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Intro: You're listening to audio from one of our third Thursday webinars on Parkinson's research. In these webinars, expert panelists and people with Parkinson's discuss aspects of the disease and the foundation's work to speed medical breakthroughs. Learn more about the third Thursday webinars at [Michaeljfox.org/webinars](http://Michaeljfox.org/webinars). Thanks for listening.

Maggie Kuhl: Hi everyone. Thanks for joining us today. My name is Maggie Kuhl. I'm on the communications team at The Michael J. Fox Foundation. I usually produce the webinars, but today I'm joining as moderator. And, we have a really fun episode this month with some of our Foundation leadership. We are going to look back at a couple highlights from 2019, and then we want to spend most of our hour answering the questions that you all have. We hear so many different types of questions through our webinars, through in person events. So, we are going to give almost our full 60 minutes this month to just addressing what you all are wondering about. So, let's meet our panelists today with me is Rachel Dolhun, our vice president of medical communications and movement disorder specialist. Hi Rach.

Rachel Dolhun, MD: Hi.

Maggie Kuhl: And, Brian Fiske, PhD is our senior VP of research programs. He leads our targets and therapeutics portfolio. Hi Brian.

Brian Fiske, PhD: Hi.

Maggie Kuhl: And, Mark Frasier, PhD is also SVP of research, and he leads our biomarkers portfolio, how we measure PD. Hi Mark.

Mark Frasier, PhD: Hey Maggie, thanks for having me.

Maggie Kuhl: Yeah, so let's go in and discuss some notable programs and initiatives from 2019. So Rachel, why don't I turn it over to you and you talk about a couple of the things that you've been working on this year.

Rachel Dolhun, MD: Sure, I'd love to start. So, two of the things that I'm most excited about that I've been working on, one is the guide on cognitive changes, which you have in your resource list. So, through my role, I often talk with patients and families, and one of the things that I regularly hear is that they're very concerned about cognitive changes in Parkinson's disease. This is a symptom that can happen through Parkinson's disease, and people with Parkinson's and their families often express that they don't know when this can happen, what this can look like, and how to manage these symptoms. And, so I worked with people with Parkinson's, their care partners, and clinicians who care for people with

Parkinson's and their families, to develop a guide that helps people understand what these symptoms are, what they can look like, and how to manage them. And, so as I said, this is a pretty comprehensive guide that people can download and can take from this guide what serves them most.

The other thing that I'd like to mention, as you see on the screen, is the Edmond J. Safra Fellowship in Movement disorders. So this is a global program that trains movement disorder specialists, which are neurologists who have additional training in diagnosing and treating people with Parkinson's disease. We often talk about how important it is for people with Parkinson's to get this expert care if possible, but we don't have enough of these movement disorder specialists. So, in 2014 we worked with our partner, the Edmond J. Safra Foundation to launch this program, which every year grants funding to five academic medical centers around the world, which each train a new movement disorder specialist. So, since 2014 we have graduated 10 new movement disorder specialists around the world, and we have 16 more who are in training right now to become movement disorder specialists.

Maggie Kuhl: Brian, before I let you go on... Rach, building off the fellowship program, we actually just got a question about why someone would need to see a movement disorder specialist, especially if they really like their neurologist and feel that their doctor's competent. Can you just quickly talk about what role that person plays on a care team?

Rachel Dolhun, MD: People with Parkinson's who see movement disorder specialists, typically report feeling better informed about their care. And, movement disorder specialists, as I said, because they do have that additional training in diagnosing and evaluating people who have Parkinson's disease, typically are better equipped to manage Parkinson's disease. Parkinson's is a very complex and complicated condition, and because they see more people with Parkinson's disease, movement disorder specialists are more up to date on the research, more equipped to manage that complicated condition, and all the symptoms that can come with it. Both the movement symptoms, the non-movement symptoms, managing the medications that can go along with it. If you have a neurologist, and sometimes it's hard to get to movement disorder specialist because there aren't ones in your area, you can see a neurologist for your regular care. But, it is good to see a movement disorder specialist at least once for if you're around the time of your diagnosis, and then at least once or twice a year for a good check-in, if you can.

Maggie Kuhl: Okay. So it's not so much an either or, it can be an and. Which is nice to know.

Rachel Dolhun, MD: Absolutely.

Maggie Kuhl: Okay. Brian, why don't you talk to us about expanding genetic analysis in diverse populations?

Brian Fiske, PhD:

Sure, sure. So, I think you had mentioned kind of at the start, I think the last webinar that was really popular, around sort of the progress in therapeutic development for Parkinson's and sort of what that therapeutic pipeline looks like. And, I think one of the key drivers of that progress over the years has been our increased understanding of the genetics of Parkinson's. So, it was sort of the underlying genetic differences in people with Parkinson's that might at least explain some of their risks for the disease. And, that's actually, I think been a big sort of driver, again, of that progress in the pipeline. But, perhaps not surprisingly over the last 15 or 20 years that where we've seen that progress, a lot of that study and a lot of that research has largely been done in people of Caucasian descent. So, sort of traditional kind of white European Caucasians.

And, so over the last, I would say couple of years, there's been a growing interest in desire to increase the sort of diverse understanding of the disease across lots of different populations outside of just the traditional Caucasian groups. And, so this year in particular, I was particularly proud of sort of leading some of the efforts here at the foundation to increase some of that diversity in some of the genetic projects that we've been funding. And, since the start of the year after some initial conversations with some different groups, we've now deployed...actually, a little over 5 million or so dollars of research to focus specifically on increasing genetic information from various populations around the world. And, some of these populations are, for example, groups in populations in India, populations in East Asia, populations in Africa, and more recently have funded a group to expand work in Latin America and particularly in South America.

So it's really, really important we think to increase this diversity, because there's a lot of still unknown genetics around the potential causes and contributors to Parkinson's that we think we can find. And, we think looking at some of these populations is really important, not only for better understanding Parkinson's in those groups, but again, because of the combined sort of insight we'll get broadly about Parkinson's around the world. Related to that, I think in addition to genetics, I think we're seeing the growing pushes and increases in just increasing the diverse voice of Parkinson's patients in the community and other types of studies. And, so kind of in parallel to looking at genetics, we've also been working with various groups to just think about how can we better engage the broader Parkinson's population, and what are some of the unique recruitment challenges and other challenges that might exist in engaging some of these populations.

And, so some members of our team have been working on different types of strategies to do that. And, finally I would say, just in this sort of broader theme of diversity, I think one thing we're starting to see too is even just our better understanding of the diversity of Parkinson's disease. So, even beyond sort of the traditional kind of define Parkinson's disease, thinking about sort of the broader Parkinson isms, as they're called, that have sort of core Parkinson's features, but that might have other types of symptoms and components to it. So, I think we're seeing this sort of broader diversity conversation across a

number of different dimensions that are impacting some of the work we're doing and funding.

Maggie Kuhl:

Great. So Parkinson's and these similar disorders are really global problems and it's going to take all of us working together to find the cures for everyone living with these diseases. I know we're going to touch on later in our hour, diving into some of those Parkinsonisms and also genetic testing and the role that people can play in the research. So, more to come on that. And Mark, it's so important to be able to measure Parkinson's. To predict, to diagnose, to track PD. Can you tell us about some of the projects that are working towards those aims?

Mark Frasier, PhD:

Yeah. Maggie, one of the big challenges in Parkinson's disease, and really all of the brain disorders, is to understand and know what's happening within the brain when people are living with Parkinson's disease. We have no way right now to take a biopsy of the brain in a living person and look at it under the microscope.

So, one of the ways we get around this challenge is to try to develop ways to visualize what's happening in the brain through things like brain scans. And, in 2019 there was a lot of progress in developing novel ways to view the brain through imaging tools. In particular, there's been some progress demonstrated in developing a tool to visualize this alpha-synuclein protein that clumps in the brains of people with Parkinson's. This would be really important to see clumped alpha-synuclein in Parkinson's patients, not only to understand and help diagnose and understand how the disease is progressing, but to know whether new treatments that are in clinical development are actually changing this, what we think is pathological, this bad protein that accumulates in the brains of people with Parkinson's. So, there were some initial progress reported that there were some tools developed that were tested in humans to visualize alpha-synuclein, they're not perfect, but that was a milestone to be able to test in humans and they're optimizing the molecules even further to improve their ability to visualize alpha-synuclein. And, we also at the foundation, launched a large initiative called the Ken Griffin Alpha-Synuclein Imaging Competition, where we're supporting up to eight and a half million dollars worth of research to groups that are going to compete to develop this tool that's going to be able to visualize synuclein in the living brain.

So, that's really exciting. And then in addition to imaging and visualizing, what's happening in the brain, there's been a lot of progress in identifying molecules, proteins, and other types of molecules that change in people with Parkinson's in bio fluids. In things like blood and cerebral spinal fluid that can actually be sampled in people living with Parkinson's. And, so there's a lot of excitement around the ability to use blood tests and spinal fluid tests to develop more precise ways to diagnose Parkinson's and then track how the disorder is progressing. And, as I've mentioned, these could also be used not just to understand what's happening in the disease but to be used as a tool to understand whether new medicines that are being tested are actually changing the underlying biology and the underlying progression of Parkinson's.

Maggie Kuhl: I think a brain scan or a blood test for Parkinson's would be really helpful on a number of levels. We just got a question on if we could use this technology to look into people who have Parkinson's risk factors but have not been diagnosed yet or not showing the motor symptoms. What would their utility be and at risk populations, Mark?

Mark Frasier, PhD: Well, you can imagine if you can treat earlier, you could potentially have a higher likelihood of preventing the disorder from actually developing. So if we had a, for example, a brain scan that image alpha-synuclein, we know for a fact that some of the changes to the brain can occur up to 10 years prior to developing symptoms of the disease. And, if we had a tool that or a brain scan that visualized alpha-synuclein prior to developing symptoms, we could potentially intervene earlier and stop the accumulation of these bad proteins and actually demonstrate that drugs are stopping the accumulation of the protein through this tool.

So, it would enable earlier treatment and potentially ultimately the goal of prevention.

Maggie Kuhl: And, that is our goal to stop PD before it starts. So, thank you guys for these highlights. Before we move on, I just want to say that a lot more on these topics, both what we've done so far, and there will be more to come as we move forward on each of these programs on our website, our blog, our social channels. So, please keep following. And, want to call out Rachel, your cognitive guide is linked in the resource list, and here if you download the slides as well. So, thank you guys for all your hard work. And, why don't we turn ahead to the FAQs, the frequently asked questions. So, people with Parkinson's come to us, like I said, through webinars, through in person events, I would say that the number one question is how close are we to a cure? I know a lot of you are already writing in about this today. I want to call out that we did do a full hour on this last month, so there's a lot more information in that. But Brian, why don't you give us a quick snapshot of where you think we are today?

Brian Fiske, PhD: Yeah, yeah. So, obviously this is of course the critical question, and the one certainly here at the foundation where we're asking every day as well, in guiding our programs to try to get to that day even faster. But, often when I get asked this question, I try to break it down, because I think one of the things you have to think about when answering a question like where are we with cure for any disease, you have to make sure you have a clear sense of what do you mean by cure. And, so I tend to break this down in a few different stages, and then I can kind of indicate sort of where I think we are progress wise at each of those stages. But, probably for me the first sort of version of the definition of a cure is can you help someone with the disease today address their and alleviate the symptoms they have. And, basically make their day to day function better, sort of increase their quality of life, and sort of get rid of some of the disabling aspects of Parkinson's.

This doesn't mean you've necessarily cured the disease, and at the sort of basic biology since it doesn't mean you've completely replaced what has been lost, things like that. But, at least you are better able to help address those symptoms. And, in this case we've actually come quite far. I mean, many of course people with Parkinson's already get prescribed dopamine medications that largely help with their motor symptoms. We are seeing more and more in the last couple of years, approvals of drugs that can help address some of the non motor symptoms as well. And, I think we're going to see certainly in the next few years, more of those types of drugs I think coming online. So, in that regard, I think we actually are pretty close and pretty far along on our ability to at least help people alleviate and live with the symptoms of Parkinson's disease in a sort of better way, so that they can have improved quality of life.

Of course, that's not the ultimate goal of what we're trying to do. So, the second sort of definition of a cure, I tend to think about, is can we slow the disease process itself down, reduce, and sort of slow that kind of accumulation of disability that happens over time with the disease like Parkinson's. And that's a much harder question and sort of harder problem to solve, because it requires us to have at least some better understanding of what we think that disease process actually is. In that regard, that we've actually [inaudible 00:16:46] I think pretty far along. I mentioned before during the highlight section, sort of our increased understanding of the genetics of Parkinson's. And, although everybody doesn't necessarily have a strong genetic cause to their disease, what the genetics have given us, is more biological insight into the mechanisms in our bodies that when disrupted can actually lead to disease like Parkinson's.

And because of that, there are number of companies now that have developed drugs, and these were probably mentioned in the last webinar, have developed drugs that can target some of these disease mechanisms that are actually now testing those in human trials today. So again, it's still a few years off for those trials to truly report out. We won't know really the results of those efforts. But, at least we have drugs now that are being tested in people that we think are targeting the disease mechanism with the ultimate goal of slowing it down and potentially slowing that accumulation of disability. So, that's kind of the second category of getting to a cure. The third category, I tend to think of is, okay, so in someone who has the disease, maybe they've had it for a few years, they've lost some of the cells in the brain that produce the neurochemicals that are sort of involved in the symptoms of Parkinson's.

What can you do to actually sort of fix and repair what's been lost. So, even if you could slow down the disease process in someone at that stage, they still have that sort of lost parts of their brain, and are not sort of fully functional. So, you could obviously combine that with some of the symptom treating drugs, and that can certainly help. But, could you actually go in and sort of replace and fix and repair some of what's been lost? And that's kind of where we're seeing, again, some of the approaches, and I think we'll talk about this in a little bit, in a moment. Cell replacement type of approaches. Can you go in and actually kind

of give back people that dopamine cells that have been lost in the brain, for example. And, that's still a little bit further away.

There's a lot kind of technology development and sort of assessment that we have to do to really understand whether that is truly something that we can do in someone's brain. The brain is still a very sort of complex organ. We don't know a lot about it just at the fundamental level to be able to go in, and say and rewire it, and fix it from the ground up. So, that's still a little further away. But, there is at least some effort in some groups that are out there looking at ways to sort of try to replace some of those lost dopamine cells or restore some of that function. In fact, if you think about it, a deep brain stimulation, which is a surgical approach that's available today, is actually in some ways an attempt to go in and try to fix the sort of circuitry problems that are sort of that go awry in someone with Parkinson's.

So, to some degree we do have at least some attempts to try to do that kind of restoration approach. And, then the last category really, and Mark alluded to this, is can we identify people before they really get the symptoms of Parkinson's and actually prevent them from getting Parkinson's all together. For me that would be kind of the ultimate definition of cure. That you basically prevented anybody from getting Parkinson's in the first place. That of course is much further off and is largely driven by the needs we have to identify people at those early, early stages. And, we don't really have all the sort of biomarkers and sort of signals yet to figure that out. But, we're actually making some progress in some of the big investments we're making now through, for example, through our large Parkinson's Progression Marker Initiative, is attempting to try to like move that line even further back, sort of peel away that early stages of the disease so we can actually find those individuals before they get that sort of symptoms of the disease.

Maggie Kuhl:

Great. So I want to keep us moving along, but just to reiterate what you've said, it seems like we are closer than we've been. We have so many irons in the fire, which I think is really heartening that there are a lot of varied approaches, varied targets, different drugs and strategies against this disease that we're supporting and that scientists are moving on. So, there's a lot of reason to be hopeful, and we're also working on better tools to do this all much faster. So, we are probably going to touch on some of the stuff that you covered in subsequent questions, but let's move on to... My animation is being a little funny, so you'll see two of them on your screen. But, the second one is, how do I get genetic testing for PD linked mutation? So, you talked about genetic research, more diverse voices and backgrounds in genetic research. I think a lot of people have this question about, how can they find out their own genetic status? And, the difference between genetic testing for your own personal understanding and genetic research. I want to get into, but Rachel, why don't I turn to you and you talk to us about what to consider before learning your genetic status. If you carry a mutation linked to PD.

Rachel Dolhun, MD: I think a lot of people are really interested in genetic testing to learn more about themselves, or their risk for Parkinson's, or if they have Parkinson's, to learn more about their disease. You raised a really good point about genetic testing to learn more about yourself or your disease being different from genetic research. But, I think to get to the first point about genetic testing, this is pretty widely available now through online services. People are very aware of things like 23andMe, and there are some considerations around that. As I said, there are different ways to do this, 23andMe or other online services. You can get through this through your doctor's office and it's important to know what's being tested. So through 23andMe for example, there are certain genetic mutations linked to Parkinson's that are tested. Through your doctor's office you may be able to get different or more genetic mutations linked to Parkinson's tested. But what I think is an important caveat to mention about this is genetic counseling is really important both before and after testing because there are certain things that genetic testing can and can't tell you about your disease or about your risk for Parkinson's and about what the implications are for you and potentially your family.

So working with a genetic counselor who is an expert in mutations that are linked to Parkinson's and other brain diseases and other diseases is really important as you think about genetic testing and as you get your results and interpret them for yourself. So thinking about genetic testing and genetic counseling, whether you get it online or in person and your doctor's office is really important. And then just mentioning genetic testing versus genetic research. Again, genetic testing is for the purposes of learning more information about yourself just to have that information. Genetic research is getting genetic testing or getting your genetic information for the purposes of research.

So there are genetic trials for example, where you could participate and not even learn your genetic information because the trial does not disclose that information or for example, because you didn't want to learn that information so you could participate in genetic research for the sole purposes of participating in research, not for learning that information about yourself.

The last thing I will say about genetic testing at the current time, it doesn't change our clinical management in the sense that if I were your doctor and we were going to do genetic testing on you to learn more about your genetic status and if you had genetic mutations linked to Parkinson's, it wouldn't change what we did with your medications or with your clinical management in the current state of what we know about Parkinson's and the treatment of Parkinson's. That being said, there are clinical trials that are going on right now that are testing drugs and therapies that target these mutations that we know about that are linked to Parkinson's. So we could for example, change what you do about participating in research.

For example, if you found out through genetic testing that you had LRRK2 mutation or GBA mutation, you might be more inclined to say, "I want to know what trials are going on that are targeting drugs against LRRK2 or against GBA."



So there is some information that could inform your participation, for example, in these ongoing clinical trials, but it wouldn't necessarily change what your doctor does with your medication management.

Maggie Kuhl: Anyway, some of those trials are recruiting for people who have been diagnosed with Parkinson's already, but carry these mutations but there's a lot of studies that are enrolling people who are carriers of these mutations, not yet showing signs to better understand that progression right. So we just got a question on if I have family risk factors, what could I do? And theoretically you could join genetic research if you carry one of those mutations and help us move toward that prevention model. Is that right?

Rachel Dolhun, MD: Well, that's a good point. In general, research needs people both with and without Parkinson's, family members of people with Parkinson's, friends of people with Parkinson's. If you're interested in participating in research, we need people to serve as what we call control volunteers to help us understand what normal aging looks like compared with Parkinson's. What as you said, people who carry these mutation who don't yet have Parkinson's or don't have Parkinson's to compare what this looks like and to participate in research. So that's a very good point that research needs all types of volunteers.

Maggie Kuhl: It's a personal decision, but it's really valuable for research if you do decide to learn your genetic status. So let's move on to stem cells. Brian, I'm going to ask you to comment on the science a little bit about the therapies in development. You alluded to those when we hit the first bullet. But Mark, after that, I want you to chime into on how stem cells can help us learn more about the disease. I was just looking at some of the new grants that we've made and it seems that a lot of them are using these disease in a dish from pluripotent stem cells. So I want you to explain that, but first, Brian, why don't you just give us a primer on where we are with stem cell therapies?

Brian Fiske, PhD: Sure, yeah. Again, just a quick refresher what stem cells are. They're essentially cells in our body that have the capability of making lots of other types of cells. And probably the classic stem cell that everybody tends to think about is the embryonic stem cell, which is an early, early cell during development that can basically make all the cells of the body and that's the ultimate stem cell. As we grow and develop, different parts of our body, different organs in our body can establish subsets of so-called stem cells that are more there to help generate new cells of the same tissue type and sometimes we call those adult stem cells. You might hear a fancier name somatic stem cells, but again, those are a different type of stem cell population, but with the same general concept that they can be used to make other cell types.

A more recent discovery and approach, it's almost an artificial version of a stem cell that researchers about almost 10 years ago discovered but has really, I think, revolutionized the field is that we can actually create artificial stem cells from existing cells in the body in particular skin or blood cells and you may hear us sometimes talking about a type of stem cell called the induced pluripotent

stem cell. It's just again a fancy name for saying a stem cell that we've essentially created in the laboratory to have all the features of a stem cell that can then be used to make other types of cells. So there are a whole variety of different types of stem cells.

Now why we are excited about them therapeutically and then I'll let Mark talk about some of the research side of the use of stem cells. But therapeutically is the idea of course is that can you use them to generate replacement cells for what is lost in a disease like Parkinson's in particular, the dopamine cells in the brain, and then you take those cells, those newly generated cells and put them back, transplant them back into the brain and restore some of the function that's been lost in Parkinson's disease. And so that of course I think has been something that people have been really excited about for a number of years.

In fact, some of the earliest therapeutic approaches that were tested and developed for Parkinson's back even in the '80s and '90s was to use, not necessarily stem cells because they hadn't really been discovered yet at that point, but actually tissue from early developing brain tissue as a tissue replacement for people with Parkinson's. And there were a number of trials that were actually done in the '90s and the early 2000s that attempted to use this approach shot in people with Parkinson's. Unfortunately for lots of different reasons the trials did not show as much promise and progress as hoped, there were a few people I think that maybe potentially benefited from the transplants, but a lot of people either had no benefit and then in a few cases there were actually some adverse symptoms, some side effects of the transplants.

That put the field back a few years, they had to go back to the drawing board a bit and try to make sure they understood what these transplants were actually doing in the brain. But during that time, that's actually when the stem cells were really discovered in the brain and people realized that they could maybe move away from the tissue transplants to actual stem cell transplants. And so today we have a lot of groups that are working on efforts. We have a handful of programs that are in early therapeutic testing and development, and so we're starting to get, I think, and we'll be continuing to get a little bit of more insight into whether these types of replacement approaches can hold benefit for Parkinson's. Right now in their current form as sort of replacement therapies, they will only probably ever be as good as Levodopa, which is the more drug based pharmacological approach to treating and replacing dopamine in the brains of people with Parkinson's or deep brain stimulation, which is an electrical way of correcting the circuitry in the brain and improving motor symptoms and disease.

So no one right now thinks that necessarily, the current versions of these stem cell approaches will necessarily do much better than those approaches but would offer a different way of replacing that lost dopamine in the brain and partially maybe even restore some of the function in the brain. So that's why people are excited. Now there's a slight corollary to how people are using stem

cells therapeutically that I just want to mention as well because I think we tend to hear a lot about these in the news and it's a different type of way of using cells as therapy. And that is not so much about replacing what is lost but using different types of stem cells in the body that we think might produce different types of factors, potentially protective factors essentially as little factories that can go in and maybe provide factors to existing dopamine cells in the brain that remained in the brain of someone who'd Parkinson's and that maybe these factors can help protect and prevent those cells from, from dying.

And so it's a slightly different way of thinking about use of stem cells but it is one of the approaches that we often see mentioned in the news and this is more on the unfortunate side. There are a lot of clinics out there around the world that tend to claim that they're using these types of stem cells and they will offer for individuals who want to pay for it to infuse these stem cells into your body in different ways and "cure" your Parkinson's disease. And this has been kind of a particular challenge in the field because it's really hard to assess what some of these approaches are doing. A lot of these clinics aren't necessarily doing work that is certainly not approved by any regulatory body. And because of that, it's really hard sometimes to distinguish what is a true rigorous research that's being done by number of groups out there on these types of approaches versus these clinics that are offering them, I think to patients who are willing to pay for it for them. And so that particular type of approaches I think become a little more complex in the field.

Mark Frasier, PhD:

Maggie, maybe just to add on the research side why we're excited about some of the stem cell development. Brian described this technology that's evolved where you can actually take a skin sample or a blood sample from a human with Parkinson's and then generate what's called an induced pluripotent cell that could then develop into any type of cell in the body. And what we've seen in the last year or so is a lot of excitement in using these types of cells. There are a number of studies that have generated repositories of these cell lines from people with Parkinson's disease and controls. Also people that harbor some of the mutations that were discussed earlier and researchers are taking these cells, putting them into a Petri dish, and doing two things really that I think are exciting. One is to understand the biology of what's happening with Parkinson's and with some of these genetic targets.

There is really no better environment than actually having a human cell with the human gene from a human to understand what that gene is doing biologically and look at it under a microscope and manipulate it in the dish. So a lot of research into underlying biology of these genes associated with Parkinson's disease in the human cells, which is exciting. The other thing that's exciting is that a lot of drugs are being tested on these cells in the Petri dish. So we think that having these cells available from people with Parkinson's and people that have some of the mutations associated with Parkinson's will provide a more predictive model, a more predictive disease in the dish as you indicated that we can test novel molecules, novel drugs against and see if they do what we think we'd like them to do. And that can be done a lot quicker than using animal

models or other types of models. And so having a better predictive model for drug testing is a really useful way to utilize these stem cells.

Maggie Kuhl: Nice. So it's science fiction. Stem cells are a therapy in themselves, although we're not there yet, so let's exercise caution until then and also a tool to get to new treatments. So a lot of excitement there. And again, a plug for a previous webinar, we did go into stem cells earlier this year if that's something you want to learn more about. Okay, next question. Mark, let's stay with you. So DaTscan, a dopamine transporter scan what is it and should I have one? Whether I have been diagnosed with PD or if I'm at risk?

Mark Frasier, PhD: Yeah, maybe I'll start and then ask Rachel to jump in from a clinical perspective. So a DaTscan, as you said, is a dopamine transporter scan. It's a brain scan that's currently approved by the FDA to be used as a tool for diagnostic purposes and what it does, we've mentioned that in Parkinson's disease, one of the primary changes in the brain is the loss of these cells that make dopamine and the DaTscan, brain scan is a way to visualize the cells in the brain. So they inject a dye intravenously and then use a special camera essentially to take a picture of the brain that allows a neurologist and radiologist to see the level of dopamine cells in a person's brain. And so the current utility is to confirm a diagnosis by a neurologist that is used in parallel with the assessment of the symptoms of Parkinson's disease.

It is a biomarker, it's a brain scan and what some of the research is showing is that in early people with Parkinson's, newly diagnosed patients over the first year or two, the DaTscan actually can change about 10 to 15 percent in the first several years. So from a research perspective, this is really important because it's a useful measurement and useful tool that drug developers can use and incorporate into their clinical trials to assess whether their new drug that they're testing is actually changing the progression or the changing the loss of dopamine by DaTscan. In terms of whether someone's been diagnosed and whether it's useful to have a scan, I'll ask Rachel to answer that question.

Rachel Dolhun, MD: So the diagnosis of Parkinson's is really what we call clinical. So when you go see your movement disorder specialist or your doctor, they're looking at your symptoms. They're looking to see if you have the movement symptoms of Parkinson's, that tremor, slowness, stiffness, potentially walking and balance problems. They're also looking for some of the non-movement symptoms that can go along with Parkinson's. They want to ask you questions to see if you have these symptoms of Parkinson's and they're basing your diagnosis on those symptoms because we don't have what Mark been talking about, a biomarker, an objective measure of Parkinson, a scan or a blood test that in and of itself can diagnose Parkinson's.

And so DaTscan in and of itself by itself without a doctor's visit or a doctor's opinion cannot diagnose Parkinson's. Now if the diagnosis is in question, so for example, if you don't have those classic symptoms or if you're not responding to the medication or if things aren't going along as we'd expect them to. And in

one particular case, if you have a tremor that we're not sure if it's another kind of movement disorder called an essential tremor, which is typically where both hands are shaking when you're moving them or when you're using them rather than the tremor of Parkinson's, which typically at the beginning is in one hand or in one side when you're resting it or when you're not moving it. If we're not sure which kind of tremor it is, a DatScan can help us tell the difference between those two.

So it can help us tell the difference between Parkinson's and between an essential tremor, because in essential tremor, the dopamine system is not affected like it is in Parkinson's. So the DatScan can be particularly helpful in diagnosing those two different conditions. But you're looking at some of the other different conditions that can look like Parkinson's, which we will talk about a little bit later. There are some diseases that can look like Parkinson's, we call them atypical Parkinsonisms. They're things that have these long acronyms like MSA, CBD, PSP, and things like that. A DatScan cannot help us tell the difference between those because the dopamine system is affected in all of those and the DatScan will be abnormal in both Parkinson's and in those conditions. So it wouldn't help us in that situation.

Maggie Kuhl:

So are useful tool, but we still need better ones. Okay, and the last of our frequently asked questions, which is maybe after the first one, the most frequently asked, what about medical marijuana? Rachel I'm sending this one to you?

Rachel Dolhun, MD:

Yes, a very popular topic and as you said, we did a whole webinar almost entirely devoted to this. So I'll just give a short answer to this, but medical marijuana is... it has evidence to support that it could be potentially beneficial in Parkinson's. So our brain and our bodies have receptors that respond to the chemicals in marijuana. This is called the endocannabinoid system and the highest concentration of these receptors are in a part of the brain that's affected by Parkinson's, which is called the basal ganglia. So as I said, it makes sense to wonder whether marijuana would be helpful in Parkinson. There have been some clinical trials of medical marijuana and or cannabinoids in Parkinson's disease looking mostly at the tremor or the movement symptoms or dyskinesia, which is that involuntary uncontrolled movement that can come on after many years of Parkinson's or using Levodopa.

But mostly the data to date has been inconclusive, meaning that some studies look like they're positive, others look like they're negative. And so we really just don't have the data to date to support the use of medical marijuana. In Parkinson's disease for the non-movement symptoms like pain or sleep, there have been some small studies as well or some surveys of people reporting their youth that say that this could potentially be beneficial for symptoms like pain or sleep. The problem is that these studies have studied all different kinds of medical marijuana, so different doses, different formulations, different combinations of THC, which is the part that has the psychoactive component versus CBD. So we really just don't know yet and don't have good

recommendations on what could potentially be beneficial and what would again be the right formulation, the right dose.

And so we just need more data on this right now. And I would end by saying studying this is hard because there are a lot of regulations around this. It's a schedule one drug, so it's hard to study. There are also a lot of people who are using it. So again, there's a lot of... Researchers are describing the wild West. There's a lot of people using it. It's hard to get data and there's a lot of potential side effects with it. So we know we need more data. There are ongoing trials and our online observational study Fox Insight will be launching a survey in the coming year to learn more about how people are using this and what their potential benefits and side effects with it are.

Maggie Kuhl: All right. And I'll just say on that webinar, we had the members of our patient council share his own experience with cannabis use and it was a very interesting conversation. So tune into that one too. Okay, I'm going to ask you guys, you've been giving such thorough answers, which I think everyone appreciates, but we have so many questions and our time's dwindling. So I'm going to start going through some and do a lightning round, so I'll ask you to answer thoroughly but succinctly if that's possible. So [inaudible 00:43:48] ones that we got submitted in advance. Rachel, are muscle cramps part of Parkinson's.

Rachel Dolhun, MD: Typically, when people talk about muscle cramps, it's more muscle spasms, which we refer to as dystonia and that's more muscle spasms that pull a body part into an abnormal position. So, the most common is toes curling under or a foot turning in. This can often happen when medication is wearing off or like in the morning when medication's not working as well. Treatments can be medication adjustments, botulinum toxin or Botox being injected into a body part that's affected, or physical therapy and exercise.

Maggie Kuhl: Mark, what are the Parkinsonisms? We've talked about these a little bit, Lewy body dementia, PSP, MSA, CPT. Can you run through some of those and the differences?

Mark Frasier, PhD: Yeah. Well, just briefly, Parkinsonisms is an umbrella term and actually Parkinson's disease is included as one of the Parkinsonisms and it just happens to be the largest. There are other acronym diseases like PSP, MSA, CBD, all of these present with Parkinson's-like symptoms. But, if you look into what's happens in the brains of individuals with these different disorders, it is slightly different.

It is a challenge though, particularly early in the disease course with all Parkinsonisms, to really diagnose individuals and separate them into the different categories, because, as I mentioned, they all present early on with a lot of the similar movement disorder symptoms. So, as the disorders progress and other symptoms might develop, that gives neurologists clues about what disorder they might have. But, I would say, many of the research questions that we're tackling are addressing all Parkinsonisms. They have a lot of the same

features and if we were to develop treatments for Parkinson's disease, it is likely that many of the treatments may be beneficial for the Parkinsonisms.

Maggie Kuhl: Rachel, so some people have a less aggressive Parkinson's disease than others, and if so, why?

Rachel Dolhun, MD: Parkinson's is a very individualized and what we call kind of heterogeneous disease, so everybody does have an individualized and unique combination of symptoms and individual progression. So, there are some people who do progress at a slower rate than others. We tend to, or we have tended to, historically kind of lump people into these very general categories of people who have more tremor at the onset versus people who have more walking and balance problems at diagnosis or onset. In general, people who tend to have more walking and balance problems and less tremor when they're diagnosed, or at the beginning of their Parkinson's, do tend to have a little bit of a faster progression as compared to people who have more tremor and less or no walking and balance problems at the outset.

There are some other factors we look at in conjunction with that and we're researching more in our PPMI study and other studies to try to find out better ways and more ways to predict who progresses at what rate.

Maggie Kuhl: You mentioned PPMI, I don't think we've shared that acronym thus far in this discussion. It's our Parkinson's Progression Markers Initiative. It's our largest study of nearly 1500 people around the world, where we're following the disease and trying to better understand its progression so we can better measure and treat it. Brian, any of the genetics work inform maybe what form aggressive wise of PD someone might have?

Brian Fiske, PhD: There's some early work on this. We do know, for example, that some of the genetic forms might have a slightly slower progression of the disease than sort of more traditional Parkinson's. They might start earlier, at an earlier age, than more traditional Parkinson's, and in some cases might actually have some other non-motor features that might even be more aggressive than more traditional Parkinson's.

So, it's early days because we don't have the large cohorts of people that we've followed for extensive periods of time quite like we do for more traditional Parkinson's. So, knowing the progression of some of those different genetic forms is still a little bit earlier stage research, but at least we're able to start gleaming some of the differences. And as you said, in that large PPMI study, we do include some people with genetic version of Parkinson's and are starting to explore some of those questions.

Mark Frasier, PhD: Just to add, I think it's a really important point that the PPMI and other studies are pointing towards and leading towards is to have a better, more objective way to predict how one might progress and what symptoms might develop, and

there are certainly genetic tests that can be done. We're learning more about the progression of these types of genetic associated disorders.

But I think there are also other imaging and fluid based markers that can be useful ultimately as a constellation, as a panel, to predict how one might develop in their symptoms and in terms of their progression.

Maggie Kuhl:

So, not just if you'll get Parkinson's but what it might look like if you do. Brian, I'm going to stay with you and pivot a bit. A lot of questions about mannitol, can you tell us what that is and where we are in testing it for PD?

Brian Fiske, PhD:

Sure, sure. So, so mannitol, for those who don't know, essentially it's a sugar substitute, kind of used as a sweetener. Often, I think, it's used in foods that are for people with diabetes because it doesn't absorb into the body quite the same way as more traditional sugars do and therefore doesn't increase blood sugar levels. You can get that sweet flavor without the rise in blood sugar that is a problem for people with diabetes.

But, in laboratory research over the last few years, there've been some groups who are researchers in Parkinson's disease who identified Mannitol in a screen of different types of molecules that seems to impact and reduce the clumping of the protein alpha-synuclein. I'm pretty sure we probably talked about how this nucleon in past webinars but alpha-synuclein, and the abnormal clumping of the protein alpha-synuclein, is a key pathological hallmark of Parkinson's disease. We find these clumps of the protein in the brains of pretty much everybody with Parkinson's disease, or classically defined Parkinson's disease, and so we think that must have some fundamental feature contribution to the disease.

So, the idea of mannitol is that it might have some ability to go into the brain and target these clumps and in some ways reduce the clumping or target the clumping in some way. And again, all of that has been done really just in laboratory models and research in that effort. Because of that, and because it's essentially a pretty easily available nutrient that you can access, a lot of people, of course I've been very interested in taking mannitol as a potential protective factor for their Parkinson's disease.

So, there's not a lot, of course, good data to suggest that that really does have impact in Parkinson's yet. There actually is a trial being run out of Israel right now in about, I think, 60 or so people with Parkinson's that is actively trying to test some of those questions. It's being designed mostly as a safety tolerability study, because we don't know yet the level of dosing you might need to take mannitol to have any benefits, or is that going to be safe and tolerable in people with Parkinson's? And so, of course, the trial is looking at that primarily, but they all are also exploring some measures, potentially, of impact it might have on clinical features of Parkinson's as well.



So, some more data to come from that trial. I think it just really launched last year and I think won't really report out until probably the end of 2020, if not early 2021, but that's because obviously they want to do a good rigorous assessment of the treatment. So, as of right now, if you're someone with Parkinson's who is interested in taking mannitol, it's certainly not, it's not going to harm you in any significant way, at least as long as you're using it in approved levels of amounts that your doctor thinks is okay.

It's important of course to talk to your doctor first, but there really isn't a lot of evidence yet, certainly not human data, to really suggest that it is going to profoundly impact your Parkinson's disease or slow the disease down. I think we'll need more rigorous clinical data before we could make that kind of assessment.

Maggie Kuhl: Okay, so in the trial, more to come. Rachel, a lot of questions on levodopa, carbidopa, brand name Sinemet, how long should I wait to start on medication? How long before side effects arise? Why does it become less effective over time? Can you give us some background?

Rachel Dolhun, MD: And you want me to be really succinct on that? So-

Maggie Kuhl: Those three questions, you have one minute.

Rachel Dolhun, MD: Yeah. These are such common questions and really hard ones to answer, because if and when to start medication, particularly Sinemet which is the gold standard medication for Parkinson's, are really individualized and personal decisions. There are no real hard and fast rules around medications. There's no cookbook approach to this, because as we discussed, Parkinson's is very individualized and very unique.

Medications, including Sinemet for Parkinson's, all treat the symptoms. So, when symptoms get in the way of what you want or need to do, including exercise, go out with your friends, play with your grandkids, travel, whatever it is, medication is there for you and you should take it. Now, there's long been a debate about if and when to take Sinemet versus other Parkinson's medications, particularly in young people, because of the potential, with long-term use, for side effects or complications, particularly like dyskinesia, which are those involuntary abnormal uncontrolled movements.

That being said, not everybody gets dyskinesia and if you do get dyskinesia, it's not always bothersome or uncontrollable, and we have ways to treat it including medication adjustments, adding other medications and ultimately, if necessary, deep brain stimulation, so there are a lot of ways to manage that. That's all to say if you need medication now, you need ways to help your quality of life and improve your quality of life now, you don't want to sacrifice that or hold medication now for a potential complication that may never happen down the line.

Maggie Kuhl: Don't save your umbrella when it's raining. That's one of my favorite analogies. Okay, that was a good job of being succinct. Thanks Rach. Mark, hopefully an easy one. What is the difference between young onset PD and what we mean when we say early onset PD?

Mark Frasier, PhD: I don't think there's any difference, really. Young onset is typically below the age of 50, I think. Right, Rachel?

Rachel Dolhun, MD: Yeah, I think this is more of a vocabulary thing and it's been evolving over the years. I think typically young and early are synonymous, so we've been typically calling that before the age of 50.

Maggie Kuhl: Okay. If we say early stage PD though, I think, when we talk about some of these studies looking for people who've just been diagnosed, that might be what they were referring to. So, no matter what age you get PD, when it's within, do we usually say two years? That's kind of early onset, that's when a lot of studies are looking for you.

Brian Fiske, PhD: Or often it before you really start medications, sometimes. You might hear us say the word denovo, from kind of early diagnosis when that's often a sweet spot for some trials because they want to test the medication in the absence of other medications at the early stage of the disease.

Rachel Dolhun, MD: Yeah, it depends on the study. So as Brian said, it may be three years, five years, but I do think that's an important point that people often aren't aware of. Some of these studies that are testing the what we call disease modifying medications or therapies that are aiming to slow or stop the progression of disease, they're looking for people who have not yet started medication. So, that's something to take into consideration when you're thinking about medication.

Maggie Kuhl: Okay, and we're approaching one o'clock but I want to ask one other good question. Brian, I'm going to send this one to you. The gut bacteria Parkinson's connection. What do we know about Parkinson's in the gut and is there any therapeutic intervention at this point? What do you think is going on there?

Brian Fiske, PhD: All right. Like Rachel, a very complex question and very little time to answer it. So, I guess at the highest level-

Maggie Kuhl: We can go over one, I'll give you some time.

Brian Fiske, PhD: Yeah. There is this idea, largely based on when we look in people with Parkinson's, at where the different pathology lies, there does seem to be this progression people have reported, that where they see some of the early earliest stages of Parkinson's, even before some of the symptoms show up, there seems to be pathology in the gut nervous system, the parts of the nervous system that control gut function. With later stages of the disease, you start to see the pathology and other parts of the nervous system and ultimately the

brain. So, this idea that the sort of Parkinson's might start in the gut and sort of make its way into the brain has been, I think, a powerful idea really for probably the last, certainly the last 15 years or so.

Now, the other question is the role of gut bacteria in the intestines and the role that might have in either triggering or contributing to Parkinson's. I think this is also an interesting area that's been emerging in the last few years, especially as our techniques and laboratory methods have gotten better at being able to actually measure all of those different critters in our gut, and being able to actually look at that in people with Parkinson's versus people who don't have Parkinson's, for example. And I think we're starting to learn a little bit about the gut makeup, micro microbiome as we call it, in people with Parkinson's and people who don't have it.

And so, through that, I think, we're starting to uncover some different ideas that might be able to be converted into potential therapeutics, with the idea of whether they are causal for the disease or maybe contributory to disease, by targeting that microbiome there might be some ways to help with with some of the issues in Parkinson's.

There's actually one interesting, it's less about the disease cause, but we do know that people with Parkinson's do have problems with their gut function. They actually, through constipation and things like that, and there's even one aspect where it's where it's hard for the food to kind of get from the stomach into the intestines and things like that. And so, one idea, what that can lead to is then your traditional medications that you take for your Parkinson's may not work as well, simply because it's not getting through the gut system quite so easy.

Some ideas are out there about targeting the microbiome to help improve that function with the idea that that would actually just make your existing medications work a little bit better. And so I think there are some reasonable to efforts that are starting to look at those kinds of approaches. But again, I think thinking about whether changes in the gut or the microbiome are actually causing or contributing to Parkinson's disease mechanistically, I think, is still a little bit early stage, but there's a lot of groups that are starting to explore that idea.

Maggie Kuhl: Interesting. I might have to steal critters in your gut for some of my future communications.

Brian Fiske, PhD: Sounds like [inaudible 00:16:05].

Maggie Kuhl: Exactly, yeah. I'm going to steal a technique from my longtime partner in these webinars, our beloved Dave Iverson, and want to go around the table and just share a last thought from each of you. We have less than two weeks in 2019, it's been a monumental research year, and just want to hear what you want to

leave our patient audience with. Message of hope or inspiration, what do you want them to walk away from today with? So, Mark, why don't I start with you?

Mark Frasier, PhD: Well, I mean, we've said before, this is the most robust pipeline of new treatments that we've seen in our existence. We've also seen a lot of progress in developing better ways to measure. So, coupling the new treatments with better diagnostic and measurement tools is a really exciting prospect.

Maggie Kuhl: Great. How about Brian?

Brian Fiske, PhD: Yeah, I mean, I agree 100 percent with Mark's assessment. I think just that that pipeline is becoming so exciting and we use it as a core metric internally here to know how to cater our funding programs, and just seeing that progress has been amazing to see.

You know, I guess for me, I kind of harken back to my highlight from the start, which is I think also this growing need and desire to increase those diverse voice of people with Parkinson's around the world and bringing them into that whole research effort, I think, is really, really critical. And exciting that there are a lot of efforts now to really try to do that, both on the research side and the engagement recruitment side in the studies. I think more to come on that, but I think that, for me, is also very exciting.

Maggie Kuhl: And Rach, last word.

Rachel Dolhun, MD: It's hard to encapsulate just in a couple of words, but I think we all feel so privileged to be doing this work and you see the diversity of it. I bring clinical perspective, but I bring that from the patients. So, something like this, where we're able to hear from you all and your questions and get that to inform our work, and your priorities and bring that to our educational resources, but also our research initiatives as well, is really a privilege and a priority for us.

Maggie Kuhl: Great. Well, thanks to the three of you and thank you to everyone for a great year in our webinar series. I hope that you completed our survey on your screen to let us know what you want to hear more about next year. And I hope that you listen to this event again, share, listen to the other ones from this year in the library. And you can already Mark your calendar for our next webinar on January 16th, where we'll discuss diet with Parkinson's, both what you should be doing to eat healthy, but also how to travel and enjoy a glass of wine and also live your life with PD as regarded diet. So, thank you as all again. Have a great rest of the year and we'll see you next month.

Michael J. Fox: This is Michael J. Fox, thanks for listening to this podcast. Learn more about the Michael J. Fox Foundation's work and how you can help speed a cure at [michaeljfox.org](http://michaeljfox.org).