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Speaker 1: Welcome to a recap of our latest third Thursday webinar. Hear directly from expert panelists as they discuss Parkinson's research and answer your questions about living with the disease. Join us live next time by registering for an upcoming webinar at michaeljfox.org.

Larry Gifford: Thank you for joining us today. I'm Larry Gifford, a member of The Michael J. Fox Foundation Patient Council and Co-founder and president of PD Avengers, a patient-led global alliance people and organizations committed to adding urgency to the cause of ending Parkinson's. It is great to be here with you and with our panelists. Today we'll discuss a complex connection between the environment and Parkinson's diseases, how things like pesticides and pollution are linked to Parkinson's. We'll also discuss less obvious environmental contributors, socioeconomic factors like access to care and healthy foods and gyms and grocery stores that can affect the development and progression of PD and the health outcomes. But before we get into the environment and Parkinson's and all your questions, we have some breaking news to share. This is very exciting. You may have seen in the Wall Street Journal that a recent publication showed a skin test can now detect the biology of Parkinson's disease. This presents a very exciting research opportunity in the new biological era of Parkinson's.

We've got a lot more information on that at the end of today's webinar, but first we want to talk about the big topic for today, Parkinson's and the environment. And with that, we will introduce our guests. We have a lot to discuss. Dr. Beate Ritz, a distinguished professor of epidemiology, environmental health and neurology as well as the Vice Chair in Epidemiology Department in the School of Public Health at UCLA. She also co-directs the UCLA Center for Gene Environment Studies for Parkinson's disease. Her research focuses on the health effects of occupational and environmental toxins on chronic diseases, including neurodegenerative diseases like Parkinson's. Beate, thanks for being here. We also have Dr. Joohee Jimenez-Shahed with us today. She is a neurologist and movement disorder specialist at Mount Sinai and an associate professor of neurology at the Icahn School of Medicine. She's also the medical director of the Movement Disorder's Neuro Modulation and Brain Circuit therapeutics.

Joohee is also a co-chair elect of the Parkinson's Study Group, which is a nonprofit clinical trial site network. She's also the chair of the PSG's working group on healthcare outcomes and disparities. Thank you for being here.

Joohee Jimenez-Shahed: Thank you.

Larry Gifford: And finally, we have Ted Thompson, the Senior Vice President of Public Policy at the Michael J. Fox Foundation. Welcome to you, sir.

Ted Thompson: Thank you. Glad to be here.

Larry Gifford: And we are glad that you're all here because we needed to get the best experts we could because this is a tough topic. There's a lot here. It's a question many people have, including myself, why did I get Parkinson's? What caused it? Joohi, can you walk us through what we know and maybe what we don't know about what causes Parkinson's?

Joohi Jimenez-Shahed: Yeah, as you said, that's a kind of complicated question. And I do get that question a lot from my patients as well, "Why did I get Parkinson's disease?" And I think a lot of folks certainly have the question in their mind whether it was some sort of inherited reason, was there some genetic cause for their Parkinson's that made them develop this condition or were there other things going on in their life that may have created this situation for them? So I think the short answer that we tend to give patients is that it is a mix of genes and environmental exposures. When we think about genetic causes of Parkinson's disease, that's probably really only about 10 to 15% of all cases, meaning that there was a gene that one-to-one was linked with the development of Parkinson's. But for the vast majority of individuals, we know that there might be some degree of genetic susceptibility. So other genes in your sort of genetic makeup that perhaps increase the risk of starting to lose those dopaminergic neurons combined with some kind of environmental exposure.

And those could be a variety of different things that then work together with that genetic predisposition to produce the neuronal changes in the brain that end up causing the symptoms of Parkinson's disease. And then of course we know that just as sort of a general rule, the risk of developing Parkinson's increases with age, and we also know that males have a higher risk of developing Parkinson's compared to females.

Larry Gifford: So I think it's important here for us to note that not everyone who has these genetic mutations will get Parkinson's, and that there are people who get Parkinson's without these known genetic links. In fact, only about a quarter of PD cases have clear genetic drivers, so the environment must play a large part. And then even those people that are exposed to environmental factors don't always necessarily get Parkinson's.

Joohi Jimenez-Shahed: True. Yeah.

Larry Gifford: So when we are talking about the environment in this context, it's not just climate and parks and green spaces. What does a scientist mean when they talk about the environment when it comes to Parkinson's disease risk factors? Beate?

Beate Ritz, MD, PhD: First of all, the environment can be easily described as anything that's not genetic, but that's probably too broad. But generally, we mean environments that we can actually change, where we have some policy opportunity for change and some environments we cannot change because they have already happened to influence your disease risk like what happens in utero and after you're born, there's no way to change it, but we still want to understand what happened and why it happened so we can prevent it for the next people. But basically it's lifestyle, diet, physical activity, anything that's related to your personal behavior that you might be able to change. Then there are geographic differences in terms

of what you are exposed to, how much sunlight you get, whether you are exposed to certain pollutants, whether you are able to avoid being exposed to pollutants in a smaller geography because you are of a higher socioeconomic status, you can move away from polluting industries or you can't.

So socioeconomic factors play a role in terms of how much exposure we might be getting and how we can handle these exposures or whether we can avoid them. And head injury is one of the environmental exposures. And clearly head injury, we usually consider them accidents, but think about all of the veterans who had no choice about their head injuries when they were in conflict, and we certainly have now a lot of veterans who are suffering from the consequences of head injury. So these are almost occupational hazards. And clearly occupational exposures are very important because they are usually high level and they are continuous in a way more than other types of intermittent exposures might be. We mostly think about chemicals, but there's a lot of physical stress through heat or, for example, through injuries. Farmers, for example, also have a lot of head injuries, and then of course the chemicals.

Larry Gifford: Right. There's been a lot of research done already into the environmental factors that increase Parkinson's risk. Ted, can you talk a little bit about what we know?

Ted Thompson: Yeah, we know quite a bit and there's still more to learn, but there are some chemicals that are very directly connected to Parkinson's, paraquat being a major herbicide that's used in the United States. It's banned in nearly 70 countries around the world, including the world's second largest population, China, yet we continue to use it here in the United States and the use is actually increasing. Trichloroethylene is another one that has been widely used throughout the years. EPA earlier this year announced a comprehensive ban on TCE within one year. They haven't finalized the rule. So we're making some progress from that perspective. Other items, heavy metals, rotenone, and then there are many other pesticides that have a correlation with Parkinson's. Just this week, research came out that an additional three pesticides are related to PD, so there's a lot out there and our goal from a policy perspective is to eliminate these known triggers of the disease.

Larry Gifford: Is there a registry of chemicals known to cause Parkinson's?

Ted Thompson: There's no comprehensive registry, I don't believe. And keep in mind, the research shows the correlation, but because people's exposures happen over time, sometimes decades before, it's hard to create that kind of a list, and the fact that we're still learning more through research, I don't know that we'll ever have a comprehensive list per se.

Larry Gifford: Yeah, we did have a question come in asking, "Is Paraquat banned in the US and Canada?" It is not banned in the US but it is banned now in Canada just last year.

Ted Thompson: Yeah, Canada did the right thing.

Larry Gifford: That's right. One last thing, the traumatic brain injury. There was a 2023 study using data from MJFF's online study, Fox Insight, that found that participants with the history of playing organized tackle football had a 61% increased chance of Parkinson's or Parkinsonism. Wow. We're getting a lot of questions and one of the attendees wants to know, given equal exposure to environmental factors, why are some people more likely to get PD? Joohi, why is it that two people can both have the same exposure but only one gets diagnosed?

Joohi Jimenez-Shahed: Yeah, I think that's a really good question and it gets maybe a little bit back to the question of what the exact exposure was, maybe the dose of the exposure, the time period over which that exposure occurred. But then if we tie that back to our understanding of the combination with the genetic susceptibility, we know that certain of these exposures may have more of an interaction or more of a chance of developing the neurodegenerative processes that lead to Parkinson's disease when certain of those genetic predispositions are present. So for example, coffee and the effects of coffee or maybe even the effects of smoking and things like that might be different in an individual who carries certain of these genetic risk factors compared to others.

Beate Ritz, MD, PhD: If I may jump in. I have done a lot of what's called gene environment interaction studies, and they were mostly concerned with pesticides. Why I think this is really important to understand is that there are genes that are helping us detoxify toxins in our body because they are metabolized and hopefully excreted through either the fecal matter or through urine, and these enzymes that turn over toxic matter in our body can actually have a slow or a fast metabolism rate. And it's known, for example, that paraoxonase, which metabolizes organophosphate pesticides that are highly toxic and very widely used insecticides. Paraoxonase is that enzyme that can have a forty-fold difference in how fast it can turn over this pesticide. So if you are exposed to exactly the same amount of organophosphates as your neighbor over a long period of time, you may get Parkinson's because you could not turn this agent over and detoxify it, but your neighbor could.

And that is one of the explanations why we might have exposures that drive disease risk in subpopulations who then get Parkinson's, but not in your wife, not in your neighbor because they have a different genetic makeup. Interestingly to understand is, these are not Parkinson's genes at all. These genes would never give you Parkinson's. They're just helping you get rid of toxins in your body.

Joohi Jimenez-Shahed: So it's kind of almost like a double hit sort of story. If you have the susceptibility, as Beate was saying, whether it's susceptibility specifically related to Parkinson's or susceptibility to other things, and then in a system that's already maybe not functioning as well, you get an exposure that really can trigger the process, then the likelihood of the process actually being triggered and beginning is different in different people for those reasons.

Larry Gifford: And then you don't know it for a while because the onset takes a while and the symptoms don't start showing up for a while. Yeah. Here's a question from the audience, "I did not grow up on a farm or work with toxic chemicals. Is this still part of the science for determining cause for toxins?"

Beate Ritz, MD, PhD: Yes, we've emphasized pesticides because there's so much research done on pesticides, but as Ted already mentioned, there's also TCE. We don't really know where... I mean, we know where TCE is used heavily, that certain metal industries because it's a solvent that's used by industry, but it can also be in the drinking water or it could be a contaminated site that your house is built on top of if you think about TCE exposure, but what we haven't really mentioned yet is another pollutant that is coming into focus and that's air pollution. So particulate matter air pollution, and we think probably mostly from car exhaust and combustion engine exhaust, ships, airplanes, cars, anything that moves and has a combustion engine that puts particles out. These particles are quite toxic and we now have more and more data to show that high exposure to air pollution, if you're living near a busy roadway, might also increase your risk for the same reason we explained with pesticides because maybe your body is more susceptible than your neighbors'.

Larry Gifford: That makes sense. Ted, here's a question from the audience, "I'm an Iraqi veteran with PD. What do we know about burn pits and other environmental exposures of increased risks for developing PD?"

Ted Thompson: Thanks for asking because we should have mentioned burn pits by now. Yeah. There is evidence that exposure to smoke from burn pits in the Middle East wars has a triggering effect of Parkinson's as well. Roughly 10 to 12% of all people living with Parkinson's are veterans of military service. I think a lot of people know that Agent Orange from the Vietnam era is a trigger of Parkinson's as well. So I do want to note that because of all these known service-connected prompts or triggers for the disease, we do have a research program... By we, I mean the Parkinson's community has a research program at the Department of Defense that was initially only focused on toxic exposures. It is now more broadly focused on PD, but Congress a couple of years ago created a specific toxic exposure research program with about \$60 million in it in order to study the toxic exposures of military veterans.

Larry Gifford: That's great. Another question from our audience relates to... "Once a person gets PD, do environmental factors continue to contribute to furthering the disease or are those factors just relevant in impacting the risk of getting the disease in the first place?"

Beate Ritz, MD, PhD: That's an excellent question. And of course you have to study individuals from the beginning of the disease to their deaths eventually and basically measure the rate of progression. We have been trying to do that in California in my studies now for the last 15 years to answer exactly those questions, and I can tell you that we are finding some contributions once you have Parkinson's, for example, these OP pesticides, organophosphates that I mentioned, we found are not contributing to your motor symptoms anymore, but they might also contribute to your cognitive decline or other symptoms of Parkinson's. So we actually then need to look much broader than the motor features of Parkinson's and try to figure out whether these pollutants, these environmental triggers then also support your progression towards all of these other kind of features, but there's much less known about that.

Larry Gifford: This question's for Ted. If these known environmental factors increase the risk of developing Parkinson's, what's being done to prevent people from having these exposures in the first place?

Ted Thompson: Well, we are working on that. We're on a seven-year journey now to try and ban Paraquat, for example. In fact, when the EPA re-registered Paraquat a couple years ago, our only option left was to sue the EPA because we believe that they're absolutely wrong in their analysis, and in fact didn't follow their own procedures for analyzing the health risks of Paraquat, nor do we believe they took into account the cost-benefit analysis. So we're pushing on that. On the TCE front, we've also been working on that for several years, and like I mentioned earlier, the EPA has proposed a ban on that, so we applaud them for that. We also are supporting legislation in Congress by Senator Cory Booker and Congressman Jim McGovern called the Pact, but I'm not going to give you the acronym, but essentially it's a pesticide reform bill that would alter how approvals are happening in this country adopting the precautionary tale that Europe has because right now, the onus is on the injured party to prove that the chemical caused their problem, and we think that should be reversed.

The other thing that this legislation does, it would specifically ban Paraquat, but it would require the EPA to re-evaluate roughly 90 chemicals that are banned in the EU that are still used here in the U.S.

Larry Gifford: Wow. Okay. Well, that's a lot. So we have these known risk factors, but researchers are continuing to work on understanding what environmental factors link to PD. In fact, the Michael J. Fox Foundation has funded almost \$5 million in research looking at environmental risk, including exposure to toxicants, lifestyle factors and social drivers of health, which is something we're going to dive into a little bit later. We are getting a lot of questions from the audience on pesticides exposure. Here's one, "What level of exposure to pesticides is associated with PD?" Beate, you had a recent paper on pesticides and dopamine neurons, and this study was funded by the Michael J. Fox Foundation. Can you walk us through that?

Beate Ritz, MD, PhD: Yes. So pesticides, of course, a lot of different agents. We have registered in California 650 active ingredients, active meaning they're causing exactly the harm to what we call pests that is intended. But all of these are also mixtures, so they're so-called inactive ingredients. Some of these inactive ingredients I can tell you are not harmless at all and should also be looked at. But basically we have a big mixture, and the problem is that if you have a big mixture, you need to figure out what the individual components are actually contributing to risk. And in a human population, that's really hard because if you're exposed to paraquat for two years and organophosphates for five years and pyrethroids for another 10 years, who was the bad actor? We don't know. Most likely each of these exposures contributed in some part to the overall demise of the dopamine neurons.

So there is no real level of exposure that you would need. You have to look at it in combination and figure out whether these combinations might even be more toxic or the sequence of the exposure might even be more toxic than just a single

pesticide. We have started to do that in a department of defense funded project where we are taking our clues from the population, the farmers and residents in the Central Valley of California to see what combinations of pesticides actually exist and expose individuals, and then we are applying these pesticides to cells from humans who have an increased Parkinson's risk. And these pluripotent stem cells, we call them, are then being used as a model to see whether combinations of pesticides are more toxic to these cells than individual pesticides. But this is just in the very beginning of our research. We hope that we can really advance that and do it much faster and broader for a lot more pollutants in the future.

Larry Gifford: And there was another study supported by the foundation on increasing evidence that air pollution is linked to Parkinson's. Beate, can you talk about that research?

Beate Ritz, MD, PhD: Yeah, I can't talk about that study. It wasn't mine. But yes, I applaud Michael J. Fox for supporting air pollution studies. I believe the one that Michael J. Fox supported was Honglei Chen's study that is still ongoing. But there are now multiple studies that are looking at air pollution. Actually, I probably did one of the first ones in Denmark because I had access to the Danish hospital registry where you could identify almost 2000 Parkinson's patients and then draw from the Danish population the controls. And the Danes have really modeled air pollution since the 1970s, so we could go really far back. Denmark has better air pollution or better cleaned up their air quite a bit, so we saw actually a link to air pollution, but it was a fairly small increase in risk, maybe a 10% increase in risk in Denmark. We published that in about 2016.

We now have redone this in the Central Valley of California, which is actually known for the worst air pollution in the U.S in terms of particulates due to traffic but also inversion layers and wildfires and farming and gas and oil extraction in the valley. So all of these contributors to air pollution seem to increase the risk a lot more than in Denmark. We published a paper on that showing that the risk increase between the lowest and highest exposure is almost twofold.

Larry Gifford: Wow.

Ted Thompson: Larry, can I jump in real quick? The Biden administration, the EPA recently issued new air pollution standards, particulate matter standards, so we're moving in the right direction. I wanted to note that Congress has the authority to overrule regulations, and there's currently an effort in Congress to overrule these new stricter air pollution standards. So I don't believe that, well, it won't succeed because the president would veto it, but unfortunately there's still some partisanship around things like air pollution.

Larry Gifford: Okay. There are some groups of veterans, Ted, with an increased risk of Parkinson's. I think we've all seen the commercials, some research last year that revealed the PD rates for 70% higher for veterans stationed Camp Lejeune as compared to Camp Pendleton. What are you learning from veterans firsthand?

Ted Thompson: Yes, we've heard from a lot of veterans about this issue, and when that study came out, we immediately called for the EPA to ban it, for the VA to provide additional benefits to those who've been exposed and for the DOD to take action

because of the exposures at Camp Lejeune. We've also actually brought patients to meetings with the EPA, both on Paraquat and on TCE, to tell their stories and very powerful stories because of the impact on their lives. There's nothing more powerful than the firsthand account of somebody living with the disease, or in the case of one of the gentlemen, he was in such bad shape, his wife had to speak for him as he sat behind her pretty much motionless, and that was Paraquat in that case, but the impact of these chemicals is just devastating.

Larry Gifford: Yeah. Beate, you're doing a lot of work with the microbiome and how the different bacteria that live in and on our bodies, especially in our gut, can affect brain health. How does that work and how does the environment affect microbiome makeup?

Beate Ritz, MD, PhD: Yeah, this is actually a really new study, although we are now in our fourth year of collecting this data, and it took me almost 10 years to get this study funded, so it sounds like it's already long-term, but we haven't really learned enough. But what we do know is that for some people, there's a good chance that the pathologic process that causes Parkinson's in the brain might actually start in the gut. And the reason is that alpha-synuclein, this protein that clumps together in the brain and is a hallmark of what neurons go through when you develop Parkinson's disease, you can also find this protein in the gut, and it has been shown that the protein that misfolds and then clumps together when it's in the brain can actually be moved from the gut, from the colon, through your vagus system, through your nervous system to the brain, and then it can cause other proteins in your brain to accumulate.

And now the question would be, why would this protein do this? And what are the conditions in your colon, in your gut, that may actually contribute to this happening? And that's where we are. But we also think that the microbiome is really a chance for us to understand how our body can defend itself against toxins. For example, we know that the microbiome can break down pesticides, it can break down organophosphates, and if you have a microbiome that's rather active and breaks down toxins before they affect you, then you are, of course, resilient more than somebody else. And what we already have learned from the pilot data that we generated in my lab is that a good healthy diet actually supports a good healthy microbiome, even in Parkinson's patients. So we asked Parkinson's patients what their diet was, we looked at the microbiome, we looked at unhealthy and healthy diets, and you could see that the microbiome was much healthier in those who ate their greens.

Larry Gifford: Are there any other factors that people should consider when they're talking about the microbiome other than diet?

Beate Ritz, MD, PhD: Yes, of course. When we hear gut microbiome, we always just think diet, but diet is actually not necessarily the most important factor. There is, for example, antibiotics can wipe out your whole microbiome and then you have to reestablish it. And it does, it comes back after treatment. But you also need to think about other medications you're using, it's also known that certain microbiota are actually not very helpful because they're breaking down your levodopa too fast, so medications are on a high interest list for the microbiome. But also really a lot

of common chemicals that may be in your diet, pesticides on your fruits and vegetables. I just said fruits and vegetables are good, they are, but they may also come with a load of pesticides, maybe heavy metals. Anything that can get in your diet of course will also affect, eventually, your microbiome.

Larry Gifford: Thank you. There is another really critical area of the environment that we should be talking about and thinking about, and that's called social drivers of health, sometimes also referred to as the social determinants of health. Joohi, what are the social drivers of health and why are they important?

Joohi Jimenez-Shahed: There's many of them that are proposed to have an influence on how patients deal with illness or their approach to illness or the manifestations of illness. And I think, really, one way to look at this is that these are the parts of our lives that maybe affect a person's experience with Parkinson's disease or maybe affect their healthcare for Parkinson's disease, and maybe also, to a certain extent, influence the risks that they have and the exposures that they have for developing Parkinson's disease. So it's a really broad list here. It can range from things like somebody's socioeconomic status, as was already mentioned, which may have an influence on the access to healthcare, maybe race or ethnic issues that have an effect on how individuals may interact with the healthcare system. These things are important because they may lead to differences in the rate at which people are diagnosed, how quickly they're diagnosed with Parkinson's, the way that their Parkinson's is treated, what access to medications they may have because of these sort of interactions with the healthcare system.

There's also things like your education level, which we know may relate to, again, your health seeking behaviors, where exactly you might receive your healthcare. People who live in more geographically remote areas may not have access to the same levels of Parkinson's expertise as other individuals. So a number of these different things. This list is almost too long to kind of go through on an itemized level. I think there are multiple lines I think that can be drawn from all of these aspects that ultimately come down to, again, as I said, what somebody's sort of lived experiences with their Parkinson's and the healthcare that they received for it.

Larry Gifford: Yeah, I had a deep brain stimulation in October. It was a miracle. It was great, but I think as somebody like in Bangladesh, they've only ever done four DBS surgeries there, so it's not available to most people. So can you talk a little bit about that? I know you've done some research on that.

Joohi Jimenez-Shahed: Yeah, so we were able to conduct a pilot registry of patients with Parkinson's disease who are undergoing deep brain stimulation. And I think the findings from that study and particularly related to access, I think typical of what happens in a lot of clinical studies in Parkinson's disease is that the information we find out is about the patients who are accessing care in those institutions where these procedures and these treatments are being performed. So in our registry, again, we had a predominance of males, we had higher educated people, we had predominantly individuals with private insurance. And I think, again, this is just a function of where we're conducting these studies and which types of patients are likely to access care in those areas. We don't yet have enough information to talk

about how outcomes may differ, but you could certainly imagine, based on some of the things that I was mentioning, that we could see disparities in the outcomes that patients have from different therapies, including deep brain stimulation, because of, again, all of these different issues.

And that can take the range of all the way from specific Parkinson's symptoms in particular populations of patients, or it could have to do with other comorbidities that they might be experiencing other health issues, maybe if they have comorbid diabetes or cardiac disease or things like that.

Larry Gifford: Can I just interrupt you there? Can you explain comorbidities to the audience?

Joohi Jimenez-Shahed: Oh, yeah, sorry. Comorbidities is just all the things that are going on in life from a medical standpoint in addition to the Parkinson's disease. So a Parkinson's patient may also have heart disease, may also have diabetes. These are considered to be comorbidities. So I think a person's experience with the disease itself may differ based on some of these other issues, which also may then be influenced by their lifestyle and their habits. So there's definitely this sort of snowballing effect that can happen when you start considering all these different variables.

Larry Gifford: Well, I know inflammation's been talked about as sort of a trigger for Parkinson's. What kind of effect does stress play in the onset of Parkinson's?

Beate Ritz, MD, PhD: I don't know about what it has for the onset of Parkinson's, but we actually did a study where we asked Parkinson's patients about stressful events like losing a partner, losing a home, losing a job, et cetera. And we definitely saw that the risk of developing depression on top of your Parkinson's, and depression is, of course, a common feature. I mean, you see it a lot in Parkinson's patients more than in the regular aging population. So that risk is definitely increased by stressful situations. It's not good. And we know that depression has really bad influence on progression in Parkinson's as well in every way because then people don't move, don't eat well, et cetera.

Joohi Jimenez-Shahed: Yeah, I was going to say something similar. I mean, I think we all have our own types of stress, and there's several different... The term stress can be so widely kind of applied in the various experiences that people have, but I think when people are experiencing more of these stressors, it can have so many other adverse effects on just, again, on lifestyle issues. So whether it's mood, whether it's depression, whether it's anxiety, whether it's insomnia, all of these things kind of can come together and sort of worsen the experience of Parkinson's disease for individual patients. And so we'll often see that being able to intervene on any of these aspects can actually indirectly improve a person's functioning with Parkinson's. So their medications may start working better, they may be able, as Beate was saying, to engage more consistently in exercise, and then that can have downstream effects on how the Parkinson's symptoms are manifesting and how somebody's able to cope with those as well.

Larry Gifford: So get your MDS to write you a prescription for a vacation.

Joohi Jimenez-Shahed: That's right.

Beate Ritz, MD, PhD: Actually, I would say go and see your support group because I think everybody goes through these stressful times in life, and what we as human beings need the most is social support and a support group and your family can give this to you, but sometimes the family is not enough.

Larry Gifford: Beate, you had some recent research that relates to clinical profiles and disease progression in rural Latino populations.

Beate Ritz, MD, PhD: Correct. Yes. That actually fits also really well to what is available to the community in terms of resources or are there higher exposure burdens on this slide mentioned. And in the Latino communities in rural California, we have basically both. We have much higher exposures because they are the ones who live close to the fields that we apply pesticides on, or they work in the fields and they play in the fields, right? The kids. So they have this really high burden. They are low socioeconomic status. Some of them have no or very little health insurance. So when we enroll them in our studies, they're often younger, but much more advanced already in their Parkinson's disease. And they then don't have the same care that maybe another person who is young on set would have because they're also remote from any facilities with movement disorder specialists. So overall, there's definitely a great disparity in the community.

Larry Gifford: There's a term called exposure burden. What does a scientist mean when they say that?

Beate Ritz, MD, PhD: Yeah, basically what we can measure as an exposure, pesticide exposure or air pollution, and the burden just means that you have a higher level of those where you live, where you work, the environment that you basically frequent.

Joohi Jimenez-Shahed: And it's also, I mean not just for an individual exposure, but it's also a question of the numbers of different exposures, as we've been talking about, not just the pollutants and the toxicants, but then also the lifestyle things and as I said, all these things that accumulate.

Beate Ritz, MD, PhD: Yeah. And for example, I have probably a really great example there, we found that when you are paraquat exposed and you have had a head injury, your combined cumulative risk to get Parkinson's is much greater than if you have one or the other. So if you combine these exposures, you may actually put yourself at a much quicker route to disease.

Larry Gifford: Yeah, I did an experiment once where I tried to look at all the risk factors and then what I hit, I had 10 of them. I was like, no wonder I got it. Hey, Ted, there's so much we don't know because there just aren't enough studies, but we see that minority populations are underrepresented in research. Why is it important for everyone to be represented in research?

Ted Thompson: Well, for a lot of reasons. One of which is that diseases present themselves differently in different populations at times, and so it's really important that we

have a great representation of the overall population in these studies. Unfortunately, the participation rates have been lower for non-white people, but it's really important. And for example, last year we announced a significant breakthrough based on our global Parkinson's genetics program, JP-II, where we identified a gene that is specific to people of African descent. So that is a very specific result from our research across... This is worldwide research. So that's a really important factor. I believe that our overall efforts to try and expand the research paradigm, not to say that it's always been focused on white people, but typically health research has focused more on white people. And the other thing I'll mention is too often we treat our studies, not we, but the foundation, but society-wide, the focus is typically more on males than females, and diseases can present themselves differently based on sex. So again, we just need the broadest possible participation in these clinical trials.

Larry Gifford:

Well, that's a great point. And on that note, a quick word here. Parkinson's is a disease that affects people from all walks of life and to fully understand Parkinson's and develop new treatments, research needs to include people with diverse experiences. Our landmark study, the Parkinson's Progression Markers Initiative, or PPMI, is enrolling people from all backgrounds. People from diverse backgrounds play a valuable role in research. Historically, studies have focused on individuals of European ancestry, leaving a significant knowledge gap about the disease in various populations. We are committed to making research more representative so that all communities may benefit from scientific advances. By enrolling in PPMI, you can contribute to a better brain health for all. Join the study that's changing everything. All right, so we've discussed some really heavy topics, racism, the economic inequality, big systematic problems, nuanced, complex. It's important to acknowledge all that, and I think it's easy to feel overwhelmed with this topic. For now, there are some simple steps we can take, and I'm going to run through some here.

Dr. Okun, Dorsey, Schere and Bloem wrote this book called Ending Parkinson's Disease. If you don't have it, get it because it's awesome. And they have a prescription for action in there. And as part of that prescription for action, it's drink clean water, test your well water, use a filter on your tap water, breathe fresh air, eat healthy, avoid contaminants, wash foods that could still have trace amounts of pesticides or herbicides and whenever possible, eat a Mediterranean diet, exercise vigorously, drink modest amounts of caffeine, avoid activities with a risk of concussion, use the MJFF platforms to contact your lawmakers and push for more research funding, share your story, join a clinical trial or sign up for surveys at home like Fox Insight. Those are just 10 of them. They have 25 of them in there. You should read the whole book. It's delicious.

And I will say that Dr. Dorsey, I heard him on a podcast once and he said, if people with Parkinson's don't start sharing their story, there's no way we'll get enough awareness to raise enough money to do enough research to do anything about this, so I encourage everybody to go out there and share their story.

Beate Ritz, MD, PhD:

Yeah. May I just add one thing?

Larry Gifford:

Sure.

Beate Ritz, MD, PhD: An example of advocacy that really worked, in the year 2000, one of the advocates of a Parkinson's foundation started talking to me about a Parkinson's registry similar to the cancer registry. And that became, after four years of lobbying, a law that was signed in California in 2004 but didn't have a mandate for funding. And so the Parkinson's Registry on paper existed, but never was funded, never happened. We spent another 10 years lobbying Sacramento to fund this bill. And they finally did, and now we have a Parkinson's Registry, and you can believe me, a lot more research will happen in California because of this bill and the funding for this registry. And that's what advocacy can do, and hopefully we will learn so much more about Parkinson's just in the same way that we know a lot about cancer because cancer registration started in the seventies.

Larry Gifford: Ted, did you want to add on to that? You're doing some work in that area.

Ted Thompson: Yes, and I will say that that California Registry was purely driven by advocates initially, and so that's just highlighting the power that an individual or group of individuals can have. We did jump into it once it got moving and secured funding for the registry, and actually a couple of years ago, we pushed to expand the registry to be a neurodegenerative disease registry, which it now is. And one of the reasons we did that was that a lot of these diseases, they're not in silos. There are commonalities, so the broader the data collection is, the more likely we're to have some successes. I will just note also that we have a state team that have gotten state Parkinson's registries enacted in about a dozen additional states now, so we are going to have a lot more data than we've ever had before. It takes a few years to get them up and running, but that has been really helpful.

Joohi Jimenez-Shahed: And I'll just add that when we're talking about research participation in Parkinson's, a lot of discussion goes around participating in clinical trials and drug trials, which are certainly important, that's the way that we get new therapies to market for patients who are living with this condition, but by the same token, participation in these types of observational and registry studies is equally important because that's where we're really getting the opportunity to discover new links and new areas of potential research. And ultimately that will also lead to additional therapeutics, but equally important to participate in non-therapeutic trials as well.

Larry Gifford: Joohi, one of the questions we get a lot is how an individual can boost their brain health.

Joohi Jimenez-Shahed: Yeah, no, I think some of those things were definitely on that list that you mentioned from the book. I think brain health is certainly important for a lot of different reasons, and I think there's certainly everyday things that people can do to try to promote that. And we've touched on a lot of those already in the course of this discussion, but things like keeping healthy in other ways. Again, we talked a little bit about this comorbidity and how there's other health conditions that people may be experiencing. It's important to keep on top of those just as much as it is to keep on top of the specific Parkinson's management. Diet is a question that we get a lot of, and Mediterranean diet has been mentioned as a way of healthy eating and healthy living in that way, but making sure that you are

engaging in the appropriate diet for all of your health conditions and not just specifically for Parkinson's.

Sleep is certainly very important. We are increasingly understanding the adverse effects of poor sleep and poor sleep habits, and I think in our technology world where we're up late at night playing on devices and doing all of these things plus just the other effects on sleep that just the Parkinson's itself can have, this is an area where we can also be proactive and to allow that sort of full rest and recovery that is required on a daily basis. And then I think the last thing that I would mention is just paying attention to mental health and getting those issues managed. I think support groups were mentioned previously by Beate. I think that's a great way to boost mental health, but then also if there's other stressors, if there's other things to actively tackle those issues as well. That could be through mental health services, but it could also be through things like exercise, which can also help the other things like sleep and mood and other non-motor symptoms of Parkinson's as well.

Larry Gifford: You mentioned sleep, and I'm going to do a shameless plug here. The PD Avengers currently has a sleep survey on pdavengers.com, and we want people with Parkinson's and their care partners to fill it out because it affects both equally in different ways. And so that'd be great if folks could go over there and do that. Ted, I've heard something at the VA called the PADRECCs, and this question says, "Since there are 1 million Americans living with Parkinson's, and of those 11% or 110,000 are U.S military veterans who may have been exposed to dangerous toxins during their service. How is the Department of Veterans structured to provide comprehensive care?"

Ted Thompson: Thank you. The PADRECCs have existed for I think about 20 years, and it is the care model within the VA system for people with Parkinson's. Interestingly though, since the creation of the PADRECCs, the population of veterans with Parkinson's had risen by nearly 40%, but the PADRECCs had been flat funded for the most part for most of those years. Over the last two years, and this shows another impact of advocacy, we've been able to secure a 74% increase in funding for the PADRECCs. And that funding is not only going to shore up the existing program, but will hopefully result in the expansion of the PADRECCs to one or two additional states. Currently it's a hub and spoke model, and they do great work, great people, dedicated folks there, but we are going to continue to push until it's funded at a level that it can truly provide the care that they've been charged with under the law.

Larry Gifford: Great. We're going to shift to just the Q&A here with the questions from the audience. This is a toss up. Anybody can take it. What is known of time of exposure until appearance of symptoms?

Beate Ritz, MD, PhD: Wow, that's a really important question we try to answer, but I'm afraid we don't really have an answer for it. From the best epidemiologic studies out there, we believe that it's at least a seven to 10 year lag between even prodromal stages of Parkinson's and when you make the diagnosis due to the motor symptoms. So there's a lot happening before you even notice that you have Parkinson's. I actually sometimes tell people that I think there's even a prenatal exposure phase

where you can harm the development of the dopamine neuron in the fetus, and there's probably relevance to childhood exposures, but mostly what we are knowing about now and what we are studying are all these adult exposures that are cumulative over time. And so they might kill one neuron at a time, but if you have killed 80% or 60% of your neurons, that's when you see Parkinson's. So we have to be vigilant of everything we do throughout our life, but generally, I would think it's five to 10 years prior to your diagnosis that is most relevant.

Larry Gifford: Yeah. Ted, there's a lot of chatter about the registries here. Can you explain how they work, how you get on them, and how do you find out if your state has one?

Ted Thompson: Sure. To find out if your state has one, you can go to our website or you can just email us at policy@michaeljbox.org. We are currently working in four additional states this year, Connecticut, New Jersey, New York, Massachusetts. We've had registries enacted in Missouri. Now I can't remember all the states, but we've got about a dozen enacted, but our website or that email is the way to go. In terms of how you get on the registry, it depends on each state. Most of the states, it's a requirement that the physician or the healthcare provider report the data into the state, and so that's how the state collects the data with an opt-out, of course, so that if a patient doesn't want to be in the registry, they don't have to be. But one of the reasons it's so important is being able to get population-wide data on the Parkinson's community in a given state can really help to identify possible clusters of where people are living that relate to the exposures.

Dr. Ritz mentioned the California Pesticide Registry, which is the most comprehensive pesticide registry that can be used to overlay with a California Parkinson's registry as well. So that's a sampling of what we can be doing. I did want to also mention, because I know we're running out of time here, but Congressman Jennifer Wexton from Virginia a year ago on World Parkinson's day, she announced her Parkinson's diagnosis, but then several months later she announced that actually she's got progressive Supranuclear palsy, PSP. We've been working with her and her office very closely, and one of the initiatives that she took great interest in was a grant program at the NIH from about 15 years ago that focused on Parkinson's and environmental risk factors, and then it was expanded to include neurodegenerative diseases. But I've been working with her office. We've been putting together actually legislation to create a permanent grant program at the NIH focused on the intersection of environmental risk factors in Parkinson's and neurodegenerative.

The diseases that we've identified that have an environmental risk factor component are Alzheimer's, Parkinson's, ALS, PSP, and there could be others. So this bill, it's called the HEALTHY BRAINS Act. Congress always like to have great acronyms. It's Harmonized Environmental Analyses and Launching Therapeutic Hubs to Yield Bolstered Research And Innovation in Neurological Science. So anyway, HEALTHY BRAIN...

Larry Gifford: Now I remember.

Ted Thompson: Yeah, this would create a permanent research program with a \$50 million per year allocation specifically toward this. To my knowledge, there has never been a

permanent federal program focused on the interception, and to me and a lot of people, the environmental risk factors is essentially low-hanging fruit that we should be focused on because if we identify the factors and then we eliminate the factors, we're able to prevent Parkinson's in an entire cohort. So that bill is going to be introduced in April. We'll be putting more information out about that.

Larry Gifford: I've heard it called Parkinson's is mostly man-made, so it could be man unmade.

Beate Ritz, MD, PhD: Yeah.

Larry Gifford: Parkinson's was first discovered and identified over 200 years ago. Why do we spend so much time attributing modern day environmental factors to the development of the disease?

Beate Ritz, MD, PhD: Well, it's true that in 1817, James Parkinson's described the phenomenon first. We believed that Parkinson's of course existed prior to that time. But first of all, you have to get to a certain age to even see it, which is usually 60 plus. We have luckily not too patients before age 60, and then think about the world population who made it to 60 in the 18 hundreds and before, not too many, so that's probably why we didn't see it earlier. But of course, 1817 in England, and this was James Parkinson's in England, was the industrial Revolution, right? And what do we know? They introduced the combustion of coal at a grand scale. And so pollution not only to combustion products, but to metals, to everything was at a grand scale then. And so I wouldn't be surprised that if some of these patients came down with their Parkinson's because of that reason.

And we have a growing population and we have growing pollution problems and new agents are introduced, and we are introducing new neurotoxic agents at quite a rate, probably without knowing that we are doing it because there are hundreds of thousands of chemicals used in the chemical industry that were never tested for their neurotoxicity.

Larry Gifford: That's all we have time for. So I really appreciate all your expertise and insights. Thank you for being here. I also want to thank you for being here, being part of our community, and for joining us today. And thanks to our panelists for sharing time. We hope you found today's discussion helpful. Thanks everybody. Have a great day. Thank

Beate Ritz, MD, PhD: Thank you, Larry.

Joohi Jimenez-Shahed: Thank you.

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