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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: Good afternoon, good morning, good evening, whenever and wherever you are joining us from. Thank you so much for being with us. I'm Maggie Kuhl, the Vice President of Research Engagement at The Michael J. Fox Foundation. I'll be your moderator for today's webinar, a year like no other in Parkinson's research. Our 2023 in review. With me today are three colleagues. Sohini Chowdhury is our chief program officer. Thanks for being here with me Sohini. And our co-chief scientific officer is Mark Frasier and Brian Fiske. As always, Mark, Brian, nice to chat with you as well.

So today we are going to first introduce our patient-centered strategy. So The Michael J. Fox Foundation was founded by a patient. We are a patient-centered organization. Really what we wanted to start off with was our commitment to centering people with Parkinson's at the heart of everything that we do. We learn about Parkinson's disease, the biology, the clinical experience, and that directs our strategy toward better trials, better treatments, and better care.

So today we're going to share across the spectrum, things that the foundation staff are talking about, places where our donor-raised dollars are investing, and helping improve quality of life, cure disease, and perhaps prevent the Parkinson's process from ever starting. So with that, we are going to cover so much today. There is so much progress that has happened in the last year. We are going to keep things at a little bit of a surface level, but we have included a lot of links in the resource list and in the slides, which you can download in the resource list.

So, if you would like to learn more about a specific topic, you can click through and read or watch another webinar even on your own time. Or, if we get to the Q&A section and you haven't heard enough about something, please bring it up at that point. So with that, why don't we move into our first topic? We would be remiss to start any Parkinson's research year in review without talking about the biomarker breakthrough. There are a number of very deep dives. We did a previous webinar, we've done a whole newsletter on this. And so, we wanted to just give a little bit of background. Mark, why don't you remind us what is the alpha-synuclein seeding amplification assay and why is it so important for research?

Mark Frasier: Sure. Thanks, Maggie, and thanks for having me today. This alpha-synuclein seeding amplification assay, or SAA for short is a relatively new biomarker and

the foundation has been supporting efforts in biomarkers really for decades since we started in the early 2000s. And the reason we think this is so important is to have a more objective marker of diagnosis that can help doctors or neurologists in the diagnosis of the disease and particularly early in the course of disease, when the symptoms may be very slight. And until recently, this sticky protein alpha-synuclein, we've known for many, many years that it accumulates in the brains of people with Parkinson's disease. And there was really no way to measure alpha-synuclein until someone passes away and a pathologist looks at the brain under the microscope. But that has all changed recently and the development of a laboratory test. And this test actually was funded by the foundation, started in the university and now has been spun out into a company.

And this laboratory test is called the alpha-synuclein seed amplification assay. And very simply what happens is that we take a drop of spinal fluid, put it into a test tube with normal alpha-synuclein. And in people with Parkinson's disease, this normal synuclein seems to seed amplification of clumped synuclein. And this clumped synuclein after shaking for a day or two can be visualized in using a fluorescence reader. And so this laboratory test is really exciting because about 90, maybe sometimes 93% of people with Parkinson's test positive for this seed amplification assay. So it's really the first time where we have a pretty accurate objective laboratory test that can assist with the diagnosis of Parkinson's and detect this synuclein in a living human person.

Maggie Kuhl: It really is a groundbreaking discovery enabled by the contributions of many volunteers. So thank you so much if you've participated in one of the studies that have led to the discovery of this biomarker test. Thank you as well to the future volunteers who are going to help us improve it because there is still much work to do in making this test more accessible and more useful for trials. And so there are some projects already in place even well before this biomarker was announced in April of 2023. Our foundation was focused on improving its utility. And so, Sohini, maybe you can push us through to a couple of these next steps in this biomarker development.

Sohini Chowdhury: Happy to and hi everyone, really pleased to join you today. I guess there's sort of two levels of activities in terms of really bringing this breakthrough to the next level. The first level of activity is really focused on the technology around this. As Mark mentioned, this test at the moment is run on cerebral spinal fluid, which is collected through a lumbar puncture. And that is not the easiest procedure to go through. It's a very informative procedure, but certainly it limits the ability to be able to really use this test on a wide spectrum of individuals. And so, one of the things that we're really focused on is on transforming this particular test into something that's more accessible like a blood test or given the post-COVID world we live in perhaps even a nasal swab. So there's a lot of work that's going on to try to translate this test from being run on cerebral spinal fluid into something that's more accessible and easier for individuals to undergo.

A second technical component that we're looking at in terms of optimizing this particular test and improving it is really focused on making this test a quantifiable test. So at the moment as Mark illustrated, this test tells you whether you do or do not have that alpha-synuclein protein clumping of interest. What it doesn't tell you is do you have a lot of it, do you have very little of it? Is it changing over time, et cetera. And so the second sort of technical kind of work that we're really focused on is to try to make this less of a yes/no test and more of a test which could give us a sense of the spectrum of clumping that is happening and kind of correlate that spectrum of clumping to what an individual is experiencing with the disease. And so those are kind of the two main buckets of activities that are focused on improving this test on a technical arena.

But there's more that's happening, and this is really about ensuring that we're leveraging this test to its fullest when it comes to Parkinson's R&D and particularly Parkinson's therapeutic development. And as Mark mentioned, alpha-synuclein is a hallmark of the disease. It's the pathological hallmark of the disease. And so one way we're really focused on leveraging this breakthrough is really driving home the fact that this test should now be utilized in all clinical trials. Why? Because, well if you're really looking to test your therapeutic in a Parkinson's population, then you should make sure that that is the population that you have enrolled in your clinical trial. And the way to do that is to say, are the individuals enrolled? Do they have this pathological hallmark of alpha-synuclein? And now we're able to test that through this SAA test. So we're really focused on making sure that as many trials as possible where it is applicable, that they're utilizing this test to make sure that they really have the right people enrolled in the study so they can get the right sense of whether this drug or this therapy is really having the intended impact.

The second way that we're really looking to kind of expand how we can utilize this test is that there have been some very interesting data that has come out of the development of this test, that has shown that this test not only can detect alpha-synuclein in individuals with Parkinson's compared to those who don't, but interestingly, it's able to detect the presence of synuclein in individuals who do not yet have symptoms of the disease. So it may be a way of being able to identify people before symptoms start. And what that has allowed us to start to do is kind of begin to define Parkinson's disease, not just based on the symptoms that an individual may have. Do they have tremor? Do they have bradykinesia? Do they have gait or balance issues? But to actually define the disease based on do you have this biological hallmark?

Do you have other aspects of the biology such as dopamine degeneration, et cetera? And the reason why this is so exciting is that it helps drug development makers be able to kind of understand what they need to target. Can they target a reduction of alpha-synuclein? Can they prevent having synuclein and then go on to develop dopamine degeneration? Can they intervene so they stop that? And staging allows you to kind of have a framework by which you can orient

your therapeutic development programs. And so that's really exciting. The last component is that Mark mentioned that about 93% of Parkinson's patients test positive on this test. That means that 7% don't, and that what we have also found out is that depending on a genetic mutation, you may actually have a higher chance of not being SAA-positive, not being positive for this test. That begs the question of what else is going on?

And so this starts to open up avenues for us to really understand what are the different biological processes that are under this umbrella of Parkinson's disease. And this is so exciting because for the first time it really allows us to think about how do we get to a precision medicine approach for Parkinson's disease? How do we look at an individual and not say, "Oh, well tremors back today, or this is the symptoms this individual has," but actually say, "This is what's biologically going on in this person and this therapy is targeting that biological process." So it allows us to really make sure that we're thinking about the right therapy for the right individual at the right time. And that matters. That's how you really make sure that a therapy is having the greatest impact for an individual.

Maggie Kuhl: You stole my transition. I had just written down right therapy, right person, right time. That's something that we say a lot at Fox, but it's true and it's what we're going after. And to build on what you said as well, Sohini, what I heard too was we are running as far and as fast as we can because we know patients are waiting, but we are also looking for the next improvement that's going to allow us to go even farther and even faster. And as you said, there's a lot of complex biology at play in Parkinson's. There may be people who alpha-synuclein doesn't resonate.

There are things that are working together and if the more that we can measure and understand the better position we're going to be in. And so this alpha-synuclein SAA test is not the only biomarker that we are looking for by any means. And Mark, I wanted to perhaps toss you to give just to highlight these three are again, by no means what we are looking at exclusively, but perhaps some of the things that people have heard about. So what's new with other biomarkers? What are we talking about at the foundation?

Mark Frasier: Yeah, I think this is just the beginning, Maggie, and you'll see a number of breakthroughs over the course of the next year or so. Already we've seen some progress in an area to try to visualize and see the clumped alpha-synuclein in the brains of people with Parkinson's. And we've been funding this work for over a decade to try to develop neuroimaging approaches to really see a snapshot of synuclein in the brain. And this picture on the left is just one example of a study that was recently reported where they could see alpha-synuclein in the brains of people not with Parkinson's, but Parkinsonism called multiple systems atrophy. But we're really excited. There are multiple groups working on this and we expect a number of different neuroimaging approaches to be tested in humans in the next year. So we're seeing a lot of progress and

that will only just compliment the work of the SAA, because the SA work, that laboratory test really doesn't tell you where alpha-synuclein is in the brain.

And having these pictures really can show you the real estate. And then with a therapy show you if you can reduce the alpha-synuclein using these neuroimaging techniques. But as you both mentioned, there's a number of other biological pathways that we know are affected in Parkinson's. It's not just accumulation of alpha-synuclein in the brains of people with Parkinson's. So there's things like cell biology processes like lysosomal processes, which we like to call the garbage disposal for the cells. And we know mitochondria in the cell, which is like the powerhouse, the batteries of the cell, those are affected in Parkinson's. And what's exciting is that there are now tools being developed to measure lysosomal activity or mitochondrial dysfunction in people living with Parkinson's. So we think there will be a number of different biologic markers that will be able to characterize this unique biology that's happening in individuals with Parkinson's, and ultimately target individuals with those precision medicine approaches that are targeting and going after the biology that is occurring in the individuals.

Maggie Kuhl: And I want to call out too, that it's not just for overall progression. Some of these markers are tied to the type of Parkinson's that you have if you will go on to develop cognitive changes or if you'll progress at a faster or slower rate. And so back to Sohini's comment about right therapy, right person, right time. And so some of this work extends not only to slowing or stopping disease, but for people who have been living with PD for a while and giving them the best options to manage their disease. Which brings us to a question that we get very often, which a lot of you sent in during your registration, which is what is coming to market soon? What should I know about? So the good news is that there are a lot, so Brian, maybe I'll toss to you to give an overview of what might be on shelves in the next few years.

Brian Fiske: Sure. So we talked at the beginning when you introduced the topic today about the different stages of Parkinson's disease from the early risk to the early stages to the advancing disease. And I think what's exciting is what we're seeing really in the later stage pipeline and actually what's some of these cases actually being up for FDA approval are treatments that we think can really help those people at the later stages of disease where you're dealing with some of the complications of the existing medications and trying to increase your quality of life throughout the day. And so there's a number of approaches here. A lot of these focus on kind of a common theme that we've obviously had for many years in Parkinson's around the impact of giving people back dopamine into their brain, which is the loss of dopamine cells in the brains that people with Parkinson's is what really drives at least the movement problems that people suffer.

And so these approaches are really a sort of novel twist on how we can bring that dopamine into the brain and sort of more optimal ways and ways that

maybe you can reduce some of the complications that can come with these types of treatments. And so a few of these groups, so AbbVie has an approach, ABV-951. A lot of these are named by numbers right now until they come up with the incomprehensible brand names that we'll hear about later. But for now, a ABV-951, Indio-612, these are two approaches that are looking to deliver dopamine medications through a pump delivery. So something that would be worn on the belt and sort of infused through the skin basically to try to deliver these dopamine medicine in a kind of more continuous way throughout the day. And some of the trial results have looked good. These usually help people, they increase the amount of good on time they have throughout the day reduce some of the bad off time people might struggle with. So just to get better ways to improve and improve those treatments.

Mark Frasier: A lot of these approaches are engineering approaches. So they're repurposing existing approved drugs, but engineering them in a way that makes the delivery more efficient or quicker and reduces side effects. And it's been remarkable to me to see the evolution of this field, because I would say 15 years ago you talked to people in drug development and they really thought that delivery wasn't an issue and having Sinemet and levodopa was available, it was generic and there really wasn't an unmet need. And I think it was through efforts of the foundation and others to really advocate and educate drug developers that there are significant side effects and issues with some of the existing dopamine approaches. And seeing these engineering approaches that are delivering it in a better way to reduce side effects and improve the symptoms more effectively is really exciting. And it's not just one or two, but you can see it's a number of different approaches. So I think it's a testament to the education that the field has really had around the needs of people living with Parkinson's disease and their both motor symptoms and non-motor symptoms.

Maggie Kuhl: Which you on this call today I'm sure need no introduction to. So as Mark said, the education and really coming from the patient need, as we were saying at the top, listening to what matters to people with PD and responding our strategy. Sohini, for you, it's great that new drugs are coming to the market. How do people with Parkinson's disease make sure that their doctors are aware of these new treatments so that they can have them and have access to them? What is that link between approval, your doctor can actually prescribe it, they're aware?

Sohini Chowdhury: Yeah, so it is actually more complicated than just getting FDA approval. And then while I won't go into all of the steps, I think one of the biggest things, and all of you who are listening to this webinar right now can attest to this firsthand, is it's really critical to be able to understand the reimbursement component of new therapies because that often plays a very strong factor into how doctors think about the therapies that they're prescribing for the patients that they're interacting with. And so, we have a policy team and many of you are advocates for our policy team and for our policy priorities. So you're familiar with it. But one of the big things that we do is that as we see that drugs are in late stage

clinical development, that therapies are nearing that stage of FDA approval is we reach out and we try to understand what is going on with the reimbursement process. Are there attempts being made? What is the state of it, et cetera.

Sometimes there's a lag and that's kind of just the nature of all of the steps involved. Sometimes it's set up beautifully so that once there's FDA approval and it's actually being marketed and it's available, reimbursements are already covered. But I think the most important thing is to have a frank conversation with your doctor. Many of you probably see movement disorder specialists who are at the forefront of really knowing about a lot of these new drug developments and often they're running some of the trials that are testing the efficacy of these therapies, so they're very familiar. But many of you may not be seeing movement disorder specialists and your doctors may not be as familiar with some of these new therapies that are coming out.

And so I think you have a role to play in also being an advocate as you hear about this and asking your doctor to find out more, to read the literature, to direct them perhaps to information that maybe we even have on our website or others may have, so that you can really have a proper conversation about which of these potentially new therapies may be the right therapy for you to try out.

Maggie Kuhl: Absolutely. Be an informed consumer of information, which attending this webinar is a great step toward that. So I think Mark, perhaps it was you who mentioned that people with Parkinson's experience a lot of limitations with current therapies and also a lot of unmet needs, especially around non-motor symptoms. So wanted to turn to what is happening in other therapies that are perhaps a little less close to market but still moving through the pipeline and development because again, we know that these are the priorities of the Parkinson's community. So Brian, maybe you can kick us off. We had a really, really exciting stem cell trial report earlier this year that you and I did a podcast on, which is linked in the PowerPoint slides there that you can download from the resource list if you want. But why don't you recap that conversation. What was the news that we shared?

Brian Fiske: Sure. No, and it's exciting. I mean, I think the idea of stem cells have been around for probably a couple of decades now, and it's always been a lot of, I think excitement and maybe even a little bit of hype around them. But I think that the recent news was great because this was a company Blue Rock Therapeutics, they've developed a stem cell replacement therapy. And so I use that word specifically, I think when we talk about stem cells. Sometimes it can get confusing, there's stem cell approaches that are trying to provide protective factors and we'll talk about maybe another one in a moment. Then there are stem cell approaches that are trying to actually create new dopamine cells that can be transplanted back into the brains of people with Parkinson's. And so in this case we're talking about Blue Rock is developing a stem cell replacement therapy.

And what they did, it was an early phase one study, so it was only in a handful of people, but it was really one of, I think the first times we've seen a true stem cell-derived dopamine transplant approach tested in Parkinson's disease and in a good sort of well-done study. And they did it over about a year period and a handful of people. And I think the good news is it was safe, so that was of course question number one they wanted to ask and make sure that they're delivering these types of approaches into the brain. They're transplanted through a brain surgery approach, were going to be safe. But they also did some imaging just to see if the cells were still present and so there could be any evidence that the cells were there and doing what presumably dopamine cells should be doing in the brain and the data are looking good.

It looks like the cells are there and that they're actually functioning as they should. So, so far so good. It was good certainly news for the company and for us to hear the outcomes of this and companies now working on plans for the next larger trial to start testing this forward. And I think it's just good news for the field because I think there are other approaches that are approaching the clinic as well that are also going to be delivering different types of stem cell replacement approaches. And I think this is always good news when the first companies step into this space and try it out and get some of the initial data, it really kind of opens the flood gates for others to move into this space. So my guess is we're going to see more companies and more approaches like this moving to the clinic.

To be clear, this isn't a cure necessarily for the disease. So the idea of what these treatments in their current form are doing is just putting some dopamine cells back into the brain. You still have to take your dopamine pills for the most part, at least most people probably will, and that'll be converted into dopamine in the brain. And what these cells are doing is just giving you more of that sort of a dopamine factory factory back in the brain so that you can make a more dopamine and hopefully get the benefits on your movement symptoms. But it's not a cure in the sense that we're not stopping the disease process.

We're not somehow changing the underlying Parkinson's disease itself, but if we can get people back a little bit of what they've lost, I think that'll be really important, especially again, as we talked about at the start of the call today for people especially in the more advancing stages of disease, when the maybe traditional types of protective treatments may not necessarily be as beneficial because the disease has already progressed to a certain point, these types of approaches then become even more important to offer to people.

Maggie Kuhl: Yes, I think the words restore function, people are really happy to hear those I'm sure. Move on down to walking and balance issues. We know that this is an unmet need and a lot of the available therapies, even though you think of them as movement symptoms, don't actually do as well with walking and balance problems, which are very challenging for independence and socialization and confidence in moving through our world. So we launched a funding program

earlier this year focused specifically on better understanding the mechanisms and measuring mechanisms behind and measurement and treatment of walking and balance issues. And we had more than 100 applications, which was extremely promising. We're already funding some very exciting work around this. Sohini, tell me why do you think there was such a big response? I think 100 plus applications for a sort of narrow focus RFA or request for applications for funding is pretty high.

Sohini Chowdhury: Yeah, it is. And I think it's also exciting to see because I think if you were to ask people living with Parkinson's or those around them, freezing of gait issues or balance dysfunction issues, everyone's going to experience it usually towards the later having had the disease for a longer period of time, but not exclusively. And certainly the worries that come about as you articulated when you're worried about being able to move with confidence and to have that sense of security that you can move about that is limiting if you don't have that. And so I think what's especially exciting about the response to this particular funding program is that there's a recognition in the scientific community about what a huge unmet need this is for patients. And I think that is very, very exciting because there is a lot that can be done in this area.

There's a lot in terms of understanding the basic biology and pathophysiology that underpins this. It's not about dopamine. Otherwise, the medications we have would be helping this is about something else and what is it, and trying to get an understanding of that. But importantly, what can we do to try to address it both in terms of pharmacological approaches, taking medicine or non-pharmacological approaches. Innovative technologies that may help address some of the gate imbalance issues. And so seeing the response we got, it was rewarding and it was exciting because it's recognition by the scientific community that this is a huge unmet need and there's a lot that still needs to be done.

Mark Frasier: I agree. And I would just add, I think it's a reflection of where the science is and our understanding of what causes these gait and balance issues. And there's been a lot of progress and understanding the brain and the areas that control walking and gait and balance. So I think the field has progressed and that's why we're seeing a lot more research in this area.

Sohini Chowdhury: And I think that's a great segue, if I may, Maggie, what Mark just said. You've mentioned here about spinal stimulation and as we've actually learned more about the science around this, we've actually been able to leverage advances made in other fields and see whether that can be applied to Parkinson's. And this spinal stimulation project that's listed on this screen is a great example of that, where a team has actually been able to restore walking in individuals who have had paralysis due to spinal cord injury. And their hypothesis is that the mechanism by which they were able to do this could hold true for Parkinson's as well. And so the foundation is funding this study.

It's a small scale study to really validate because they've already done this in two individuals, but to validate this in more individuals and really see whether spinal cord stimulation could address some of these gait imbalance issues. And so these things can only happen as we have a better understanding of the science. As Mark articulated, we're able to see what's going on in other fields and could that help us in Parkinson's.

Brian Fiske: Yeah, I remember from my graduate school days, we talked a lot about how you tend to think the brain is where everything happens, but the spinal cord actually, there's quite a bit of circuitry in there that if you stimulate in the right way, it can actually activate some of the basic things that we do, like walking, some of these basic behaviors that we have. So to see this kind of technology apply to that concept, I think is really exciting to see. And that might actually then have benefits for people with Parkinson's.

Maggie Kuhl: Absolutely. I want to take a quick detour here, because listening to you describe the challenges and the opportunities in treating something like walking and balance brought to mind that we received a lot of questions that started with how do I adjust to balance issues? How do I know what treatment's best for me? How do I get my husband motivated who has Parkinson's and is experiencing apathy? And so I wanted to make a quick plug for our buddy network, which is a great resource if you or your loved one is living with Parkinson's disease, to gain information like ones that we're sharing more about studies and research, but also just about how you navigate Parkinson's disease and how others are doing that. And so a lot of this, especially walking and balance, I've heard so many anecdotes of different queuing techniques or different devices that people are using for assistance.

So I think it's linked in the resource list. If not, you can Google Fox Foundation Buddy Network, but all of those how questions and while we're working toward better treatments that are randomized trial proven, there's also just a network out there that can help you navigate life with PD. So please check that out if you're not already. In the essence of time, I'm not going to go too deep into our last three bullets here, but I did want to call out that we know that there are so many other aspects of life with PD. These symptoms that we have listed here are some of the ones that we most frequently hear. As Sohini was saying really challenging, really limiting confidence, independence affecting quality of life. So we have a number of projects that are using everything from repurposed drugs to apps, to spinal stimulation to try and uncover exactly how we can improve quality of life while we work toward therapies that will not require all of these different approaches and hopefully will treat Parkinson's overall.

And with that, I think we'll transition to our next part of the conversation, which is cures. And I always put an 'S' because I think the theme of our talk here is that it's not going to be one cure, it's going to be many really personalized for your own biology. So there is a lot in the pipeline. There's been some exciting progress this year. Brian, why don't you give us an overview perhaps just

starting with some of these targets that people may have heard of. We've already talked about alpha-synuclein. I think people hopefully are pretty aware that inflammation is a concern in Parkinson's disease and any others that you'd want to mention?

Brian Fiske: Yeah, no, so when we look at the therapeutic pipeline for Parkinson's and the team here spends a lot of their days kind of digging through that and trying to make sure we understand what's moving forward and what challenges exist. Obviously, a big part of the therapeutic pipeline today are treatments that are targeting again this alpha-synuclein protein that we keep talking about. And now that we have this additional biomarker tool, I think we're going to see that tool be used and sort of integrated into a lot of these trials going forward to think about how do we really and match these therapies to the people who are hopefully most likely to benefit from them. But there's been a lot of great work, some of the leading groups in the pipeline that have these synuclein targeted therapies. There's a company, Roche, that's working on an antibody approach.

This is an immunotherapy. Basically they've created a synthetic antibody that can go in and target the aggregated clumped aspects of the synuclein protein, and through that process try to get rid of it much like our antibodies normally do when we're sick. This is a way to just give you the antibody directly and then hopefully it'll help remove that synuclein. So they've been working on this for a while. They had some initial results a little bit ago from their trial that suggested some possible benefits of the therapy that continue to look at those individuals for a number of years now and had done some additional analyses and they reported on some of this over the last couple of months suggesting that they're continuing to see those benefits over time, at least on the movement scales that they're using in those trials. So it's continuing to potentially promising that targeting synuclein, this way might have some potential benefits.

Obviously they need to do a more larger trial, a well-controlled trial to really demonstrate that more fully, but at least the signals right now are potentially promising. But it's not the only target in the pipeline. We see a lot of diverse other mechanisms being looked at as well. You mentioned inflammation. I think that's a really exciting area. The idea that maybe inflammation, whether it's causing Parkinson's or it might be contributing to the cell loss over time. I think scientists are still sort of debating that idea, but at a minimum the idea that we could be targeting the inflammation process directly is a very powerful one in Parkinson's. And so we're seeing a lot of approaches looking at that. Some of them are using more traditional small molecules and trying to target specific components of the inflammation pathway to see if they can alter that process.

Others are using other kinds of approaches like we mentioned earlier about stem cell approaches. Stem cells seem to produce a lot of interesting factors that might offer different kinds of protection. Some of those might be growth factors that act like fertilizer in the brain. Others might be factors that help modulate the immune system. And so there's a trial actually ongoing that we've

been supporting for the last couple of years that's using, so-called mesenchymal skin cells. These are a type of skin cell that's found a lot of different places in the body, but particular in places like the bone marrow and things like that. And so this investigator is using that approach infusing these stem cells and the people with Parkinson's to see if they can show benefit over time with this approach. It's nice, because the investigator in particular is taking a very rigorous approach to this.

There are a lot of efforts out there that are offering these types of mesenchymal stem cell infusions to people with Parkinson's often at a cost and direct-to-consumer type of approaches. There's very little data on whether those approaches are really offering any benefit and data isn't really being collected about long-term benefit of those approaches. So for us, it was really important to then work with a scientist who could really rigorously test this. So we're hopeful to have some results from that trial next year and that'll help us inform whether these types of approaches might also offer some benefit.

Again, really trying to focus on these different biological aspects of the disease that we think are relevant. And as we talked about repeatedly before, this idea, we're at a point where we really can start using some of these measurement tools now to really try to match up people to these different mechanisms and these different drugs that are targeting those mechanisms. So I think the idea of this sort of decision medicine, I think is less a future and it feels like more of a present now. So really exciting to see all this moving forward.

Maggie Kuhl: Yeah, I want to ask too, there's been some in the news or people might've heard of, there's been some testing of drugs that are very well-known around diabetes and weight loss. These GLP1 receptor drugs, the brand names are Ozempic or Wegovy or Mounjaro, people may have heard of, but they've been in testing for some time for their impact on Parkinson's. So what are we watching around that?

Brian Fiske: Yeah, and I'll back up for a second and to say a lot of these approaches sort of fall into a category of therapy that we tend to call repurpose drugs. So these are drugs that are generally approved for another indication. There's maybe some biological evidence or rationale to think that it might be beneficial in Parkinson's. And so people will then try to test these in people with Parkinson's to see if they might see that kind of benefit. Drugs that target this mechanism, GLP-1 are an example of that. There have been others historically, a number of other repurposed approaches. I think I saw in the question thread, someone asking me about Nebraxol, for example. That's another repurposed therapy that's being looked at for a different mechanism in Parkinson's and there's some ongoing trials there. But GLP-1 is interesting. It's the GLP-1 itself and the receptors that it activates in the body, really involved mostly in metabolism.

They really help us deal with blood sugar and modulate blood sugar in the body. So they have some really important metabolic effects, and that's why they have

been originally approved for diabetes to help with blood sugar and that more recently with obesity where it seems to be helping people to lose weight. But over the last several years, there've been some data to suggest that it might have some protective benefits and laboratory models of Parkinson's disease. And so a few years ago, some researchers started looking at this. They used a different GLP-1 drug called Exenatide that's been available, and did some initial trials. And actually the foundation funded one of the phase two trials for one of these drugs a few years ago that suggested that there might be some effects that these drugs might actually have some benefits potentially at least on the clinical measurements that those trials used around sort of movement and things like that.

More recently in the last couple of years, there've been a slew of other trials that have tested not just Exenatide, but some of these other similar GLP-1 drugs. And in the last year in particular, there's been a flood of these initial reports from these trials. Again suggesting not always consistently. That's I think, important to remember that to be clear about. Not every trial is sort of seeing the exact same thing, so there's kind of something odd going on, but they're seeing some clinical benefits of these drugs and people with Parkinson's. And so there's this, I think, interest in thinking about what these results actually mean. Are they actually signals of real benefit? Are they something else related to... again, these are drugs that alter metabolism and do all kinds of things. So we don't know for sure how that might be influencing the body, but we're monitoring it. We're excited to see where this goes. There's a large trial in the UK that should be reporting out next year with exenatide have I think, more data from that trial to inform where this is going.

Maggie Kuhl: We have a lot still to learn about Parkinson's. We have so many targets. We have hundreds and hundreds of targets. These big ones like alpha-synuclein and inflammation, these genetic markers or something semi-connected to a pathway that we are just identifying and learning about, but we know there's a lot of darkness that we need to shed more light into around what causes and drives Parkinson's. So we have a number of efforts. One of the biggest ones is called the Global Parkinson's Genetics Program or GP2, which is in partnership with our partner, the Aligning Science Across Parkinson's or ASAP Initiative. It reported a really big finding this year. Mark, why don't you share that with us?

Mark Frasier: Yeah, I mean, really Parkinson's has been studied mostly in the Western European Caucasian population. And it's really important, not just socially but scientifically to understand Parkinson's globally. We know it knows no bounds. And if Parkinson's occurs all over the world, and the Global Parkinson's Genetic Program is an effort to collect DNA samples from individuals, particularly underrepresented people in Africa, Asia, South America, to understand the genetic contribution to Parkinson's disease in these underrepresented populations. And it's a relatively new program.

And what's exciting is even just as it's beginning, there was a report just this year, that in people of African descent, both in the US and in Africa, there's a specific DNA change in the GBA gene that contributes to Parkinson's. It's actually a different DNA change than other GBA mutations that have been identified in other populations. But it really just shows that this role of the GBA gene and protein that is involved in this garbage disposal process is really important in Parkinson's disease. So we expect more discoveries to come out of this program to really understand Parkinson's at a global level and the biology that's occurring in everyone with Parkinson's.

Brian Fiske: One of the, I think also really powerful points about that GBA finding and people of African descent was obviously found a variant or a DNA change and a gene we sort of knew about from other studies, but how common that change was in people of African descent was much greater than it is in people in other ethnic populations. And so I think it just again reflects the idea that even if we go out in the globe and find that we all share maybe similar biology for some populations, that biology may be much more sort of relevant to their form of Parkinson's disease.

And I think that's really important to get back to this concept of precision medicine. How do we offer groups of people the right treatments that really would impact their lives? And so people in these populations, you might then want to really consider these types of treatments that focus on the GNET lysosome biology, the GBA biology that you alluded to, that would be more relevant to a group like that than it might be another population. So it's really exciting to see these kinds of data come out and really again, put genetics in kind of this global context, which is really, really important.

Maggie Kuhl: Very exciting finding. And as you said, Mark, more to come from GP2, absolutely not the last or even perhaps a little bit of what you are to hear from that program. I wanted to go back to something that we had chatted about earlier, which is access to care and treatments and building an informed and educated Parkinson's community that can help us achieve our shared goals of better care today, better treatments for tomorrow, better access and coverage for all. So Sohini, there's a couple things on this slide. We've already referenced the policy program, so you can chat about the national plan for Parkinson's disease, which again, hopefully many on this call have already heard. And the PDIQ+You events, which we host are a great opportunity. And there's a couple coming up in 2025 to mark on your calendar. So just quickly before we can go to the Q&A, anything you want to highlight around these programs?

Sohini Chowdhury: I would just say that if you are close to the locations that are mentioned here, please do consider attending a PDIQ+You event. These are really meant to kind of talk about how to put together the right care team for your needs and really gives a much broader sense of the research that's happening. But importantly, it also highlights and exposes attendees to the local resources in the community that can be leveraged as one goes through one's journey with Parkinson's

disease. One thing I will just say about the National Plan for Parkinson's Disease is that for those of you who are not aware, this is a no-cost legislation that was submitted to Congress.

It enjoys a very significant bipartisan support. But what it's really about is mandating on a government scale, mandating the existence of a coalition of agencies, federal government agencies, key opinion leaders, Parkinson's advocates, patient representatives, et cetera, to really think about how the government can help support and accelerate efforts to make Parkinson's a thing of the past. And so right now, it is going through its normal sort of machinations as it goes through the two houses, but at some point, we fully expect that it will be approved and then we're really going to be looking for many of you to partner with us to really make this happen and to form something that will have a lasting impact on Parkinson's. And so with that, I'll leave it there. We have a lot of information on our website about it, but it's an extremely exciting effort.

Maggie Kuhl: Yes, please advocate and share with your legislators the importance of this program. So with that, we're going to transition to the Q&A. We received 700 questions before we even began today. I've seen the hundreds that you all are sending in. Sohini asked me how long I wanted for Q&A, I said 20 minutes. We had so much to share. We've got nine. We're going to cover as much as we can in nine minutes, I promise you. So team, succinct. There's lots more on our website. Sohini, starting with the policy theme, where are we with movements to limit exposure to environmental risk factors that we know raise risk of Parkinson's disease?

Sohini Chowdhury: So there has been advancement in two particular areas. One is TRICHLOROETHYLENE or TCE for short. Many of you may have seen a pretty devastating report that came out about exposure to TCE at Camp Lejeune, I believe is how it's pronounced. And that really spurred a lot of activity in a positive way. And so the team has really been working on this and chances are that government's looking at this and that there's a chance that the use of it is going to be dramatically reduced or banned. The second area of interest is paraquat, which I know we've talked about for a number of years. The foundation has worked with other groups interested in this area and has met with officials at the EPA. And so the EPA has signaled that it is willing to re-look at its decision in 2021, where they basically said, "We have no concerns with paraquat." So they've opened the door to reconsidering that decision and reconsider that the first step in really trying to kind of move the bar when it comes to paraquat.

Maggie Kuhl: Amazing movement there and things that we know should not be so widely used with their high likelihood PD. Mark, how many years in advance, and I think I put that in quotes, I think that's the answer to the question, can a alpha-synuclein SAA test detect Parkinson's Disease?

Mark Frasier: Oh, that's a great question. We don't know the answer to it, but the data suggests that in terms of the temporal pattern, alpha-synuclein seems to change first before the dopamine neurons are lost, or at least before we can detect the dopamine degeneration using a dopamine imaging agent. And then subsequent to that, symptoms develop. So we're supporting studies to understand how early that happens. Previous studies have suggested that some of the pathology can occur five to 10 and sometimes even 15 years prior to symptoms developing. So I would guess somewhere in that range, but we really need to generate additional data to understand how early that happens.

Maggie Kuhl: So the disease is starting, and this is where I make a plug for our PPMI study, which is where a lot of the results around the SAA tests are coming. Which side banner? My PPMI banner behind me. And it is recruiting anyone age 18 or older in the US. There's lots of different ways to participate. It's linked in the resource list. Please help us achieve everything that we are saying that we all really need by joining PPMI. Brian, the glove. The Stanford glove. What is new with the Stanford glove.

Mark Frasier: By stimulating the fingers through these vibrations, it seems to reset the circuitry and at least anecdotally reduce some of the symptoms including tremor and slowness or stiffness. As far as we know, there are clinical trials that are ongoing to test this more rigorously. As I mentioned, it was more anecdotal evidence of people wearing the glove that seemed to have reduced symptoms, but we really need controlled studies including people that might wear a glove that may not receive the stimulation or a different stimulation to really control that placebo effect that we know is common in Parkinson's disease. So I think those studies are ongoing. Currently, it's not available, I think, to the population and really needs additional data to make that available.

Maggie Kuhl: Brian, I'm beginning to think that Mark has planted some device so he can just finish all [inaudible 00:51:08]-

Brian Fiske: He wants there to only be one CSO, not two, I think. It sounds like you guys ended again, more data [inaudible 00:51:16].

Maggie Kuhl: Yes, there'll be more questions for you. Stay with us. But Mark, staying with you for a second question on if we're using artificial intelligence for Parkinson's research.

Mark Frasier: Yeah. This is popular across not just medical research but research in general. But there's two main areas that we've supported AI in Parkinson's research. One is to analyze sensor data. So this is wearable data using smart watches, or smartphones that collects massive amounts of data and to try to identify patterns that might occur with Parkinson's disease in a living normal environment. We've supported studies that collect a lot of wearable data and then now have funded work to analyze the data using AI, or machine learning approaches.

The other is in molecular data. There's been a tremendous wave of really deep molecular data, genetic data, but also protein profiling data and fluids. There are now approaches to measure different metabolites and fluids alongside complicated imaging data. And so we've supported some AI approaches really to combine different types of data sets and again, understand different subtypes of Parkinson's disease, try to identify individuals that might progress faster versus slower and what might predict that from occurring. So it's really an effort to combine a lot of large data sets and identifying patterns that human traditional statistical approaches would not recognize.

Maggie Kuhl: That's why we need lots of data and lots of people to participate in research. So I'm going to take a page from my own webinar mentor, Dave Iversson, and do a little around the room to end us. It's the end of a monumental year, a year like none other in Parkinson's research. What are you walking into 2024 feeling, hoping, collecting? Mark, why don't we start with you?

Mark Frasier: Yeah, I mean, what I'm really excited about, it's not just the breakthrough, the biomarker breakthrough and having these tools that measure and can detect Parkinson's biology earlier, but also the therapies that are developing in parallel with those tools and the biomarker tools. And it's really a convergence of having the measurements and also the therapies that can go hand in hand and make clinical trials smarter and more efficient and really hopefully slow the disease.

Sohini Chowdhury: Yeah, I think when I think about what I'm walking into in 2024, I think I'm walking into it with a really open mind, because I think to what Mark said, the entire landscape for how we think about therapeutic development and how we think about Parkinson's disease has changed in 2023. All of a sudden, we can look beyond the symptoms and actually start to understand what's going on in an individual. And we're starting to recognize that what is going on in an individual is different person to person, who's dealing with Parkinson's disease.

I think that opens up huge doors for us, both in terms of how we think about building on this concept of what precision medicine could be for Parkinson's, but also thinking about how we can leverage all of this knowledge that we've built over the past couple of decades and really refine our understanding of what's happening for each individual and how to intervene in the best possible way in the disease that individual has. And so, I don't know exactly what that means yet, but I feel that we are on a cusp of a total seismic change of how we're thinking about this in a way that is really going to resonate and create impact for people living with the disease.

Maggie Kuhl: And Brian, thanks for being such a champ in overcoming the difficulties. So the last word is yours.

Brian Fiske: I mean, I'll just echo Mark and Sohini and just say, I think it's a really exciting time. This biomarker tool, we can't talk about it enough because it's something we've wanted for so long. We're going to see its imprints all over the

therapeutic pipeline in the coming years. Look forward to next year. They're going to be probably some new approvals for at least some of these more advanced programs that we talked about. So look forward to that, but also look forward to progress in the pipeline as some of these other approaches start moving forward as well. So if we're going to get a lot of data next year, we'll know hopefully next year when we're doing this webinar, we'll be able to talk about those exciting updates as well.

Maggie Kuhl: Thank you all. And thank you all for attending. Please access the resources. We had so much to cover. You asked so many questions. We hope the foundation is a resource for you to become empowered, informed, and true partners in our shared pursuit. So thank you for joining us.

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