Michael J. Fox: This is Michael J. Fox. Thanks for listening to this podcast. Learn more about the Michael J. Fox Foundation's work and how you can help speed a cure at michaeljfox.org.

Speaker 1: In this episode, you'll hear a recap from our latest Third Thursdays webinar. Expert panelists will discuss the latest in Parkinson's research and answer audience questions about living well with the disease. We hope you find the discussion helpful.

Jimmy Choi: Hello, and thanks for being with us here today, everybody. I am Jimmy Choi. I'm a Parkinson's advocate. I'm a world record athlete, and I'm a seven-time American Ninja Warrior, and I was diagnosed with Parkinson's in 2003. I'm also a member of the Michael J. Fox Foundation's Patient Council. Now, today we're going to be discussing what causes Parkinson's disease and why the answer to that question is critical to develop therapies that will treat, slow, or stop Parkinson's progression. Now, I'm often asked, "What do you think caused your Parkinson's?" What do I think caused my Parkinson's? If I'm being honest, I can come up with a whole list. Repeated head trauma, years of exposure to chemicals driving through farmland throughout Indiana and Illinois, and even drinking well water from these same areas. Those are all possible contributors. But the truth is today, science can't tell me what exactly pulled the trigger for me.

But if you zoom out away from me as an individual to the population level, science can give us some answers. We can say after studying hundreds of thousands of people and say that aging, genetics, lifestyle, environmental exposures, these can all increase a person's risk of developing Parkinson's. But when you zoom back into that one person, it's almost never just one thing. It's a combination. Different factors that could be stacking, that could be interacting with each other, lining up at a moment in time to an individual's biology that actually posed the trigger. So I'd like for you to keep that in mind today throughout our discussion. As we continue, we just want to make sure that we're mindful of the discussion that we're looking at is from a broader view. Now, we've got a lot to discuss, so let me introduce our panelists.

First, we have Todd Sherer. He's the Michael J. Fox Foundation's Chief Mission Officer involved in guiding the foundation's research strategy. Thank you, Todd, for being here with us today. We also have Dr. Caroline Tanner, who is the Roger Evans, an Ipenacia endowed professor in Parkinson's disease at the University of California, San Francisco's Weill Institute for Neurosciences. She's also on the Parkinson's Progression Marker Initiative or PPMI leadership team and is the principal investigator for Fox Insight. Welcome, Dr. Tanner. And also joining us today is Andrew Singleton, who is a neurogeneticist who leads the steering committee of the Global Parkinson's Genetics Program. He is also the chair of PPMI's genetics working group. Thank you, Andrew, for joining us today as well. Now, I've mentioned that there could be many factors when it comes to my own onset. My wife and my parents seem to think it's years of playing American football in the '80s and '90s where concussions was something that you just shook off.

You got right back into the game, banging heads with 300 pound linemen. But I also grew up around farmlands and all through high school and college and could literally sometimes just sit there and watch some of these crops being sprayed with chemicals. So I will probably never know exactly what factors cause my Parkinson's. So Todd, I'm going to ask you this first question, and I think this is a great place to start, is why is it important? Why is this area of research important?

Todd Sherer, PhD: Yeah. So as you mentioned, there's a lot of factors that could lead to Parkinson's in the environment, genetic factors that we'll talk about, particularly Andy will talk about today. And this is an important question from a research perspective for us to understand and to really get more insight in. For example, in the environment, one thing that this research could point us to is areas of prevention. If we could identify specific things in the environment that increase the risk for Parkinson's, we could then work to try to get those out of the environment to prevent future cases, Parkinson's disease. I think more specifically in studying the environmental factors as well as the genetic factors that link to Parkinson's, it also gives us great insight into what might be triggering the disease in the cells of the brain that are impacted by the disease. And that understanding could lead to the development of diagnostic tests for the disease and importantly, directions to develop new treatments that can really target the underlying cause of the disease, which would lead us hopefully to treatments that could slow the progression of the disease and even prevent its onset as well.

Jimmy Choi: Dr. Tanner, I want to turn my focus over to you here for a second. We're going to get into more details on all of these in a bit, but at a high level, what do we know about how genetics and the environment and aging and how they intersect when it comes to Parkinson's?

Dr. Caroline Tanner: It's a combination of all of these factors and every individual is likely different. So some people may have a strongly associated change in one of their genes that's connected to Parkinson's. Others may have lots of very small changes that affect how they metabolize things that they're exposed to from the environment. People are exposed to lots of different things in the environment, so essentially anything that isn't genetic is environmental, and some of them are positive and some of them may increase your risk of Parkinson's. And then as we know with aging, lots of things don't work quite as well as time goes on, and that includes some of the inborn defense mechanisms that the body has to protect against either a genetic or an environmental factor.

Jimmy Choi: Andy, many people have heard about early indicators of Parkinson's such as loss of smell and REM sleep behavior disorder or RBD. These are indicated as early signs, but what's the difference between a risk factor and an actual cause of Parkinson's?

Dr. Andy Singleton: That's a great question. So thinking about this from the perspective of genetics, right? The geneticist, so that's the way I think. We know that there's a whole gradation of risk of genetic factors that impart risk for disease. One way to think about these is as a switch. So on the one side, you have a genetic factor that's essentially causative. If you carry it, you have a very high likelihood of getting

disease, and that's like a simple on off light switch. And then all the way down at the other side, you have something that just imparts a small amount of risk. So it brings you towards this threshold of disease, kind of like a dimmer switch. It doesn't turn the lights all the way on, but it gets you part of the way there. We know that there are hundreds of genetic risk factors, and most of them fit in this risk factor area.

They're not causative, they're not sufficient to cause disease, but they impart risk towards disease. And of course, the reason we study those is to understand the disease at its most basic processes so that we can try and find ways to intervene, try and find therapeutics that are targeted towards the disease process itself rather than the symptoms that are suffered.

Jimmy Choi: Yeah. And I think it's a very important distinction for our audience to understand here because I get a lot of people coming up to me and ask me like, "Hey, what are some little known things about Parkinson's now?" I often mentioned RBD as one of those or loss of smell. They're like, "Oh my God, I lost my smell during COVID. Does that mean I'm going to get ..." No, we want people to understand that. No, just because you have one of these things, it could be an indicator, but it doesn't mean that you're going to have Parkinson's. I want to dive a little bit more into the genetics now. We have a community question from my fellow Fox Foundation patient council member who was diagnosed in 2016, and she lives in Arizona. And let's watch this video together.

Sheryl Lowenhar: Hi, everyone. This is Sheryl Lowenhar. I'm in Scottsdale, Arizona, and I was diagnosed in 2016, so it'll be 10 years living with the disease this year. I knew I had Parkinson's because my father had Parkinson's and I was starting to look like him. I can just imagine the way I was walking, the way I was dragging my feet. I wasn't swinging my arms, and I said, "What's going on?" And so what I did was I went to the Michael J. Fox website and checked it out that they had a PD IQ + You conference coming up in Phoenix. So I went, there was a thousand people there. I saw all the speakers, and at the end of it, I walked up to Dr. Shill, who is head of the Muhammad Ali Parkinson's Center, and I asked her about genetics and said, "Do you think Parkinson's can be part of a gene variation?" And she said, "We're studying up on that right now.

You should join PPMI program out of Michael J. Fox." So went home, looked it up on the web, signed up for it, and they sent me a kit in the mail. I swabbed my mouth, sent it back. A couple weeks later, I got a phone call from a genetic counselor and we set up an appointment and she told me that I had the GBA mutation and that only 6% of people that have that mutation get the disease. And I said, "Well, it's 100% in my case. I pretty much know it." But we've signed up for the program for the clinical study to the PPMI. And as soon as I walked in the door, Dr. Sprecher was the head of the study said, "You have Parkinson's." Got diagnosed that way.

I'm very interested in the genetic mutations and the research that's going into it. I keep track of all that, but I'd like to know why do some people get Parkinson's disease that have the GBA mutation and some people don't. It seems like the majority of people don't. So why is that and what triggers it?

Jimmy Choi: Yeah, Andy, I'm going to start with you there as we talk about genetics and you already alluded it in the very beginning, but what do we know about the role of genetics in Parkinson's?

Dr. Andy Singleton: So we've made a huge amount of progress over the last 20 years or so on understanding the genetic basis of disease. And really this started by looking at very rare families where disease occurred much, much more often than one would expect and really finding these genes that are causative. Typically, they're fairly, fairly rare. Over the last 15 years or so, we've been able to look at a different type of genetic influence in disease, and that's genetic risk. And we do this by looking at tens, hundreds of thousands of people with disease, comparing them to people without disease and looking at genetic differences between those groups. So far, we've identified around a hundred regions of the genome that contain variants that impart small amounts of risk, individually small amounts of risk for disease, but collectively, those come together to bring you towards this threshold of disease.

So we know the identity of those risk factors in typical Parkinson's disease, and we know that those risk factors in typical Parkinson's disease also modulate risk in people who carry a GBA1 mutation or people who carry a LRRK2 mutation. So at least part of the answer to Sheryl's question is genetics. Genetics is part of the reason why one person who carries a GBA mutation gets disease, one person doesn't. As Carly and Todd said earlier, of course, environment is also important. I think a really key concept for us to think about and recognize is that every single case is genetic. Every single case is environmental. Every single case is to do with age, and it's about the proportion and the amount of risk that each of those in part. So it's been an amazing 20 years of discovery. We still have a long, long way to go and still a lot of research to do, but the path so far has been great for genetic discovery.

Jimmy Choi: Just because you have a genetic risk factor, it's the combination of all the other factors and the amount of it in which that can trigger the onset of Parkinson's. Did I sum that up correctly for our audience?

Dr. Andy Singleton: Yeah, you did. There are not many genetic factors that are deterministic. There are not many genetic factors that if you carry them, you are definitely going to get disease. Those are very, very rare. Generally, when we're talking about genetic risk, these are things that just increase the likelihood of getting disease. They don't mean you're going to get disease.

Jimmy Choi: Yeah. In Sheryl's video, she mentioned 6% in her case. That might not sound like a lot to people, but I think that in general population sense, Parkinson's is right around 1% or maybe even less. So go from that to six, that's a big deal. Now, Dr. Tanner, we have many people in the audience with a family history of Parkinson's. Now, they're probably wondering what their likelihood of developing symptoms are moving forward. How should people think about family history and their own risk?

Dr. Caroline Tanner: Yeah. So importantly, just because there's someone in your family who has Parkinson's doesn't necessarily mean that you yourself will get Parkinson's. So

that's the first really important point. There are things that one can do to try to understand, especially whether or not you have one of the genetic changes that has a stronger association with Parkinson's. And the best way to do this is probably to work through your own healthcare provider and to connect with genetic counselors who can help you think about this and whether you want to have genetic testing to identify whether you have any of the genes that, as Andy just said, are more strongly associated with Parkinson's risk. This can be helpful because it can give you some insights into possible future treatments, which we'll talk about a little bit more in a minute. But also there are many things that people can do that are more lifestyle-oriented changes that also can be important.

Importantly, even if you don't have an identifiable genetic change, these lifestyle changes, so exercise, healthy diet can make a big difference for anyone in terms of lowering your risk of Parkinson's and in general, improving your health.

Jimmy Choi: Yeah, thank you. I personally, I've done genetic analysis and personally, I don't have any of the genetic markers associated with Parkinson's. And in my family, I'm really actually the first person in my family that's been diagnosed. However, years after my own diagnosis, my grandmother at age 93 exhibited all the signs of Parkinson's, but she was dealing with other issues. And 93, we just didn't bother telling her. We just added her medication into her entire list. So this factor, and you guys can tell me if I'm wrong about this, is that I tell people all the time that just because you have a family history and if none of you have the genetic connection to Parkinson's, then what it is that a lot of family members all grew up in the same environments. So that is something that you do have in common. Thank you, Dr. Tanner.

Todd, how does a deeper understanding of genetics point towards biological pathways and future targeted treatments, including for people like me who don't have known genetic links?

Todd Sherer, PhD: Yeah, I think one of the important, in addition to trying to understand how or why someone may have gotten Parkinson's by looking at the genetics, the other important result that this gives to the scientists is it really gives us a very tangible biological cause of the disease that we can identify that a change in this particular gene through some mechanisms is leading to the disease in a person. So that's very fundamental knowledge for us to build on to then try to understand what is happening in the cells that are affected by the disease and how can we actually change that cellular process that's impacted in the disease. And this really, one of the first genes that were uncovered for Parkinson's have pointed to a number of overlapping biochemical pathways that we now believe are linked to the onset and the progression of the disease. And what's really interesting and important is that many of those same biological pathways, when we study people who don't have the mutations, those same pathways are impacted in the disease.

So the genetics uncovered shined a light in a certain area that otherwise we may not have known to focus on. And now we're seeing that those same biological pathways are likely at play in people who have Parkinson's, but not due to the genetic mutations. And importantly and interestingly as well, as we have identified some of the environmental factors that are linked to Parkinson's and we

study how those different environmental factors may impact the cells in the body, the same biochemical pathways are also impacted by the known environmental factors. So this gives a lot of confidence now to the scientists that these are areas that we should really focus therapeutic interventions through because we believe that these biochemical mechanisms are involved in the disease, both from a genetic perspective and an environmental perspective.

Jimmy Choi: Thank you. And what I'm hearing, whether or not you have a genetic connection to Parkinson's, it is important that all the research is kind of helped when research being done in one area is helping research done in another.

Dr. Andy Singleton: I think you're right, Jimmy. Just to clarify one point, because I think it's really important, is that we often talk about, I have a genetic form, I don't have a genetic form. The vast majority of genetic risk that's involved in disease is extremely common in the population. So everybody has a genetic contributor to their disease. When someone gets tested for a genetic variant, it's generally only the high risk things that get tested. We know that these lower risk variants that alter risk for disease sometimes protect you against disease, everyone carries these. So there's a genetic component to all of the disease. I think this kind of opens up another reason why we do genetics on top of trying to find mechanisms that we can then target. It's so that once we have therapeutics matched to a particular mechanism, we can then tell which patient those mechanisms are going to work best in by understanding their genetic risk, by understanding what other environmental risks they may have and how that leads to a particular mechanism.

Jimmy Choi: That's very important and thanks for the clarification. I certainly learned myself a new way how to help describe this to people that come up to me with questions. Sheryl, I just want to take a quick second to call out PPMI. Sheryl mentioned it in her video. PPMI is still recruiting volunteers. It is the Michael J. Fox Foundation's landmark study that is looking at the many causes of Parkinson's and how to measure and to stop Parkinson's. People from all backgrounds with and without Parkinson's can participate and help move research forward. I'm encouraging everybody to join the study if you're not already a part of it. Join a study that's changing everything. So I want to kick off the next part of our discussion around environmental risk. We have a community question from veteran Rich Point who is based in Michigan.

Rich Point: Hi, my name is Rich Point. I live in Harrison Township, Michigan. I'm a Marine veteran. I joined the Marine Corps right out of high school in 1985, did six years of active duty, was deployed to the Desert Shield Desert Storm during that time. And then in about 2017, 2018, I started noticing my gait was off. I would go on a run, I'd trip and fall over nothing. My left arm was kind of not swinging right. My family said I should tell my doctor about this. So I told my primary care doctor about these issues and he sent me to a neurologist who diagnosed me in 2019 with Parkinson's disease. So immediately when I got that diagnosis, I kind of realized my Marine Corps career was over and fortunately I had 20 years to wrap up. So I applied for retirement, got my 20-year package put in.

Yeah, so I kind of wonder, my exposure to the neurotoxins in the Gulf War, could they have caused my Parkinson's disease? If so, how does that affect your brain, this exposure to neurotoxins they keep talking about?

Jimmy Choi: He brings up a very valid point when it comes to environmental exposures. Then he brings up a question many of us ask, but for him specifically as a veteran. So Dr. Tanner, when we say environmental exposure, what does that mean and how do we know that these exposures relate to Parkinson's at the population level?

Dr. Caroline Tanner: Yeah. So at the population level, we know that exposures to specific chemicals can be associated with a higher risk of Parkinson's. And that's basically by looking at large numbers of people, some people who have Parkinson's, other people who don't, and looking at their life histories or their experiences of exposure and understanding if you're exposed to this particular chemical, for example, do you have a bigger chance of developing Parkinson's at some point in the future? So for example, in the military, we know that service members who were served in the Vietnam Korean War era and were exposed to what's called Agent Orange, which is a combination of herbicides, have a higher risk of Parkinson's as a service-related disability. We know that people who have traumatic brain injury, which is more common in military settings, also common in other kinds of occupations like farming, people with those exposures are at higher risk of Parkinson's.

And then a very specific situation in Marine Base Camp Lejeune, there was a large number of years where the water supplies in Camp Lejeune was contaminated with the solvents, trichloroethylene and perchloroethylene, and people who were military residents there had a higher risk of Parkinson's compared to people who lived at Camp Pendleton where the water wasn't contaminated, but who had otherwise similar experiences. So those are some examples. I'm looking at big populations and saying, oh, the folks in this group who had these exposures are more likely to get Parkinson's compared to the people who didn't. We can't do that on the individual basis and say, "Oh, that's why you've got Parkinson's," but we can look at big populations and through those patterns of increased risk.

Jimmy Choi: So is it safe to say veterans out there, they're put in positions where they're exposed to these environments where your average person, non-veterans may not be exposed in high concentrations, for example. So is it safe to say that that is why it seems like a lot of veterans are being diagnosed with Parkinson's versus the general population or

Dr. Caroline Tanner: Yeah, it's the risk of the job means you're more likely to be exposed to chemicals or situations like having head injury, blast injuries, things like that, that increase your risk of disease. So it's not just veterans, people who served in the military, but people with other kinds of occupations that give them those kinds of risks of exposure may also be at greater risk. For example, farmers who are pesticide applicators are also often in a situation where they're exposed to chemicals that are associated with Parkinson's risk.

Jimmy Choi: Todd, we got a question from the audience. Dr. Tanner mentioned head injuries or head trauma, and I mentioned myself, why are concussions linked to Parkinson's disease?

Todd Sherer, PhD: It's a great question and has also a concussion survives of great interest to me as well. So we really don't know the answer to this. We do know that head injuries can initiate a number of processes in the brain, whether it's aggregation of protein or an inflammatory response. And these are some of the pathways that I mentioned earlier that have been linked to neurodegenerative diseases like Parkinson's. So that's at least one of the hypotheses now is that a head injury and frequent head injuries could start to initiate some of these processes in the brain that then can make you have an increased risk of other neurodegenerative diseases like Parkinson's.

Dr. Caroline Tanner: One other thing that can happen is that there's a protective mechanism called the blood-brain barrier, and with head injury, that can be interrupted. So if you have head injury, and for example, you're in a military combat situation where you might have exposure to chemicals, that might even further increase your risk.

Jimmy Choi: So Dr. Tanner, we're on the subject of ... It's very interesting because the head injuries affecting the blood-brain barrier is not common knowledge, so I want to thank you for bringing that up. So what are some challenges in studying environmental exposures that you're facing in your work?

Dr. Caroline Tanner: Yeah, so the hardest thing is that there's no way to look at a population, say, "Oh, these are the people we know are likely maybe at risk for Parkinson's." So we need to look backwards after someone already has been diagnosed with disease and see what their experiences were. And for an individual, that's really, really difficult because of course we're exposed to all kinds of things all the time and most of the time we don't know it. I grew up in farming country. I can't go back and tell you even what the pesticides were that were used in the crops around my home. I have no idea. I was a kid. So it's very hard to really know that. And we have to take advantage of populations like the Camp Lejeune situation, farmers who have to keep track of the pesticides they use so we can go to the farms and see what they use because they have the farm records that we can look at.

Situations like that in an occupational setting where we can actually document exposures that people had before they developed disease and then compare them to people who don't have disease. And that's the way we come up with these ideas, but they're not individual, they're big picture population. It's actually amazing given how difficult it is that we do keep seeing these associations over and over again.

Jimmy Choi: Yeah, it's almost like you're reverse engineering from a person has diagnosed. Todd, given that there's indications of certain environmental exposures that increase risk, what are some actionable items that we can do today or right now for in reducing these environmental exposures?

Todd Sherer, PhD: Yeah, this is a big effort at the foundation and the Parkinson's community to try to see what can be done to get some of these high-risk environmental toxicants

out of the environment. So there's efforts the foundation's doing at the state level, active now, for example, in Minnesota and Vermont to try to get certain pesticides banned. And this is something that people should want to advocate for this, get to the foundation website and sign up and see how to get involved to try to bring more attention to this, to see if we could get some of these toxicants out of the environment to decrease the risk in the future of people getting exposed to these that could increase their risk of diseases like Parkinson's.

Jimmy Choi: And I've been hearing a lot of talk from people on social media about Paraquat. Can you tell us, first of all, what that is and why it's important to limit those?

Dr. Caroline Tanner: So this is an example. So Paraquat is an herbicide and it has been associated with Parkinson's risk, starting with some work that we and others did looking at farming populations. So people exposed to Paraquat have a higher risk of Parkinson's. And interestingly, people who are exposed to Paraquat and who have a change in some of their genetics that help to rapidly break down toxicant and exposures, people who can't do that genetically are at much higher risk if they're also exposed to Paraquat. So that's an example gene environment interaction that we were talking about earlier that applies in this case. So Paraquat is an herbicide associated with Parkinson's risk. We found it to have actions in the body that are similar to other chemicals that we know cause Parkinson's like MPTP, which was a cluster of people who were exposed to a toxicant chemical. So there are a lot of plausibility factors for Paraquat being something that may be dangerous for populations in general and associated with a higher risk of Parkinson's.

Jimmy Choi: I want to move forward and want to talk about the role of aging when it comes to Parkinson's. Now, Dr. Tanner, how does aging contribute to Parkinson's risk?

Dr. Caroline Tanner: Aging sort of has a slowdown effect, not just on watching people move or watching people think, but looking at all of the processes within the body that help protect us and keep us healthy are not quite as good with aging. So stresses that are normally ones that we can compensate for very well as a younger person become more challenging with aging and it makes us a little bit more vulnerable to changes that can be either inborn, so a genetic risk factor or can be an environmental exposure. We're just not quite as good as compensating as we grow older. Understanding more about the type of Parkinson's that people get, I think is something that we're still working on. You mentioned earlier PPMI, and this is one of the things we're studying in PPMI is understanding the individual trajectories for each person and looking at the different aspects of what we call biomarkers that can help us see changes in people that may predict this person is going to have more problems with motor slowness, this person may have cognitive changes.

So we're trying to understand that we can't do that yet, so that's still a research area, but it's safe to say that all of the things in those boxes do contribute to a more rapid risk of developing Parkinson's disease or an increased risk rather, not more rapid of developing Parkinson's.

Jimmy Choi: Thank you. Now, Todd, this is a question that hits me right at home. I was diagnosed in 2003, I was only 27 years old back then. If age is such a contributor, why are people being diagnosed with young-onset Parkinson's? And it seems like to me that in more recent history that this seems to be something that's growing.

Todd Sherer: Yeah. So I think for young onset, there's some different hypotheses on whether it's growing and what might be the reason for that. I think could be an increased awareness and diagnosis of the disease. There could actually be an increase in the onset of young onset. So this is still being investigated. In general, I think it's a belief that younger onset is more likely to have a genetic component than more later onset disease. When we think about the role of aging, I do think it's important to remember that the genetic changes you're born with. So the impact of those genetic changes on the nervous system do accumulate through aging. So even with young onset Parkinson's, if there is a genetic component, there's still a role of aging in terms of when the symptoms actually do come on board for the individual. But this is an area of really active research to try to understand what's happening in the demographics of the disease and what the trajectory of the diseases could be for young onset versus a later onset disease.

Dr. Andy Singleton: We know for sure that younger onset cases tend to have a much higher genetic load. Again, lots and lots and lots of small genetic factors that combine to bring you towards risk for disease. I think this concept of aging is one that's really important too. One of the areas that I think we're starting to coalesce around as a field, one of the mechanisms involved in disease is your ability to deal with bad things as they happen. So your ability to metabolize toxicance, as Carly talked about, your ability to deal with infection, your ability to deal with a process, it's a little process that's gone wrong. And certainly the genetic risk factors and the downstream mechanisms of those genetic risk factors often point towards these damage dealing processes, these processes that are within the body that help us deal with inherent damage that we accumulate or that just occurs, occurs over time.

Jimmy Choi: Dr. Tanner?

Dr. Caroline Tanner: Yeah, I wanted to also comment that while it's a theory, it's not known, but it's a topic of research, there is the idea that perhaps there may be more younger age of onset individuals being diagnosed with Parkinson's, partly because awareness, as Todd said, that maybe possibly also because of changes in the environment, the idea that there may be more exposure to toxicants. There may be other factors that are contributors that mean that the disease onset is younger. For example, in the study we did in the Marines in Marine-based Camp Lejeune, the age at onset in that population was in the 50s, which is relatively young for Parkinson's. On average, it was in the 50s because it's still a relatively young group of people. So whether or not there are going to be more and more Marines who develop Parkinson's as time goes on who live there, we don't know, but we do know that it was a relatively younger age of onset in people who were exposed to that toxicant chemical.

So possibly the multiple small genetic factors, the contributions of aging, and then also environmental factors could all be contributors here.

Jimmy Choi: I want to move on to our next section here, concerning research and the causes. Dr. Tanner, we talked at length about these risks for developing Parkinson's at the population level, and we framed this entire conversation about speaking at the populations level. So let's zoom it in a little bit, and how might these factors combine in an individual?

Dr. Caroline Tanner: So as we've been saying, everyone has Parkinson's likely due to the combined effects of their inborn genetic characteristics, what happens to them during life, so their environment, including chemical exposures, but also healthy behaviors like exercise and healthy diet, and then aging, which means you become less and less able to compensate for those other factors that may predispose you to risk. So everybody's individual. I think the helpful thing though is that the work we've talked about with genetics, also looking in the laboratory and understanding the effects of some of the chemical exposures we've identified that increased Parkinson's risk lead us to clues about ways to be able to develop effective therapies and ways that people can either get better treatments or even looking backwards, have healthy behaviors that may prevent or delay the onset of disease.

Jimmy Choi: Andy, in your research, when it comes to genetics, what research is currently going on into new pathways linked to Parkinson's?

Dr. Andy Singleton: Yeah, there's a huge amount. I would say the vast majority of mechanistic-based research, so research that's aimed at understanding disease processes is centered on genetic risk factors. So we've highlighted a whole series of mechanisms that we believe are involved in disease, again, around maladaptive response, response to the way in which a cell gets rid of a malformed protein as an example. So all of these things are leading to potential therapeutics. And maybe this is something that Todd wants to talk about, but there are now several trials that are focused on the targets that we've highlighted through genetics and using genetics to understand disease processes. So you've got this genetics feeding the beginning, fitting our understanding, and then at the end saying which patients would do well to be matched to that particular therapeutic. As Carly said, overlaying environment on top of this is key, and I'm sure that these things will coalesce around viable targets and viable treatments for Parkinson's disease.

Jimmy Choi: Yeah. One of the biggest takeaways from what I hear you say today, Andy, is that because your specialty is in the genetics and individuals without a genetic component, or so it might seem like myself, doesn't mean that we shouldn't pay attention to the work that you're doing because I think it's important for the audience to know that just because you're looking at from a genetics perspective point of view, it doesn't mean that those of us who might not have, at least on the surface, a genetic connection can say, "Oh, that doesn't apply to me. I want the audience to know that. " So thank you. Now, Todd, does the cause of Parkinson's matter in terms of treatment and how that is being handled today in clinical trials and in the future?

Todd Sherer, PhD: Yes. I think for the most part, right now for the symptomatic treatments like the dopamine-based treatments, there's not a dramatic difference in how the clinicians will handle the disease based on the underlying cause of the disease.

But going forward, and this is what Andy was just referring to, with all the progress that's been made with the genetics of Parkinson's, we now have specific therapies that are being developed against some of these gene changes in the disease. So one area that's active is in the LRRK2 area, which is one of the common genes that's been linked to Parkinson's. The question before that mentioned GBA, there are specific therapies that are in development now to target the genetic changes in GBA for Parkinson's. So there are actual active clinical trials now that are recruiting people into the trial based on the genetic cause of their disease. So they're looking, for example, for people with Parkinson's who have a LRRK2 mutation or people with Parkinson's that have a GBA mutation because it's believed that these therapies could have a specific effect in those populations.

To the point we raised before though, many of these same therapies are also being tested in people that have more what's called idiopathic or sporadic PD, which would be a Parkinson's disease not directly linked to one of these known mutations because it is believed that these same therapies may benefit those individuals as well. But I think where we've come since Andy and others started working on genetics and Parkinson's is quite a long way because it's not just now in the area of understanding the cause. This understanding has been converted directly into the development to potentially treatments that are now in the clinic being tested based on that understanding and identifying individuals who may have the best chance of benefiting from those therapies.

Jimmy Choi: We have about 10 minutes left that I want to get into a lot of the questions that we're getting. So before we get into that, I want to thank all of our experts here for their insights today. I think that you guys are providing a great topics of discussion and a lot of thought for people to think as we see in these questions coming in. So the first question is something that I've been wondering myself as well as I've been living now 23 years with Parkinson's. Dr. Tanner, if you're already diagnosed today, should you continue to reduce environmental exposures or is it, "Oh, too late. Sorry?"

Dr. Caroline Tanner: Yeah, that is a great question. There's a little bit of work that's been done, some of it done in PPMI that suggests that changing your behavior, having healthy lifestyles, and as much as possible, avoiding environmental exposures that may be associated with increased risk of Parkinson's can help to change the trajectory of your disease, so make you less likely to have a more rapid progression, less likely, for example, to develop cognitive changes. So one of the things I tell patients is go look under your kitchen cabinet and look in your garage and see what's there. And you can be amazed at the toxic and chemicals that are there, some of them may be even associated with Parkinson's risk specifically, try to avoid those. We didn't mention it, but there's some evidence that air pollution is something that increases risk of Parkinson's. It's easy to use air filters, be careful on wearing a mask, possibly not doing heavy running, exercising on a polluted day.

So those are things that people can do. And then healthy lifestyle. In general, exercising, in general, eating more of a plant-based, low animal fat diet is really important for people.

Jimmy Choi: Thank you. Personally, this is out the same way, just because I've been diagnosed for such a long time, I do make a conscious effort to minimize my own environmental risk. I jokingly tell my wife, "No, I don't want to mow the lawn because there's pesticides out there or herbicides out there." So tell the kids to do it. But thank you. Todd, we're getting a lot of questions in the audience about Alzheimer's and Parkinson's. First of all, are they the same things that cause same things that cause Alzheimer's as in Parkinson's? And are there any overlapping research?

Todd Sherer, PhD: I might ask both Carly and Andy to talk about the causes because I know they've studied this, but there's certainly great overlap in a lot of the cellular mechanisms that are involved in the two diseases around how the cells handle protein, how the immune system interacts with the nervous system. This is a significant area of study within the PPMI program to try to understand the role or involvement of cognitive symptoms in Parkinson's disease and what is related more directly to Parkinson's versus what could be related to Alzheimer's. And we are finding a lot of overlap in the biology between the two diseases. So this is an area of very active research and a lot of findings that are coming out of Parkinson's disease are advancing Alzheimer's and vice versa. But in terms of the causes, I know Andy has studied a lot of, for example, the genetics in both Parkinson's and Alzheimer's.

So I think it might be interesting to hear his comments about where there are overlaps and where there are distinctions.

Dr. Andy Singleton: So we do see some overlap. Some of the genes involved in inflammation, for example, are involved in both diseases. However, it's surprisingly minimal from a genetic perspective. I would've said beforehand that I would've expected to see a lot of genetic overlap and we really don't see a huge amount. So there are distinct genetic origins for the diseases, but as Todd points out, there are common mechanisms or common features of the diseases, which I think we can use to understand both diseases, and we can also use the differences to understand the differences between the diseases and what mechanistically that means.

Jimmy Choi: Dr. Tanner, since we're all chiming in here, would you like to add something in? Yeah,

Dr. Caroline Tanner: Well, I think as Todd pointed out, one of the really important things we're learning in PPMI is that there seems to be more of a continuum and less of a, this is Alzheimer's, this is Parkinson's. And there are commonalities of markers of misfolded proteins that we can see when we evaluate people that are seen in Alzheimer's as well as in Parkinson's. We're still trying to piece apart exactly what that means in terms of predicting what someone's trajectory of disease will be. But I think it highlights the fact that this long-term is going to help us develop therapies that may be very individualized to the one person. So we may measure your genetic characteristics, measure certain biomarkers and say, "Oh, the best treatment for you is going to be this particular treatment or this particular combination." So this personalized medicine approach that can come from the work that we're doing now in PPMI and in other populations, looking at each individual's biomarkers as well as their clinical trajectory.

Jimmy Choi: Andy, there's a lot of questions about genetic testing in the Q&A. One of the things that people sometimes ask me is, I don't want to know my genetics. I don't want to know if I'm risk, but so what is your opinion on whether or not people should get genetically tested and how does that lead to a path to get tested for research?

Dr. Andy Singleton: Yeah, sure. Great question. It is a very personal decision, so I can't give you advice as a group. I think exploring this with your physician or with a genetic counselor is certainly worthwhile. To my mind, there are now a couple of upsides. Probably the most prominent is that, as Todd pointed out, we are now starting to see therapeutic trials which are geared towards genetic forms of disease. So knowing if you have that genetic form of disease or not can potentially be important as you think about trials. So this is something that is kind of actionable now. There are a few paths to getting genetic testing. You can go see your physician, they can order a test. There is a study called PD Generation, which provides genetic testing services, and I believe that MJFF will be working with PPMI to provide more testing over the near future.

The good point about getting involved in a study like PPMI or my PPMI or PD generation is you can opt in to your samples being used for research also. So there's kind of a double whammy there. You get some information back. It tells you about potential ability to take part in genetic-based trials, and you also contribute a sample for research.

Jimmy Choi: Thank you. If you guys wouldn't mind helping us close out this webinar with what you are hopeful for the next few years. And we'll start with Dr. Tanner.

Dr. Caroline Tanner: Yeah, so I am really hopeful that we are close to having therapeutics that may be able to actually target mechanisms of disease for people with genetic disease, but also for the rest of people who don't have the strong genetic link and be able to find treatments that will slow disease progression. I think we're close to that, and that's really very exciting.

Todd Sherer, PhD: Todd? Yeah, I have the same view. I guess I wanted to just start by saying 25, 30 years ago, we said that the cause of Parkinson's was idiopathic, which I think the Greek translation of idiopathic is we have no idea what the cause is. And from the work of Carly and Andy, we now have very, very vast understanding of both the genetic and environmental causes of Parkinson's. And this has now moved from being a theoretical question of what could cause the disease to actionable items and findings that are moving into the development of treatments that are being tested in people today with Parkinson's. So it's a very important inflection point where we are in the field now that we've taken this understanding and it's really now moving to the potential for really transformative and innovative therapies. So I'm quite excited about that. And it's a testament to the incredible hard and diligent work that's been done over time, and we're fortunate now to be at a cusp to benefit from all that hard labor and thinking.

Jimmy Choi: Yeah, I'm excited as well. Andy, would you like to close this out?

Dr. Andy Singleton: Yeah, I'd agree with everything that's been said. I hope that we continue to accelerate in discovery in the way that we have done over the last few years, because then a treatment is inevitable. I think that the field has been transformed over the last two decades by Michael J. Fox Foundation, really driving research forward and thinking about the disease in lots of different ways, thinking about therapies, thinking about how to diagnose people before they even know they have disease, and all of this is bearing fruit. We're making incredible progress. I hope we continue to accelerate.

Jimmy Choi: Yeah, thank you so much. And personally, as a person living with Parkinson's, I'm personally hopeful because when I started down this process, I remembered looking at all the research pipelines back 20 years ago. To me at least, it was non-existent or nothing in terms of disease modifying, but today we know we're working on several or some of these clinical trials are moving on into Phase II and III, and they are listed as disease modifying. And that's why I'm hopeful and that's what's exciting to me. So thank you all for being a part of this discussion today. I want to thank our community for joining us and another big thanks to the panelists for sharing your time and your expertise. And we hope you found today's discussion very helpful and I hope everybody have a great day. Thank you.

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