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You're listening to audio from a recent panel discussion in New York City. Foundation staff shared the latest in Parkinson’s research with members of our grassroots fundraising community, Team Fox. Listen to the Q and A session from the panel in a separate podcast on our website and in your podcast app.

It's great to be here today. Again, my name's Dave Iverson. I've stepped away from most of my connections with The Michael J. Fox Foundation in terms of being on the patient council and many of my duties of hosting podcasts and webinars and the like, but I can't seem to step away entirely. I said to a few people yesterday when I was at the Foundation that coming there is like coming home and that's because of the extraordinary nature of the Foundation and the community of which we are all part. So it's a great pleasure to be here today and thank you for all that you do, all through the year, and for being here today.

What we're going to do for the next 50 minutes or so is have a conversation about where we are currently with research and the latest in new developments with both symptomatic treatments and disease modifying treatments and where we think we may be going. And then at the end of that session, we'll have time for your questions. So you should see on your table little index cards and there should be pens there as well. So if questions come up during any of our conversation, jot down your questions and then towards the end you can just kind of hold them up and if I'm on my game, I'll remind you to do that. Then we'll collect those questions, staff will come around and pick those up and we'll spend our last half-hour, 20 minutes to 30 minutes answering those questions.

So let's get started and I'm going to advance to a slide of some of the topics that we're going to be talking about. We want to talk about some new developments with new symptomatic treatments, things that make a difference in terms of how those of us who have been diagnosed and live with Parkinson's deal with our daily lives. And this was a significant years in many ways, Rachel Dolhun, because of several new drugs that have been approved or a drug and a new treatment that have been approved, one that's we hope nearing approval, and that the Foundation played a key role in. So let's talk about one item in particular, which is things that focus on off-episodes, when your medications aren't working. And this has been a long unmet need. And there was a key one ... Let's talk first about something called Inbrija, which is newly and that the Foundation played a key role in getting started.

So Inbrija, as you mentioned, is a new medication. It was approved in December of last year, just hit market I think last month. And this is an inhaled form of Levodopa. So many of you are familiar with Levodopa. It's our gold standard medication for treating Parkinson's. It's very effective for the movement symptoms, tremors, stiffness and slowness. Most people take it at some point in the course of their disease, with the course of their life with Parkinson's. And
this medication is an inhaled form, as I mentioned. So it's sort of similar to an asthma inhaler. The way that it's a little bit different from the Levodopa that many of you are familiar with is that it's used as needed. So it's added on to your regular regimen of Parkinson's medications and it's an on demand medication.

So when your symptoms come back, maybe in between medication doses or suddenly or unexpectedly, or in the morning before you take your first dose of medication, this can be used as sort of a rescue type therapy that you can take a puff of and get you on quickly. In trials it worked as early as 10 minutes and lasted up to about 60 minutes, so that it can sort of bridge that time when your medications aren't working and you're off and can't function as well as you need to and want to and then your regular medications can kick in. So this really met an unmet need where people were having a lot of off-time, where symptoms were coming back unexpectedly or being very unanticipated and were limiting people's quality of life. They said "I didn't want to go out in public because I wasn't sure if I was going to be off," or "I was having trouble at my job because I was going off, or my medications were wearing off." So this can be sort of an add-on, as needed, on demand medication that can be used in addition to your regular medications.

Dave Iverson: I'll always remember my colleague Steve Dewitt telling me once that he had a friend who was an electrician and that if you're an electrician with Parkinson's, off-episodes are a really bad idea. So it's a real difference that I think the Foundation has made. Before we get to the other almost there we think a therapy for off, why don't you chime in for a moment, Sohini, on the role the Foundation played, because it represents a key first for The Michael J. Fox Foundation.

Sohini: Yeah, you know, the Foundation has long been known for breaking down silos and for basically trying to encourage the collaboration and the partnering across a lot of the different stakeholders that are required in getting a drug into a patient's hand. And so one of the exciting this about the Inbrija case is that this is a great example of what we call our de-risking strategy. And in a nutshell what we mean by de-risking is being able for Foundation funds and support to be able to push things along in the early stage of development, to the point where it can move forward in sort of later stages of development because there's more funds available. And in this case, Inbrija got funding from the Foundation to support some of its early clinical testing of the drug. And after that funding was no longer really required, we continued to play a role in helping to support its recruitment efforts.

And I think it's a wonderful example of showing how the Foundation's sort of support in both the early and the late stage really accelerated things. It accelerated it in the development plan by giving it the necessary funds and sort of the stamp of approval to be able to move forward with its drug development. And then in the later stage development phases, we were able to utilize our knowledge in how to communicate to the Parkinson's community, our best
practices of recruitment, to ensure that the study could be run in the most efficient way possible and really, as quickly as possible, get to the answer. Is this drug making an impact on patients' lives?

Dave Iverson: And it's also I think an interesting example of the time it takes and the long view you have to have to get these things done. I remember interviewing Glen Batchelder who was the head of the group that started, I believe, this drug Civitas. And it was probably five or six years ago when the Foundation I think first became engaged with it. Five or six years seems like a long time, but actually in the world that you live in and that you worked in in the pharmaceutical industry, Marco, that's kind of ... That's quick. And it shows what a difference that kind of intervention that the Foundation did can yield that eventual result.

Marco Baptista: Yeah. Drug discovery takes a long time and I think one of the central roles of MJFF is to try to speed it up and we do it in many different ways. In this example, we did it by working with Civitas and I think the metric of success from this is twofold. One, that you now have another company that has more of the funds to be able to push it over the line, Acorda purchasing Civitas. And then secondly, it's now available for Parkinson's patients.

Dave Iverson: And let's talk then about another off-therapy for off-episodes, Rachel Dolhun, that has a lot of appeal, seems to have worked well throughout the clinical trial process, but the FDA has sort of put a hold on it for now. We're still quite hopeful about it, as I understand it, but bring us up to date on that one and perhaps as a way of showing that there are always bumps in the road sometimes and you have to find your way through those too.

Rachel Dolhun: Yeah, so this is, as you said hitting a little bit of a speed bump, but we hope it's going to get over that little hurdle and make it through to the end and it's under FDA review right now. So this is what we call sublingual or under the tongue apomorphine. And apomorphine is a drug that's used in Parkinson's. It's what we call a dopamine agonist. So it mimics the effect of dopamine, that brain chemical that goes missing in Parkinson's. And this drug actually is currently available for Parkinson's right now as a rescue medicine for when people go off unexpectedly or between medication doses, as I was describing earlier. But it's an injection. So injections, for many reasons, are not the most attractive thing. So it can be hard to give yourself an injection in the middle of an off-episode. You might not want to give yourself an injection for many different reasons. And so this medication had been reformulated into a strip that you can just sort of pop under your tongue and it dissolves, similar to a Listerine breath strip.

And so the idea very similar to what I was speaking about earlier with that asthma inhaler type inhaled Levodopa is that you would pop this strip under the tongue when you go off, or when you're wearing off in between medication doses, and it would take you back on and control your symptoms fairly quickly. In trials it's worked in as quickly as about 10 minutes and lasted similarly about
30 minutes to up to an hour. So again, it bridges that gap that can happen when medication isn't working very well.

Dave Iverson: And any thoughts or any forecast, Rachel, as to kind of what's next in terms of what still needs to happen for it to meet FDA approval?

Rachel Dolhun: We're not very sure about that. I think that some of what happens with these medications that are sort of devices, like the asthma inhaler and this strip, it doesn't sound very much like a device, but there's a little bit that goes into making sure that it's administered correctly. So the right part of the strip that has the medication on it is going to the right part of the mouth at the right time. So the FDA, I think, wants to make sure that people are administering this medication correctly. And so I think that's a little bit of the glitch that we've hit here. And so it's really a matter of making sure that we get over that hump.

Dave Iverson: Let's talk about one other approval that happened in this past year, which is something called focused ultrasound, which in some ways is a bit analogous to the apomorphine strip as compared to an injection. Ultrasound has some of the same benefits as deep brain stimulation, but it's without the surgery. So describe what it is, what it's useful for and touch on the role that the Foundation has played in supporting it as well.

Rachel Dolhun: Focused ultrasound is sort of a non-invasive surgical procedure, if that even makes sense. And this was approved late last year as well, for tremor in Parkinson's that doesn't respond to medication. And focused ultrasound is sort of the new trick on an old surgery. So even before we had deep brain stimulation, we would do surgery for Parkinson's. So doctors would actually open up the brain and go in and actually damage brain cells, very small area of the brain, but create a little what we call lesion and damage brain cells that are involved in that circuit that's misbehaving that's causing the movement symptoms. And then many years later we developed deep brain stimulation. So we would actually put electrodes in, in that same circuit, and interrupt that abnormal, that misbehaving circuit with electricity that's delivered by those electrodes.

And that became very attractive because we can modify that electricity and it's reversible. We can take it out if it's not working or we don't like it or there's a problem with it. Now, we've sort of moved ahead and gone back to the old surgeries with focused ultrasound. And what focused ultrasound does is focus ultrasound beams from outside the skull onto that area of the brain where the circuit of cells is misbehaving. And similar to those old surgeries I was talking about, it creates damage to those cells. So it creates an irreversible lesion or spot of damage to those cells that can't be undone, just like those old surgeries couldn't be undone. It interrupts the motor circuit that's misbehaving, so it stops the symptoms, but we can't undo it. We can't reverse it like we can with the brain stimulation. So it's a good option, it's a new option for people who maybe can't undergo deep brain stimulation for one reason or another, or don't
want deep brain stimulation or one reason or another, and it's expanding our available options for doctors and patients.

Dave Iverson: So it sounds like there are a few trade-offs with it, that on the one hand it has some pluses, you don't have to go through surgery, you don't have to worry about battery replacement like you do with DBS. On the other hand, it can't be undone in the way that DBS actually you could sort of turn it off. And this way there's no turning it off once it happens. Let's widen this out a bit more and talk about the philosophy behind bringing these things to fruition, like we've just heard, but form a philosophical standpoint of the Foundation. Sohini, as the Deputy CEO, but also then from a science standpoint. How do you take that philosophy and make the choices you do as scientists? So unmet needs, we've talked about as something that's key. Finding gaps in care as something that motivates the decisions that the Foundation makes. What else is part of that matrix that governs the way in which the Foundation says "We're going to fund that, but not that?"

Sohini: Yeah, that's a great question. It's one that we often get, because at the end of the day, although the Foundation is able to raise and, thanks to many of you in the room, quite a lot of money to pour into Parkinson's research, it's never quite enough. And so we are asked to make trade-offs about where we're going to prioritize allocating those funds. And so when we think about it, we sort of think about it at the highest level in two areas, if I can call it that. One is how can we best impact Parkinson's patients today? What can we do to improve quality of life, to improve the management of their symptoms, et cetera? And that can fall both into supporting therapeutic development, like we heard, helping these therapeutic approaches, go through the phases of development and make their way into patients' hands.

But it can also include, and I know that we'll touch on this a little bit later, what we can enablers, things that aren't about the therapeutics, but they enable the therapeutic development to happen. Things like biomarkers, or research tools, or clinical scales. And so we dedicate a lot of our resources in understanding okay, in the activities that could really make an impact in patients' lives today, where should we play a role, either because people aren't paying attention to that area and we want to stimulate activity there, or because there is activity that's happening but it's not happening as quickly enough? And there's a role we can play, to Marco's point, to accelerate things by putting some extra funding, to putting know-how, to create the necessary tools, et cetera.

Dave Iverson: Well, let's talk then about a specific example that we see on our screen now. It says funding 3,000,000 in technology to treat gait and balance issues. Covered Levodopa many of us in the room take. It's great at certain things, not so great when it comes to gait and balance in particular. So this is an example of this. And this is something that the Foundation has decided to make a push on and to do it with a pretty expedited timeline. We only want to fund things that will happen in a couple of years. So now as a scientist, Dr. Baptista, how do you go about sort of making those determinations? And then Rachel, I want you to
chime in a little bit on how you see that from a movement disorder specialist standpoint. So how do you do that?

Marco Baptista: Yeah, so the scientist on staff at The Michael J. Fox Foundation, part of our role is to identify scientific gaps. And scientific gaps that we feel that if we don't bring people together, in groups together that normally wouldn't be working together, that the answer will not be solved. At least it won't be solved in a short period of time. So it's with that perspective that we always go into work and think about the scientific gaps. And then I think something that's great about the Foundation is that we are such a neutral brand. We're here to find a cure for Parkinson's disease and nothing else.

Dave Iverson: As Michael always says "Purity of motive."

Marco Baptista: It's purity of motive and people understand that. And we start to build a culture where we can actually get around the table pharmaceutical competitors that normally wouldn't be talking to each other, but they understand what the scientific gap is, they understand that they're not going to do it alone, and you start to build a culture that if they're feeling that if they're not around the table, that all of a sudden they're at a competitive disadvantage, which is a really interesting way that we can change the culture so that it's not a culture of being in competition and not sharing data, because I think not sharing data and having that open flow of communication really slows down already a very slow drug discovery process.

Dave Iverson: Sort of when Andy Singleton in the video we all said makes the comment at the very beginning of that video, is a noted geneticist, that the idea of bringing academics and research together and pharmaceuticals 15 years ago would have seemed like "How are you going to do that?" It's a bit like what you teach kids in preschool. You've got to share, right?

Marco Baptista: Yeah, yeah. And I was ... Exactly. And I was in the pharmaceutical industry and I know that if you're presenting to upper management what work you're doing, there's always going to be slides that you show about what your competitors are doing. You have a competitive landscape slide that you show. And I think we're changing the culture so that if industry folks are talking to their upper management about what they're doing, they're going to be asked "Are you working with The Michael J. Fox Foundation? Because we know that our competitors are working with The Michael J. Fox Foundation and that puts you at a disadvantage."

Dave Iverson: So let's bring this into the world of gait and balance, Rachel, and sort of how we're approaching that, the kinds of things, strategies that are being funded and the role that patients are ... Two of my colleagues on the patient council [inaudible 00:18:34] played in reviewing some of those proposals and focusing them on things that can help and help now, as opposed to 15 years from now.
Rachel Dolhun: And for every reason you just detailed, this is one of my favorite projects we're doing right now because it has the potential to help one of the most troubling and bothersome symptoms of Parkinson's that you can't get at well with medications, with surgery, with focused ultrasound, with the new treatments we just described. And these new out-of-the-box, out of medication, somewhat sci-fi sounding therapies have the potential to help now. So while we work toward disease-modifying therapies, while we work toward better symptomatic therapies in other ways, these are just these really cool, novel, merging technology with other ideas that have the potential to help now. And they brought in the patient voice. So where we heard from people in the community saying "This is a really tough symptom. It interferes with my life. It limits my independence. I don't want to go out. I can't do the things I want to do. I can't exercise as well as I need to and because of my walking and balance problems."

And that's all a long way to lead into saying we decided we were going to fund gait and balance projects that weren't just based on medication, but brought in technology. And with that we brought in the voice of two of our patient council members, Israel Robledo, who is here, and Ken Cater, to not only say what's a good idea, what seems to make sense, would you use these vibrating socks that will vibrate when you're frozen and will get you going again, but also does this protocol make sense? Can we make you go off your medication all night and bring you in to test this? And they're like "I don't know about that." So getting that voice from the get-go, what makes sense, what will you use, along the way, is really important, that I think these have the potential to really make a difference in people's lives today, or within the next two years.

Dave Iverson: And you were only funding ... One of the criteria was you would only fund something that could be brought to fruition in two years.

Rachel Dolhun: Right.

Dave Iverson: Which is like lightning speed. So just one follow-up on that and then we'll move to our next topic, but I'm curious, Marco, within your world again, as a scientist, I'd love to imagine you being at some group of scientists presenting and you're saying "Well, the latest thing we're funding at The Michael J. Fox Foundation is vibrating socks."

Marco Baptista: Right.

Dave Iverson: But that's in a way, to me, that's sort of perfect because it shows that the Foundation isn't afraid and is willing to kind of go places.

Marco Baptista: Yes, we definitely are very open. All the scientists are extremely open to new ideas and we want to think out of the box. We don't have this hubris into thinking that we have all the answers, so we're very open to seeing what people have to present to us and I think this gait and balance technology review that we did was both innovative, as Rachel was saying, both in what we did fund, like
vibrating socks, and how we actually conducted the review. That is a very
innovative way, very patient-focused way to do a review and it's not a common
way to do it, but I hope to see more reviews being carried out like that.

Dave Iverson: Yeah, I think it's a terrific example of what the Foundation is and how the
Foundation approaches things. Let's move to another topic which has to do with
cognition and the cognitive impairment that often happens in later stage
Parkinson's disease, of particular interest and focus of Rachel Dolhun.

I think this again is a huge unmet need. I think probably everyone here in the
room today either knows someone who is dealing with that or who may be
approaching that problem, or if you have a Parkinson's diagnosis, you worry
about that as happening to you at some point.

This is as personal as it gets, and it should be personal. That's also I think part of
what's key to the Foundation, is that it's personal. Walk us through a little bit of
what's happening, because this is a new area that the Foundation is really
focusing on.

There are a couple of new areas of treatment that involve everything from
blood plasma, to looking at the role of inflammation in cognition. What are you
looking at? What are your hopes for that Rachel?

Rachel Dolhun: Just like gait and balance, cognitive problems in Parkinson's are a tough one.
They don't happen to everybody, but they can. There's a wide spectrum of
them. There's mild cognitive impairment where there are changes in memory
and thinking that are noticeable but don't impact your everyday life. You can
still get around them to do everything you want and need to do.

Then there's the opposite end of the spectrum, which is dementia, a very scary
word we often equate with Alzheimer's, but in Parkinson's may impact more
thinking more problems, processing, decision making, judgment, and does so to
such a significant degree that it does impact your everyday life. People need
help to do things that are part of their everyday activities.

This wide spectrum of cognitive problems in Parkinson's is something that we
don't talk about enough because it's a scary topic. It's this thing that has a lot of
stigma attached to it. It's something that we need to address more because
much more research and work needs to be done in this area.

We need to understand more about it, so understand more of which brain cells
are involved, how they're involved and why. What brain chemicals are involved?
To what extent and how we can target those?

There are a couple different projects looking at inflammation in the brain and
how that can impact and be a potential marker for dementia in Parkinson's.
Looking also at the protein that we associate with Alzheimer's, the amyloid beta
protein you hear a lot about, and how that is involved in the brains of people with Parkinson's. How that might correspond with other proteins that are involved in Parkinson's and have a synergistic effect in causing cognitive problems or dementia.

Then we're looking at ways to measure these; inflammation, measuring the proteins. We can't see these proteins very well until autopsy. Can we image them in a living brain? Also, developing scales to accurately measure how a person is living with any kind of cognitive change.

There's a lot of difficulty because people are slow with Parkinson's. Defining is slowness because your movement is slow, or slowness because your thinking is slow? Separating exactly what is cognitive problem in Parkinson's, how we can define that and track it over time, and validate it so that the FDA sees that and recognizes that as a measure for our studies when we're looking at these new drugs.

Dave Iverson: If I can just underline that for a moment, because I think that's another key thing the Foundation does that's not always super sexy, it's not as exciting as, "New drug approved." In order to get that new drug approved, sometimes you need the measurement device, that scale.

The FDA says, "How do we know that it makes a difference?" The way you know it makes a difference is if you have a way to measure it. Developing those scales actually plays a really critical role in something eventually getting that sexy headline.

Rachel Dolhun: That's exactly right. Sometimes we need that scale before or in addition to the drug development to move it forward. Those are helpful field wide.

Lastly, there are many things in the pipeline to help with everything from mild cognitive impairment all the way to dementia. As Dave mentioned, there are things like, it sounds science fiction-y but there's something called young plasma; taking plasma from younger people and infusing it. There are thought to be proteins and factors that stimulate the development and regeneration of cells that are helpful for cognition, new drugs that work on new targets.

There are many things in the pipeline that are working on mild cognitive impairment which we don't have medications for right now in dementia and Parkinson's.

Dave Iverson: One quick thing before we move on to our next slide Rachel, you're also developing a guide for how to deal with this problem, for both patients and their loved ones to contend with cognition issues.

I think that's going to be so important and so helpful to this really difficult problem. When will that be coming out and what can people look forward to?
Rachel Dolhun: We hope to deploy this guide in June of this year. The idea behind this is that as we mentioned, this is a hard topic to talk about, it's not talked about enough.

What we want to do is open the door to conversations with you, with your families, with your doctors about what happens with cognition and Parkinson's. I think people don't focus on it enough whether it's because we don't want to know what may happen, doctors are focusing more on movement symptoms and don't mention that this can be part of Parkinson's.

The idea is that this will help understand what you may be experiencing now or in the future, how to navigate all those aspects of cognitive problems in Parkinson's and understand the ongoing research and connect to it.

Dave Iverson: Great. All right, let's move on to the other big topic within our world, which is all these things we are talking about help with the symptoms of Parkinson's, but what about stopping the disease itself, which is of course in the end what we most want to accomplish.

We're going to drill down into some of the genetic areas in just a moment, but as a way of setting that up a bit, Sohini, take us back again to the overall mission of the Foundation. If we could stop progression, then you'd never wind up with those cognitive issues because that happens late in the disease. If we could just put it on hold, that in itself would be a huge accomplishment.

Sohini: Exactly. If you get back to what I was saying earlier about our philosophy and how we figure out where to put the money that we raise, that the Foundation has as its disposal, I talked about thinking about the patients in the here and the now. Today, what can we do to improve lives?

The other part of what we're focused in is, again if you want to think about it in its broadest terms, cure. What exactly do we mean by cure? For us, a lot of this science around the concept of cure is this concept of disease modification. How do you modify the disease to either slow the progression of it or halt it completely from progressing?

If you think about it real world terms, the day that an individual is diagnosed with Parkinson's disease, what if you were given some sort of intervention and that's it? It will never progress further. You having Parkinson's will stop at that point and you will live with the state that you're in at that moment.

It may not be considered "a cure" in the purest sense of the word, but for many people I think in this room, patients and loved ones who have seen the effects of Parkinson's disease on individuals they know, you would probably argue that pretty much would be considered a cure.

I think that is the second part of where we think about, "Where do we allocate our funds? How do we move that concept of disease modification from that, a
That can again involve a real broad strategy of enablers, tools that are required to help progress things, generating knowledge about the disease, how and when should you intervene? Finally, helping to actually develop that therapeutic.

Dave Iverson: Let's move into some of those areas now. We'll start with some of the genetic possibilities out there that are now, and this is incredibly exciting I think that many of these are now in clinical trial. Five years ago, we wouldn't have had any I don't think. Is that right? Any disease modifying drug in clinical trial.

Sohini: Yes.

Dave Iverson: Now five years later, here in 2019, we have something like 40 different disease modifying things that are being tried. Not 40 different ones, but 40 different clinical trials.

That's an extraordinary achievement. Genetics are key to this Marco Baptista. We sometimes think, "Gee, genetic mutations only account for a relatively small percentage of those of us with Parkinson's, why focus on that?"

Begin with that if you would Marco, why focus on that? And some of the really exciting news from this past years that some of those things that we're learning from genetic defects may actually be of help to everyone.

Marco Baptista: Yes, I get that question a lot; why are we so interested in a genetic cause of Parkinson's disease when we know that the majority of Parkinson's patients don't have genetics that are driving the pathogenesis of the disease?

The answer is that we don't know the cause of Parkinson's disease in general. If 10% of the population we know has a genetic cause of the disease, that means 90% of the patient population, it's completely unknown. Scientifically, there's a lot of value to latch on to something which we know with the genetics is causing the disease.

Dave Iverson: Not that I often quote Donald Rumsfeld, but it's the known known.

Marco Baptista: I can't believe you just ... Yes. With the 10% that we know that there's a genetic cause, we've been digging really deep into trying to understand that particular part of Parkinson's disease.

What we've been finding is that even though genetically it might be different from the 90% that don't have a genetic cause, the biology is actually quite similar. That's really exciting.
It's almost like we're taking what's happening in the cancer field, which is more of this precision medicine, where right now we talk about cancer in a particular way that's very specific to the individual type of cancer that exists. That's happening in Parkinson's disease, but we do see that the learnings from the genetics is going to be generalized to the rest of the population.

I think you alluded to a publication that came out recently that in example of one genetic cause of the disease, LRRK2, that there is now building evidence that even in those individuals who have no mutations in the LRRK2 gene which increases the risk of Parkinson's disease, they were seeing increased LRRK2 activity in those cells.

It's enough that it's actually driving companies to think that they are going to be able to develop drugs that were designed specifically for those genetic carriers, but they think that they can extend it beyond.

Dave Iverson: To go a bit deeper on that example Marco, LRRK2 is a gene that makes a protein. Everyone has the LRRK2 gene, it's not just people-

Marco Baptista: Almost everyone has it.

Dave Iverson: Although only a small percentage have a mutation that puts you at risk, what we're learning is that that protein, whether you have the mutation or not, may be a clue to solving the riddle of Parkinson's for everyone?

Marco Baptista: Yes, exactly. As you mentioned, you get a LRRK2 gene from your mother, you get a LRRK2 gene from your father. If one of those genes has a mutation, and all that means is that there is a disruption in the DNA code so that it's product, in the case of LRRK2 it's a protein which has a function in the cell. If it's mutated and not functioning properly, you have over your lifetime about a 25%-30% increase likelihood of getting a Parkinson's disease.

The underlying biology that we're learning about LRRK2 by studying people who have the mutation and by setting those individuals that don't have mutations, is that there are commonalities. There's a thread that is a common denominator that we think is linked to alpha-synuclein, which I'm sure we'll talk about, which is part of the pathogenesis that most if not all Parkinson's patients have. It ties into inflammation, which we're starting to understand a little bit better, that is linked to Parkinson's disease. Also, your recycling centers that you have in your cells, we call these lysosomes.

We're seeing that all of these different genetic causes of the disease are linked to these pathways that we think are disrupted in all patient with Parkinson's.

Dave Iverson: It feels like we're beginning to piece some puzzle pieces together. That we know inflammation is important, we know how the cells get rid of stuff is important.
Many of these things are linked that then lead to that sticky protein alpha-synuclein killing off the key brain cells.

Is there a scientific sense of that, that this giant puzzle is getting a bit closer to being put together?

Marco Baptista: Yes. The idea of a unified theory of what's causing the disease, that's a holy grail that we're trying to achieve. This is what the science is leading us to. At MJFF, what we try to do is fund the best science and then follow where the science is taking us.

Right now, the science is taking us to those pathways that we think are common in all Parkinson's patients. We've learned a lot from genetic carriers of the disease that we think can generalize to everyone.

Dave Iverson: Briefly Marco, just give us a quick snapshot of where we are with the clinical trials with not only LRRK2, but also GBA and these other trials that we're also now testing drugs that might fix that mutation problem.

Marco Baptista: Yes. To your point earlier when you said that in the last five years there wasn't any real disease modifying therapies out there in the clinic, when I was learning about Parkinson's in school, we didn't talk about a genetic cause of the disease. When I used to go to conferences, we'd always talk about dopamine.

Now you can go to a conference and there's barely any discussion about dopamine, or indirectly dopamine through these genetic causes that we're studying.

Maybe I can give you an example with LRRK2 and give you a sense of how long it takes for drug discovery to happen and how MJFF has been trying to shorten that time. The discovery that a mutation in the LRRK2 gene can increase the chances of you getting Parkinson's disease happened back in 2004.

Two independent labs made that discovery, 2004. 2017, the drug went first in human. During that time from 2004, it was a lot of laboratory bench work that was being done, all these what we call pre-clinical studies are being conducted. All the way until 2017, it was deemed for this one particular company Denali, which we had worked with quite a bit. We worked with them also when they were, a lot of them were in another company called Genentech.

In 2017, a human for the first time took it. Now they're have been well over 100 individuals, mostly healthy individuals that have taken a LRRK2 kinase inhibitor. In 2018, for the first time it's gone into Parkinson's patients.

That does seem like a long time, 2004 to 2017. In the grand scheme of things of normally how drug discovery works, this was pretty fast. I think a big role in Denali openly makes these statements in public, that they feel like The Michael
J. Fox Foundation really helped accelerate them getting into the clinic. We did it in many different ways.

Dave Iverson: I think it's also a reminder of what all of you have done who are in this room today is so key in why we have to keep our shoulder to the wheel for the long journey. Whether it's Pancakes for Parkinson's, or Fox Trots, or whatever it happens to be, that's what pays for making these things happen. We have to keep flipping those pancakes and running in those runs.

If you could take this, I'm really fascinated by this idea Rachel, and maybe you can bring this together a little bit further from what Marco has already said; this word inflammation that we keep hearing about, and that it might play a role in cognition, that it might play a role in what LRRK2 is doing, that it might play a role in the cells that aren't working quite right in getting rid of stuff.

I'm interested in your perspective on that as someone who saw patients as a movement disorder specialist and who knows plays the role you do at the Foundation; tell us what that means exactly, inflammation? We sort of think inflammation as, it's what happens when you have an infection or something. How does that translate into what's going on in the brain?

Rachel Dolhun: Inflammation is a tough one. We know that there is inflammation associated with Parkinson's. That on the simplest level means that the cells involved in creating an inflammatory reaction, that as you mentioned, is a normal reaction that happens with infections that we want to fight, or other bugs or things we want to get rid of, is there.

It's there in the brains of people with Parkinson's, we see it. What we don't know yet is whether that's causing Parkinson's or it's a consequence of Parkinson's. There's been a lot of especially early work to understand more of all these mechanisms. There are a lot of cells and a lot of factors we call them that are released from cells that are involved in the immune response and in inflammation.

Talk about a puzzle, this is a big puzzle to understand which cells are involved, how they may be involved, if they're causing damage to the movement cells, to the cognition cells, how they're causing that damage, if we need to interfere to stop that damage, how we need to interfere to stop that damage, to what level?

Again, you need an immune response to fight infection and do good things. It's a matter of balancing that.

Dave Iverson: Let's talk about two other treatments that in some ways also touch on this question of inflammation. These are what we call repurpose drugs, drugs that were designed for another purpose, but now we think may apply to Parkinson's.
One's showing a lot of promise, Nilotinib, a leukemia cancer drug. Another, Inosine, which is designed to boost uric acid urate levels, which hasn't worked out. Both tied in some ways to this same question. Marco, tell us a little bit about what's going on with Nilotinib because that's gotten a lot of attention. Also, what we learned from failure in a case like the Inosine trials.

Marco Baptista: Sure. Just in general, just so you understand how we deem something of priority enough that we make an investment in it; for a repurposed drug, meaning something that is normally been designed to give for another disease indication besides Parkinson's disease, it's either data that is pre-clinical data, data that's done on the bench that indicates that potentially it might have a neuroprotection effect. Or it's through epidemiological studies, so looking at correlations.

For the example with Inosine, Inosine is a precursor to urate, there's a correlation of higher urate levels with less of an incidence of Parkinson's disease. Those two sources of data that we take into account to then make a determination if we think there's some promise and we support it.

Nilotinib is more of the former, it's more that data was that generated pre-clinically that was suggesting that potentially Nilotinib, which is a second generation cancer drug originally for chronic myelogenous leukemia, that it potentially could be protecting cells by working through inflammatory pathways or through that recycling center that I was talking about inside the cells.

Currently, there are several trials that are ongoing right now. We're supporting one called NILO-PD, we've just successfully completed recruitment, which by the way is a big deal. It's something that really slows down drug discovery process in clinical trials, is getting people to participate in clinical research. Quite an accomplishment with Nilotinib that we've reached our recruitment goals.

Now we're analyzing the data to actually see if something that originally was designed to help cancer patients can help Parkinson's disease. We yet don't know what the answer to that is, and we'll keep everyone updated.

With regards to Inosine, we now do have the results. Again, Inosine is the nutraceutical to increase urate levels. It didn't reach its primary endpoint, it wasn't helping the Parkinson's patients as was originally designed for the clinical trial. But these were, it was a very well-designed trial and we think about that quite a bit when we're going to make an investment. Given the attrition rates in the clinic, given that the last numbers I saw something not higher than 9% of clinical trials that start in phase I actually make it to FDA approval, so it's very dismal numbers and we always have that on our radar, what can we do to ensure that we support very informative trials, and for the inosine trial, the trial's called the SURE-PD3, and the way that we support it in the past, we made sure that we incorporated wearables into that study. We incorporated brain imaging scans, we incorporated other types of outcome measures so that we can extract as much information as possible.
Dave Iverson: So are there lessons learned from that.

Marco Baptista: Hopefully there are lessons learned and more data that we can analyze.

Dave Iverson: And from a Foundation, again, standpoint, from the management and direction of the Foundation, that you and Todd share and lead, is it important not to be afraid of failure?

Sohini: Absolutely. I mean the reality is drug development is extremely complex, it's extremely risky, and there's no greater engineering that exists in the world than our own human body so chances are many of the things that we're going to try are going to fail, but the point is I think we all know that's going to happen, there's going to be a high failure rate, but to Marco's point, how do you make failure informative? Because it's one thing to fail, it's another thing to fail and be able to get data out of it that will then be able to allow you to design something better down the road, improve something, add something, so that we continue to kind of raise our chances of moving from failure to success.

And I think that one of the things we've realized is that even if we don't have a direct funding role in a study and in this case, the inosine trial is a phase III NIH funded trial, we can still play a role in the design in helping to support the addition of imaging and other factors that will make it much more informative, so even if it fails, we're not walking away with nothing. We're walking away still with a really important pool of data that will continue to build our knowledge about the disease and about what's going on in an individual as they're being given different things targeting different pathways.

Dave Iverson: Let's use that then as a way to move on to our next topic, which is some of the things that the Foundation does that go beyond actually the role of funding, and in about 15 minutes or so we're going to start taking your questions, so if questions have come up in the things we've said, even though I know we've been incredibly clear, if there's anything that you'd like further clarity on or just a completely different question, jot those down, hold them up, and someone from the staff will pick them up and get them organized and they'll bring them up to me in about 15 minutes. So go ahead and write those questions down, hold them up and we'll get to them.

Okay, let's talk some about some additional things that the Foundation plays, the role that the Foundation plays. One of the first things we see on the slide, Rachel, is the Edmond Safra Fellows in Movement Disorder, and movement disorder specialists of course are the neurologists who specialize in Parkinson's disease and other movement disorders. They're crucial for those of us who live with that condition, and not everyone gets to see one. The fact is in our patient council meeting yesterday, Hadley Ferguson, who's from Montana made the point there's not a single movement disorder specialist in the state of Montana. There's like one in the state of Oklahoma where another one of our ... Nicki Jarvis who lives in the state of Oklahoma. There's a tremendous need for this.
What are we doing to try to encourage more movement disorder specialists to entering the field?

Rachel Dolhun: Right. There aren't enough of these specialists, there aren't any in certain areas, and we need more now and we're going to need more in the future. Movement disorder specialists, people who see them say they feel better about their care, they feel more informed, they're more up to date on research, so this is a really important resource is a movement disorder specialist, and lack of funding for their training is one of the biggest issues. So in 2014, we established this initiative in partnership with the Edmond J. Safra Foundation where every year we fund five academic medical centers around the world that then train a new movement disorder specialist over two years so that over those two years, this movement disorder specialist becomes not only an expert doctor in caring for people with Parkinson's and other movement disorders, but also an expert researcher. So they have that unique skill in that they're not only caring for people but also getting those insights directly from their patients to inform the research that patients need.

So we've already funded enough for 21 fellows who are in training or already graduated and we've got enough to graduate 41 fellows up to the year 2025.

Dave Iverson: And just make sure one of them goes to Montana and Oklahoma and many other places that are in great need of course. I'm going to go a bit out of order here and ask you something that you referenced earlier, Sohini, first and then we'll come back to the workshop and their kind of expert convening role that the Foundation plays. Again, tools sounds not very interesting stuff, like what are you doing? What does that mean? I have, when I think of this image of like a workshop or a warehouse and in some ways that's informative because if you think about a workshop or a warehouse, they'd not only have to build something, they'd have to make the tools to build that something, it would slow that down. They wouldn't be able to just manufacture what they wanted, they'd have to make the tool that makes that thing. That's some of what you do in a sense, is you free scientists from creating those Petri dishes or mouse models or whatever it happens to be, so that they can get right to the science.

Sohini: Yes, that's correct. So again, when I kind of think of this concept of enabling, enabling and accelerating therapeutic development. What we want to do with our tools is basically create those things that will allow a lab to be able to test easily, to get access to the models that will give them the readout they need to say this is promising, this is not, and move it forward.

One of the especially unique things that I don't think we often highlight but is really germane to the concept of tools and moving things forward is that by creating a catalog of tools that are available for the community. We're also in essence providing a sense of uniformity in how things are being tested in the lab. So rather than homegrown models or tests or whatever occurring from lab to lab, you have a pool of resources that we all know that have been characterized, that have been published on, etc., and things are being tested on
those pools, and so we're able to have greater confidence in understanding what the results are telling us, because it's not this one sort of homegrown kit that something has been tested on.

Instead it's something within a tool catalog that we know we're much more informed about, we have greater sense of assurance about understanding the positives and the way that tool is working versus where it still may have some deficits and need to be improved upon, and I think adding that sense of uniformity and enabling labs to not have to focus their attention on developing the tools but be able to just access it and input it into the therapeutic pipeline all goes towards this concept of acceleration. How do we get things to move forward rather than having to spend three years establishing a model in your lab?

Dave Iverson: Well and it also speaks to what you were saying before, Marco, about sharing data. In order to be able to share data, you have to know that it's all been done or generated according to the same rules, that lab X isn't doing one thing and lab Y another, and that allows that to happen.

So use that perhaps if you would as a way of talking a little bit about the role that the Fox Foundation plays in bringing people together, to make that kind of sharing happen and to solve problems.

Marco Baptista: Yeah. Maybe something that people may not realize and might find strange is that when we are bringing people together, when we've identified what a scientific gap is or a big scientific question that we feel one group can't answer, not only are we bringing groups together that naturally wouldn't be coming together, like different companies sitting at the table and sharing information and sharing tools, but we also reach out to people who don't do Parkinson's research. I know that might sound a little strange, but what we're focused on is what questions we want to get answered, and sometimes where the science leads us and where the questions lead us will lead us to who we feel might be the experts in that area and we get them excited about doing Parkinson's research.

Actually, just recently I was talking to a professor at UCSD in San Diego, Dr. Susan Taylor, she's a really big name in the field of kinases, which is a class of proteins. Her claim to fame is solving the structure. She understands the anatomy of a particular kinase, a protein kinase A, that's what she's really known for. If anyone thinks of her, they think of this PKA kinase. And just recently I was talking to her and she's been doing a lot of work for us, she's made some huge breakthroughs. She's coming to one of these workshops in a couple of weeks where we have industry groups and academics.

She had never done Parkinson's research before and she's making some great breakthroughs, she's all excited about the science and she told me that she used to wake up in the morning and all that she would do is think about PKA and now when she wakes up in the morning, she's thinking about LRRK2, i.e. she's
thinking about Parkinson's disease and we're reaching out to the best minds regardless of what their academic background is because there's a certain question that we feel we need to bring that group in. That's something that we don't talk a lot about and we do it more and more and we see success from it.

Dave Iverson: Well that's a great example I think of sort of the final area that we're going to get into, and again, if you still have questions, we're going to get to them in about five minutes, so if you have more and if you've got some ready for me, we do, okay. Well, good. So we're going to be really quick.

Let's lead into this because I think if I had when I was diagnosed with Parkinson's, if someone had said to me, data analytics is going to be really key to you, I would have said, say what? But that's kind of where we're moving, Sohini. If we look at this last point on here, The Michael J. Fox Foundation has done a ton in the pursuit of finding a biomarker. Started this thing called PPMI, for Parkinson's progression markers initiative almost 10 years ago. It's accumulated now an extraordinary amount of data that's telling us a lot about the disease. So begin with that, where we are with that, if you would, Sohini, and then we'll move on to our next slide about where that will take us.

Sohini: Yeah, so just as a quick background, PPMI, the Parkinson's progression markers initiative, is a study that was initiated in 2010 with the goal of really understanding what is going on in the body of an individual with early stage Parkinson's and comparing what's going on with individuals who don't have Parkinson's, and the way that we try to do that is by literally doing everything under the sun to those individuals who've enrolled in the study. We image, we have different imaging modalities, we ask them to undergo a lot of different clinical assessments, we collect a lot of different bio samples, which are then analyzed, we incorporate genetics, etc. The result eight years later actually, or nine years later now, is that we have the most well characterized group of individuals that comprise 1400 individuals and it's remarkable what's coming out of that.

First of all, one of the things I'm especially proud of about this study, it's one of the ... it's probably the first really major Parkinson's study that is an open access dataset. What that means is that anyone in the research community can access the data in real time from the study. The study is continuing to go on. That's very unique, because usually when you talk about some of these studies that we mentioned earlier, the only individuals who really see the raw data are the people who are working on the study, and then what's shared with the community is a sort of high level data summary that is included in a manuscript or in a publication or in a talk.

So we have an enormous amount of data that are being accessed by the research community and actually as of today, we have had almost 3.5 million downloads of PPMI data that is just extraordinary. It's global, it's worldwide so it's truly having an impact in the community, but when you talk about what impact it's really making, you talked earlier today about the fact that five years
ago we didn't have these disease modifying studies happening. I can tell you that 10 companies, the companies that are involved in the 10 studies in phase I and phase II that are focused on disease modification, each and every one would tell you today the reason they're able to be in the clinic is because of PPMI.

It all comes back to the patient and understanding the disease and by going into the patient and understanding what is going on in the patient, and PPMI is providing that data and that data are being utilized to understand what should we incorporate in trying to measure whether our drug is having an effect in a phase II study, what type of patient should we be focused on enrolling in our study, because we think we may have the clearest read out of whether the drug is having effect, because we think that drug, to Marco's point about precision medicine, that drug is tailored for that type of individual.

We didn't have this before PPMI, we now have it and it's enabled these studies to get into the clinic. I think it's one of the most exciting things that's happening is that we're incorporating real patient data into our scientific knowledge that's thereby enabling these studies to happen, and PPMI is a very unique example of that.

Dave Iverson: So does that mean then, Rachel or Marco, either of you could take this, but that Marco mentioned a while ago that only 10% of all drugs once they start wind up actually gaining FDA approval, so that means 90% of things that go through clinical trials don't work. Part of the reason for that may be is that they're not being given to the right folks, right, so that we're learning that Parkinson's isn't just one disease but there are many variations on that, if we could get smarter about that, Rachel, does that then mean that, oh, you have Parkinson's flavor X, this drug might work for you?

Rachel Dolhun: That's the hope and not only that, but can we understand more about who will have mild cognitive impairment, who will have dementia, who has more walking and balance problems, so can we understand about who will progress more quickly? We're already understanding more about that modeling from this sort of data, so it's understanding more about not only the disease so we can target it, but so that we can prognosticate and understand more about life with the disease.

Dave Iverson: So we're learning from that 1400 folks and what they have given us in terms of their bio samples and data that there are certain indicators that will say, well, you may be at more risk for this or more risk for that and then those are the people you want to enroll in a particular drug trial.

Rachel Dolhun: Absolutely.

Dave Iverson: Yeah. Let's talk then about this last point before we get to your questions then about ... sorry, I didn't move as I thought I had to our next one about where this
goes in terms of prevention, because we talked earlier about stopping would be
great, preventing would be even better. So what are we now trying to do with
this idea of enrolling people and studying risk factors so that we might learn the
most we can about people who are at risk for the disease but hopefully
intervening before the disease actually begins?

Sohini: So I think that one of the byproducts if I could call it that from PPMI is that a
group that we enrolled in PPMI were individuals who did not necessarily have
Parkinson's disease but had a risk factor, meaning they had an increased risk of
potentially developing that disease and they fell into three buckets. One was
having a diagnosis of a disease called REM sleep behavior disorder, which is
basically acting out your dreams, another was having a smell deficit, and
another was having one of the genetic mutations that we referenced earlier,
GBA, LRRK2, synuclein.

Coming out of those studies, we realized that the time is right now to be able to
do a feasibility study, basically figure out how would you set up a prevention
study? How would you be able to identify with a high degree of certainty those
individuals who would go on to develop Parkinson's disease? What we're
looking at in a new study is basically the development of what we call "a risk
algorithm." Can you create a risk algorithm that will give you a sense of certainty
that an individual will go on to develop Parkinson's within a finite period of
time, within the next year, within 18 months, two years? Because if you can do
that, you actually are beginning to talk about a slightly different question, not
just slowing and halting the disease once it's been diagnosed by a clinician, but
actually potentially intervening before the symptoms even start, preventing the
onset of those symptoms.

That's an extremely exciting approach. It is something that a lot of fields are
doing, notably Alzheimer's. They're trying to go into this prevention model and
that's really kind of a parallel step that we're beginning to kind of focus our
attention on in addition to sort of that focus on alleviating or addressing the
symptoms of today, figuring out how to make disease modification a reality,
now we're really trying to target how do we make the concept of prevention of
Parkinson's disease a reality as well.

Dave Iverson: In some ways that's sort of the ultimate unmet need, right?

Sohini: Absolutely.

Dave Iverson: Stopping the disease before it ever starts.

Sohini: Exactly.

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