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MJFF: Welcome to a recap of our latest Third Thursday Webinar. Here 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.

Brian Fiske: Hello and welcome to our webinar today. I am Brian Fiske. I'm co-chief scientific officer here at The Michael J. Fox Foundation for Parkinson's Research, and really excited to be hosting our great panel today in discussion about all the progress that we're seeing in Parkinson's research. So it's near the end of the year for us here and our teams are really busy trying to get out the last grants for the year and planning for next year. But it's always a great opportunity to pause for a moment and just talk a little bit about the progress we've seen this year. So I'm really excited to do that.

We're going to talk about a lot today. We're going to try to run through this pretty quickly, but we want to give you as much insight on progress as possible. We'll talk a little bit about new treatments that we're seeing coming through the pipeline. We're going to talk about some of the advances we're seeing and how we can better measure and track Parkinson's disease. And we'll also talk about some exciting work that we're doing around the idea of potentially even preventing Parkinson's altogether. So we have a lot to discuss. But first I want to introduce my colleagues and our panelists today.

So first I'd like to introduce Dr. Shalini Padmanabhan, who is our Vice President of Discovery and Translational Research. Next we have Dr. Jamie Eberling. She is Senior Vice President of our Research Resources Group. Hi, Jamie.

Jamie Eberling: Hi everyone.

Brian Fiske: And finally we have Dr. Katie Kopil, who is Senior Vice President of our Clinical Research Team.

Katie Kopil: Thanks. Excited to be here, Brian.

Brian Fiske: Great, great, great. So let's get started. We have a lot to talk about. So before you get into talking about the progress we're seeing, I think it's important to always start with an understanding of what we're trying to do. What's the problem we're trying to solve? And so we like this sort of slide because it helps frame, I think, what the real challenge of Parkinson's disease is. That it's not this sort of static disease, but it's a progressive disease. And what that means is that really when someone is initially diagnosed with the disease, and that's usually defined today by someone coming to the doctor and presenting certain movement symptoms, so slow movement, rigidity in the muscles, maybe resting

tremor, that's really just sort of a symptomatic moment in time of what is really a progressive disease that maybe starts symptomatically at that point but then continues to advance with other symptoms and other complications becoming a problem over time.

But even before that moment, we know that the disease is happening. That it's sort of simmering underneath, leading to maybe some early symptoms that people don't necessarily always think of as Parkinson's disease, but maybe predictive of later Parkinson's disease and certainly an underlying biology that is being impacted at those early stages. So this framing, I think, is important 'cause you're going to hear us talk a lot about over the course of the next hour the different ways we're thinking about this sort of progressive disease and how we think about treatments and how we think about measuring along the spectrum, and even ultimately how we might even be able to find those people at the earliest stages and maybe even delay the onset of the disease altogether. So we wanted to start here just to get this into your brains and have you thinking about this framing.

So wanted to start off first, clearly with thinking about treatment. So this is, I think, obviously where many people are excited to hear about progress in Parkinson's. And so when we're often asked what's the latest and how close are we to the cure, this is really a good place to start. 'Cause I think it's important to know what types of treatments we're seeing and what types of treatments we think will be available soon. So Shalini, I'm going to start with you in this section to help me walk through the progress we're seeing. And I know our team is probably following, I think, last I checked, more than 170 therapies in clinical testing, meaning that they're actually being tested in humans today. And that's really exciting to understand that. But obviously with so many different treatments, we can't cover all of them. So it's probably helpful for us to break this down a bit.

And we thought what we could start first with is actually sort of reorder this slide a bit is let's talk about first of how we can treat symptoms today. So we have obviously a lot of approved drugs. It's been great. Since 2014, I think 18 drug approvals for Parkinson's, which is amazing to think about, all seeking to target and reduce the impact of symptoms of Parkinson's disease. And so I wonder if you could walk us through some of the advances we're seeing there. And I know there's some exciting updates about some potential new approvals coming up soon as well.

Shalini Padmanabhan: Yeah, sure, Brian. So yeah, as everybody knows here, levodopa carbidopa is really currently the gold standard medication for people with Parkinson's. And what it does is that it provides dopamine to the brain to basically help with movement. So this is a symptomatic therapy, Brian, as you highlighted, which means that it only helps manage the symptoms but doesn't really treat the underlying cause of the disease, which is why we are investing so much in research to understand what the cause is. However, even with symptomatic treatment, many patients have to work with their doctors to find a dose that

works for them. So they don't experience many off periods, which are the periods between doses that causes the Parkinson's symptoms to reappear and also to prevent some of the side effects of the medications, especially with prolonged use. So over the last few years, we've seen many approvals that help manage some of these issues, and these have generally been tweaks to the way the medication is delivered.

And we have two more in this category that are now awaiting a decision from the FDA. So these include AbbVie's new formulation of levodopa that can be infused under the skin, so to provide more of a continuous dosing of levodopa. So patients experience fewer "off" periods as well as we have a second drug, which is from Amneal Pharmaceuticals, which is a pill that contains both of an immediate release as well as an extended release, which means you'll have some part of the drug that's released to the body immediately and some that's released slowly over time. Again, this is to better control the symptoms for a longer period of time and to prevent patients from experiencing a lot of off periods. And both of these, as I mentioned, are with the FDA now and we will be hearing from the FDA early next year. So very, very exciting new formulations in this category. We also did see one recent approval of Dhivy, which is basically an easy-to-break tablet of levodopa carbidopa, so you can more precisely control the dose. Some people may want to stagger their doses over the day and some people may need lesser early on in the disease, so these kind of treatment options really help with managing symptoms currently.

Brian Fiske: Yeah, no. And so it's exciting to see these, again, new approaches to maybe an existing type of drug. Again, you're replacing dopamine is something we've been doing for many years, but I think when we see innovation like this to help, and as we talked about before, especially as the disease advances, it can get complicated sometimes even just simply delivering dopamine. And so new ways of doing that can help, I think, reduce some of those complications. So we're always excited when we can see advances in that space. So let's talk about, diving a little bit deeper into the pipeline, some of the other sort of symptom areas that we're really looking at and really excited to see progress.

Shalini Padmanabhan: Sure. So I think this is very interestingly because when surveyed, actually 50 percent of people with Parkinson's had indicated that their symptoms related to movement were most bothersome. And even within this category, it was gait and balance, those related to precise movements, that seemed to really affect people the most, especially as the disease advances. So to begin to tackle this issue, we are now funding a company called Takeda to test a drug for improving gait. So help people walk better, balance better. This is a Phase II study, so we learn if the drug looks promising or not to address the symptom. Interestingly, this drug will also test if it can improve memory and cognition in people with Parkinson's. So kind of testing two symptoms with one pill. So very, very exciting funding in this area. This is a challenging area to study because especially, I think, with laboratory models, it's not easy to study gait and balance because these are all very relevant and specific to a human condition.

And so we earlier in the year actually hosted a workshop that brought together drug companies, researchers, talk a little bit more about gait and balance in Parkinson's disease. And we are now working through some of the recommendations which just includes how do we better measure some of these aspects in people with Parkinson's disease? How do we understand the underlying mechanisms that contribute to some of these issues, especially as the disease progresses, and how do we then better treat it? So a lot of work to be done in this area, but we've heard time and time again that this is an important area of research for us to consider. I think similarly, I think, as I mentioned, 50 percent said that it was their motor symptoms that were most bothersome, which means that at least 50 percent of people indicated that it was a non-motor symptoms that were most bothersome.

And amongst this, I think things that keep coming up over and over again are cognition, pain, sleep, et cetera. And these are very, very challenging for us to study. So I think we need to really go back to the basics because it's very different circuits. We don't understand what really goes wrong in people with Parkinson's. Are they the same mechanisms that are at play or are they different for people with Parkinson's disease? So we actually launched a funding call earlier this year to bring in ideas from the community to better model some of these symptoms in the laboratory setting so we can better understand the circuits or the mechanisms that are at play, both not only in the development of Parkinson's symptoms, but also in how they progress in these models and then hoping that we could find better treatments. So we got a lot of interest from the research community. We have lots of ideas that we are now kind of scanning and evaluating and our hope is that we'll fund at least diverse set of symptoms that we can tackle in the coming years through our funding programs.

Brian Fiske: And I think that that last point is really critical. We've wanted to see more therapeutics being developed against some of these other symptoms, and there are a few approved ones over the last several years. But like you said, I think the complexity of the biology underlying some of those other symptoms is sort hard to crack, and so we may have to put a little bit more funding and sort stimulate more research in those areas. So it's exciting to see that happening. So let's move from the more symptom treating approaches and really think about, I think, what many are hopeful for as kind of the holy grail is treatments that can actually maybe slow the disease process down so they can target the sort of underlying mechanisms. And certainly over the last 20 years, we've just seen an explosion of research that's really, I think, increased our understanding of these mechanisms and now have moved those ideas actually into drug development and including some approaches that are in clinical testing now. So talk us a little bit about what some of those critical mechanistic targets as they call them are and what kind of progress we're seeing.

Shalini Padmanabhan: Sure. So as I mentioned, I think in order to identify drugs and therapies that can either slow or modify the disease course, we need to better understand the underlying mechanisms that play a role. And this has again been an area of active research because we are now learning that there are multiple triggers of

the disease. Genetics, environment, a mix of the two. And these are different in different individuals and different stages of the disease. So you can quickly see how complex this biology gets. However, what we have learned is that in a vast majority of individuals with Parkinson's, there is misfolding or aggregation of a protein called alpha-synuclein, both in the brain as well as in the body. And now we have about 15 different therapies in clinical trials that aim to either decrease the amount of alpha-synucloein, increase kind of disaggregation of clumped or aggregated synuclein, and prevent spreading of alpha-synuclein.

So as a disease advances, you want to prevent that spreading. So of course most of our treatment strategies are attempting to hit one of these areas. So just wanted to highlight a couple of trials that focus on maybe preventing the spread of alpha-synuclein from one cell to another. And these are antibody or vaccine based approaches, or more broadly categorized as immunotherapy approaches. So most of you heard, Roche is one company that tested an antibody to neutralize the alpha-synuclein that's transferring from one cell to another. We have another approach, which is the approach from Vaxxinity, which is more what we call as an active immunization approach, which means we actually inject a fragment of alpha-synuclein that causes your body to then produce an antibody to tackle these toxic clumps as they're transferring from a cell to cell, from one cell to another.

So these approaches are both in Phase II and Phase I respectively, and will actually be a good proof of mechanism studies for the field because we've done enough studies around these approaches in pre-clinical models in the lab. And I feel like now the final test is really in the clinic. So very, very exciting times and we will learn a lot more as a Parkinson's disease kind of community. The other thing that we are also learning is about the genetic causes of Parkinson's disease. And there are two genes, LRRK2 and GBA, both of which have been implicated in Parkinson's disease, and we are now testing several drugs against these gene targets to determine if they're actually beneficial in patients who carry mutations in LRRK2 and GBA. So just wanted to highlight one quick one, which is a recent partnership between Biogen and Denali that has enabled Phase II and Phase III studies of a LRRK2 inhibitor.

Interestingly, these are being tested not only in individuals who carry the lymph mutation, but also in one of the trials. These are being tested in people who have PD but don't carry the LRRK2 mutation. So this is making the drug more widely available to the community. And that's because the underlying biology between these two groups of patients may be similar at least in a subset. So that's again an interesting kind of proof of mechanism study that we will be seeing that's being tested in human studies. Again, Brian, these are just a few examples or highlights. We have many more targets for Parkinson's that are being tested and these cover a wide spectrum of mechanisms. Some that improve the energy producing functions in the cells, some that aim to restore the recycling capacity of cells, and some that even modulate the immune system. So there's a lot of exciting things and hopefully by next year we'll have some more kind of moving into the clinic.

Brian Fiske: Yeah, no, and I think that that's an important point too. Because I think from our perspective at the Foundation for us to look at the therapeutic pipeline for Parkinson's, we want that diversity in mechanisms being looked at and explored. For us, it's sort of a key measure of the health pipeline. If they were all only looking at one idea...

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Brian Fiske: The health of the pipeline, if they were all only looking at one idea, that would be, I think a little bit too risky in our view. And so we'd like to see these different mechanisms. So we're going to move on here in a second, but just a call out to the participants today. If you want to learn a bit more about some of these therapeutic areas, you can check out this year in review publication that's listed here on the slide. I think it's also link in your resources page on the screen and you can learn a little bit more about some of the areas that Shelly and I talked about. So let's move on and talk about another really critical part of this. So we can think about all these great therapeutic ideas that we can sort of target and try to address in clinical studies. But one of the real big barriers to that is if you don't know how your drug is ultimately working in the body, it can be really hard to assess whether you're actually seeing any real impact of these therapeutics.

So this idea of measures and tools and biomarkers, you may heard us talk about ways of measuring the underlying disease biology. These are just really critical needs for the field. And so we're going to talk a little bit about some of what we're seeing as really critical approaches for thinking about how we can measure and track the underlying disease of Parkinson's. So Jamie, I'm going to switch to you. You're our sort of leading expert on a really important type of measure in particular, which is this idea of being able to image the brain, sort of what's going on under the hood, as I like to often say. And it's I think really exciting that we're seeing some real progress, I think recently in our ability to detect some of the important biology linked to Parkinson's. So I wonder if you kind of walk us through that, what some of that exciting progress is.

Jamie Eberling: Sure. Thanks Brian. So as Brian mentioned, we believe that these different types of biomarkers are really critical for drug development. We want objective ways of measuring the progression of the disease, even the presence of the disease, so diagnostic markers, the progression of the disease as the disease advances and the symptoms become more severe. And then also response to treatment, objective ways of knowing if a treatment is working. So by objective, I mean we don't want to just rely on assessing symptoms because symptoms vary from day to day, even at different times during the day. And different clinicians will assess symptoms differently. It's subjective. So we want objective markers. And one type of marker would be a brain scan, imaging markers. And there are different types of brain scans. One that we think is really critical and would be a game changer for Parkinson's therapeutic development would be a way of seeing alpha-synuclein in the brain.

So as Shalini mentioned, alpha-synuclein is a protein that accumulates and clumps in the brain in Parkinson's disease. And as the disease progresses, it spreads and that spread is associated with worsening symptoms. So if we could actually image alpha-synuclein in the brain, we could then image patients periodically to see how that alpha-synuclein is changing. So it could initially be a diagnostic marker, we could see is there alpha-synuclein in the brain? Maybe we can see it even before there are symptoms. And we could potentially, if we have the therapy, prevent symptoms from ever developing. But then we could also use this to see how the alpha-synuclein spreads over time. So we've been supporting work to develop a brain scan, a PET scan to image alpha-synuclein for over a decade now. It's a very challenging thing to do, but over the last couple years we've seen some real progress and it's really exciting.

At some point you start to think maybe this isn't even possible to do. It's difficult, maybe it's not even possible. But now we've got some real hope and we believe it is possible. And so I'd like to tell you about what has happened just this year. One of the companies that we've been supporting called AC Immune, they're a Swiss company, has been working on developing an alpha-synuclein PET tracer for a number of years now. And we've been supporting that work. And a PET tracer is, you can think of it as a drug that contains a radioactive label and you inject the drug into a patient, it goes into the brain and it targets alpha-synuclein. So it binds to alpha-synuclein and then using a PET scanner, a type of brain scan, the areas that light up on the brain scan show where that radioactivity is. And the radioactivity is where the alpha-synuclein is.

So it allows you to actually look into the brain, it's like a window into the brain, the living brain, and see the pathology. So AC Immune tested their PET tracer in humans over the past year. They tested it in both patients with Parkinson's disease, subjects that didn't have any kind of neurological disease, and then patients with a disease called multiple system atrophy or MSA, which is often was mistook for Parkinson's disease early on because they share similar symptoms. So it's often difficult to diagnose MSA early on because it gets misdiagnosed as Parkinson's disease. But then as the disease progresses, which is usually pretty rapid in MSA, it's an aggressive disease, one realizes that, oh no, it's not Parkinson's disease at all and we shouldn't be treating this patient like they have Parkinson's disease because they won't respond to that type of treatment.

So when AC Immune tested their PET tracer, they found that they didn't really see anything in the Parkinson's patients. So they looked at the brain scans and it didn't look like anything. They didn't see any radioactivity that accumulated suggesting that either the tracer doesn't work or there's no alpha-synuclein there. But then when they tested their tracer in MSA patients, they saw that on the brain scans, they could see that it lit up. So if you look at the image on the screen, these are from two patients with MSA. There's on the left it's two levels in the brain, so it's the same brain but two different parts of the brain. And you can see on the bottom two images that there's these areas of red and yellow. That is alpha-synuclein in the brain. And this is the first time that we've been

actually able to image alpha-synuclein pathology in a living human. So it's really exciting.

The fact that we didn't see any in Parkinson's disease, that's less exciting, that's disappointing, but this does show us that it's possible to image alpha-synuclein in the brain. Why didn't it work in Parkinson's disease? We don't know. But there are at least a couple potential reasons. One is, as I mentioned, MSA is a very aggressive disease. It progresses rapidly and we think that there just may be more pathology in the brain. And so it's easier to see it on a PET scan, that we would need something more sensitive in order to see alpha-synuclein at lower levels. And the lower levels may be in Parkinson's patients, especially early in the disease.

So the fact that it does work in MSA is extremely exciting for the field. And I think it's really kind of been a shot in the arm for other groups that are working on developing an alpha-synuclein PET tracer because again, it shows that it's possible to do and we think we're getting close. And in fact, the Fox Foundation is funding several groups that are ready to test their PET tracers in Parkinson's patients later this year. There's at least three groups and we just need one of those to work. Maybe all three work, maybe none of them do, but we're really hopeful that we'll have some more good news later in the year. But I think this was really a big step forward for the field.

Brian Fiske: Yeah. No, you and I were at a conference earlier in the year where we saw some of these first results presented. And I just remember this sort of almost like gasp in the room sort of sense that we might finally have something that could detect synuclein in a living human brain and just the excitement. I think you've spent so many years I think as our internal champion on this, and it's so great to see this kind of progress happening and obviously more work to come as you said, but certainly a great milestone for the field, so.

Jamie Eberling: I'm pretty sure I cried during that meeting.

Brian Fiske: So I know maybe before we talk about some other types of measurements, I know Jamie leads an effort here at the Foundation too that's really about trying to help support different types of imaging agents. And brain imaging is such, I think, a critical tool for our ability to really measure and track the disease. And so it's something the Foundation has really put a lot of effort in and Jamie's been a leader in really moving this forward. So we're excited to see that continued investment. Now, besides brain imaging, there are some other types of measurements that we're really excited to see advancing. And these are more sort of traditional, sort of blood based or other kinds of body fluid type measurements, biochemical measurements of the different aspects of Parkinson's disease biology. There's a really promising technique that we're been supporting and we're seeing some real advances in that can detect similar to how Jamie describing able to see alpha-synuclein in protein in the brain, some ways to detect that synuclein protein in other body fluids.

And in particular being able to detect forms of that protein that we think are more pathological, sort of more like the type of sort of bad, if you will, alpha-synuclein that can happen in the brains of people with Parkinson's. And there's a tool called a seeding assay, which basically has the ability to detect whether someone's synuclein is particularly sticky, if you will, is maybe one way to think about it, where if you run it through this test, it'll sort of show whether that persons synuclein tends to clump versus someone who maybe has a sort of normal a synuclein in their body. And so that test is really showing some real promise and it's helping us to think a little bit about how we can better identify people who we think have more of this sort of robust kind of synuclein flavor of Parkinson's disease. And that could be a really powerful tool in addition to the brain imaging to find people who would be most appropriate for treatments that target that biology.

So again, in parallel, I think these biochemical tests along with the advances we're seeing in imaging are going to be really, really critical and powerful as we continue to move the field forward. We want to just maybe pause for a moment because a lot of the work that you've heard, especially the work around biomarkers and different ways of measuring Parkinson's, have really come from a great deal of work over the last number of years. But in particular from a study that the Foundation launched a little over 10 years ago called the Parkinson's Progression Markers Initiative or PPMI and this study is really important. It's been following people newly diagnosed with Parkinson's, but then several years ago we started adding in people who don't yet have the symptoms of Parkinson's but carry certain risk factors. And this study has really allowed us to truly understand the progression of the disease.

So that again, if you remember that first slide I showed about how Parkinson's is progressive, being able to actually measure that and track that and understand that I think has been really critical. And PPMI has been just foundational in our ability to really understand that with lots of data coming from it. It's exciting because the study is still looking for volunteers. So if you are someone newly diagnosed with Parkinson's who are not yet on medication, we invite you to sort of check out the links in your resource page to get more information about the study. But even if you're not someone who's newly diagnosed with the disease, if your someone who has Parkinson's already for a few years, as well as if you are, as long as you're 18 years and older in the U.S., you can actually join the study even if you don't have Parkinson's, because we're really interested in understanding and identifying factors that may lead to sort of risk for Parkinson's disease as well.

So check out this link if you want to join. We have also, in addition to the core PPMI study, we have what is called PPMI online, which allows you to sort of join this larger study as well. So take a look, get more information, and we would love to have more people participating in this study. All right, so we're going to switch gears a little bit. And again, we've talked a lot about people with the disease who have the symptoms and how we can sort of help address some of those symptoms, how we can measure some of that biology, obviously how we

hopefully maybe might be able to slow down some of that biology in people with Parkinson's. But we know the disease starts many years before the motor symptoms really show up. And so there's a lot we're trying to understand about risk for Parkinson's. And so Katie, we're going to switch to you and kind of help us walk through this. What are we talking about when we think about understanding risk for Parkinson's and what are we looking to detect and why is it so important?

Katie Kopil: Yes. The good news is that we are listening more to the Parkinson's community, and if you are living with Parkinson's, Parkinson's is in your family, you don't wake up one day and have it. There's a constellation of symptoms that are accumulating that force somebody to say, Hey, I need to see a doctor about this. And the idea here and what we're learning, especially from PPMI, thank you for those of you that are participating in this study, it's a gift. What we are learning is that the biologic process of Parkinson's disease can start many years, even decades before the onset of symptoms. And the onset of symptoms are not just those motor symptoms that push somebody to a neurologist to get a diagnosis of Parkinson's disease, but some of those symptoms, which you see on the slide here, include non-motor symptoms like issues with sleep, constipation, loss of smell.

So the opportunity that the field is excited about and The Michael J. Fox Foundation is excited about is to better biologically define Parkinson's disease at its earliest stages so that there might be an opportunity to intervene. Either we've talked a lot about pharmacologic or drug treatments for Parkinson's disease, but even intervene with very serious lifestyle changes for people that better understand their risk for Parkinson's because of genetic factors, because of biologic factors like the seeding...

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Katie Kopil: Factors because of biologic factors like the seeding assay, Brian, that you mentioned, or environmental exposures like exposures to pesticides or traumatic brain injury. So the opportunity that we have as a field to learn more about how we classify Parkinson's as a disease, how we make it more objective like what Dr. Eberling was talking about, and try to do that early, is opening up a whole world of possibility in terms of treating Parkinson's early, before symptoms start, before symptoms worsen. And I'd like to point out also that prevention also can mean lots of things to different people. So this could also be preventing worsening of symptoms even if you already have the disease or preventing more advanced symptoms that can come with longer duration of living with Parkinson's disease. But it's all anchored to this piece of biology and how do we better biologically define the disease and then find the right treatments for the right people at the right time.

Brian Fiske: So yeah, I think this finding people at this sort of early stage I think is really critical. And I think it's important like you said, prevention can mean a lot of different things where you are in your progressive journey, it's trying to prevent

you from getting further down that road as best we can. And could you talk though a little bit about, I know one important direction we're headed is this idea of how do you think about designing the right kind of study to actually do that, to actually find those individuals and potentially offer them something that could prevent that further progression. So if you could talk a little bit more about that.

Katie Kopil: Yes, there's a lot of excitement here and a lot of different smart people thinking about this problem and opportunity globally. One way that The Michael J. Fox Foundation in partnership with clinician scientists in the PPMI study are thinking about it is understanding those individuals who are likely at risk for Parkinson's and developing or getting a diagnosis of Parkinson's in the next two to three years. And trying to map out what are those risk factors that would make somebody not likely to develop Parkinson's in 10 years or 20 years, but rather those individuals who are likely to develop Parkinson's in two to three years. We think some of those measures include things like changes in DAT scan. It could include this seeding assay measure, something that is getting more proximal to the onset of motor symptoms.

And within the context of the PPMI study, trying to design clinical trials that may be able to test interventions and understand whether they prevent further changes in biomarkers like DAT scan or prevent worsening of motor and non-motor symptoms, ultimately preventing a diagnosis of what we know today as motor Parkinson's disease. There are other studies that are also upcoming that the Fox Foundation is going to be supporting. Also looking at lifestyle interventions, at people at earlier stages of risk because of genetic factors or other lifestyle factors that don't necessarily have that two to three year horizon of risk, but a longer potential for risk, so that there's opportunity to develop a really robust set of tools that people hopefully in the future will have to arm themselves to live well with Parkinson's now, prevent getting it no matter where they might be in a biologic state of Parkinson's disease.

Brian Fiske: So really exciting I think for us to even be even conceptualizing this idea that we could potentially do this. And I feel like advances in the last few years have really positioned us with I think almost a real opportunity to try this out. So it's exciting that we're able to leverage some of the infrastructure we have in place to actually potentially do this and try it out. So really exciting.

Katie Kopil: And I'll highlight also that we're not just building on learning and infrastructure in Parkinson's disease, but we're taking cues from other diseases. There has been this approach in the Alzheimer's field. Brain health overall is becoming increasingly important across different types of diseases, how do you promote healthy aging? And so we're learning a lot about this opportunity to promote better brain health. I think there's a guide that's also listed in the resources here about ways that you could intervene and promote healthy brain aging right now.

Brian Fiske: Great. So you've heard a lot about the advances and panelists have touched on from therapeutics to measurement to maybe even slowing down and prevention. There's still a lot of work needed and a lot of ways that you actually can get involved in that. So we've listed a few things here. The ways that you can stay connected in the community, join some of these initiatives, some of these efforts. Consider participation in PPMI. You can join Team Fox, you can register for some of the events that are related to that. You have a buddy network for those who have Parkinson's and want to connect with people like them. An important advance though this year that we're really excited about is what is called the National Plan To End Parkinson's Act. And this is actually an act that is going through Congress right now. It's been presented both in the House and the Senate, that really is seeking to elevate the importance of ending Parkinson's at the congressional level.

And this is work that's been led in particular by members of our policy team here at the Foundation for quite a while. And we're just really excited to know that this is potentially something that will actually be an act if Congress is able to pass it. And so the bill is really about trying to build, I think more resource and awareness around Parkinson's disease at the congressional level. And so we're really excited that this could be passed and hopefully maybe this year, we'll see. But we need your voice, so we need your help in really advocating for this act. And so far more than 6,500 people have been reaching out to Congress, but we can always have more. So you can find in your resource list information for how you can add your voice to let Congress know how important ending Parkinson's really is. And hopefully we can get this act passed.

Larry Gifford: A landmark study that could change the way Parkinson's disease is diagnosed, managed, and treated is recruiting participants now. PPMI or the Parkinson's Progression Markers Initiative, needs people with and without Parkinson's, especially people aged 60 and up who have close relatives living with the disease. Take a short survey today at michaeljfox.org/ppmi to see if you're eligible. That's michaeljfox.org/ppmi.

Brian Fiske: Let's move on. I think too, we're ready now to start answering all your questions. So really excited to do this. So our team here has been, hopefully been posting some questions in the Q & A box. Our team here has been going through and sort collating some of these. So we're going to go through a few questions and maybe I wanted to start off with a question that I know we get a lot, which is the importance of stem cells in Parkinson's disease and why stem cells might offer benefit? And maybe I'll pause for a moment just for those of you who don't know what stem cells are, these are cells in our bodies that have the potential for being converted into any other type of cell on the body. So it's sort the classic stem cells or the stem cell of all stem cells, of course is the embryonic stem cell that we all come from when we're first born.

But there are other types of stem cells that can be accessed and developed, including different types of techniques people have used to create stem cells even from adult tissues like skin tissue and other types of body tissues. So it's

really exciting that we have this ability to use stem cell technology to convert them into, at least for Parkinson's disease, an important cell type that we would like to replace, which are dopamine cells. And so this idea that you could take a stem cell, make new dopamine cells and then transplant those back into the brain of someone with Parkinson's to help deliver more dopamine is a really powerful idea that's been looked at for a number of years now. So Sohini, I know we've done some work here, we have some investments here. I wonder if you could talk about some of the recent projects project that we've supported that is trying to do this and why we think it's a worthwhile idea to try out.

Shalini Padmanabhan: Sure. So I think there's a lot of interest in this area around stem cells. And Brian, as you highlighted, it is currently being tested as a replacement strategy. I would say mostly with potentially seeing if there could be disease modifying effects. But I think at this point it's mainly kind of to see if we can actually replace dopamine or restore cells in that general vicinity where the cells are lost in Parkinson's disease. There are many different approaches, and I think you highlighted one Brian, I feel, I mean stem cells, you can take a healthy stem cell and convert it into a dopamine neuron and then inject that in the brain for people with Parkinson's disease. And we have a couple of studies here, one that we had previously kind of supported that's now going on to clinical trials with BlueRock and another one that we just supported this year with Arizona University where they're actually injecting dopamine neurons into a population of Parkinson's disease patients where motor disease is the primary cause of the Parkinson's disease.

And so there are a couple of different studies, at least with this strategy, but the other approach is actually taking patients own cells and converting that into dopamine neuron. So it's more of a personalized medicine type of approach. This of course would be more expensive, would take time, but this is also something that's being tested by another company. And a third of course is you just inject undifferentiated stem cells. And this is where I think we should be very, very careful about what's being marketed out there because we definitely don't want to take something that's not been tested. And so we would always put a word of caution, especially if you're being asked to pay for some of these treatments, it's something that you should definitely discuss with your doctor.

Brian Fiske: Yeah. So again, the way I often like to frame that, I think it's a potentially groundbreaking type of approach obviously if you could replace what is lost in the brain of someone with Parkinson's disease in the context of these dopamine producing cells, but it's still I think early days. And so we're excited that we're seeing progress, like you said, a few companies with treatments in clinical testing and some work even that we're funding on this, but it's still nothing approved right now. And I think unfortunately there are a lot of clinics out there that are offering, "stem cell therapy" that if anybody's looking at those, I think it's just really important that you talk to your doctor first, that you really understand what those clinics are truly offering before assuming that it's a treatment that will actually help your Parkinson's disease.

All right, so looking at more questions here and we have a couple more sort of therapeutic ones. There was a question about the use of focus ultrasound, and I'm going to use this maybe as an opportunity to back up higher level for a second and just talk about the idea of, we talked early on a lot about the different types of traditional drug treatments for Parkinson's, replacing dopamine for example, or other types of brain chemicals that might help with the symptoms of Parkinson's. But another type of approach that has been approved for use in Parkinson's disease involves the idea of using technology to modulate the brain circuitry that is affected in Parkinson's disease. And so there's one approach called deep brain stimulation, which uses kind of a pacemaker for the brain in a way, that uses a stimulator that gets implanted along with an electrode that goes into a part of the brain that provides a signal to help modulate the circuits that are impacted in Parkinson's and can actually improve movement in individuals who receive this surgery.

There's another type of approach that uses a slightly different twist, which is, rather than stimulating the brain, goes in and tries to actually remove a small portion of the brain. So lesioning it as they say. And this was actually a surgical technique that was developed years ago and was used early on in the disease. But more recently technology has advanced where now they can do this using something called focused ultrasound. So it uses sound waves that are just directed to a very specific spot in the brain. So you don't have to do the usual open up the skull type of brain surgery, you can just do this with the focus ultrasound and it can sort of lesion a portion of the brain that somewhat similarly can impact the underlying circuit that is impacted in Parkinson's and provide some potential relief in motor symptoms and other types of movement symptoms in Parkinson's.

So these two techniques, neuro-modulatory type techniques, I think have been really powerful additions to the way we can think about treating Parkinson's. But focus ultrasound is kind of interesting because it offers maybe some other opportunities as well in addition to this lesioning approach. People are thinking about it in other ways as well. And I was going to maybe either, Katie or Jamie, if you want to jump in about what are some of the ways that people are thinking about focus ultrasound beyond that sort of just traditional lesioning approach?

Jamie Eberling: I mean, I can say that one way that's being explored is you can actually use focus ultrasound to make a small opening in the blood brain barrier. That's this protective brain barrier that prevents toxins from entering the brain, but it also prevents some types of therapies from getting into the brain well enough to have an effect. One example would be growth factors. It's been explored for the delivery of growth factors, which are extremely difficult to get into the brain without surgery. So this would be a way of making a small opening in the blood brain barrier and getting these growth factors into the brain to have, hopefully trophic restorative effects. Now it's not very advanced, it's something that's been explored, but there's certainly more work to do. But it could also be used to get other...

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Jamie Eberling: ... certainly more work to do, but it could also be used to get other types of therapeutics, like antibodies don't get into the brain all that well. It could increase how well antibodies get into the brain and perhaps make them more effective. I should also just point out that this opening in the blood brain barrier is not permanent. It's a temporary opening that then closes again. I think there's still work to be done to know how safe that is, but there's not, at this point, a reason to think that it would be necessarily not safe.

Brian Fiske: Right. Right. Right. This idea then, again, of using a technique like that to help deliver drugs that normally wouldn't really make it into the brain, I think would be really powerful and a real advance for ways to treat Parkinson's. Katie, I know you've spoken maybe to some of these groups that are trying this type of work. I don't know if you have any other insight you want to add.

Katie Kopil: That was a great summary. I know there are a lot of questions.

Brian Fiske: Okay. Okay, great, great, great. There were some questions here that relate broadly to some of the types of measurement tools that are available out there. I think one of the exciting advances in measurement in addition to the great exciting advances that Jamie talked about in brain imaging is the idea of using wearable approaches. The things we wear on our wrist and carry in our pockets and other types of ways that we can measure Parkinson's disease with these approaches. Katie, I know you've had a long history at the Foundation and working in some of these spaces, and I wonder if you could talk a little bit about how we're thinking about the use of digital wearables as a tool for measuring Parkinson's.

Katie Kopil: Sure. It's the sexy new thing. Everybody's wearing watches and has smartphones, and so, there's a lot of enthusiasm, not just from Michael J. Fox Foundation, who helped incentivize focus in this area early, but there's many, many groups working in this space. I think there's probably two flavors of groups looking at wearable measurement tools because there could also be wearable tools that stimulate various nerves or parts of your body to treat the disease, but in the measurement space, many groups are looking at wearable devices that provide insight into accelerometers, gyroscopes that look at the movement of somebody and give a more fine-tuned and continuous picture of what someone's Parkinson's movements look like that is helping design smarter clinical trials and helping groups decide is this treatment worth moving from a Phase I to a Phase II clinical trial or Phase II to Phase III because you have a more sensitive and continuous way of measuring this.

Flipping from the research to the care space, there are also groups that are invested in looking at this continuous measurement of somebody's motor symptoms largely, and then trying to time that with of an E-diary of when did you take your medication, how well is that medication working, and trying to move the Parkinson's field from where we are today, which is seeing a specialist

or a doctor once or twice a year to optimize the Parkinson's treatments that someone's receiving to where the diabetes field is, where you take daily blood sugars and you're able to empower patients to really monitor their disease and take control of the ways that they understand their medications are working and have smarter conversations with doctors. Nothing is at the point that this is the one that everybody should be using, but the field is moving in both those directions; better measurements for smarter clinical trials in the context of research, and then also pairing those measurements with a real life experience of living with Parkinson's and being able to better translate movements into care.

Brian Fiske: Again, as these continue to advance, I think it's just exciting to see the different ways they could be used, sometimes maybe in ways that we don't fully appreciate today that later on could end up being really, really, really groundbreaking. A few minutes still left and I'm noticing a number of questions people have around different pathways, biology linked to Parkinson's and how we're thinking about that in the context of different treatments. The way we tend to think of it is how do you deliver the right treatment to the right patient based on their form of Parkinson's disease?

Shalini, I might have you help me with this as we think about the different biology that have been linked to Parkinson's. We've talked a little bit about obviously alpha-synuclein. There are other types of pathways that have been associated like inflammation and things like that. How are we looking at these different pathways in the context of developing therapies for Parkinson's? You can touch a little bit about that.

Shalini Padmanabhan: No, Brian. I think the ultimate goal really for us is to match the right person to the right clinical trial and maybe at the right stage of their disease, as you correctly highlighted during the introduction here. I feel like we've made tremendous progress with therapeutics, lots of drugs in clinical trials, but we are seeing that many of them actually fail in clinical trials and we don't understand if they're failing because the mechanism isn't right or if they're not being tested in the right patient population. I think also with our increased understanding of what Parkinson's disease is and what the triggers are, what we are learning of course is that no two people have the same Parkinson's.

Trying to understand what is unique to a particular person or what is their subtype really. We believe, at least internally now, that there are some subtypes of Parkinson's disease. We don't know how many and how they can be classified because you can think about subtypes as somebody who has a motor dominant subtype or a non-motor dominant subtype, but you can also think about that at a very basic biology level. What's the mechanism that's contributing to their Parkinson's or how many different mechanisms do we really have within Parkinson's disease?

I would say despite years and years of research, I think we are narrowing down on the same four or five mechanisms that keep coming up over and over again,

and one is around protein aggregation or clumping, and that can be synuclein or it can be other proteins as well. A second one is, as I mentioned, around the energy producing components of your cell, which are the mitochondria, so around mitochondrial mechanisms. The third one is around lysosomes or the recycling centers of your cell and how can you better improve the health. The fourth one is around immune regulation or your immune system, so inflammation-related endpoints.

We all agree that these all play a role in some way in Parkinson's disease, but when they kick in or what happens first and what comes later is still a topic that we are researching and learning more about, but I think what we are trying to do now is trying to identify drugs that target many of these mechanisms. As I mentioned, we have drugs that are actually targeting the mitochondria to improve mitochondrial health, targeting lysosomes, targeting immune system.

When you think about mitochondria or immune system, it's just not one thing that you can target. There are multiple aspects of that pathway or mechanism that you can target. We are trying to get a holistic view of what that mechanism is in Parkinson's disease and see what makes sense to target when at what stage of the disease, and then more importantly, trying to identify in that broad population that we call the idiopathic PD population, what are the different subtypes that are actually present?

Do we have a mitochondrial subtype of patients and can we direct them to the mitochondrial therapies and do we have a [inaudible 00:56:20] or lysosomal subtype that would be better benefit from [inaudible 00:56:25] or lysosomal therapies? That's a major effort at the Foundation, and it's not only in the preclinical space, but studies like PPMI and many patient-driven studies are actually contributing to our understanding of these subtypes and are driven by also technological advances. I maybe stop there because I feel there's a lot we can discuss in the space, but there's a lot of interesting work that's coming along, moving along [inaudible 00:56:47].

Brian Fiske: Yeah, certainly, this idea of precision medicine is something that we're excited to see move forward. We have one or two minutes left. I might invite the panelist. Maybe highlight one thing you would love the audience to take away from today. Maybe what you thought was the most exciting thing this year or an advance that you're really looking forward to. Katie, I'll start with you just because you're top of my screen. What would you like [inaudible 00:57:18]?

Jamie Eberling: Anybody who knows me probably knows what I'm going to say. I think broadly, the emerging biomarkers, there's been just so much progress made in the last two years that the assay that Brian spoke about, but then of course, the imaging, the alpha-synuclein imaging in particular, and I think that we'll see more progress pretty quickly in that area. I think my dream of having an alpha-synuclein PET tracer that works in Parkinson's isn't far off.

Brian Fiske: Katie, what about you?

Katie Kopil: I'm excited that we know more about Parkinson's disease than ever before because of research participation, and no amount of research funding is going to bring new treatments to the community without participation in clinical trials, so I'm excited about the awareness of clinical trials that's been raised through the COVID experience and I'm very grateful for everybody that's been willing to raise their hand to participate in online surveys or in-person clinical trials. Thank you for that gift. You're making our understanding of Parkinson's disease immensely more rich and patient centered.

Brian Fiske: Shalini, finally, with you.

Shalini Padmanabhan: Yeah, I can't beat those two, so maybe just to provide some variety, I would say there's a lot of studies going on around genetics. What we learned about genetics 20 years ago is just the tip of the iceberg. I feel now with the studies like GP2, we're going to learn much more about the genetic causes of Parkinson's disease. It may not be just one or two genes. They may be a mix of genes that may be contributing to different people's Parkinson's, so I'll leave you with that and that's something that's super exciting.

Brian Fiske: Great. With that, we'll close today at the top of the hour. Again, thanks for participating. Hopefully, this has been helpful to you and informative to you. Again, check out the resources that we provided, including that year in review publication, which touches on some of the advances that we talked about today if you want to refresh your memory a little bit about what we discussed, and again, just wish you a happy end of the year and look forward to talking to all of you again. Thank you.

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