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.

Bradford Casey: Hello, I am Bradford Casey. I'm a scientist at The Michael J. Fox Foundation, and I am very excited to be here with you and our panelists today. Today, we are going to be diving into an exciting topic, basically how a Parkinson's treatment gains approval from the US Food and Drug Administration, also known as the FDA, and how that becomes available to people living with Parkinson's disease. So we've got a lot to discuss, so let's go ahead and get started. Let me first introduce our panelists. So today, we have Dr. Brian Fiske, who is Chief Scientist at The Michael J. Fox Foundation. Thanks, Brian, for being here with us today.

Dr. Brian Fiske: Good to be here.

Bradford Casey: We also have Dr. Maria de Leon, who's a movement disorder specialist, who is actually diagnosed with Parkinson's disease in 2008. She's also a member of the Fox Foundation's Patient Council.

Dr. Maria de Leon: Thank you.

Bradford Casey: And then lastly, we have Dr. Stuart Isaacson. Dr. Isaacson is a movement disorder specialist. He is the director of the Parkinson's Disease and Movement Disorders Center of Boca Raton, Florida, and he's also a PI for the Parkinson's Progression Markers Initiative site in Boca Raton. Welcome, Dr. Isaacson.

Dr. Stuart Isaacson: Good to be here.

Bradford Casey: So it's been a big year for Parkinson's disease research, and there have been three new treatments approved by the FDA in just the last year, so let's start there. Stuart, what can you tell us about these new options for patients, and what sets them apart from previous treatments available for Parkinson's?

Dr. Stuart Isaacson: Well, it's really exciting. I mean, we strive so hard trying to find ways to ultimately stop the progression and cure Parkinson's disease, restore those brain cells that have degenerated in the brain, but until then, we have to find better treatments to treat the symptoms, both motor symptoms and non-motor symptoms. We relied very heavily on levodopa, which of course, becomes dopamine, the chemical that's being lost in Parkinson's. The problem though, is that when we take levodopa, we ask people to swallow it, and we wanted to go to the brain and become dopamine, an essential neurotransmitter. And the miracle is that when you swallow it, in early Parkinson's disease, it gets the brain-improved symptoms in 20 minutes. That was the miracle. The irony perhaps though, is that the esophagus, the stomach are very slow to deliver levodopa. It may get stuck in

the stomach when it gets into the intestine, where it has to be absorbed to a special protein to get across from the gut into the blood.

It can be difficult for you to get across in the bloodstream, it only stays there for 90 minutes, not such a long time. It has to get into the brain, across the so-called blood-brain barrier. It has to become dopamine, and it has to bind to dopamine receptor proteins to improve movement. There's a lot for it to go to, a lot of challenges. So many people begin to experience that, When you take a dose of levodopa, it may take longer than usual to work, maybe in the morning or around mealtime, or some other time of the day, or maybe it works well but it doesn't last long enough in its benefit, and it begins to wane after a few hours. So we're trying to get doses of Carbidopa, Levodopa that might work quicker, or last longer. Or how can we get it to work more continuously throughout the waking day, or overnight, into the morning.

And this is what we've seen this year. Crexont is a longer-acting formulation of Carbidopa-Levodopa. It works just as quickly, but it has what's called a mucoadhesive polymer. Fancy words, but what it means is that when it gets through the esophagus and stomach, and gets to that part of the intestine where it has to be absorbed, rather than just passing through as food and medications do, and whatever gets absorbed when it's moving through will get absorbed. Crexont sticks there, it adheres to the inside of the intestine, and it sticks there for about five hours, so it lets out levodopa over five hours, so it can be absorbed there for five hours, maintaining blood levels instead of for 90 minutes for five or six hours. So benefit from a dose of levodopa, when it's found at the right dose, can last for five or six, in some people, seven or eight hours.

Indeed, as an early treatment, Crexont is used twice a day. And even in later, when people may be taking immediate-release Carbidopa-Levodopa, four, five, six, maybe seven or eight times, depending on each individual person. Crexont is only used three or four times, and that fourth dose would be at bedtime. So really, a much longer duration. I think it's a great option to have now. And then we have another Carbidopa-Levodopa that actually stays in the bloodstream 24 hours, and it's delivered just beneath the skin, where it's called the subcutaneous, through a device about the size of an iPhone, a little bit bigger than an iPhone. And it has a little tubing, and it goes to a little patch on the skin. And inside the patch, is a tiny little plastic Teflon catheter that goes right through the skin, and you don't really feel it going through the skin, and it goes just beneath the skin to deliver the medicine continuously through this pump device.

So it gives Carbidopa-Levodopa just beneath the skin, and there's blood vessels beneath the skin, so the medicine gets in, gets right into the circulating bloodstream. It can keep levels of Carbidopa-Levodopa even for 24 hours. It's one 24 hours. And then we just had just a week or two ago, the approval of Onapgo, which has been available in Asia and Australia and Europe for decades. And my colleagues in those areas of the world have told us. I've actually seen patients in their homes with the Onapgo over the years, and we've had patients at our center and research programs using all these medications for the past 10 years. I think we could talk about that later, how early access is so important to these medicines. But rather than putting Carbidopa-Levodopa just beneath the

skin, this uses a little bit smaller pump, and it puts apomorphine, which is a dopamine-like molecule, it's called the dopamine agonist, but it's not like the oral ones we have that can have side effects because they only bind to one type of dopamine receptor protein, called D-II.

And apomorphine that's in the Onapgo, is much like dopamine. It looks like dopamine, and it binds in the brain like dopamine, so it works more like dopamine. And this is more than just during the waking hours, it's put on in the morning, worn throughout the day, and taken off before bed. So lots of new options for people to try to see what works best for them, what's best tolerated, any side effects, lots of options. So I think 2025, we have a lot of new things approved, and of course, there's so many things in trials that give us great hope that we're going to have new things later this year, and into 2026 and 2027.

Bradford Casey: Yeah, thanks. That's a really great introduction. And one of the things you talked about is kind of how these are some new treatments, but each of them really represents options in addition to existing treatments. Maria, could you tell us a little bit about why this variety of options is important for patients?

Dr. Maria de Leon: Well, I think that one of the big reasons is that we know that Parkinson's is a very complex disease. It's not homogeneous, and everybody is an individual. Everybody tolerates medications differently, responds to them differently, and so that's one of the big reasons why we need so many different types. And also, as Dr. Isaacson said, is that the challenge of getting it from the gut to the brain is different in everybody, and is more pronounced as the disease progresses. That's been my experience, because then you have so many other issues, problems with the gut getting slower, and other medications that interact, so that's one of the reasons I think that is so wonderful that we have so many new medications available, so that we continue to provide a better quality of life for patients, and have more options.

Bradford Casey: That's a great introduction. And obviously, the treatments that are available have changed over the last 25 years. Brian, I know you've been in this space a long time, perhaps you could give us a little bit of historical context on how these treatments have changed.

Dr. Brian Fiske: Sure, sure. Yeah. No, it's been interesting to sort of follow, I think, the evolution and the progression in the therapeutic pipeline. So the pipeline being just sort of the whole body of therapies that are being developed and tested for Parkinson's. And you looked at that prior to 2000, in the decades prior to 2000, so the first sort of dopamine-directed therapies really being explored and approved in the 60s and 70s. And then leading up to 2000, the end of the 20th century, a lot of the focus there was really, again, about the different ways you could deliver the dopamine medication at that time. There was some rising of the, Dr. Isaacson mentioned dopamine agonists, so different ways to target the dopamine system were also being explored at that time. The first deep brain stimulation approach, surgical approaches, were also being approved in those sort of early periods.

So by the time you reached the start of the 21st century, we already had a fairly good foundational basis of therapies, mostly targeting a dopamine system as

options for people with Parkinson's. And so within what you kind of saw after that, which was, I think, where we started really seeing sort of an uptick in approvals, was really driven by a few things. One, we continued to want to optimize, I think, the dopamine therapy, so you continue to see innovation and sort of additional approaches, different ways to target the dopamine system to maintain elevated dopamine in the brain. Some of the newer delivery approaches, including, of course, now, the even more recent delivery approaches for how to get dopamine into the body and into the brain, in better ways. Really, again, with this goal of how do you extend the benefits of dopamine for even longer periods of time over the course of the disease, as the disease progresses.

But what you also saw during that time, which was interesting, was a few other things. One, you started to see a little bit greater attention towards some of the non-motor aspects of Parkinson's, in the kind of Parkinson's-specific therapy pipeline, with some new treatments that we're focusing on different aspects of Parkinson's disease, sort of the low blood pressure problems that some people have, some of the thinking sort of psychosis, hallucination problems people have. So you were starting to see in the last 10 years or so, treatments really directed towards some of those non-motor aspects, non-movement aspects of Parkinson's, which again was really exciting to see. Again, a focus more holistically on disease, not just on the movement issues alone.

But I think for us, what I think certainly the foundation are excited to see, is this emergence, and sort of evolution now, in the pipeline of, and it represents probably a good 40 to 50% of the current clinical pipeline when we look at it today, of treatments that we think are now targeting the underlying biology of the disease. So these are now treatments that are not just about focusing on how do you mitigate and reduce the symptoms of the disease, but actually might be targeting the underlying triggers that are leading to why certain brain cells are lost in Parkinson's, and maybe slowing that process down. So you see a lot of now, new treatments that are starting to be exploring the different biologies that we think are underlying that. And that, I think, for us, is really exciting, because these are then the treatments that we hope will start showing promise in the near future.

Bradford Casey: Yeah, that's great, Brian. I think these are important points. Obviously, you and I spend a lot of time looking at this on the research side. Dr. Isaacson. I know that as a clinician, you see a lot of patients that are coming to you with these concerns. How do you approach these new treatments and patients through ask about them in the clinic?

Dr. Stuart Isaacson: Well, I think we have so many options, it can be difficult for both clinicians and patients, and their families and caregivers, to really decipher what would be best to do today, in the next couple of months, this year, next year. How do we plan for now and the future? It's really very complex because we have so many medications. And of course, there are many physicians and neurologists who have a lot of expertise in Parkinson's disease, but never enough, because Parkinson's disease is so common. So it's really a big challenge in trying to raise awareness among clinicians and patients and their families, to raise education, and things like this. That's why it's great to be involved in these types of things.

And also to consider all the options, so of course, non-pharmacological options of exercise and healthy living, good diet, good sleep is so important. The right medication balance, how to adjust for each individual person for their symptoms, for that couple of weeks or months.

How we adjust the medications, which ones we try, which ones we use, and which ones we stop because maybe they're not doing enough, and we try something else. And not having inertia, always being hopeful to try something new to try to make something better is really important. And research medications, I might consider part of that discussion. I don't think research medications are something we do after what we have approved doesn't work. There are always options, and it might be a better option for someone than something that's already approved, depending on their symptoms and needs, and what's necessary. I think research medications give us hope for tomorrow, but it also gives us access to future therapies today. That's a really important point I try to discuss, and to integrate our clinical medications that are already approved with research medications that we hope to pass muster and be approved, and to really integrate this discussion.

I think it's so important to have these types of things, what Michael J. Fox does to really put this all together, because we need to get as much awareness and education out. We need to know what's the biggest problem that's happening. What's a day like? Why do you wake up with symptoms? What happens when you take your first dose of medicine? What improves? How long has it improved for? When do the symptoms come back? What symptoms come back? When is the next dose? To really try to map out and fine-tune the timing, and talk about the different medicines. I always suggest to my patients, "Try it, maybe you'll like it. And if not, we can try something else."

But to always have that hope to try something new, and having all these new options available. We have over a dozen medicines in the past 10 years, or maybe even more medicines, from everything from motor symptoms to non-motor symptoms. And it's been amazing to see that things that when they get approved can now be used, but for the 10 years before they're approved, they're available for people who really need them through these research programs.

Bradford Casey: I think that's great. Now, Maria, I know that as a person with Parkinson's, this is all very personal for you. How do you think about these new treatments? What do you consider when you're evaluating your own care, and what do you hope for? I'm curious, especially as you think about some of these treatments that are moving into post-clinical trials for the affordability aspects.

Dr. Maria de Leon: Yeah. Well, first of all, I'm always excited to hear there's new medications available. And not just for myself, but I think of all my patients, and the disease and the advances. But I think as a patient and as a clinician, my thinking is the same. You want to find the medications that not only are going to improve the symptoms of the patients, but have fewer side effects, and be able to maintain them in a lifestyle. They're able to function, have a good quality of life, be able to do the things they want to do. And as a patient and a physician, that's what I always want to do, maximize the benefit, but minimize the tolerability, the side effects, how often you have to take the medications. And that's the one wonderful

thing about having this new medications that you can do 24 hours or 12 hours and bypass the gut, because then you are providing a different mechanism.

Also, longevity, because I tell you from experience as a patient, after the pandemic, I had COVID, and my Parkinson's went up like three times. And I went from taking medicines three times a day, to having to take the levodopa to six times a day. I felt like I was having to just live my life around the medication. It's like, "Did I take it? Am I going to take it? Am I going to miss it?" And there is no way to live it, okay. I tell you that, I can't even imagine what it was like for patients when we told them to take half a tablet every four hours, or every two hours. I mean, I just cannot fathom that. So that was the one big thing that for me, that's like I cannot live my life just around the clock thinking about when is my medicine due?

And so when I see this new medications, and the first thing when the nearest before this came out that provided a 24-hour relief, I said, "I need to be on that. I need to try that, and let's see if we can do it." And fortunately, it worked for me. It's not always the case. And Dr. Isaacson said, "You have to try it." Everybody's different, sometimes you have to make adjustments. Sometimes it works well with one medicine but not another. So you have to be open-minded, that unfortunately, we don't have a magic ball that say this can work. It works in some people, it doesn't work in everybody, and there have to be some adjustment in some period of this honeymoon, or whatever, that you have to try it. So that's the way I think about it, trying to minimize the medication, the effect that you have on the patients, and maximize the quality of life.

And with every new medicine, it's like "Am I providing me longevity of life? Is this medicine going to keep me another five years going, another 10 years going, until something else comes up, or the cure comes up?" And that's my goal as a patient, as a physician, it's like "How long can I go on doing what I like to do and being active with this medication?" Of course, there's lots of up and downs, and as a disease progresses, you get older, a lot more complications. But another reason why you want to minimize medications and have something that lasts longer so you don't have to take 20 medicines at a time to be able to function. And so that's my hope, that every time you have something new you're getting closer to maybe someday you may be finding a cure to perhaps not all of Parkinson's at this rate, because it's such a complex disease, and it's such an umbrella of so many different things. But perhaps we will find a cure for a subtype, then we'll open the doors and a key to the next subtype, and so on.

So that's the way I view it, and always want to ask and encourage patients to ask their physicians, "Is there something new? Is there something better that I can take that will keep me functioning, or functioning better, or that I don't have to be taking six pills a day, six times a day, or have to have my life around this?" So especially when you're younger, well, at any stage, but when you're younger and you have kids and family and jobs, and all that, you really want to be able to have the least amount of things you can have to function. So thank you.

Bradford Casey: I think these are wonderful points, and I know that we all join you in that hope that we'll continue to see these improvements. Maybe now would be a good time to talk a little bit about how things go through that process to actually gain FDA approval, what that looks like, and what that means for the downstream availability of these treatments. So Brian, maybe you could briefly walk us through what that overall process of seeing a treatment approved looks like.

Dr. Brian Fiske: Yeah, yeah. So I mean, different approaches can obviously follow different paths. But just kind of conceptually, obviously there's a huge body of work that initially starts with the biological idea, the thing that you think is relevant to Parkinson's that you want to target with your therapy. And so there's a whole body of what we call kind of pre-clinical research very often, that goes into that, and this is just figuring out, okay, is this biology? Can you even target it with a therapeutic approach? Which direction do you need to target it? Do you want to increase its activity, lower its activity, whatever you need to do to sort of change the biology in a way that you think is beneficial? Is it safe to do so, things like that. So there's a whole body of work that we kind of call pre-clinical studies, that really are focused on that, answering those types of questions. And those ultimately lead up to a data package of pre-clinical, again, safety and other kinds of evidence.

Then investigators will then submit to the FDA to say, "Okay, we think we're ready to test this in people, living human beings. Here's all the data and the safety, and why we think we can do it, and sort of the approach we think we would start with to move it into human testing." And then they will get an FDA approval to be able to start clinical testing, and sometimes they may have to go back and fix a few things, collect some additional data before the FDA would give them that approval. But it's an important sort of initial milestone for a lot of therapeutic companies and groups to be able to pass that sort of entry into the clinical testing phases. So once they're in there, it becomes a fairly straight, I'm not going say straightforward, it isn't the right word for it, but a clear set of steps that you have to go through to try to get to a point where you can then ultimately seek a final FDA approval.

We often talk about the clinical sort of phases, phase one, phase two, phase three, these are sort of progressive stages of clinical testing for a therapeutic, really with the idea of initially starting first with is it safe? So you just want to test it in a very small group of people. Very often, these might be healthy individuals, where you just really testing in a small number of people whether the doses, the approach you're using is safe. Depending on the drug, you might test that also in the individuals who exhibit the disease, in this case Parkinson's disease. But really that first phase one is about getting some safety data, maybe a little bit of biological data to suggest what the dosing you need to use, and things like that. Then you move into phase two, phase two is really the first time when you start to get a little bit of hint about the potential effects, or the efficacy of the drug.

Again, these are usually smaller, still relatively smaller trials. They're very often, and should be, controlled trials. Usually, that means you have a group of individuals who aren't receiving the treatment, receiving some type of control drug. It could be a placebo, it could be some other sort of comparison that you

would use. But really with the idea of comparing that to then people on the actual drug that you're testing to try to see if there's actually an effect or not. Often these, again, they're small, so the effect may be really looking for sort of hints of effect that may not be statistically-powered enough to see a really subtle effect. But you're using this sort of as your initial test bed, if you will, for really seeing if there's an effect there or not.

Once you have that, then you move into phase three. And phase three is really the big pivotal trial. This is really in a larger number of people. Again, it's controlled, so you have an effective control group. One thing about phase two is you might also test a few different doses possibly, to see if there's one dose that might be more effective. But usually, by the time you get to phase three, you've kind of got a lot of that figured out. You have your dose, you have what you really want to test, and you're doing it in a large number of people, really to get a real sense of whether the drug is working or not. And once you have those data, assuming they look positive, that's really when you start having the full data package that you're ready then to submit to the FDA for approval for use of that therapy in your indicated population, Parkinson's disease in this case.

Bradford Casey: That's great, Brian, I think covers a lot of ground, and maybe speaks a little bit to the many challenges that different therapies may face throughout that pipeline. But one of those I specifically want to talk about is the actual experience of people that might participate. Dr. De Leon, maybe you could tell us a little bit about what people might expect from participating in a trial, either from personal experience or from your experience as an MDS professional.

Dr. Maria de Leon: Thank you. And I to say something that I guess is relevant to this, why you would want to participate in trial, that I forgot to mention before when you asked me about why I'm excited about new medications. Because at times, we have unmet treatments for symptoms or gaps in treatment, like non-motor symptoms and things. So when we have new medications, you're hoping that you're going to be able to get some effect, or some treatment of those symptoms that we don't have a lot of control. That's one of the reasons too, to participate in a trial. There's some patients that just not been able to tolerate medications, have not being able to get the effect they would like to have, or have other comorbidities that have prevented interacting. And so that's one of the reasons that trials are important, and everybody can participate in trial.

And as you said, there's different phases. You can do phase one, phase two, and sometimes you don't even have to participate in trials that unnecessarily involve medications or new medications, you can participate in trials, like for instance, post-marketing and phase four trials, when a medication has been approved. And you're needing something different, and you like to try, but perhaps it's not available, or is too costly, or something, so then you can talk to your physicians about perhaps enrolling in some of these trials, and be able to have the benefit of knowing whether this medication worked for you without having to incur the cost necessarily. And also, perhaps for underserved communities it is good, because then you have the eyes on you, that perhaps you may not be able to have the access to care that you would, because now you have a team that is looking at you more regularly and seeing what is going on.

So that's one of the reasons that perhaps considering trial participation is something important, because not only are you helping yourself in many ways, having a physician look at you, providing the medications, new medications, but also improving the science. Because then a lot of times, when we do research before it becomes approved, there's a lot of strict criteria, and I know from personal experience, I'm not able to participate anymore in a lot of trials because the criteria is so strict and I have other comorbidities. So they're like, "Well, you're excluded." But then when it becomes available, people in the general population, like me, are going to take it anyway. So then you get information about what is going on and how these medications really affect other populations, or other comorbidities and things. So I think that that's one of the reasons to keep in mind, and we gain knowledge.

Bradford Casey: It really again, speaks to both the importance of people participating in trials, and then the many different types of trials that one can participate in throughout that approval process. So maybe we'll want to move on and think a little bit about how basically we support researching the biology of the disease, and of course, that's the starting point for all of these things. Brian, I know that you had spoken previously about the preclinical work that goes into developing a new therapeutic approach, maybe you could tell us a little bit about what it is that makes those good targets for diseases like Parkinson's.

Dr. Brian Fiske: It's an important question, and it's certainly one that you and I, and others on the team, spend a lot of our time thinking about how do we enable those, that biology, to get into the therapeutic pipeline in the first place. And I think there's a lot of factors that go into that. It's very certainly a complex science, but you're often looking at some very specific questions. Is the biology really related, for example, to Parkinson's disease? And there's a number of ways you can kind of explore that. Maybe there's genetic association between the biology and Parkinson's, meaning that there are genes that are altered in some way, and we know that they are then sort of cause Parkinson's disease in some individuals, so you can use that as a basis for some targets. Or maybe there's just evidence when you look in people with Parkinson's, that there is sort of evidence of altered biology, and again, you can then explore that biology a little bit more closely to see if there are targets within that biology that you could go after.

So there's a whole sort of body of... An important thing is here, is it's biology IN people with the disease that were the best model, if you will, of looking for these targets. So that's why genetics and other types of human-based studies are really important for initially finding these. Once you have it though, then there's a whole, again, we talked about this earlier, body of work that you have to start looking at to try to see, "okay, yes, this biology seems to be linked to people with Parkinson's, but is it actually something you can target therapeutically?" And there's some biology that probably just isn't really touchable, because maybe it's very fundamental to just living, and you really can't target it with a therapy, at least with current technologies. So there's a lot of questions you have to ask about the drug ability, if you will, of going after a particular biology that you think is linked.

So you start looking at that more closely. You'll look at laboratory models in different... Could be cell models taken, created from people with Parkinson's, or other types of laboratory models, where again, you're just trying to manipulate that biology, and you're seeing maybe does it protect dopamine cells in the brain if you do that, or maybe it actually causes those dopamine cells to die. So you want to look and try to really understand the directionality, for example, if you suppress the biology, or if you enhance it, what are the effects? So there's a lot of basic questions you start asking about it. That often requires tools, and so a lot of the work we often do to help enable this is to help work with the research community to identify what types of tools they need to actually go in and manipulate the biology and measure it, so that we can help them kind of build that database, that data set they need around the target to see if it's really potentially worth pursuing or not.

And really, just ultimately trying to work as best we can to, what we like to call, de-risk the biology. So is this, again, not only associated with Parkinson's, but is it actually sort of translatable? That's another word we often use, is can you translate the biology into the language of therapeutic development so it can actually be tested and developed as a therapeutic for Parkinson's, and move that forward. So there's a lot of work that we do around this from the tool development, working with researchers who are expert in that biology to see if they can manipulate it in the right types of model systems. And then ultimately, obviously working with companies who are interested in maybe pursuing that biology therapeutically, and helping them, and enabling them to explore those ideas, and hopefully move them forward in the pipeline.

Bradford Casey: Yeah, I think there's a lot there. Obviously, really critical to think about the complexity of that space. And maybe one aspect of that complexity is ensuring that the research that is completed is representative of people that might face Parkinson's. Dr. Isaacson, maybe you could tell us a little bit about the importance of ensuring that we do include everyone in research.

Dr. Stuart Isaacson: Well, it's really important, because we all want to find new treatments. But we all do it together, none of us can do it alone. It requires everyone working together to be part of the research effort, to see if something will work, and to get it known sooner. We don't know what causes Parkinson's for most people. We don't know what causes many of the symptoms, but we're learning lots of different targets to see what can help. And everyone may be same in some ways and different in other ways, and one drug may broadly help lots of people, or one drug may only help a few people. We know about genetic causes, for instance, in this ongoing research. So we have to really begin to look at each individual person, but the people can't all look alike. There's all different types of people, with different genetic makeups and ethnicities and colors and personalities and families, in different parts of the country and world.

And we really want to get therapies that work individually, in groups, in people, but also drugs that work broadly. And we want to know not only how they work, but also how safe they are in different populations. So there's been a big effort, and we've been part of trying to open research access to people across the land who can join this. One of the reasons why we've opened our research centers in

California and in New York, in addition to our Florida sites, to more broadly be able to reach people who might be interested in being part of solving the problem today, and trying new things now. Because not only are these medications often tested, as you described, against placebo, but after 12 weeks or six months, depending on the drug, usually there's a program that opens it up. Not always, but usually opens it up, and everyone gets to use the medicine until we find out how it works. And if it works, it's so-called open label.

So it's really a way to get access to a medicine today, that may give us the hope for tomorrow's solution. So really important that people consider this, but there's lots of barriers, and we work together trying to overcome those barriers.

Bradford Casey: Yeah. I think these are really important points, and again, kind of remind us all about how important it is to engage with our community as we think towards that research at the Fox Foundation, but more broadly, for patients that may be considering participating in some of those opportunities that might arise. So maybe we could go ahead and talk a little bit about one of those study opportunities, our Parkinson's Progression Markers Initiative. So we're mostly talking about treatments in clinical trials today, but there's really some critical research that's happening in the observational trial space as well, and this is one of them. Our study, again, what we consider the PPMI study, is actually recruiting volunteers again, including people from all backgrounds with and without Parkinson's, all able to really participate and to help move this research forward.

So I think that I would just be disappointed if I've missed the opportunity to share a little bit about that. I'd encourage people to look into the study. Brian was talking earlier about the importance of looking at all of these different data sets as we think towards identifying new therapeutics, and then moving them towards clinical programs. And programs like the PPMI, Parkinson's Progression Markers Initiative, are really a critical piece of that as we build out that data, make that data available to the research community, and it's a great opportunity for people to get involved.

So again, I think maybe we'll move on and just talk a little bit about that, that robust research pipeline that we've discussed a little bit about. Brian, maybe I'll turn this back to you. Can you tell us a little bit about the research pipeline, what that means to us, and then a little bit about how it's changed over time at the Fox Foundation?

Dr. Brian Fiske: Yeah, yeah. And I know I touched on some of this earlier too. I think for us, when we look at it today, again, when we talk about 150-plus treatments, we're really talking about these are treatments that are actually being tested in people today. This isn't just stuff that's in the laboratory, on a laboratory bench being looked at. So it's really exciting that we have such a robust, I think, pipeline, that's focused on Parkinson's. And it's, again, represents a range of ideas, and you can see that half or so, or a little bit more actually, are focused on this idea of disease progression, meaning that these are treatments that are targeting biology, that we think might actually be able to slow the disease process down, versus

treatments that are focused on more symptom management and symptom reduction, which are obviously still critical pieces, but we want to see this mix.

We'd like to see this mix in the pipeline, that we're have a good diverse portfolio, if you want to use the investor terminology here. And this is really something only in the last few years, that I think that we've really seen an I emergence of. Before, it really was very sort of focused predominantly a little bit more on the symptom side, which again, was important. We were seeing a lot of innovation still happening there, including increased focuses on non-motor features, and things like that. But for us, I think it really this emergence of the biology-directed therapies that are focused on progression, and they really represent a whole range of different ideas people have. Some of them are driven by some of the genetic understanding we have of the disease, so there are a handful of biologies that have come out through the genetic studies, that a number of the therapies in clinical testing right now are trying to target.

You may hear us often talk about the protein alpha-synuclein, so there are a number of therapies that are directed against that sort of pathological protein, looking at ways to try to reduce and get rid of that pathological clumping of that protein in the brain, which we think might be relevant. But there are other treatments that are targeting other aspects of biology, again, driven by these laboratory findings, to try to see if altering those can be important too. And so again, it represents, I think, a real range, and a lot of that, again, really have come about really in the last 10 years or so, advances into clinic, as companies start figuring out ways that they can actually target that biology and test it.

So we see, looking forward, continued, I think, progress here. Every few months, we see entry of a new company that has a therapeutic against some of the biology, moving into clinical testing. And it's a risky pipeline, there's a lot of barriers, obviously, to get these things effectively tested. And we'd love biomarkers, for example, and maybe we'll talk about that more in a moment. But I think for us, it's just, again, a continued excitement to see this continued push towards really maintaining this robust, healthy, and diverse, I think, pipeline of therapies being tested for Parkinson's.

Bradford Casey: Yeah, that's great. Obviously, it takes a lot of different perspectives to make sure that this work is reflected. Dr. de Leon, I know that advocacy has been a huge piece of your work with our patient council, but also with the Parkinson's community more broadly. Could you tell us a little bit about how you've advocated, both for the community and for yourself, to get some of these concerns addressed by researchers?

Dr. Maria de Leon: Yeah, I've been very privileged to work with The Michael J. Fox Patient Council, which has allowed me to really build on this platform of advocacy and be able to work with different stakeholders, from pharmaceutical companies to clinicians, scientists, the government, to try to advance the science to discover at both ends, one, how can we prevent, how we diagnose earlier, the disease? What are the markers? Are there biological markers that we can count on, say specifically, somebody's going to develop Parkinson's 100%, and then we can develop preventive measures, or start early treatments. Because I do believe that early

treatment and early diagnosis really does make a huge impact in the quality of life and the development and progression of disease. Of course, then we also wanted to work on the other end, finding a cure and finding better treatments for late-stage disease, which is a big still unmet need. There's still a lot of problems in that arena.

But I've been privileged enough to work with the [inaudible 00:38:40] PD to try, again, to discover what are the symptoms clinically, or what are the markers so that we can diagnose, or be more confident in saying somebody will develop Parkinson's versus Parkinsonism or something else. And also working with Michael J. Fox and other, the Department of Defense and NIH, in assigning grants and funding basic science research, it's also clinical research that would help target those unmet needs, target those areas where we know there's really very few treatments, or very few answers, and we haven't really come up with different ideas of why this happens, like sleep, for one, or autonomic dysfunction. And so we're trying to work on that.

And then with the clinicians, again, trying to make sure that we recruit the right people, that we have more people researching, participating from different backgrounds, different ethnicities. Somebody say comorbidities, meaning that they have other diseases, like blood pressure, diabetes, other things that we know are going to be part of the community, but we sometimes are excluded from basic research because we don't want to throw in a variable in the disease when we're studying a drug. So we try to make it as clean as possible, just Parkinson's or nothing else.

So that's what I've been doing, and trying to advocate also changing the policies so that more people have access to care and to medications. Because we have so many new medicines, but it doesn't do us any good if nobody's able to take it or afford them. So trying to be able to have this access is what my advocacy has been for in the last 20 years, trying to really have a holistic view of the person, as a patient, as a clinician, trying to find those target areas where we really need to work on, so that everybody can have a better life, better quality, and we can have more choices as doctors also. That's it in a nutshell.

Bradford Casey: I think that's wonderful, and thank you so much for all that you've done in those advocacy forums on behalf of our patient community. Brian, maybe we could talk a little bit about the business side of science for a second. Obviously, clinical trials are very expensive, and pharmaceutical companies are by nature risk-averse. Dr, how are treatments really supported at this step, and how might we support them as we move things through that pipeline?

Dr. Brian Fiske: Yeah, it's a tough business to be in the business of, I think, drug development. So there's obviously the scientific risk, which we've talked about. Just at the end of the day, these are hypotheses that people are testing. So like any laboratory experiment, whether you're doing it in the lab or doing it in a clinical trial, there's the risk that the outcome's going to be negative, that you're not going to see the effect that you want to see. And that's actually good science process. That's actually how science should work. We shouldn't go into these experiments assuming an outcome, we should actually be looking for the data to tell us what

the outcome is. But because of that, it makes it a risky business certainly to invest money into, so a lot of companies, it really depends on what stage they're in, who they are, are they a small company, are they a large company with multiple programs, where they can draw from different sort of funding sources?

So it can be very patchwork, I think, for companies too, that think about where they get their money. So some companies will do a combination of getting philanthropic funding. For example, we're a major philanthropic funder of drug development for Parkinson's. We have a lot of companies that have come to us for help, especially when they're early in the process and they're just trying to still figure out whether the idea has any sort of therapeutic legs or not. Or they're looking for more long-term investors, so people are actually investing in not just the program, but maybe also the company itself, helping to make the company succeed. So it's a whole range of different places that companies can get money from, and it's again, it can be a very fickle business. So right now, the investor community is very risk-averse when it comes to CNS disorders, because again, there's not a lot of clarity sometimes on the path forward for some of these therapies. There's not a lot of good biomarkers necessarily, for moving Parkinson's trials forward.

So for some investors, that's a very risky business to get into. A lot, of course, of what we do is try to convince them that there is real opportunity. So not only in the science, how can we de-risk the science a little bit, make the science more clearly linked to Parkinson's, or more viable? But also all the work we do around biomarker development to show them that we actually do have some tools. We actually do have some ways we think we can assess the biology in Parkinson's that can actually maybe help support clinical trials. Even the work we do to help identify people and volunteers to be in trials, to show that it is feasible to actually do these types of trials in people with Parkinson's, even if they might be sort of selected people maybe carrying certain genetic differences, or forms of the disease, we can help support and enable these companies. And again, kind of make the whole path feel a little bit less risky, and hopefully then help increase interest among investors who can step in and provide the significant resources to move things forward.

Bradford Casey: Yeah, thanks. Dr. Isaacson, obviously we're talking a lot about what it looks like to participate in these trials and what they mean. Could you tell us a little bit about how someone volunteers to participate in research trials? And importantly, maybe also why it is that some people might be eligible and others might not be eligible for specific studies?

Dr. Stuart Isaacson: Yeah. Well, it's a big challenge. I think there's been estimates that each individual research program, especially when I gets to phase three, needs about 300 people in the country to volunteer. And once they volunteer, we would, six months later, have an answer for each person. And when everyone volunteers, we can get the answer and maybe the drug can go forward. If it takes three years for 300 people to volunteer, well, that's two years longer than if it takes one year for 300 people to volunteer. So I think we're all in this together trying to understand who can volunteer. So really, volunteering just means, well, I'm going to sign a permission slip to participate, and I'm going to answer some questions and have a

blood test and a urine test and EKG. Maybe they check spinal fluid or do a brain scan. And if I pass muster, meaning everything looks like it's within the range of normal, so I'm not at a high risk of having a side effect.

That's really where the exclusion comes in. We want to exclude people who might have a side effect from this particular therapy that's being tested based on what we've learned already in prior studies, or in some of the pre-human work. And if someone qualifies, then we have to see, well, are the symptoms the right symptoms? Are they occurring to the significant enough severity to see a difference between people who might take a therapy or might take a placebo? And that would be the inclusion criteria. And if you meet all the criteria and you qualify, then you'll be asked to come in and do some of the testing, and tapping the fingers, and walking, and these types of tests that we do. Sometimes there's wearables that we use. Sometimes we confirm a diagnosis of Parkinson's with that scan, brain imaging or skin biopsies, or the seed assay. And then you get the medication, get it right there at the clinical. And you take them, and you come back, and we see how you're doing.

So it's not very different than being prescribed a medication at a clinic visit, then agreeing to taking it and go into the pharmacy to get it, and then taking it and seeing if it works, and what dose, but it's done in a more regimented recipe-like way. So I think it's important for people to consider is this something they're interested in, and then to put their foot in the water, and then see. Until you actually get the medicine, you can always change your mind and drop out. And when you get the medicine, you can still change your mind and drop out, so no one's committed. So I think trying is probably better than fearing something that's an unknown, because many people who are part of these trials enjoy them, like to be involved, and learn a lot about not only what's being studied, but also about their own symptoms, because some of the questions are insightful and can make people think about things.

So we always try to encourage people to think about being involved. And not only themselves, but people they know in the community, for helping volunteers and other family members perhaps who might want to be involved.

Bradford Casey: Thanks very much. I think these are critical points, and it's obviously something that people should really think about. A lot of different ways to get involved. Dr. Isaacson, maybe I'll direct one of the first questions to you. So we're getting a lot of questions about inflammation, the potential role of inflammation in Parkinson's disease. Could you tell us a little bit about what's known about the potential role for inflammation?

Dr. Stuart Isaacson: Well, as we've heard, it's a complex problem, Parkinson's. It's not how we used to think about it as just being a problem in the dopamine cells in the brain. And if we could just understand and fix that, we'd be moving forward. But it involves the entire nervous system, not just the brain and dopamine, but serotonin and norepinephrine, and you can see the choline and so many neurochemicals and neurotransmitters, not just the brain and the brainstem, but the autonomic nervous system and the enteric nervous system, and the gut. And we even have a skin biopsy that looks at the nerves, the sensorimotor nerves in the skin, we can

see markers of degeneration, the synuclein protein. So it's very complex, and we don't know what makes some of these cells not function so well. What role things like synuclein and oxidative stress and inflammation play in the role? Is this something that's a marker of damage, or something involved in causing damage, or something that's involved in starting damage, or just a bystander that we see when we look at things later?

We don't know. We're working hard, it's why it's called research, because we research and research again, and search again, and research again, to try to understand how all these components, and inflammation is one of those components. And there seems to be some evidence that it's involved in the Parkinson's process, both from some of the genetic work and genes that have been involved, as well as some of the markers in the bloodstream, as far as how we think about the gut and synuclein, and different things. We don't know precisely what role, and there's a lot of targeting, trying to reduce inflammation, neuro-inflammation. There's ongoing research programs looking at this in different ways, at different parts of the inflammatory pathways. And hopefully, as we learn more, and some of these medications hopefully show some signal, we'll be able to refine them and move forward to try to understand better how we can interrupt Parkinson's degeneration, stop it, and then try to reverse it.

Bradford Casey: Yeah, these are all critical pieces of the puzzle, obviously. One thing that I think about a lot as one of the foundation scientists, is how we can get to those answers. And I've seen a number of questions come through about AI and its potential power, in terms of getting to those answers, and I think that that's really where these approaches can be really valuable. As you mentioned, there are many things that need to be looked at, and many variables at once, and so this is an area where we have actually partnered with experts in AI, artificial intelligence and machine learning approaches, another computational approach, to try to really dig into the big data sets that have been generated, both within the Fox Foundation studies and then across the Parkinson's research field. We're very hopeful that that type of approach can touch on a couple different things.

One, is in understanding how these different symptoms, or different features of disease, might come together to tell us more about the mechanisms that Brian mentioned previously. But in addition to that, we're hoping that some of these approaches might be valuable in discovering new potential therapeutics, and so we continue to partner with experts in this area to try to understand that a little bit better.

So the next one, maybe I'll send over to Brian. Brian, I know that we've been following the Exenatide study for a while, maybe you could tell us a little bit about that study, what the recent results that we've seen mean for Parkinson's disease applications.

Dr. Brian Fiske: So maybe I'll back up, and just for people who maybe don't know what Exenatide is. So Exenatide is a type of drug that targets a biology called GLP-1. People might think of this biology more in its probably better known, more famous or infamous form of the weight loss drugs. So like Wegovy and others that are out there, Ozempic, that are focused on the same biology for weight loss. Originally

for diabetes actually, and then later for weight loss. So why it's been looked at for Parkinson's, I think, is based on a lot of earlier, over the last probably 10, maybe almost 20 years of initially preclinical research, exploring whether targeting this mechanism might have some benefit in Parkinson's. And there's been some data that suggests that it might, again, in preclinical research. And so about 10 years or so ago, investigators started looking initially at Exenatide, which was one type of approved drug that targets this mechanism, to see if it might pull some benefit in people with Parkinson's.

And some of those early trial results suggested there might be some effects in possibly slowing the disease down. Some other groups have looked at a few different types of GLP-1 drugs. So there's a drug called Liraglutide and Lixisenatide, they all had sort of slightly similar but different sounding names, but kind of all target the same biology. And so there'd been this growing body of research that suggests that there might be some potential signals there. Most recently, was a large phase three trial, so again, this would be a large trial in a larger number of people that was run in the UK, looking again at Exenatide to see if given over a long period of time, this was over a several-year period, would you be able to replicate and see the same effects that were seen in the earlier trials. Unfortunately, that trial read out recently and did not see any effect of the drug on really any measure that the investigators used in that particular trial to see if there was benefits.

So it's early days to sort of interpret what that means. And I know the investigators, and many in the community, are continuing to look the data and try to understand is there a signal? Why would we see signal earlier and not see a signal now? So there's a lot of, I think, still open questions about how to interpret the results. I think importantly though, and this is something I've spent a bit of time over the last couple of years diving into this literature, there's a lot of effects these drugs might have. They're actually really hard to test in clinical trials, largely because... We talked about controlling trials, for example, earlier, and needing to have sort of a group that isn't on the drug. But usually, when you do that, you do that in a blinded fashion. You don't want people who know what drug, if they're on the drug or not, because you want to be able to truly understand the effects of the drug, sort of unbiased by any perceptions people have about whether they're on the drug or not.

Unfortunately, for these drugs, because they do things like cause weight loss, among a variety of other effects, it's really, really hard to do that type of blinded study. You can try to design it that way, but it's really hard to do. So there could be a lot of effects that these drugs might be having that, just frankly, are hard to sort of control in clinical trials, and could explain earlier results, could even explain maybe the lack of results in the latest trial. So it's a really complex drug, I think, to try to test for Parkinson's. And I think what we're seeing you can interpret, at least how I'm interpreting these recent results, is really a reflection of the complexity of testing that hypothesis in Parkinson's.

Does that mean these drugs have no path forward? Uncertain, I think there's still a lot of analysis to do on the existing data, and actually, we're starting to talk with different groups about the different types of analyses that might be helpful to

guide the field, those next steps. But I think we'll just have to really dig into the data to really understand. But as of now, it's clear that Exenatide, given to a large number of people over several years, did not show any benefits in those individuals. And that's kind of the data as we have them today, and so we have to kind of, I think, interpret that in the context of our understanding of this particular biology.

Dr. Stuart Isaacson: It's interesting what you say too, because the data that's accumulated is really a win. So even though the study didn't show what we wanted to show, boy, we learned so much from any study. And people who participate in these studies should feel so encouraged and hopeful that we just learned so much just looking at what happens in the body, the safety, and any other markers we might see. And in the blood, and then spinal fluid that saved, that we can come back and look at biomarkers that we're going to learn through PPMI, because all these programs really, really work together. So really, we learned so much from observational programs, from studies, just because we picked the wrong way of looking at it, the wrong glasses, the wrong test, the drug may have worked, or may not have worked, we just couldn't prove it. But we learn a lot, so I think people should really feel very happy that when a study is completed and we find something safe, we know there may be something there we can adjust or change, or come back and research it again.

Dr. Brian Fiske: Yeah, no, I 100% agree. And it can obviously feel disappointing and frustrating in the moment, but every outcome is a, like you said, is a win because it tells us something additional about how to target and treat this disease.

Bradford Casey: Yeah, thanks both. I think, again, very important to keep in mind that even a failed trial, so to speak, can still be a win for the scientific research that it supports. I just want to take a moment to thank everyone for joining us, especially our panelists here today. But really thank you everyone for being part of our community and for taking the time to join us for today's webinar. We really hope that you found today's discussion helpful. I have found it very interesting, but want to just take another moment to say thank you very much and have a great day.

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