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MJFF: Welcome to a recap of our latest Third Thursday Webinar. Hear directly from expert panelists as they discuss Parkinson's research and answer your questions about living with the disease. Join us live next time by registering for an upcoming webinar at [michaeljfox.org](http://michaeljfox.org).

Mark Frasier, PhD: Hi, everyone. Welcome. My name is Mark Frasier. I'm the Chief Scientific Officer at The Michael J. Fox Foundation and we're really excited that you can join us today. Today, we're going to be talking about the latest in Parkinson's research, particularly the latest advancements that have occurred in the last 12 months.

Mark Frasier, PhD: I'm excited. We have a great set of panelists today. So, I'd like to introduce them to you today. First, welcome Dr. Beate Ritz. Dr. Ritz is a professor of epidemiology, environmental health sciences, and neurology at the University of California Los Angeles. Our Foundation has funded Beate for her work and pesticide exposure and links to Parkinson's disease. Welcome, Dr. Ritz.

Mark Frasier, PhD: We also have Dr. Irfan Qureshi, Dr. Qureshi is Vice President of Neurology at Biohaven Pharmaceuticals. He's a board-certified neurologist and a physician-scientist with years of experience in research and patient care. Thanks so much for joining us, Dr. Qureshi.

Mark Frasier, PhD: And finally, we have Marion Fioretti. She's joining us from Connecticut. She's an active community member of The Michael J. Fox Foundation. Marion was diagnosed with Parkinson's disease in 2010. Thanks so much for joining us, Marion.

Marion Fioretti: Pleasure to be here. Thank you.

Mark Frasier, PhD: Great. So, as I mentioned, today is our annual year in review webinar. And what we'd like to do is highlight the latest progress in Parkinson's research. We do have a lot more to cover than we have time in this hour or so, but we'll do our best to get as much covered as we can.

Mark Frasier, PhD: We're going to be talking about some of the latest technology advances in Parkinson's disease, talk about some of the latest treatments and some of the news that have come out in the last 12 months, as well as understanding what causes Parkinson's disease and environmental exposures that may lead to Parkinson's disease.

Mark Frasier, PhD: Patients are the heart of everything we do. So, in order to be successful and in order to develop new treatments and ultimately a cure, we need you, which is why we're so thrilled that everyone is joining us today. So, let's dive right in. We'd like to start just talking about the latest advances in treating some

Parkinson's symptoms and before we talk about the recent results, I'd like to start by just asking Marion just to talk a little bit about her symptoms, what bothers her, and her path to diagnosis. Marion, can you talk about your disease?

Marion Fioretti: Certainly, Mark, thank you very much. As you mentioned, I was diagnosed in 2010. Luckily I feel like even though it's been close to 11 years now, that I'm doing quite well. I don't have tremors, as that seems to be the normal or the standard that people look for in Parkinson's. But what happens to me is if I have off episodes, I have problems with my movement of my feet. My feet sometimes feel like I'm in cement block shoes or something. Or even things like crossing through a doorway where I get into an almost freeze and my husband says it looks like I'm going to tilt or something or fall over.

Marion Fioretti: Luckily sleep has not been a problem with me. I seem to be able to sleep quite well through, but one of my big pluses is my exercise. I've always exercised throughout my life. But once I was diagnosed with Parkinson's, exercise became very important to me. Back in 2015, I did the Tour de Fox. I started off where we did a hike up Mount Mansfield with my daughter. I've since then run 5Ks, 10Ks, Rocked the Ridge up in Mohonk, Chicago Half Marathon. Have not done a marathon yet. I'm not sure if I'm up to it. But you never know, a few more years I might give it a try. But just in general, I would say my main things is my freezing gate and getting stuck with my feet, the shuffling.

Mark Frasier, PhD: Thanks, Marion, and congratulations on all the fitness accomplishments and certainly there's a lot of, of research that suggests that exercise really can slow the progression of disease. So, I think that's fantastic that you're able to do all of those activities. You mentioned so-called off episodes where you feel stuck or frozen. And there's been a lot of advances in novel technologies and new treatments to treat some of these off episodes when drugs wear off and are not as effective.

Mark Frasier, PhD: Dr. Qureshi, can you talk a little bit about the latest we've seen in those advances and perhaps some other treatments for Parkinson's disease symptoms?

Irfan Qureshi, MD: Yeah. How, Hi, Mark. Thank you so much for inviting me and thank you to the Foundation for having me. It's a pleasure to talk with you all today. There've been really exciting progress in Parkinson's disease research that we've seen over the last year. There is quite a lot going on, both in terms of what we call symptomatic treatment or treating the symptoms of Parkinson's that people have today, as well as stopping Parkinson's disease tomorrow, what we call disease modification.

Irfan Qureshi, MD: I'll just start at a very high level. There are approximately 170 therapies that are currently being evaluated in clinical trials. That's an amazing number, 172. And of those, about 39 of them are in late stage trials, what we call phase three trials, which is really important because the next step after a successful phase

three trial is really to try to go and talk to the FDA and to get drugs approved so that they can benefit people out in the community.

Irfan Qureshi, MD: And so I want to start first talking about symptoms and particularly hard to treat symptoms as Marion just talked about, things like gait and things like off episodes. And there have certainly been a lot of advances over the last year. I'll highlight a few of them. First, I want to focus on advances that are related not to medicines or to drugs, but to other kinds of therapies and I'm going to focus on two of them.

Irfan Qureshi, MD: One is called focused ultrasound, and this is something that's really exciting. Ultrasound is a technique which a lot of people have heard of or had ultrasounds. But focus ultrasound is a way to really target in a very specific way specific brain regions that may be involved in Parkinson's disease. And focus ultrasound was first approved for patients with Parkinson's disease who have tremor in 2018. But recently over the last year, the FD has also approved focus ultrasound to address other symptoms of Parkinson's disease, which are stiffness and dyskinesia. Those are those involuntary movements that some people with Parkinson's disease have.

Irfan Qureshi, MD: And so that's a really exciting new potential therapy that is available for people. We also have advances in deep brain stimulation. DBS or deep brain stimulation is an important therapy that's been available for more than 20 years for people with Parkinson's disease. It is a surgical treatment where a device is implanted and that device helps to control the electrical signals in the brain and to reduce some of the motor symptoms of Parkinson's disease, including things like tremor and stiffness.

Irfan Qureshi, MD: And it's really exciting that the progress over the last year that we've seen with DBS allows people to personalize their DBS therapies much more so than in the past and allows people to do so while being at home and not necessarily having to have as many visits to the doctor.

Irfan Qureshi, MD: In the past, you would get DBS and after the surgery have many visits with the doctor to fine tune that DBS system. But nowadays, you can, with these exciting advances, do more of that at home. So, where you have a wifi connection or cellular connection, you can really use that to program or refine the DBS with your doctor.

Irfan Qureshi, MD: So that's really, really exciting. In addition, we know that one of the ultimate goals is to continue to refine the therapy and I want to highlight one of the initiatives from the Fox Foundation, which is the registry for advancement of DBS, the Rad PD registry, which is a way to continue to learn more and have more exciting advances in the future with DBS.

Irfan Qureshi, MD: So, I'm going to move on now and talk about medicines or pharmaceuticals that can target symptoms of Parkinson's disease. We were talking about off

symptoms, that is motor symptoms, things like movement slowing down, having more tremor, et cetera, which can occur for people. And there are some exciting new advances for medicines on that front. One example is a medicine which is an extended release form of levodopa that is new. That was studied and has positive phase three data.

Irfan Qureshi, MD: That study showed that people who were taking the extended release levodopa, this new formulation, compared to the standard levodopa had better outcomes. They had less off time with fewer dosing. So, three times a day, rather than five times a day. So, I think that's one example of the advances we've seen over the last year.

Irfan Qureshi, MD: There are quite a few other potential symptomatic treatments as well, both targeting the motor symptoms, which include for example, additional all forms of levodopa, better delivery, more personalization. And one example of that is subcutaneous pumps that deliver levodopa continuously for people.

Irfan Qureshi, MD: But the focus is not only on motor symptoms. There's a whole bunch of non-motor symptoms, which I'm sure different people experience in different ways. Those can include things like issues with managing blood pressure issues, with constipation, things with cognitive and behavioral issues. And there's a broad range of therapies, which are available that target, in clinical trials, these different kinds of symptoms. And the hope is to progress those so that they become available for people.

Irfan Qureshi, MD: And I'm just going to highlight some the mechanisms, the targets of those different medicines. For the motor symptoms, it's really dopamine. That's the chemical, the neurotransmitter in the brain that controls movement. We also have some other targets, including glutamate. That's another neurotransmitter that controls movement. As well as gaba, G-A-B-A, gaba is another neurotransmitter.

Irfan Qureshi, MD: And there are various medicines that are being studied that target these different neurotransmitters for the motor symptoms of Parkinson's disease. There's also the non-motor symptoms, which I mentioned, and there are various potential medicines that are being studied. They target other brain neurotransmitters and chemicals which we call acetylcholine, epinephrine, and serotonin. So with that, I'll take a pause and hand it back over to Mark.

Mark Frasier, PhD: That's great. Thanks Irfan. That's wonderful. I would make two comments. One is that some of these delivery approaches are not using necessarily new medicines. They're the same chemicals. But they're engineering different ways to deliver them. And while you might think that they may not be impactful, it's remarkable in some of the research that's been published how these engineering approaches really can improve quality of life, reduce off time, et cetera.

Mark Frasier, PhD: So, I think that's been really exciting to see some of these new engineering approaches or formulation approaches in Parkinson's disease march their way to approval. The other comment I was going to make was just around the non-motor symptoms that you mentioned. Cognition, depression, constipation, et cetera. The Foundation has really made a concerted effort to fund research in this area and targeted researchers and solicited applications for funding.

Mark Frasier, PhD: And in the 2021 year review that you see here on the screen, you can access this through the resource list, there's a really nice description of some of the projects and trials that have been funded out of these funding programs. And so there's always opportunities to participate in research and we'll talk about that in a moment. But if you're interested in learning more about some of these non-motor treatments that the Foundation is funding, I encourage you to look into this year end review.

Mark Frasier, PhD: Before going on, Marion, I'm curious just on what you heard from Irfan, what excites you about some of the developments that you've heard about?

Marion Fioretti: I think to the extent that I can still continue taking the carbidopa levodopa, as opposed to there's some other drugs out there that I've tried to stay away from, because I was concerned about compulsory behaviors that they might be attached to and that people have concerns. But I guess the mode that I would receive the dosage in, because oftentimes right now, if I don't plan my meals properly, if I happen to have a burger or something, and then all of a sudden take my meds. I'll be out of kilter for the next hour or two, because it doesn't get absorbed properly. Because I have that conflict between, is my stomach and my intestines going to absorb the medicine or the protein. And for some reason I take the protein first. That's something that I'm interested in.

Irfan Qureshi, MD: Yeah. So Marion, that is exactly what Mark was talking about, right? With these novel delivery systems. It's not a necessarily a different medication, but the delivery system is way better with some of the newer technologies, because I think everybody with Parkinson's experiences exactly what you were talking about, the regimen being personalized, being affected by what they eat. And the better delivery systems we can get. We know that the Levodopa is really our main treatment for Parkinson's disease motor symptoms. So that's why there's so much emphasis there. And I'm glad to hear that you feel that way as well.

Marion Fioretti: Yes.

Mark Frasier, PhD: Dr. Qureshi we have a question from the audience before moving on just about the difference between DBS, deep brain stimulation that you mentioned and focused ultrasound. And certainly the decision on these types of treatments is a personal one that involves conversations with their individual doctor. Can you just talk at a high level about the differences between these two approaches and potential strengths and limitations?

- Irfan Qureshi, MD: Yeah, it's a great question. And I would echo what you said, which is for whoever is asking the question and others who have the same question, talk to your doctor, they're probably the best person to answer all the details. But at the high level, the differences are that deep brain stimulation is a surgery. Whereas, focused ultrasound is not a surgery. It's a non-invasive type of procedure. There's no anesthesia, et cetera.
- Irfan Qureshi, MD: So both are trying to reduce the symptoms of Parkinson's disease with focus ultrasound. It's a single treatment that aims to target the cells with beams of ultrasound and turn those cells off. For DBS, there's an implantable device, electrodes, that go into the brain and those electrodes can be fine tuned over time. And so they're just very different and what may be right for one person may depend on their personal preferences. It may depend on what the disease symptoms they have. And so I would encourage you to talk to your doctor about the specifics.
- Mark Frasier, PhD: Yeah. Great. Thank you Irfan.
- Larry Gifford: A landmark study that could change the way Parkinson's disease is diagnosed, managed and treated is recruiting participants now. PPMI or the Parkinson's Progression Markers Initiative needs people with and without Parkinson's, especially people age 60 and up who have close relatives living with the disease. Take a short survey today at [michaeljfox.org/ppmi](http://michaeljfox.org/ppmi) to see if you're eligible. That's [michaeljfox.org/ppmi](http://michaeljfox.org/ppmi).
- Mark Frasier, PhD: So, this was covering a lot of the advances in treating Parkinson's symptoms. And of course, why we exist is to go out of business and really ultimately find a cure or treatments that slow or stop the progression of the disease. And there's been a lot of advances in our understanding of the role of genetics in Parkinson's disease. And these have led to actual drug development programs that are targeting some of these proteins that are linked to the genes. And, and 2021 was an exciting year. There's been some reports of new findings, new clinical trials and new opportunities to develop treatments that slow or stop the progression of the disease. This slide lists a couple of those new advances. And I'd like to ask Irfan, if you could just highlight perhaps some of the reports that you're particularly excited about?
- Irfan Qureshi, MD: Yeah, absolutely. I think as you've said Mark, there are many researchers around the world, who are studying Parkinson's disease to better understand the disease. And everybody's ultimate goal is to go out of business to find a cure for the disease. And really the first step in that is these kinds of exciting scientific discoveries from genetics and other approaches, including some of the genetic consortia work that is funded by the Foundation. And I will say a few words about the disease modifying treatments, the treatments that are currently in trials to stop the progression of Parkinson's disease. These are really very different than some of the types of medicines that I mentioned before. The goal of those medicines is to reduce the symptoms. The goal of these trials is to

prevent the progression of the disease. It doesn't necessarily make symptoms go away.

Irfan Qureshi, MD: These therapies do that by targeting the underlying cause of the disease. And so as Mark mentioned, we have learned a lot over the past few decades about the genes and the proteins that are involved in Parkinson's disease. And so I'm going to highlight three of those. One is called alpha-synuclein, is a protein you might have heard of it deposits in the brains of people with Parkinson's disease and it's believed to lead to the death of the neuronal cells. And so that is an important potential target for therapies.

Irfan Qureshi, MD: There's also a gene and protein called LRRK2, L-R-R-K-two. LRRK2 is a common genetic risk factor for people with Parkinson's disease. And it's another target, that's very exciting where we've seen advances with potential therapies progressing into the clinic.

Irfan Qureshi, MD: And then lastly, I want to highlight a gene and protein called GBA. GBA again, like LRRK2 is a genetic risk factor for Parkinson's disease. And so, for each of these three genes and proteins that I've mentioned, they've been exciting advances in the science and in ways to target these genes and proteins. For alpha-synuclein, that's one of the most exciting, there are 13 potential therapies that are being advanced and these therapies span vaccines. So really, exciting technology to reduce alpha-synuclein deposits. As well as small molecule kind of therapies that are aimed to dissolve as some of these deposits, as well as protein antibodies, which are designed to stop the spreading of these deposits.

Irfan Qureshi, MD: So really exciting science we've seen go forward over the last year, targeting alpha-synuclein. We also have exciting therapies that are targeting LRRK2. That is a gene, which has been linked to Parkinson's disease. And so there are studies that are for people who carry that gene.

Irfan Qureshi, MD: In addition, there is some belief that even people who don't carry that gene mutation are at risk and you can still reduce Parkinson's disease progression by targeting LRRK2. So there are studies with LRRK2, two of them that are ongoing, two compounds. And lastly, for GBA, there are at least four compounds that are progressing in clinical trials. So you can see there's a really exciting group of compounds that target different aspects of the disease in a very targeted way.

Irfan Qureshi, MD: But there are other approaches too. We know that there are some general mechanisms that are probably relevant in Parkinson's disease. Those include things like inflammation. They include autophagy. Autophagy is a fancy word, that means the housekeeping, sort of that occurs inside the body, inside the cells. There is oxidative stress which can damage genes and proteins and cells. There's therapies that target the mitochondria. The mitochondria are really important parts of your cell. There are the energy factories that drive your cells, especially your brain cells. There's also cell therapies. So for example, stem cell therapies or other approaches. So there's quite a lot that's in the pipeline, as I mentioned, when we started more than 172 unique compounds with 39 in late

stage phase three development. And we're really hopeful about these progressing and showing us positive data.

Mark Frasier, PhD: Wow. Yeah, that is a lot as you say. And I mean, one takeaway I think that I have is just the momentum in this space is really unprecedented. The diversity of targets that you talked about, that are being attacked for a disease modifying treatment for part Parkinson's disease, the diversity approaches, whether it's gene therapy or small molecule or vaccine. It's really a robust pipeline. I also like to remind everyone that, these trials that are being tested for new treatments in humans are clinical trials. They are experiments. And so it is unlikely that every trial that is in clinical testing will work. But one of the things that the Foundation does is work with researchers and groups, developing these treatments, to share data, share information from both trials that are successful and trials that may not have been as successful or met their expectation, really because every experiment we'd like to learn from.

Mark Frasier, PhD: And so I think it's important as a community to appreciate that not everything will work in clinical trials, but certainly something and likely many things will be learned in every clinical trial. And that will just improve our ability to develop treatments going forward. So that's exciting.

Mark Frasier, PhD: So I'd like to switch gears a little bit and bring Dr. Ritz into the conversation. I mentioned, Dr. Ritz is a world leading expert in understanding the role of the environment and how it might contribute to Parkinson's disease. We talked about a little bit about some of the genetic learnings that have occurred in the last several years that have led to new treatment strategies. But we've known for some time that genetics doesn't explain everything in Parkinson's disease and certain environmental factors may contribute to developing Parkinson's. So before going to the latest research, Dr. Ritz, can you just summarize kind of what we know in general about the role of the environment in Parkinson's disease?

Beate Ritz, MD, PhD: Yes. So the story is actually fairly short. Even so I've been spending almost 25 years of my life on it. I have been concentrating on pesticide exposures from the beginning. And what we know scientifically about pesticides and Parkinson's is probably the most solid. And I'll explain in a minute, next in line I think are some metals, especially large exposures. There was a very good study out of Harvard and a few other studies that showed that lead exposures are a risk factor for Parkinson's. Increasing the risk almost two fold, it's long term lead exposure. The Harvard study did actually bone lead measurements, and that was important because the bone store's the lead. And so they had a really long term record of lead in the body of elderly men. That was the normative aging study, mostly veteran males in Boston.

Beate Ritz, MD, PhD: And recently one of my junior colleagues developed a very good marker for this bone lead in the blood. So long term... Because the blood lead is really a short term marker, but we believe we now have also developed a longer term marker. I can use it, we used it in my studies. We used it in a very large study that was



available publicly in Australia. And these tibia bone lead measures actually were predictive in the same way that they were in that Boston study. So lead is definitely something we need to keep out of our environment. And we all think, okay, we took lead out of the gasoline. Maybe we are done, but there's a lot of legacy lead out there in the world. A lot of airplane fuels are still leaded and they're distributed pretty nicely about urban areas.

Beate Ritz, MD, PhD: You know these kind of exposures and there are legacy oil contamination. There's a lot of lead pipes, et cetera. So I think we still need to put our feelings out to what else can we do to avoid us being exposed long term to lead? The third one that I think is new is actually air pollution. And it kind of fits lead very well because part of the air pollution we are talking about is particulate matter. And that's combustion related. It comes out of the tail pipe of cars and ships and airplanes and power stations. So combustion related particles, but part of this air pollution is actually also metals and where the metals coming from on broken tire wear. And so if we are talking about the impact of traffic, of air pollution of transportation, we always have to also think about how soil is re suspended, how brake and tire wear contributes, metals, and we are breathing this, and we know these metals on neurotoxic. We've known for a very, very long time that heavy metals are neurotoxic. The difference is that through the breakdown and the grinding up of these particles, they become so small that we can inhale them. And when we inhale them, they may get stuck in the lung, but then the lung transports the mucus up and we swallow it. And then we are in the gut and through the gut, you know, we can be exposed to all of these things that we are breathing in, even if it's not going in through the lungs.

Beate Ritz, MD, PhD: And finally, I think we also need to pay attention to organic solvents because there are some really important studies out there saying that organic solvents are not good for your brain. And we are using solvents very heavily in industries, but, you know, you can also find them as byproducts of a lot of other common uses and they are not very good for your brain.

Beate Ritz, MD, PhD: So, what do I know about pesticides? Well, pesticides are by tonnage, apart from pharmaceuticals, the largest intentionally introduce chemicals near humans in the world. And why is that the case? Well, we want to grow our crops and we want to keep insects from eating them and we want to kill the weeds that otherwise would displace our crops. So we have a good reason to do this. However, we engineered quite a lot of these pesticides to actually be neurotoxic because they're supposed to kill those pests, right? And how do we kill the pests? Well, we harm their nervous system. So it is very well known that organophosphates, for example, they were introduced first as nerve agents in World War I, and then we developed from Sarin gas we developed all of the offshoots of organophosphate pesticides.

Beate Ritz, MD, PhD: They're not as toxic as Sarin gas, don't get me wrong, but they're toxic to these little insects. And then the question is, how toxic can they become to bystanders, people who apply them, but also bystanders? And the problem with a lot of these pesticides is yes, they're not acutely toxic in the same way to you

as they are to insects. But what about long term exposure? And, you know, do you harm your brain one cell by one cell? And we know that we only have a certain number of neurons in the substantia nigra, where all the dopamine is made that you need. And every cell we are losing there is one cell too many, right? So chronic long-term exposure we should be very worried about and anything that can get into the brain or that harms the brain in maybe even an indirect way, which is immune system.

Beate Ritz, MD, PhD: And so these pesticides have shown, quite a few of the pesticides are not just known as acute neurotoxic, like the organophosphates, but some of them might just be immunotoxic or, you know, do something about your immune system not working all that well. And why is that important? Well, we have the gut and for some of you who already asked these questions, there is recently more and more discussion about what the gut does that is relevant to the brain. And all of the Parkinson's patients on this line will know, you probably have some gut issues, you probably have some constipation, or you had some constipation and these autonomous nervous system related symptoms, we think it's the vagus nerve related symptoms, they are very real and they're very much Parkinson's disease and specific to Parkinson's disease. And so what is it in the gut that, you know, might be related to these symptoms?

Beate Ritz, MD, PhD: And one focus recently has been the gut microbiome. And why is the gut microbiome so important? Well, because it's kind of another organ of ours and why am I saying that? It is just like we have a second liver in our gut. We have a huge amount of organisms that are breaking down food for us, also breaking down toxins for us, but possibly also generating toxins. And we are just starting to learn more about how all of this happens and how maybe the microbiome is what can help or harm us depending on whether it generates toxins or breaks down toxins for us.

Beate Ritz, MD, PhD: And that leads back to the question about what about the appendix? Well, the appendix is known as an immune organ, but the appendix is also known as harboring probably the microbes that you want to keep in your body, when once you wipe out with an antibiotic, your, gut microbiome for a week or two, what probably recolonize well rest of your colon is sitting in the appendix. So the appendix is kind of a holding tank for this microbiome that should be helpful to you. However, it might also be the organ where inflammation starts and where inflammatory reactions can go back and forth and stimulate immunologic and inflammatory mechanisms in your body that then affects the brain and is not good for you. And therefore the appendix has become one of the interesting organs now to study and see how it contributes to possibly risk increase in Parkinson's. But there's very little out there. We don't know much yet.

Mark Frasier, PhD: It's fascinating, fascinating work. What do we know about exposure earlier versus late and how long one needs to be exposed to certain toxicants to increase the risk of something like Parkinson's disease?

Beate Ritz, MD, PhD: Excellent question. We, we basically don't know. However, if you conceptualize that it is really a game of numbers of how many dopamine neurons are left making dopamine, and we all know, very well know that you can live and not have any Parkinson's motor symptoms up to the time when 60 to 80 percent of these neurons are gone 60 to 80 percent. So there's quite an excess capacity in the substantia nigra to produce enough dopamine. And probably those colleagues who survive, those cells who survived are doing double duty and maybe getting more stressed about this. So you can think about a scenario where very early in life, you got exposed to a pesticide for some reason or other that really did harm the substantia nigra neurons, so maybe 5 percent died, but you're left was 95 percent. So those go happily on until what age, where they start to fail.

Beate Ritz, MD, PhD: And then every leftover capacity that you have you need. So I can easily see that it is bad for you to lose that 5 percent in use, because you don't have enough capacity left once you get close to that 60 to 80 percent death of your neurons, but you can also argue that that same pattern could happen late. You know, you're 65 and you're now exposed to a high dose of an agent that kills these neurons, and that pushes you over the edge at that time. But we all believe it's a long term process in the end.

Mark Frasier, PhD: Right.

Beate Ritz, MD, PhD: It's not instantaneous.

Mark Frasier, PhD: Sure. Yeah. That makes sense. And, you know, it takes the entire Parkinson's community to develop cures. We certainly need people with Parkinson's to volunteer for research, and this could be drug trials, but it could also be research on environment and different exposures. One other way that you can be involved is the Foundation has a campaign to eliminate paraquat, which is a pesticide associated with Parkinson's disease. And if you go to the resource list on the box on the right, you can click a link to contact your lawmakers in the US to advocate for banning paraquat as a pesticide used currently in the US.

Mark Frasier, PhD: So let's move on to, I just want to talk briefly about PPMI, the Parkinson's progression marker initiative. This is another way that the community can be involved in Parkinson's research and developing new treatments.

Mark Frasier, PhD: The PPMI study is a global landmark study collecting lots of data from people with Parkinson's and people without Parkinson's. The study has been going on for 10 years. And the goal of the study is to develop tools that can be used to develop new treatments. These tools are called biomarkers, that are indicators or measurements of the disease. And these tools can be very informative and helpful in determining whether a new treatment is working or not. The study has been in existence for 10 years, and it is undergoing an expansion to find thousands of individuals around the world to participate in this study. Everyone is eligible to sign up for this study. You can visit this link that you see to answer some questions?

Mark Frasier, PhD: There's actually an online component that everyone over the age of 18 is eligible to participate in. And then as you answer more questions, you can determine if one is eligible for the advancing study and actually visiting research centers to contribute additional data. There's actually going to be a whole webinar about PPMI, what we've learned and the expansion of this study in December. So I encourage you to sign up for that on December 16th.

Mark Frasier, PhD: So I mentioned PPMI is focused on biomarkers, and we haven't really talked about that in this webinar, and I thought it would be useful just to ask Dr. Qureshi to expand on why biomarkers are important, and then I'd like to share some latest developments in new research tests for biomarkers.

Mark Frasier, PhD: Irfan?

Irfan Qureshi, MD: Yeah. Thank you so much, Mark. This is such an important point. And, you know, the Fox Foundation through PPMI is really, I think hopefully going to transform how we think about Parkinson's disease and all the people have participated in the PPMI and those that will in the future. I think everybody knows the journey of someone to get to a diagnosis of Parkinson's disease is not a straight line. It can be really hard once you go to a primary care doctor or an orthopedic doctor, or some other kind of doctor to eventually get to a neurologist or a movement disorder specialist. And it's often not at the first visit, but maybe at a later visit that the diagnosis can be really confirmed. And why is that? And for Parkinson's disease, we don't have a blood test that very easily you could look at in everybody and say, oh, you have Parkinson's disease.

Irfan Qureshi, MD: We don't have a radiology test, like an imaging scan that we can just send people for and say, okay, you have Parkinson's disease. And so when we talk about biomarkers, we are trying to really find that very special signature of the disease so that we could do a test when somebody walks into the office and say, you definitely have Parkinson's disease. And I would go even further and say, you know, in the future, we don't want to just cure Parkinson's disease. We want to prevent it from ever happening. And these biomarkers that are being studied in PPMI will help us to diagnose people before the disease even occur, and the symptoms show up in people. And that's really, really, I think, going to transform a lot of how we think about Parkinson's. We want to start thinking about prevention eventually, right? Prevention is always better than cure.

Irfan Qureshi, MD: And so that is around this issue of diagnosis, but there's a whole second issue, which is related to once somebody has the disease, how do we know if a medicine we give them is working or not? If earlier today, in the webinar we talked about disease modifying treatments that stopped the progression of the disease. And currently in clinical trials, when we try to evaluate that we use clinical measures, we examine people, we watch how they move, and that's really important, but it would also be very nice to have a tool that's a blood test. I'll think of it like a cholesterol test as an example. When you give medicines for cholesterol, you then measure cholesterol and you say, the cholesterol is lower and you know the drug is working. Or you say, well, I need to increase the dose

of the medicine because it's not working well enough. And that's what disease progression biomarkers will really help us to do. It will help us to advance these therapies in an exponential kind of way.

Mark Frasier, PhD: Yeah, it's, it's really exciting to see some of the developments and having these measurements and indicators, and even the possibility of finding individuals before Parkinson's symptoms develops. And that's why these more objective markers are so important. I thought I'd just highlight a couple of projects that the Foundation has funded this year, as examples of these objective biomarkers. And these are early in development. There are certainly some that are a little bit later stage. You can read more about this in the year in review, under the resource list. But just two examples here. One is this device it's called the Emerald device, that is a box that you can put in your home and it collects information just based on a wifi signal and actually can track individual's movement and their gait patterns, their response to medicines, just in the comfort of their own home without the person having to wear any wearable device or anything. So this is a really exciting technology that we supported a pilot study in a small number of people with Parkinson's to just determine whether it can detect symptoms of Parkinson's disease. It turns out it can. And we're excited to support a larger study to really understand how this device can objectively gather information and track information about this Parkinson's symptoms and how the symptoms develop over time. The second example is a really novel example of a biomarker, which is in the oil of skin. So the story behind this project came out of the UK, where a wife of a person with Parkinson's actually detected a difference in how her husband smelled and detected a scent that was different.

Mark Frasier, PhD: This was several years ago, and it led to a lot of research that confirmed that there, in small number of individuals, the sebum or the oil that's released from skin, there seems to be a difference in people with Parkinson's compared to people without Parkinson's. And now, some of the laboratory experiments have identified the actual chemicals that seem to be different. And the Fox Foundation is supporting a larger study to build the data set and confirm that some of these chemicals in skin oil are different in people with Parkinson's. But you can imagine how easy of a test this might be if it were scaled and available in a laboratory setting as a potential diagnostics. So these are very early, kind of innovative, new tests that are in a research setting, but the Foundation supports these early cutting edge technologies in the hopes that they will eventually lead to more standard tools and biomarkers.

Mark Frasier, PhD: Okay, I've talked about how you can get involved in research. I've talked about how you can get involved in advocacy and in advocating for removal of pesticides. Marion, I do want to ask you to comment. You mentioned Team Fox, you've been involved in a number of different ways. It does take the entire Parkinson's community to develop new treatments and cures. Can you just share a little bit about your experience with getting involved and how it's helped you and what you've learned from it?

Marion Fioretti: Yes, very gladly, Mark. As I said, I was diagnosed back in 2010. Initially, I didn't speak about it to much of anyone. My daughter actually was the first person that joined Team Fox, and we started in 2011. She ran our first fundraiser, which was a bar event that happened on the snowstorm or the blizzard of Halloween that year, but we were still successful. People didn't want to leave the bar actually to go out into the snow. But in addition to that, the exercise piece has been very critical, just running 5Ks or 10Ks or half marathons or Rock the Ridge. It's not just the physical part either. It's the camaraderie of the people. I have met so many fantastic people who I can now call friends and some of them probably closer than my family.

Marion Fioretti: So that's been very critical. In addition, I'm involved with the Fox Insight online, which is essentially, I think I have my 17th visit coming up right now, which is essentially, it takes a little while, but they ask you a series of questions based upon how you have been managing for the last 30 days or so. But it was helping them to accumulate data in terms of symptoms and how people are managing. And then in addition to fundraising, as I mentioned, that helps to raise money so we can pay for this research. And I just, Team Fox is very upbeat, very knowledgeable, and I couldn't have asked for a better place to get involved with.

Mark Frasier, PhD: Wow, that's great. Congratulations, that you clearly are doing many things, raising money, participating in research, building awareness. And that's just fantastic and glad to hear that it's been so helpful. I do want to remind everyone that you can post your questions in the box. We're going to just take some of those questions now. The first was around how to find studies. I've talked about participating in research and the Fox Foundation. Marion, I'll ask you to comment on how you found different studies. But before doing so, I'll just put in a plug for the Foundation's website called Fox Trial Finder, which is a matching tool for people that want to sign up for research but don't know where to find it. You can type in a little bit of information about yourself and your zip code. And then you can see different trials that are occurring in your area that you may be eligible. But obviously not everyone is eligible for every study. But Marion, can you just talk about how you've found different studies to participate in?

Marion Fioretti: I think you took the words right out of my mouth, which is the Fox Trial Finder. That's been very critical. And PPMI, I wish I could have been involved with it, but unfortunately I can't directly participate because of the length of time I've had PD as well as the medications that I've been on. But it's still open for people who do not have PD or are in the very early stages.

Mark Frasier, PhD: Yeah, it's a good point. And certain research studies are looking for a very particular profile of person, whether it's how long they've been diagnosed or certain symptoms that they develop. But you're right, the expansion of PPMI, what's called PPMI online, is actually open to anyone over 18. So we're excited that that has expanded. We've got a question about environmental exposure, and this is a difficult question about whether someone knows whether they

were exposed or not. Dr. Ritz, how would you advise them on whether they've been exposed and also are all of the exposures a bad thing?

Beate Ritz, MD, PhD: Right. So first of all, do you know whether you were exposed? Well, if you handle the pesticide, you probably knew that you were exposed to it. But what I have been working on for the last 20 some years is actually bystander exposure, meaning you live in communities where everybody around you uses these pesticides, and some of them are volatile enough to travel miles. And you can test them in the air, and you'll find them miles away from the place of application. So you know that anybody closer will definitely breathe the stuff. That said, in California, you can find out because we have what's called the Pesticide Use Reporting system. And all commercial applications, which includes farmers, but it also includes golf courses, right of way applications by the state, they are all in this electronic registry. And so ideally, you could actually go online and find out what's being sprayed around you.

Beate Ritz, MD, PhD: That is not the case when you go outside of California. In Arizona, I know only of one other place. Arizona has a pesticide use registry, but it's not publicly available to the public. California is trying to make all this publicly available. And in my mind, if we are talking about introducing so many chemicals into our environment, then we should hold the industry that does that also responsible for paying for surveillance of what's happening when humans come in contact and non-intentional contact with this. So I think we need to advocate for exposure registries, and the California registry has been working for more than 40 years really well. We need them in other places. With some agents, it's easier. For example, lead. Yes, you could actually have your bones tested for bone lead. It takes about an hour. It takes a special machine. It's not cheap, but you could find out what your bone lead measure is, how much lead you've been exposed to within the last 30 years. That's definitely possible. Whether that then helps you answer your question is another question. But for lead, it's possible.

Beate Ritz, MD, PhD: For pesticides, unless you use them yourself, it's not possible. And then is everything bad? Good question. We hope it's not, that the environment generally is also good for you. We hope that, for example, sunshine is good for you and vitamin D. So go and take that walk and maybe don't put sunscreen on, unless you are prone to melanoma, which we know, unfortunately, Parkinson's patients are at a slightly increased risk of developing melanoma. We don't know why, but it's a very, very small risk. So I think some exposure to the sunshine to get your vitamin D would be very good, and to get your exercise at the same time. And I totally agree, the one thing we know that slows it down maybe is exercise.

Mark Frasier, PhD: Great. Thank you, Beate. We're getting a lot of great questions. Unfortunately, we're at the end of the hour. And so I think we'll have to adjourn. I do want to remind everyone that there is a lot more information in the resource list and links to reading materials that cover a lot more than we were able to cover today. So please check out those links. I want to thank you for being a part of

the community, the Parkinson's community, and for joining us today. We hope you found this information useful. I also want to thank our panelists. Thank you, Beate. Thank you, Marion. Thank you, Irfan, for sharing your insights and expertise today. We'll be linking a link to the webinar, sending a link to the webinar that you can watch on demand very shortly. Or if you'd like to share it with friends or family, as you'd like. As I said, I hope you found this information useful. We wish you a wonderful holiday season with family and friends, and thank you for joining us.

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