us out and offer the lived experience perspective at that workshop. And you made a comment that you really had no idea how much went into designing a clinical trial. Could you share more about what was behind that comment?

Rick Grant: Well, I was amazed. I was sitting in a room with 75 of the smartest people I've ever met in my entire life. And then there was me. And everybody, there, they were all PhDs and MDs. And they were all talking about Parkinson's and their studies to eradicate it. And I thought, I'm one guy in a room with 75 people. I wonder how many other 75 room people are around the world doing this. And I

was just amazed at the number of brains are going into curing a disease. And I was just flabbergasted by the whole thing.

Maggie Kuhl: Well, I think we all agree that your brain is certainly critical, the lived experience, you're one of those very smart people in that room. And looking at this quote from our founder, Michael J. Fox, I think as you said, a lot of people in a lot of rooms are figuring out how we are going to climb to cures. And so, today our goal for this conversation is to share a little bit more about, as you observed, how much goes into clinical trials. And give context for things like biomarkers, and staging frameworks, and other breakthroughs that might seem a bit removed from a new therapy, but are actually really critical to advancing new treatments. And so, we hope that our audience members feel more informed about the process and the impact that they can have by participating in research. So, with that, maybe we'll back up and start with a little bit of a primer. Tanya, maybe I could hand it over to you. What do we mean by clinical studies and what are the different types?

Tanya Simuni: Absolutely. Let's cover the basics. Clinical study involves human research participants. And it's very important to distinguish between you being in the clinician's office as a patient and you might be in the same office as a research participant. The engagement is very different. There are two major categories of clinical studies, observational studies. And you can see the are a couple bullet points. But the bottom line is these are the studies that collect information on the clinical measures on the biological measures, including imaging measures, but there is no intervention. So, for that reason, it's an observational study. And another large category is interventional studies. Those are obviously based on the category when we are delivering some kind of intervention. Majority of people think about it as a drug, but it also can be some kind of device also falls under the umbrella of interventional studies.

Maggie Kuhl: And the first one, observational studies are really critical to the second. Is that right?

Tanya Simuni: Undoubtedly so. And as we continue the conversation, I'm sure that we'll be addressing the questions. Majority of people think, "Give me the drug. That should work." And in order to develop the drug that should work, we need to collect a lot of information to design those smart studies.

Maggie Kuhl: We're going to focus mostly on trials with that background that we've just laid. So, Niraj, maybe you can walk us through how trials take a phased approach.

Niraj Shanbhag: I'd be happy to. Thanks very much. I think the key point to get across is that trials have to move through a phased approach to make sure that whatever you're testing in the trial is safe. That's the primary driver before anything else. And so, we generally start with what's called a phase one study, you can see here on the left. And that's really just to make sure it's safe in a very small number of participants. Usually those who are considered what we might call a healthy volunteer, someone who doesn't necessarily have any particular disease. But is just making sure that seeing how the drug works in that person's body, seeing

what that person's body does to the drug, and making sure there aren't any safety concerns that we didn't know about before it was tested in humans.

If everything looks good from after that kind of trial, things move forward to a phase two where we might start to include more participants, maybe some participants with a disease of interest. And we might start to, again, we're primarily looking for safety. Let's make sure whatever we're testing is safe in a larger population of people. But we also might start to look for some sense that this molecule might have some effect, that it actually might be efficacious or provide some benefit. We can't really prove that in a phase two study. Again, we're primarily looking at safety. But we're looking for some hints that something might be effective because it'll help give confidence in moving forward and exposing even more people to that product.

So, phase three is oftentimes the biggest trial that's run by a pharmaceutical company. It's really to prove that in addition to being safe in a large population of patients, it's also effective. So, this is where we really need tools and measures that we can look at at the end of this study and say this drug did something or it didn't do something. And then finally we have what are called phase four studies. These are usually after a drug is actually approved by a regulatory agency like the FDA, it's already on the market. But oftentimes we still want to look and make sure we really understand what the long-term safety and also the benefits are in the real world.

Maggie Kuhl: A question we get a lot is about time, how long does it take to move through these? And so, I want to give you a chance to answer. But I also just want to address that I'm sure our audience is thinking that. And part of the goal of this conversation is to talk about how we can get faster. But right now, each of these phases are years on their own. Is that accurate?

Niraj Shanbhag: That's absolutely right. Each trial is years, and they get longer and longer as you move through. And that's for a few different reasons. One is certainly the time it takes to find the right patients who might be interested and might benefit from a particular drug that's being tested. And two is as you get to the later phases, particularly a phase three study, again, you really want to look for a measure that it's working. And sometimes those measures take a really long time before they become clear. So, if you're looking for effects on how someone is thinking or how someone is feeling, you might not know after a few weeks or even a few months, and oftentimes can take a year or more to really understand that.

Maggie Kuhl: So, right now from phase one to approval after phase three, it could be 10 years or more. But again with more understanding of disease, better tests, and as you said, ways to recruit participants faster, we're hoping to truncate and reduce that length from good idea to market availability. So, that is what a trial has to look like. But as we discussed, Rick, your comments, there's a lot of questions to answer in how to put together those phases. And so, sticking with you with the industry perspective. Maybe you could talk us through some of these questions that you have to answer. What's the process for actually planning a trial?

Niraj Shanbhag:

Absolutely. So, really the first question is, what do we want to target? What is the actual disease process that we think we might be able to fix with a drug? And I know we'll get to this later. But some of the work that Dr. Simuni and others have done in the Parkinson's disease space is really, really important for this question, because if we understand how a disease works, that's how we find the targets. And so, once we decide what target we want approach, then we have to understand who do we want to enroll in that study? Who are the people for which targeting that specific target might be beneficial? And again, understanding what are the molecules that are important in a disease or how does a disease change over time through initiatives like the PPMI, that's how we answer those questions. Who are the people that might most benefit from a particular clinical trial?

Understanding how much of a drug to give is the next question. And that comes and in large part from studies we do before we ever get to humans. Sometimes those are done in animals. And then those are also done from these very early studies we do in small numbers of either healthy volunteers or people with a particular disease. Additionally, how long to follow participants is a major question. It's a major driver as we discussed of the length of some of these trials. And the better markers we have of how a disease is progressing in someone's body, the shorter and more efficient we can make those trials.

So if we can look at some blood measures of something that changes quickly, that's going to then predict how someone feels months later, we can theoretically make a trial much shorter and much more efficient. And finally, I think we talked about this a bit, but really what are you going to measure? Are you going to wait? Do you have to wait two years to measure how someone is feeling at the time with a survey, or asking them how they're feeling, or checking how they're doing in a doctor's office on a physical exam? Or can we add to that measures that might change earlier like some of the blood markers or spinal fluid markers that Dr. Simuni has been working on?

Maggie Kuhl:

Yeah, I've heard it referred to as sort of go no go decisions. When you have that really clear early signal, it's a lot easier to say, "Yes, we're going to continue, or, "We're going to use our limited resources towards something else that might be more effective." Rick, you've been in a clinical trial yourself. Could you tell us about that experience? Looking at some of these questions, did you think about how the company had answered all of them and landed on how to design the trial that you were in?

Rick Grant:

Yeah. Well, about four years ago I was involved in the DNL-201, we called it the red pill. The folks through PPMI and our forensic at UPenn contacted me because I was of the right age and the right... The LRRK2 and all of that stuff. So, I was cleared into the study. As we walked into it, they said it's going to be a 45-day study or whatever it happened to be. You'd have two stays of hospitals, which in almost 60 years of life, I've never stayed a night in the hospital until then. And I asked lots of questions, what's it going to do to my body and my brain? Is there anything that's going to be over the top and caustic? And all the answers were, "No, you should be completely fine." Leading into it, we were

doing DAT scans, and MRIs, and blood and lumbar punctures, and you just adjusted out to all that stuff.

And all the questions I had asked were completely answered and were completely true. So, it was very all in all pretty good experience. And then after I was out of the study, I learned that I actually was on the pill. And people were saying as I was on the pill, "You look great, you're moving much more fluid than you ever have, or than you have recent times. You seem like you're more of yourself." And then DNL decided to not take 201 to the market and take its cousin to the next steps. So, now as you all were saying, it's years until things happen. So, hopefully I'll be able to see the effects of the 151 pill if that goes to market.

Maggie Kuhl: Yeah. What I'm hearing is some of the questions that perhaps that study was wrestling with too or others are who gets placebo? How many people get placebo versus drug? And then some studies will unblind and give everyone the drug after a certain point or such. So, all of these things really go into the trial to really balance. And we'll talk about this a bit, the participant experience with the scientific inquiry. I wanted, Tanya, maybe to shift to you. We get a question a lot. I'm looking at the words who to enroll. And we get a lot of questions on eligibility criteria. Some trials say you can't have deep brain stimulation. Some trials say you have to be younger than 80 and older than 60. And Rick, you were saying, "I was the right age, I had this right profile." Why are trials so specific in their eligibility criteria?

Tanya Simuni: Very a legitimate question. And I'm sure that some of the attendees would say, "I really wanted to participate in the study and I didn't qualify for one reason or the other." There are two major categories why the studies are very selective and in majority of cases quite [inaudible 00:14:58]. The first reason is safety. If we're talking about drugs. Those are investigational therapies. We need to make sure and we are responsible to be sure that we're not hurting individuals. So, based on the preclinical profile of the therapeutic, based on the previous experience, there will be a number of what is called exclusion criteria, people who cannot be enrolled. So, that is one category.

The other category is selecting the participants who fit the mechanism of action of the drug. Basically pre-selecting individuals where you can have the cleanest experiment. Because clinical trial is an experiment. And that can be based on most importantly based on the biological profile of the individuals. If it is large targeting therapy, you want to have the individual who the carries that they're in or here has the biology that is similar to the individuals who care that they're in. And then come the other factors that based on the mechanism you define the age of the population, specific criteria of their clinical profile and so on. So, while it's frustrating, it has to be very careful and thought to.

Maggie Kuhl: And sometimes our learnings around the disease evolve and we're able to perhaps broaden sometimes the criteria in trials or after a study, after a drug has been proven safe in one population, extend it to another. I love the LRRK2 example because LRRK2 targeting therapies did start for people who carry LRRK2 mutation. But then some of our biological understanding showed that that

pathway may be impacted even in people with idiopathic or cause unknown disease. And so, now some trials are testing those therapies in a broader population. So, to me it just all goes back to learning about the disease and there is precision medicine and matching the right drug to the right person. But the more we learn, the more we can understand if therapies might work for other groups as well. That extends too to different racial ethnic backgrounds that perhaps have not been as included in research. So, I think what I hear is there are very strong reasons to start small. But then the more we learn, the more we'll be able to drive towards therapies for all, either the same or different treatment approaches.

Tanya Simuni: And going back to what Niraj has introduced, the phases of therapeutic development, remember that there was phase four, which is post-approval studies. And that's when the drug is approved available at the pharmacy. But are there still ongoing collection of the information both from the safety standpoint... Remember that even the largest studies are just a tiny percent of individuals living with that condition. But also looking, trying to ask the questions in the non-controlled environment, no placebo arm, whether there are additional features that would indicate the efficacy signature.

Maggie Kuhl: Absolutely. Before we move on, I wanted to focus... We got a question from the audience, and this came in actually in the pre-registration forms as well around exclusion of people with deep brain stimulation. I think that's a real lightning rod in the Parkinson's patient community. Some choose not to have DBS solely because it might exclude them. And there's actually a commentary or review in the last week or so, should we rethink this? And so, curious for any commentary or perhaps more higher level just around our evolving need to be examining our own assumptions about what we should or shouldn't have, and really be centering again with the balance of science and the patient participant experience.

Tanya Simuni: Again, they're a legitimate question. The answer to that goes back to that cleanest experiment. And it's not always the right experiment, but the cleanest experiment. So, it all depends on giving the right person to the right study. When we are talking about experimental therapeutics that are being developed hopefully to slow progression of the disease historically, traditionally, those target people with just newly diagnosed disease. The earliest time that we can intervene. And those studies would exclude people with the brain stimulation, which is therapy, very important therapy for advanced stages of the disease. Or therapeutics that are being developed to treat the symptoms. And frequently those studies also exclude individuals who have surgery, who had previous surgery. And that's where probably the field should start rethinking it. Again, it's bringing everyone to the common denominator so that the participants in this study look as much alike based on their biological and clinical characteristics to answer that primary question, ultimately, does my intervention work or not?

Maggie Kuhl: That's perhaps a good shift to how might be able to speed trials. So, we talked about the timing, we talked about some of our considerations for today and designing trials. But our foundation with partners such as all three of you, work on the resources and the information that will help us advance trials more quickly. So, you see here a couple of our tenets of what we're trying to help the

field do to advance the direction and the speed of Parkinson's research studies. Maybe we'll just keep things moving by going into the first one, which is to build evidence. Niraj, as you were saying, you have to know what you're going after, what question you're answering, that you have a really solid confident reason to test this therapy. And so, maybe you could talk us through a little bit why this is a key step for industry to decide whether to invest in a trial on a specific target.

Niraj Shanbhag: Yeah, like we talked about that the amount of resources and time that goes into developing a new therapy is massive. So, we want to have as much confidence as possible right from the start that we're going in the right place. So, having valuable data, what we call natural history data or exactly what the PPMI is doing is understanding in people living with a specific disease, how they change over time, not just in how they feel, but in how these different, what are called biomarkers change over time. These could be molecules in your blood or maybe it's a finding on an MRI image, or something like that. If you find examples of things that really change over time and really correlate tightly with how people are feeling over time, those are really promising targets to at least think about testing a drug against. To see that if you change that, can you actually improve how someone feels?

Maggie Kuhl: Right. So, like you said, we're gathering a lot of data around disease and we're connecting that, not only around the biology but also how it translates to clinical experience. I want to call attention to our last bullet here on the slide about sharing data. So, our PPMI study, other studies that the foundation is involved in. More and more studies across the field are sharing the data de-identified with full consent from all participants to speed breakthroughs to put out what we have so that other great minds can be comparing, and contrasting, and looking for the next great breakthrough. Rick, when we chatted before this call, you had called that out as something that was really important to you. Could you talk through why you think as a person living with Parkinson's, that sharing of data is so critical?

Rick Grant: Yeah, being one person with Parkinson's, my perspective is once the blood is taken, the urine is taken, the spinal fluid is taken at that point, it becomes yours. It becomes the researcher appropriate at that point. And the patient has done what he or she's agreed to do. At that point, take what you all need and go with it. And someone in Australia may discover something that someone in New York hasn't really thought of using that one sample. So, I think it's crucial that I'm sure they're not... I guess your stable of volunteers is not as huge as it should be. So, take what we've given and run with it. It's something that you guys need that the world really needs.

Maggie Kuhl: We appreciate that partnership again, with all of the protections and ethical considerations in place. But that is surely what we're all after, working together to speed things forward. Maybe that's a good shift here, but I feel like we've talked a lot about the need to define the disease. And so, spending a little bit of time thinking about how we work with the patient community and maybe an entry point to this. We were just talking about sharing data and we see here about balancing ask and give. We got a question from one of our audience members about returning the results of studies, the finding from studies. Tanya, what do

you think about our need to return to the participants, what we're learning in studies and perhaps using that too to share how else you think about designing patient-centric trials.

Tanya Simuni:

So, thank you for asking the question. PPMI just is one of the examples of the studies that really is trailblazing the frontier of what used to be an absolute noll of sharing the data collected in the studies with the participants as the study is ongoing. So, as of last month, PPMI has launched the program of sharing results of DaTSCAN, which is the imaging modality used to assess the degree of dopamine loss in the brain. And actually sharing at this point baseline data. But ultimately the goal is to share it in real life. And the rationale for that, without participants, studies will not exist. Observational studies will not exist. Interventional studies will not exist. And people are contributing a lot of time, a lot of help. They are owners of it. So, it's our responsibility to share. It's easy to say it's logical, a lot of work because we're sharing research data.

It's not like going to the doctor's office, your glucose level is such, we know tremendous amount of data, what that means. Here is your glucose level. You can download it from MyChart portal within 12 hours of the test. These are research data. So, as we're sharing, we need to provide sufficient information what we know today, which might be different from what we'll know tomorrow, so that the information is factual and is rightfully positioned. So, essentially important, that's where the field of a lot of observational studies is going. And that's where the future is going. It's standard of practice that in interventional studies, once you complete the study, the participants will know whether they've been on the drug or a placebo. But it takes a lot of time. And obviously there are absolutely right reasons to blind [inaudible 00:27:15] individuals and the investigators what are of the study they're on. But shareable data is essentially important. That's the first part of the question.

Second part, how do we make the studies what is referred to patient centered? Basically discipline [inaudible 00:27:37]. Again, returning back, it's a lot of effort that goes on behalf of the participants. The best answer to that, ask the participants. Rick is so generous, contributing to the study. Ask Rick or another person, we are designing the study. And then he has to go back to fundamental questions, developing the therapeutic that ultimately targets if it is symptoms that are important for the person. Otherwise, we can develop a therapeutic that would work, that will show statistical significant change. But it's really not important for the participant. So, it goes back to what Niraj was saying, what are we developing therapeutic for? And then how are we developing it? How are we designing the study to collect sufficient amount of information, but not over [inaudible 00:28:36] amount of information? And how do we communicate it to the participants?

Maggie Kuhl:

Absolutely. Yeah. We got this question from one of the audience members, how to guarantee that we are developing scientific programs that meet patient needs. And through listening to the patient community, we do focus groups, we do surveys, we have folks in our webinar, audience Q&A who say, "Why aren't you studying this thing? That is my most troublesome aspect of living with PD." So, to me, research participation means enrolling in trials. It means enrolling in

observational studies. But also means things like, Rick, like you were doing at that cognition workshop is being in the room and being willing to speak up and share your own experience with the decision makers. Rick, anything else that you wanted to share about your experience in the trial or in the workshop around patient centricity?

Rick Grant: Well, I was just thinking about trials. There's always an out on a trial. After my DNL study, I was involved in the lighthouse study, which was a four-year study. And then they stopped returning two year study. And I knew that through the lighthouse four-year study, after a month or so, I knew I wasn't getting the pill, I was the placebo. And I thought, I know what the pill feels like, I know how I can react to it. The placebo, you're not going to learn anything from me in my mind with the placebo. So, they were turning the lighthouse study into LUMA study, which was two years. And I said, "If I'm placebo, I don't want to participate with it." And they're completely fine with that. So, there's always an out, once you agree to do something, if anything's uncomfortable, you can raise your hand and say, "Enough." And thankfully, I really haven't had to do too much of that, which is great.

Maggie Kuhl: That's true. Thank you for underscoring that. All research is voluntary and there's no commitment to see anything through. So, that's an important note. Thank you for sharing that.

Rick Grant: And there's no pressure at all.

Maggie Kuhl: And Niraj, from the industry perspective, how does a pharmaceutical company think about patient involvement in answering those questions? And two, I think it's interesting that there is, as Tanya said, there is an ethical moral partnership that we need to hold here, but it's also a smart financial decision. And industry is weighing financial investments. And so, it will make for a better trial if you engage participants early and often.

Niraj Shanbhag: Yeah, absolutely. We think about this all the time. Right now actually for another study I'm working on, but it's absolutely critical. We know that obviously participants are really interested in this. We know that regulators are interested in this, and it's for all the reasons that Dr. Simuni laid out, it's not only to make a trial as least burdensome as possible for participants and their care partners, but really to make sure we're measuring the right things. Because exactly as was said before, if we're measuring the wrong thing, no one's going to want it. And to be honest, no one's going to take it then. And then it's useless to everyone.

So, we have to make sure we understand what is most important to people living with the disease and the people helping care for them. And that the only way to do that, like you said, is to ask them. There's really no way. There's no other way to get to that question. So, to do that, we partner with foundations like the Fox Foundation or other patient advocacy groups. And then ideally connect directly with patients and their care partners to have these discussions and to find out what's important.

Maggie Kuhl:

So, what is important? Let's pivot to measuring the impact of therapies. We've gotten a couple of questions already coming through around biomarkers and how those speed through speed trials. So, Tanya, I'll pass it to you. We had a big biomarker breakthrough in Parkinson's research. Many thanks to Rick, and you, and others involved in PPMI and other studies for that. So, first of all, I got a good question that is can you just define a biomarker, and then can you maybe tell us about this breakthrough, and really how it is speeding trials, and how other biomarkers like it are speeding nutrients? So, this is a three parter, actually. Last one was a two-parter. But I know you can handle it. I give you the big question.

Tanya Simuni:

Okay, let's go. First of all, legitimate question, what is a biomarker? It is objective measure of biology in human body. Let me give you a perfect example of a biomarker. Cholesterol level is a biomarker of cardiovascular health. And each of us should and is getting it as part of our annual physical exam. And significant decisions are being made based on the biomarker, independent of the degree of symptoms. Everyone agrees that you shouldn't wait until someone has a heart attack to start treating cardiovascular disease. You need to prevent.

And in cardiovascular disease, cholesterol as an example or stress test, those are those objective measures that indicate the state of underlying disease biology. In Parkinson's, up until synuclein biomarker, we didn't have such measures. All of our measures have been clinical. So, we truly have to wait until the person comes in with the earliest signs of tremors, slowness, or other symptoms to say, "You have Parkinson's disease." Today we have the biomarker that in the research domain, not yet in the clinic. A lot of more work needs to be done where we can measure the biomarker to say that you have the biology, you have the disease because symptoms are the signs of the biology. So, the biomarker of the disease and then essentially important returning back to what Niraj was saying, find the right therapeutic target. And then moving into the therapeutics biomarker for identifying the population for the study.

If you have a therapy targeting synuclein biology, you want to have people who have synuclein positive test and not negative. Majority of people with Parkinson's will have synuclein positive tests, but not all of them. And then the next question, can I have a biomarker to measure progression of the disease? Because as Niraj was saying earlier, and as all of us know, studies are long. And if we have a biomarker of the disease progression, the studies will move much faster. We're not there yet, but those are biomarkers of the disease progression. So, that's why those are essentially important. And again, in order to develop therapeutics, those have to be identified and studied in observational studies. Returning back to PPMI. So, I answered two parts of your question. What was the third part?

Maggie Kuhl:

I think you hit them all. I think you hit them all. You said what is a biomarker? We covered. Why does it impact studies both to select participants and to assess therapeutic impact? We talked about the synuclein biomarker. So, alpha synuclein is the sticky protein that clumps in the brain cells and we believe leads to loss of dopamine. But as you said, not everyone diagnosed with clinical Parkinson's is positive on this test. And so, we still have a ways to go to understand the complexity of Parkinson's disease and related disorders, and

studies like PPMI are helping answer those questions. So, a negative test does not mean that there's no therapies for you. There's a full pipeline out there and we're really trying to bolster that pipeline for precision medicine approaches for all. Niraj, so that's the biology of the disease overall. But Takeda especially also works in some of the symptomatic therapies and we don't have as many biomarkers for some of the issues that face people with Parkinson's such as cognitive impairment or gait disorders. How do we measure the impact and select participants for those symptomatic trials?

Niraj Shanbhag: Yeah, it's a really great question and it's a challenging question. It's one that I think we in all companies struggle with. So, let me just step back a minute. When we say a symptomatic therapy, what we mean is we are focusing on improving some symptom, whether that's difficulty thinking or like you said, difficulty maybe walking. But it's not really based on fixing, necessarily fixing some underlying biology. We really just want to help with one particular symptom or two particular symptoms, whatever it is. So, in that case, usually you find participants who are having issues with those problems. So, we might have an inclusion criteria saying you have to perform at a level below a certain level on a cognitive test.

Maybe we give you a paper and pencil test in the clinic and say, "If you're performing below a certain level, you might benefit from this therapy." So, then you can come into the trial. Or maybe we are including people who have had a certain number of falls in the past year just as a measure of some way to find people who might most benefit from the drugs. But again, these are not objective markers like a biomarker. So, I think they're inherently a little more fuzzy. They're a little bit more variable. They're not quite as [inaudible 00:38:27]. But I do think at this point it's sort of the best we can do in terms of these symptomatic therapies.

Maggie Kuhl: And we're trying to make better scales. And also match the of different scales that we have to exactly how a therapy might be working. Maybe a compound use one scale versus a device that you wear uses a different scale. So, that's part of the work that our foundation is doing. Rick, again, you were in a precision medicine trial. We've had breakthroughs like the biomarker. But again, we do have some ways to go. How does it feel to be living with Parkinson's in this new biological era of getting closer to precision medicine approaches?

Rick Grant: Well, I think the biomarker news from last year I think was amazing. I think it's great. Scientists have been looking to learn bits of information over many, many years. Personally, I'm excited that we're starting to make some progress here. That these rooms of 75 people around the world are really going to solve this hopefully quicker than not. And I'm personally just excited about it. Someone asked me once, why do I do research? And I said, well, I'm not doing it for myself. I'm doing it for my kids, my grandkids, for your children, your grandchildren. So, hopefully you guys with what you're doing, no one have to worry about it anymore. And personally, I know my kids are excited to... When the news came out in 2023 about the marker, my kids were very excited about it. So, let's keep it going. Let's end it all.

Maggie Kuhl: Not to correct you, but I do think when you said what you are doing, I think it should be what we are doing because you are participating in research. And one of our underlying themes here is that we need to learn more about disease, we need patient partners.

Rick Grant: I guess you're absolutely right.

Maggie Kuhl: Not to correct you, but not to diminish your role at all.

Rick Grant: Thank you.

Maggie Kuhl: Another group that plays a big role in driving treatments to patient hands is regulators. People who are deciding what is approved or what is paid for by insurance. And so, this is another partnership that our foundation and our partners pursue so that we can be answering those questions to design trials that will be attractive and available to regulators to make that easier decision of, yes, we see this clear benefit, we think we should approve this, we think we should pay for this. Niraj, from the industry perspective, how critical is it to align with regulators early in that planning stage?

Niraj Shanbhag: Absolutely essential. There's no question about it. In fact all the different regulatory bodies, whether it's in the FDA in the US or other bodies in other countries, they all have dedicated meetings that sponsors such as Takeda and other companies will schedule ahead of time at really pre-specified steps to really make sure we're aligned on what our patient population might be, what our measures that we're measuring might be. So, it's absolutely essential. There's no question about it.

Maggie Kuhl: And Tanya, the breakthroughs just keep on coming. We had a paper last month around a new framework for thinking about Parkinson's disease, a new staging framework that incorporates that biomarker that we had discussed. Can you tell us about that development, the tool development, and also again how that's helping work with regulators on trial design?

Tanya Simuni: Absolutely. So, what Maggie is referring to is the paper that was published last month in Lancet Neurology on behalf of a large group of multi-stakeholders, including people with Parkinson's disease. That convened about a little bit over a year ago at the time when the synuclein biomarker paper was being published. And the question that we posed now that we have biomarker underlying disease biology, are we in the position to actually rethink how are we defining the disease? And can we move into the biological definition of the disease? That is the first part of the paper. And we actually are making the statement that we in the era that we can define the disease based on underlying biology as measured by the biomarker of alpha synuclein, as well as presence of dopamine dysfunction as measured by DaTSCAN today, indicate the measures would evolve, but the concept would stay. And the greatest advantage and advancement of such approach.

Again, returning back, you don't wait for the heart attack. You identify the underlying biology and ultimately also translating it into Parkinson's disease. Not to wait until someone has the symptoms of tremor, and stiffness, and walking problems. But to identify that underlying biology. So, move early in the biological course of the disease. I want to preface that is the research definition. It is a research framework. It's not ready for clinic. We need more data. But returning why is essentially important, returning back to therapeutic development, there are two parts to the paper; biological definition that we just discussed and integrated biological clinical staging system. So, once you define the disease, people who have strictly biomarker have the disease. People who have biomarker and subtle clinical symptoms like brain behavior disorder. Right now that will prodromal individuals. And it's the term that is not known to the regulators and confusing to the field.

It is an early stage of that new definition. And then people with newly diagnosed disease, that is the next stage of the new definition. And then marching through advancing clinical signs and symptoms, there is further stages of the disease. Why is it [inaudible 00:44:58]? Because that provides the framework for therapeutic development to identify the participants returning back strictly based on biomarker or biomarker and clinical features. And to decide what endpoints, how do you measure what you need to measure? Because it'll be different in individual just with underlying biology. There are those steps to measure. But as we're developing biomarkers that could measure progression, that would be the measure in that very early stage versus stage with clinical signs and symptoms. You will pick different measures to measure the effect of your intervention. And regulators are there. Regulators are part of that initiative, part of that paper because it's very important and essentially helpful for them to put it in their decision process. How do they approach whether something worked or not? How do they make their ultimate decision?

Maggie Kuhl: It's lovely that they worked with us on that because they are the ones who are reviewing it. Niraj, we're you going to jump in?

Niraj Shanbhag: I was just going to add, I love the statin example. But I also think another great example is what's happening in the Alzheimer's field right now is sort of a very, very similar biology defined framework for defining the disease and staging disease, at least from a research perspective. And it's been successful. It's now being used to identify patients who might benefit from certain therapies to track them and to really understand early on whether these specific therapies are working. And so far they've been really good at predicting who will actually feel and function better at the end of a longer trial. So, maybe you can get a measure at six months that will really predict how someone will do at the end of two years, for instance. And I think this has really contributed significantly to approvals of the first approvals in Alzheimer's disease we've seen in 20 years. And I'm hopeful that we're also headed that way in Parkinson's disease as well.

Maggie Kuhl: Yes, yes. Parkinson's field, we're always learning and working. And I think too, we are looking for biological measures of progression. But even right now in something like the framework that bases the stages post appearance of clinical symptoms based on function, right now, so many studies have eligibility criteria

based on how many years since diagnosis. And anyone living with Parkinson's or who knows other people with Parkinson's knows that two years from diagnosis can look so different. And so, if we're assigning it more towards your biology and your function versus something as arbitrary, frankly with access to healthcare issues and other confounders as linked sense diagnosis, as you said, we're just going to have a much better tool to have better studies and easier paths to approval.

So, we have so many questions, so I wanted to share it. First of all, before we get there, I have to make a plug for PPMI a bit. PPMI is for everyone. Anyone over age 18 or older can participate. There's an online platform for anyone. And then some individuals with specific factors or disease experiences can participate as Rick has at a clinical site. So, you can visit michaeljfox.org/ppmi to get started. All contributions are incredibly valuable. We've talked a lot about hearing what the most troublesome symptoms are or a normal aging path versus one in Parkinson's and all the subtypes that are under that disease umbrella.

So, PPMI is really the source of truth for Parkinson's data in the research field. And if you are not already a part of it, we hope that you will join us there. And now we will jump over to the Q&A. We got a number of questions, Niraj, maybe I'll direct this one to you, around wearables. We haven't really talked about the role of digital measures, Apple Watch, wearable smartwatch. There's lots of different devices that we're putting on folks these days to be measuring the impact of therapies.

Niraj Shanbhag:

Yeah, thanks very much. I'm happy to start. It's a very, in my mind, a complicated topic. And I think we're just at the beginning of understanding the power of these wearables. So, maybe I can start by just saying, as an example, you might use wearables in a clinical study. Something we did recently was to measure how someone is walking, how well they're walking. Instead of just saying, let's look at them and time how long it takes to walk from point A to point B, you can use some wearables to also say exactly how fast are they walking, how long does it take someone to turn, what's the variability in how they're stepping? So, the idea is you can potentially reduce the burden on participants by allowing wearables at home, for instance, instead of having coming to the clinic. But you also potentially get a lot more data out of a wearable than just looking at someone.

In my mind, I think the reason I say we're still at the beginning of this is because there's a lot of different wearables out there that do different things. And I think we still really need to prove and we need to understand exactly what you're measuring and how important those things are. So, maybe we can measure exactly how fast someone's walking. But what does that really mean? Is that really going to translate to something important? Coming back to this question of what's really important for patients and their caregivers? And then another aspect is, as I mentioned, there's a lot of different wearables out there, different companies, they have slightly different software in them that do slightly different things. I think rightly so, regulators are, I think, a little bit hesitant to just jump on and say, "Let's take any wearable and any data that comes our way and assume

it's true." So, again, I think it's really promising. I think we're going to get a lot out of these in the future. But I do feel we're a little bit at the early stages.

Maggie Kuhl: Still in that learning phase rather than full application. Great. Rick, I am going to direct this one to you. I love this question. Do patients in studies ever get to meet with other patients in the study to discuss their experiences, feelings as they travel along? Or is the goal to keep them as sterile as possible and to not cross contaminate with experiences? You've been in PPMI and interventional trials. Does anyone tell you it's like a jury situation where you can't...

Rick Grant: When I'm up in Philadelphia for treatment or part of the study, I've never actually... They haven't walked someone into the room. However, I know that PPMI, they do an annual Sunday breakfast where the participants within PPMI get together. And we sit there and we talk about what's going on in our world, which I think is very beneficial. But yeah, I haven't really been forced to sit down in a room with anyone, which I think I personally would love to do. But it hasn't happened yet. But there's still time.

Maggie Kuhl: Niraj or Tanya is that consideration in interventional trials? PPMI is different. My personal PPMI slogan is come for the QR state for the community because I think we tried to foster that. But is it different in a trial when you're trying to have different groups?

Niraj Shanbhag: Yeah, I would say I don't think this is something that generally gets... Maybe doesn't get talked about as much, but it's certainly true. Coming back to, I think Dr. Simuni's point earlier, having cleanest experiment possible. You don't necessarily want someone saying, "Oh, I had this either beneficial effect or side effect," and then potentially skewing how someone else views their own therapy. So, to some extent, it's helpful to have people somewhat isolated from other participants in the study.

Maggie Kuhl: Understood. Well, Tanya, question for you. How can patients and healthcare providers determine which clinical trials they should join?

Tanya Simuni: Your first question should be addressed to your clinician, to your Parkinson's doctor. And obviously your clinicians as they can [inaudible 00:52:55]. And they definitely have a lot of skill to treat the disease. Some of them are not that involved in clinical research. So, they will honestly tell you, "I don't know," or, "I will ask." There are a lot of resources, clinical trials... Every study is required to register on clinical trials. Go, right? So, you certainly can plug in Parkinson's disease and disease modification, but that is overwhelming.

Michael J. Fox has Fox Trial Finder, which is more of the matchmaking platform. That you plug in your basic criteria about yourself, age, how long you had the disease, medications that you take, and you get a list of trials that you potentially would qualify. Qualify for the study, still, you need to go back to your clinician and say, "Here is the list of studies, what do you think?" And even if they don't know the study, they will have more resources to direct you. If you're being treated in academic center, these are the clinicians who very frequently

serve as investigators. So, they carry two hats and will be able to address those questions more [inaudible 00:54:17].

Maggie Kuhl: Follow up question. This time I at least waited for you to answer one before asking a second one. We got a question. If you don't live in an urban environment where a large academic medical center is based, how can you participate in trials?

Tanya Simuni: Great question. It is our responsibility, because otherwise we will recruit the participants from their restricted socioeconomic background, very restricted geographical background. And we'll be answering the question only those participants. There are a number of opportunities. There are more studies that are going virtually. He cannot give the drug virtually. But you certainly can do a lot of assessments remotely and reduce the burden of traveling to the site. Majority of studies will have reimbursement, travel reimbursement for the participants. PPMI has 31 sites in the United States, which certainly does not cover the full geography of the United States. And the participants travel to our center from large geographical areas. And obviously they're committing their time, but they're reimbursed for travel. So, really it's combination of returning back to the smart design of the studies and using technology as much as you can to reduce the burden for in-person visits. And finding the studies at whatever closest, not that close academic centers that will... And majority of studies will give reimbursement for travel.

Maggie Kuhl: And I'll say in my role at the foundation, we're even looking at other reimbursement efforts. Some people, for example, to leave their pet or to leave someone who they care for to travel and enter a trial. These are the things that we're trying to think about how to balance again, that ask and that give, and make trials as patient-centric as possible. We have two more minutes. We could answer so many more questions. Thank you all for contributing and sharing your questions and your comments. I'd like to end by just going around the room and having any last thoughts. Niraj, anything that you wanted to call out about what we talked about? Or just your hope or optimism around the pace of trials?

Niraj Shanbhag: Yeah, absolutely. First, I would maybe reflect that I really think the data we get from initiatives like the PPMI, thanks to people like Rick and others, I cannot stress how important that is. And that's the source, like you said, of truth. It's where all the inflation comes from in terms of what do we want to test, who do we want to test today, and how confident are we in these molecules? So, I really want to stress how important that is, and thank Rick and all the other participants. And finally, I am really hopeful. I think I said this before, I think the Alzheimer's field is really proving this in real time, and I think we're headed that direction. Again, thanks to a lot of the effort of the people on this call. So, thank you. Thank you for having me today.

Maggie Kuhl: Thanks for being here. Tanya.

Tanya Simuni: Yeah, I very much could echo what Niraj has just said. I would start with huge thank you to people living with the disease. There are more than 800 of you who have joined the webinar now. So, obviously the topic is relevant, it's important.

Without your participation, studies will not be happening. Be the active participant. Try to remember patient-centric concepts. So, your voice matters. Your participation matters. And similarly, I'm optimistic. We live in really exciting times. PPMI has been there for more than 10 years. It's 13 years in existence. But it took a lot of time, a lot of effort of all the participants, investigators of the global community. But we have so much data that meaningfully is contributing to research. PPMI is not only studied. And again, a lot of work has to be done, but we're certainly moving forward. Thank you for inviting me.

Maggie Kuhl: And Rick, the last word is yours.

Rick Grant: Wow. I am a fairly impulsive person. And I've learned over the past six years since being diagnosed that give it some time. Getting the right mix, getting the right cure takes time. So, we're going to get there. I always say to people, my goal is to put Michael J. Fox out of business. So, once we cure this, you guys can go off, and retire, and go to islands, but we want to put this to bed. So, thank you for including me.

Maggie Kuhl: We want that too. But Niraj or Tanya, maybe I'll need a job on a different disease state when we cure Parkinson's. So, thank you for being part of our community and joining us today. And we hope you found today's discussion helpful. Thank you all for your input and have a great day.

Speaker 1: Did you enjoy this podcast? Share it with a friend or leave a review on iTunes. It helps listeners like you find and support our mission. Learn more about The Michael J. Fox Foundation at michaeljfox.org. Thanks for listening.

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.