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 MJFF Parkinson's 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.

Dr Soania Mathur: Hi, I'm Dr Soania Mathur. I'm a retired family physician, writer, speaker, Parkinson's advocate, and co-founder of the PD Avengers. I'm also a very proud member of the Michael J. Fox Foundation's Patient Council, and I was diagnosed myself with Parkinson's in 1998 at the age of 27. I would first like to extend my gratitude to you all for joining us today, and it's my true pleasure to be here with you and our esteemed panelists. Today, we're going to be talking about how genetics can influence our personal risk of getting Parkinson's, and how investigating genetics can lead to a greater understanding of this disease: why it develops, how it progresses, and even potential targets for treatment. So we've got a lot to discuss, so let me first introduce our panelists.

Aditya Boddu is a movement disorder neurologist and assistant professor of neurology at Yale University. He was an Edmond J. Safra fellow, class of 2022, a program which aims to increase the number of movement disorder specialists all over the world, which we need desperately. He also has a research interest in Parkinson's genetics.

Bradford Casey is a PhD and senior scientific portfolio manager at the Michael J. Fox Foundation. He works to foster the foundation's research into genetics.

And finally, Susan Small lives in Northern California. She was diagnosed with Parkinson's in 2008, and she carries a LRRK2 genetic variant, which we'll get into. She's involved with Sailing For Parkinson's, a regatta that raises funds for research. Welcome everybody.

So let's get started. The statistic that I hear most often is that 10 to 15% of Parkinson's cases have a clearly identified genetic variant, but let's start with the basics. There can be a lot of confusion, I think, around words like gene, variant, mutation, risk. So in very simple terms for me, I think of our genes like instructions that help tell our bodies how to work, and a genetic variant is simply a difference in those gene instructions. But let's unpack what all of that means when we're talking about Parkinson's. We'll start with you, Bradford. How do you think about a genetic variant in simple terms? We hear a lot about genetics, but what does it actually mean to have a genetic link to Parkinson's or a variant that's linked to Parkinson's?

Bradford Casey: Thanks, Soania. Yeah, it's a really important question. So obviously we all remember that we all share a lot of our genetic code, our DNA, and there's variability across our DNA, and some of those variations can actually lead to changes in how our body functions. So in this instance, we're really talking about variants that are linked to Parkinson's disease. Sometimes those variants have

really big impacts, sometimes they have small impacts. Other variants may not be involved in diseases at all. They might just be involved in things like eye or hair color or our height, but it's important to understand the ones that are linked to diseases.

Now, there are a few that have long been understood to be linked to Parkinson's disease. We've known that there are significant genetic risk factors for over 20 years now, but we're still learning more about them, and we'll talk a little bit about that today. But I would say that from the foundation's perspective, we remain very actively engaged to learn more about not only the variants that have already been discovered, but also other variants that may be out there that we don't know about yet, but may be really informative as we want to learn more about the disease.

Dr Soania Mathur: And do all of these genes influence Parkinson's in the same way, the variants that are related to developing Parkinson's?

Bradford Casey: Yeah, it's an important question. So actually we know that these genes do different things in the body. They may be active in different cells, for example. And similarly, we think that these variants are likely leading to different forms of changes in the body that can lead to Parkinson's disease. So they definitely do different things, and we think that these variations are likely linking to different risk factors for Parkinson's.

Dr Soania Mathur: Aditya, from a clinical perspective, what does it mean when someone has Parkinson's and they learn they have a genetic variant? How does it affect the clinical status of a patient?

Aditya Boddu: Well, thank you, Soania. First of all, it's an absolute pleasure to be here and have this really engaging conversation with all of you. So when you think of what a gene variant means to somebody with Parkinson's disease, I think it's clinically meaningful because it gives the patient some knowledge about their disease. It gives you an idea about what we call the phenotype, which is the set of features that your kind of Parkinson's would typically have. It also tells you about the prognosis and how your disease might be expected to evolve as you live with Parkinson's.

Another important thing is I think knowing that one may have a genetic variant has implications for other family members who may be potentially at risk. And we are at a very interesting moment in time because it's actually actionable information now if somebody has a genetic variant because it could possibly open a window into enrollment in research and clinical trials targeted to these gene variants.

Dr Soania Mathur: Right. Yeah, we'll be getting more into more details about that exciting part in a few minutes. Susan, I'd like to ask you, what does knowing your genetic link to Parkinson's mean for you, knowing that you have the LRRK2 variant?

Susan Small: Well, I think it's meant a lot to me to know this because there are trajectory of progression and treatments that are specific to the LRRK2 genome in the mutation. And so knowing that, I can work with my doctors to pick a good course of treatment.

Dr Soania Mathur: Yes, you're very right. And Bradford, we'll go into details later. And as Susan just mentioned, the LRRK2 genetic variant and addressing that variant would be important for her quality of life. But at a high level, what are researchers learning about genetics that could ultimately help all people with PD?

Bradford Casey: So we've learned a lot about the role that genetics play as risk factors for Parkinson's disease. There are many causes for Parkinson's and we don't fully understand them, but we know that genetics can significantly increase people's risk. So having a parent with Parkinson's can roughly double one's risk of having Parkinson's disease. And we've really tried to understand more about that risk because once we can measure that risk by developing genetic tests, we can tell people more about how likely they or their families may be to develop Parkinson's disease during their lives. It again can help people seek out clinical care, especially if there are questions about a diagnosis and can ultimately really improve the outcomes for those participants in studies as well as for patients in general.

We are often asked how much might a specific risk factor affect someone's risk? And it's important to understand that there is a wide spectrum of that risk. Again, we know that generally speaking, a first generation relative can really almost double your own risk for Parkinson's disease, but we also recognize that a lot of people who, again, have these genetic variants may never go on to develop disease, and we can maybe dig into that more later today.

Dr Soania Mathur: Let's take a step back and talk about something that I think is on the minds of many people in our audience, and certainly is on my mind, and you alluded to it, but if Parkinson's runs in my family, what does that actually mean for me and my children? And as a mother of three beautiful daughters, now all in their 20s, and I developed my symptoms when I was 27, I would not be telling the truth if I said I don't stay up at night worrying at times, feeling that desperation for them to not end up facing the same challenges with this disease that I face. And I wonder how I should be framing these concerns. And Susan, is this a question that comes up for you as well?

Susan Small: Yes. Well, I had my testing over 10 years ago and my children were just barely adults, in their early 20s, and it made a difference. It was a family conversation. They didn't want to be tested, though.

Dr Soania Mathur: Yeah, that's something that we are definitely going to talk about, genetic testing, and when and how to go about that. Bradford did allude to this, but how much do genes contribute to developing Parkinson's? How should people think about the difference between inheriting a genetic variant and inheriting Parkinson's disease? Because just because someone has a genetic risk, it's not the same thing as inheriting the disease itself, is it?

Aditya Boddu: No, that's an important point. So when we think of Parkinson's disease, most of Parkinson's disease across the world is really what we call idiopathic sporadic Parkinson's disease. Idiopathic because we don't really know how it came to be. We like masquerading ignorance using big words, but there's a lot we still don't understand about why a single individual may have developed it, and sporadic as opposed to not being inherited. When it comes to a genetic basis for Parkinson's disease, which is what we're essentially talking about today, most of the recent papers quote about a 10 to 15% genetic basis towards Parkinson's disease.

Now, when it comes to a genetic variant, it is not necessary that one develops Parkinson's disease, because a gene variant is essentially giving you a likelihood or a risk of developing Parkinson's disease. Now, most of the common gene variants involve, for instance, GBA and LRRK2 have something called incomplete penetrance, which essentially means that this person who has a gene variant may be a carrier, but may never really develop Parkinson's disease. So that's an important takeaway point to understand.

Dr Soania Mathur: Yeah, that's incredibly important. And Bradford, you also mentioned the fact that if a parent has Parkinson's, it's double the risk for the child. What does that actually mean? If the risk for developing Parkinson's is 2%, does that mean it goes to 4%? How does that work?

Bradford Casey: Precisely so. So again, it's important to think about all of this against the landscape of everyone's risk for developing Parkinson's, regardless of what you know about your family's history. We know that roughly one to 2% of our population is likely to develop Parkinson's during their lifetime, just generally speaking. And we do think that having a close family relative with Parkinson's disease can approximately double that, so roughly 5% if you have, again, a first generation family member. We really want to think about that as we provide guidance to people who may be evaluating treatment options, or again, for people who may have family members who are potentially at risk. We think about this a lot because, again, as Susan points out, people are really making very important decisions about their lives as they evaluate those opportunities to learn more.

We know that there are a wide variety of levels of penetrance, as Aditya pointed out previously, and that's important to keep in mind as well. So knowing that your family member has Parkinson's disease, even if you know the specific genetic risk factors, is certainly not a guarantee that you'll develop Parkinson's in your lifetime. And it's really important to keep that in mind as you evaluate these things and as you talk to other people in your family about the disease.

Dr Soania Mathur: And is there any influence based on the age at which a parent is diagnosed? For example, if a parent's onset is diagnosed after the age of 70 or 80 versus young onset Parkinson's disease, do we know about that?

Bradford Casey: Yeah, it's a really interesting question. So we know that people can develop both genetic and idiopathic forms of Parkinson's either at younger or older ages, so both are possible. However, one thing that we do know is that people who develop young onset Parkinson's or early onset Parkinson's are more likely to carry genetic risk factors for the disease. We don't fully understand that, and we

recognize that a lot of that may have to do with a combination of genetic and environmental risk factors, but we're always trying to learn more, and this is part of the reason that this remains a priority for the foundation.

Dr Soania Mathur: Aditya, is that why people in the same family can have very different experiences, why one might have developed the disease and another with the same variant never does? I've even heard twin studies that sometimes show a difference in terms of the experience of genetic mutation.

Aditya Boddu: Yeah, no, that is a really interesting and important question that you've raised. At the Movement Disorder Society Congresses, they usually have this fascinating conversation about Parkinson's disease and Parkinson's diseases, because the lived experience of Parkinson's is so varied and so different even within individuals of the same family. Somebody with Parkinson's disease may have an active and independent life, still be able to play sports even 20 years into the disease, while somebody else might not be able to do that within 10 years. So there's this large heterogeneity to Parkinson's disease.

Part of it is that when it comes to the gene variants, there's this large genetic background that every individual has, which has other modifier genes which kind of influence that gene variant that one is born with. In addition, there's so many other risk factors, environmental and lifestyle risk factors, that one is exposed to across one's entire lifespan, what we call the exposome. And as the slide alludes to, there's also the combination of aging. So it's this complex interplay between all these factors, which really determines, we think, why individuals with Parkinson's disease may have such varied experiences.

Dr Soania Mathur: Absolutely. My Parkinson's isn't the same as Susan's, for instance. There's just such a variability in how this disease presents. So clearly genetics aren't the whole story. And Bradford, how are researchers thinking about what Aditya said about the interaction between genetic susceptibility and other factors such as environmental exposures and aging? How are researchers dealing with that?

Bradford Casey: This is an area of tremendous research focus right now, and people around the world are very excited about this question because we really think that this is an opportunity to learn more, not so much about the genetics themselves, but about the underlying biology of disease. So basically when we talk to researchers that are working in genetics on one hand and environmental research on the other, we think that while they may have different fundamental causes, we may be seeing different signals for the same type of disruption in that biology. So for example, if you have a gene that might make a protein, but there's also an environmental exposure that could damage that protein, we want to understand more about how that interaction can really lead some people to develop the disease and others not to.

At the end of the day, we think that this is an opportunity, A, to help identify ways to protect people from ever developing Parkinson's disease by removing some of those exposures. But we also think that this is a great opportunity for us to understand that biology so that we can develop treatments for every form of Parkinson's regardless of its cause.

Dr Soania Mathur: Absolutely. And we'll get more into that as well. Susan, I just want to go back. When you learned you had a LRRK2 variant, you said your children decided not to get tested, but what questions or conversations did your diagnosis of a LRRK2 variant raise within your family? Did it change how you thought about your own Parkinson's or how you thought about risk for your family members? What was that like?

Susan Small: Well, certainly the risk was an issue.

Dr Soania Mathur: It must have led to very serious conversations to allow them to make the decision not to get tested.

Susan Small: Yes. Well, their personal reasons for not wanting to get tested, I won't necessarily share, but I do believe that they were glad that their father, for instance, wasn't part of the Ashkenazi Jewish race. It's like getting a double negative in your genome and knowing that I had a mutation, it was scary for them, but not anything that we couldn't overcome.

Dr Soania Mathur: Right, yeah. I think that open communication that you have within your family is definitely important, especially when you're dealing with something like your own diagnosis. And once people learn that genetics can influence Parkinson's risk in some families, and with a lot of people who haven't had genetic testing, a very natural question follows: "Should I get tested?" That question can be much more complicated than simply deciding whether you want a blood test. There can be an implication how we understand our own disease for those family conversations you just talked about, for future research opportunities that Bradford mentioned, and sometimes for how we think about the future. So Susan, what actually led you to get tested? What were you hoping to learn from that and did the experience turn out the way you expected? What was that whole experience of getting tested like for you?

Susan Small: Well, it didn't turn out the way I expected because I didn't think that I would have any of the mutations. At the time, my sister, my mother, and my aunt were going through genetic testing for breast cancer. And so when the opportunity to get tested for Parkinson's, it was like, "Well, of course this is just what you do." And so there was a familial influence in wanting me to find out what the results would be.

Dr Soania Mathur: That's very interesting because that's true. When you're getting testing done, it doesn't just influence yourself, but it influences the family. It affects the family, and then they have to make their own decisions about testing or not. But who should consider genetic testing for Parkinson's if it's not a family issue? Is testing something that should be considered for everyone with Parkinson's or are there particular circumstances where it might be especially informative?

Aditya Boddu: Yeah, that's a good question. So I think ultimately choosing to get tested for Parkinson's disease is a very individualized and a personal choice, as Susan has just shared with us. When it comes to thinking about this clinically and what it means for the patient, I generally offer it to most patients. However, I really think about the role of genetic testing in certain cases. So we just had been discussing

about young onset Parkinson's disease, or early onset Parkinson's disease. Typically, the age of onset of Parkinson's disease, at least in the United States, is around 58 to 62. And if I see somebody in clinic with features of Parkinson's disease in their 20s or 30s, I would suspect a genetic basis for that. And so that's a case in which genetic testing, I think, could be considered.

Patients who may have a family history of Parkinson's disease, as Bradford was just talking about, having a parent with Parkinson's disease could also confer a risk to you potentially, so it has implications for the rest of the family. So having that first degree relative is, again, another case that I think of. And then just from a clinical perspective, sometimes you run into cases where there's other superimposed neurological features in somebody with Parkinson's disease. So if there's another movement disorder or an unusual clinical sign, then you would suggest a genetic basis, which would potentially help with the diagnosis and eventually the management of that patient. So at least in these three cases, I would really think about genetic testing because there are pros, but there are also cons to it. And ultimately, it's really something the patient would decide after an informed conversation.

Dr Soania Mathur: That makes complete sense. From a research perspective, Bradford, if someone already has PD, what could they potentially learn from genetic testing if they've already got the disease?

Bradford Casey: So there's a lot of things that you can learn from participating in genetic testing, and some of those are relevant to you, and some of those may be relevant to those around you, and some of those are relevant to people that may not yet have the disease or know about the disease. For you, as a patient, it might help you make decisions about the types of treatments that you might want to seek out. It may help you think a little bit about your future with the disease, but it also tells you a little bit more about potential risks for your family members. And obviously this is a personal decision, but it is increasingly a decision that has consequence. So Soania, Aditya, I know that you're both clinicians, and for many years, Parkinson's has been a disease that doesn't have genetically defined therapies, which means that there are not specific drugs that are developed around your specific type of Parkinson's disease.

But increasingly, we are starting to see people thinking about that in the therapeutics that we're developing. So in our lifetime, we may very well have drugs that are developed for specific forms of disease, and we can talk more about that as well. For people who may be thinking about their long-term Parkinson's risk or risk in their families, having testing can tell you a little bit about that risk, but it might also simply tell you that you need to be more vigilant about your own health in the future, which is an opportunity for people to keep something in mind in case, again, they have symptoms that can't be resolved, in case they have issues that are affecting them that they don't have answers to. And then finally, of course, all of this is really tremendously valuable for research as well, as we want to, again, learn more about the disease and how we can treat it.

Dr Soania Mathur: So the results could influence someone's research participation or clinical trial eligibility as well, is that correct?

Bradford Casey: Precisely so, yeah. And I think that that last piece is one that's really interesting. As we think about what opportunities people may be eligible for, increasingly we are thinking about that through the lens of genetics because it can help understand better what some things may be testing or what types of experiments people may be doing with the data behind it.

Dr Soania Mathur: And Aditya, how can someone access genetic testing? And are there important differences between testing through a clinical setting, a research study, as Bradford mentioned, and direct-to-consumer genetic testing? How should someone access it or how can they access it?

Aditya Boddu: That's a good question. It gets nebulous out there with different kinds of genetic testings available and how to access it. But typically, if you're a patient with Parkinson's disease who is interested in genetic testing, the first thing is really to have established care with a movement disorders neurologist. Not all clinics, but some movement disorder clinics have also access to a genetic counselor who can spend more time in other situations. It's done by the movement disorder neurologist themselves, just discussing what genetic testing could offer for the patient. There's in-depth discussions about what the implications of a positive test result would mean or a negative test result would mean, and also possibly an unknown test result because sometimes you come out with variants of uncertain significance. So I think that's an important piece of the conversation when one is considering genetic testing.

As far as genetic testing itself goes, most genetic testings for Parkinson's in most cases are panel testings. So basically there's a list of candidate genes against which the individual's DNA is sequenced and mapped and looked at. However, the thing with panel testing is that in some cases you could still have Parkinson's disease and have missed one of the genes or the gene variants. When it comes to direct-to-consumer testing, there are issues because they probably, in most cases, they only test for one or two genes or a handful of genes, so they don't really cover the entire spectrum. So I would say the best way to access genetic testing is in a clinical setting because it's more than just the test results, because sometimes it can provide actionable information and can tie you to research and potentially allow patients access to clinical trials that are on the horizon targeted to their kind of Parkinson's disease.

Dr Soania Mathur: And what role does a genetic counselor play and why would someone benefit from talking to one before or after getting tested?

Aditya Boddu: Yeah, so a genetic counselor is somebody who can spend time discussing the results with the patients, but also talking about the potentials of risk to the other family members. Further, it can get tricky figuring out what kind of genetic testing to be used and what the insurance coverage is for something like that might be. Unfortunately, there's unequitable access to genetic testing, and that's something that a genetic counselor can really help the patient navigate.

Dr Soania Mathur: Did you have a genetic counselor, Susan? Did you have one involved with your testing?

Susan Small: Yes, yes. There was somebody who spoke to me before and after.

Dr Soania Mathur: To tell you what the results meant?

Susan Small: Yes, they did. I think that there have been some developments since I had my testing, was more than 10 years ago, so I think that there's been more information learned and that I'm ready for another consultation.

Dr Soania Mathur: Bradford, is that something you've seen yourself, that the number of genes has increased over the last 10 years that we know about?

Bradford Casey: Absolutely. Not only in the last 10 years, but just in the last two years. So as we expand the amount of research data that's available, we really have learned a lot more about these new variants that are linked to Parkinson's disease, their significance to specific features of the disease, as well as a little bit about what it might mean for people's progression trajectories, for example. So we're learning a lot more about it, and all of this is constantly changing that calculus that patients face as they evaluate genetic testing.

One thing that is important to remember is that, again, a lot of the tests that you might face clinically, if your physician were to offer you genetic testing, would be panel-based, so they might not have all of the different variants. But that said, there are a lot of providers that offer retesting with new variants that are identified as well. So these can affect your results. They might provide more clarity down the road. And as we learn more and more about potential genetic links and how that interacts with other risk factors for Parkinson's disease, I think we're learning a lot that people might be able to get down the road from future retesting.

Dr Soania Mathur: So you just mentioned retesting. Does that mean another appointment, another blood test, or does that mean they keep your blood on hand and can retest based on your previous test?

Bradford Casey: So it depends on the provider. Certainly, there are some companies that collect blood or they collect saliva, for example, and some of those retain those samples. Others may discard it after running the test, so you might have to make another visit to another collection, but there are a lot of large providers that do bank your samples and offer that service of retesting when new genes are identified.

Dr Soania Mathur: So let's now move from the question, and we've talked about this a little bit, but what genetics means for me, to another really important question, what does genetics teach researchers about Parkinson's? So Aditya, how does studying a gene such as LRRK2 help scientists understand what is happening biologically in Parkinson's? And do those discoveries only apply to people who carry LRRK2 variants, or can they teach us something about Parkinson's more broadly than that?

Aditya Boddu: Yeah, that's a good question, and one that has, I think, different pieces to it. Just to add to Bradford about the wealth of knowledge that's being added from all the

genetic studies, particularly the GP2 initiative, what we're also understanding is the ancestry of Parkinson's populations all around the world, because most of the genetic data is in European and North American ancestry, so we ignore a large part of the world which seems to have possibly an enriched risk of certain variants which you would not otherwise see. So it gives you a global picture of the LRRK2 variants across the world and how they differ across different populations. The LRRK2 gene gives you a window into the signals and the biological processes that may be implicated in one's a LRRK2 Parkinson's disease. And this is broadly, it's not just in somebody with LRRK2-related Parkinson's itself, but Parkinson's disease, because the LRRK2 kinase activity seems to be elevated even in idiopathic Parkinson's disease populations.

The LRRK2 is a very interesting gene variant because variance in the LRRK2 gene also seems to influence the pathogenesis of another disease, progressive supranuclear palsy, which is a Parkinsonian condition. Not the same as Parkinson's disease, but this seems to be a hotspot for not just Parkinson's, but possibly other neurodegenerative diseases as well. So it's really a piece of knowledge that applies and can potentially have huge translational implications, not just to somebody with LRRK2, but gives us an understanding of the biology of Parkinson's disease at a very basic level. So that's how possibly you would think about it.

Dr Soania Mathur: I think what you said is so, so very important for the community. I often say you can't cure what you don't know, and anything that gives us more knowledge about this disease process is going to benefit the whole community, which I think is really important. So Bradford, where does genetic variant target drug development stand today? What have the researchers learned so far and how close are we to having treatments that actually target the biology of Parkinson's disease that's affected by these variants?

Bradford Casey: It's a really exciting time not only in genetic therapeutic development, but Parkinson's therapeutic development more broadly. In terms of those genetically targeted therapies, as I pointed out, over the last 20 years, we've learned so much about which genes are most closely linked to Parkinson's disease risk, and we think that those are real opportunities to treat those specific mechanisms that might break. Those of you who have joined us for different calls in the past may be very familiar with a protein called alpha-synuclein. So the first genetically targeted treatments were really focused on treating that alpha-synuclein. Some people do have variants in alpha-synuclein that are linked to Parkinson's risk, and often this is with a more debilitating or earlier onset form of the disease, so it was an early target.

We've seen those move into the clinic, and we do now have clinical trials underway for alpha-synuclein-based therapeutics. And I think it's really important to keep in mind that those are not only going to be relevant to people that have those specific mutations, but other people who, again, have that synuclein pathology that really defines Parkinson's disease in humans. We also are seeing therapeutic development focused again around LRRK2 and GBA, another common risk variant that's identified for Parkinson's disease. And so we really see those moving forward. We don't have all of the answers, and there's

been a handful of clinical trials that haven't had promising outcomes. But that said, we think that this really remains a great opportunity to help target that biology specifically, help understand more about how we may be able to interfere with those disease mechanisms, and really help change the face of drug development for everyone that's facing Parkinson's.

Dr Soania Mathur: It's exciting, you're right. One of those initiatives is GP2, Aditya mentioned that. Could you just explain to us what GP2 is?

Bradford Casey: I though you'd never ask. So GP2, or our Global Parkinson's Genetics Program, is a study that is working to collect samples from around the world with the vision of trying to help build out our understanding of genetic risk factors for Parkinson's disease. So we're currently looking at collecting over 250,000 samples around the world from people of very diverse ancestries. And that last piece is super important. A lot of what we know about Parkinson's genetics and the risk associated with those Parkinson's genetics is based in Northern European populations. Because there is so much more diversity in other areas of the world, it's a real priority for us to understand more.

Because even understanding variants that may not affect your personal ancestry, we may learn a lot about the biology that could ultimately lead to therapeutics that are going to be effective for everyone. So our goal is really to bring together the smartest people around the world to help collect those genetic samples, to partner with local researchers to help analyze that, and ultimately to make sure that we are collecting and sharing all that data with responsible researchers around the world to make the most of that investment. We're really excited about this program and we're really proud of everything it's accomplished so far.

Dr Soania Mathur: I think that's so important and there's certain consequences that if you don't include certain populations that are underrepresented in genetics research, it really affects our whole understanding of the disease again, like we mentioned before. Susan, another study that is investigating these genetics is Parkinson's Precision Medicine Initiative, PPMI. What led you to join the studies?

Susan Small: Well, it was recommended by my physician, my movement disorder specialist, and it was such a fascinating opportunity to be able to contribute by participating. The lumbar punctures aren't very fun, but it's so helpful to them to get the fluid and have it be tested and tried on different medication options. It was really fascinating to me.

Dr Soania Mathur: Well, I have a lot of respect for you and other people that participate in this type of research. You're literally giving of yourselves and without your involvement, there could be no progress to finding better treatments or a cure. So thank you for that. I want to just highlight a genetic screening opportunity available through PPMI, the foundation's landmark research study. PPMI offers genetic screening at no cost to eligible individuals, which may help determine whether they qualify for certain research opportunities. And by taking part in PPMI, research participants can help researchers better understand the role genetics plays in Parkinson's and move the research forward, as Susan has done. So to learn more

about this, click the link in the "Take action" box on the right side of your screen and help our community progress towards that ultimate cure.

Now we've talked about what genetics can tell us today. Now I want to look towards the future. And one of the promises of understanding Parkinson's biology at a deeper level is the possibility of moving towards what we call precision medicine. We didn't label it, we talked a bit about it, but where the treatments are increasingly tailored to the biology of an individual rather than assuming that everyone with Parkinson's has exactly the same disease, because that's really doubtful given all the variety of presentations that this disease has. Aditya, what does precision medicine mean in Parkinson's disease and how do genetics factor into that future?

Aditya Boddu: Yeah, Sonya, you alluded to precision medicine yourself. So in a disease like Parkinson's, which is so heterogeneous, there's multiple biological pathways that can lead to this thing we call Parkinson's disease, which is so different in each person. And so a uniform standard, one size fits all approach usually doesn't seem to work. So precision medicine is really about tailoring interventions based on the specific molecular signatures of one's Parkinson's disease. And genetics is obviously an important part of this. It's an important component along other omics approaches and other biomarkers.

That's because at the end of the day, genetics gives you an actionable route, and we've alluded to this in the conversations before about trials that are underway for patients with GBA and LRRK2. A barrier to these clinical trials is when patients don't know their gene status. And so if you, for instance, know that you are somebody who has a GBA variant and has Parkinson's disease or a LRRK2 variant with Parkinson's disease, this can potentially, you may be a candidate for some of these clinical trials where there's therapies targeted to these parts of your genome.

Dr Soania Mathur: And how far are we away from using that genetic information to deliver the right treatment to the right patient at the right time? What needs to happen before genetic information can routinely guide your clinical care?

Aditya Boddu: There still remains a lot of work to be done. I think the door for these kinds of clinical trials and approaches has already opened and we are in a brave new world. I think we've had trials for GBA and LRRK2. There's now a phase two clinical trial for GBA looking at viral vector therapy in patients that is actively recruiting and whose results might come out two or three years down the road. There are phase two clinical trials for LRRK2 that are enrolling and currently recruiting patients. And so I think the future is now.

Even though for instance, we've been talking about LRRK2, LRRK2 really represents about four to 5% of the familial cases in the Parkinson's disease, but we've seen how understanding more about this can have implications for even those with Parkinson's without a LRRK2 variant. And so I think much of the basic science seems to be progressing in the right direction, but we still need to test therapies across different populations across the world and really find better

interventions. We're not quite there yet, but I think this is the start of something really exciting.

Dr Soania Mathur: And Bradford, do you find the same thing when you talk about subtypes of PD, the genetic variants, that's really affecting researchers in the lab, so to speak? It's actually making an impact on how they conduct their clinical trials?

Bradford Casey: Yeah, so subtypes are essentially a way of thinking a little bit about the disease with the goal of better understanding the individual pieces of biology. So earlier we talked a little bit about the potential for environmental risk factors of Parkinson's disease. One possibility is that that is a distinct form of the disease, both in cause but also in biology. So genetics are probably the most commonly discussed potential subtype. Again, because we do have some identified genetic risk factors, it's a very objective way that we can classify patients, understand how they may be more similar than other Parkinson's patients, and see what we can learn in hopes of better developing therapies. So we continue to look at subtypes in a broad lens to really try to think about how we can classify patients in different ways. And we really believe that that is going to help support therapeutic development for all the different subtypes as well as perhaps people who are not defined by those subtypes.

Dr Soania Mathur: And Susan, what is it like to see research and clinical trials focus on the biology connected to LRRK2, your disease? And looking ahead, what kind of advances would be most meaningful to you? Not just scientifically, but in terms of living with Parkinson's disease.

Susan Small: Yeah, so it would really mean something special to me to have an answer to the LRRK2 mutation and being able to treat that specifically, I think it would be like a leap to the moon, a blessing to have specific care for my gene mutation.

Dr Soania Mathur: Absolutely. So we've covered a lot of ground from understanding genetic variants and family risk to genetic testing, research, and the promise of precision medicine. And we know that many of you have questions. One thing that came up in the audience that's listening, and also was pre-submitted, is that, so you know you have a variant, a Parkinson's variant. What can you do, Bradford, maybe you can address this, but what can you do to lower your risk of developing the disease, for instance?

Bradford Casey: It's a great question. It's one that we get very frequently. So again, we don't yet have specific targeted therapies that have been clinically tested and approved, but again, we see that as part of the future. For now, we really encourage people to think about this through the lens of what you're going to do with that knowledge of increased risk. So if you do know that you are at increased risk for developing Parkinson's disease, our guidance is usually very similar to people who have recently been diagnosed. We often tell people to really consider the impact of things like a healthy diet and exercise, which really help people who have developed the disease to keep from progressing faster than they otherwise might. So this is one of those things that we really guide people towards.

There are a handful of lifestyle factors that may alter people's risk of disease, but to be honest, there's not enough data that really suggests that people with any of these specific variations should dramatically alter those lifestyle factors. Again, it's more about encouraging people to be healthy, to be vigilant about their own health, and to talk closely with a physician about how they may be able to prevent things. Again, there's always new research coming out, so we're really hopeful that we will understand more about how we may be able to alter those risk factors, and there's a very good chance that we may see progress in the near future on that as well.

Dr Soania Mathur: Yeah, so I really hope we do get to the point where there are actual treatments that we can implement when we know someone's at risk to prevent them from having to embark on this journey in the first place. And that would be wonderful and that's what we're aiming for, I guess. Aditya, are there ways to screen for Parkinson's or recognize early signs before the typical movement symptoms appear?

Aditya Boddu: Yeah, that's a good question and a hard one to answer. James Parkinson himself talks about how the inroads into the disease are so subtle that one may have had Parkinson's for several years and then in retrospect realizes they have the disease. But Parkinson's disease commonly is experienced by a patient when they begin to have motor signs. So early motor signs can involve things like a tremor, which is a shaking of one part of the body on one side at rest, or difficulty moving or slowing of one's gait. This is usually something that a care partner or a family member might see. So usually these are motor symptoms which may allude to the fact that somebody may have Parkinson's disease, which is why a patient may come to you to get diagnosed.

Dr Soania Mathur: Also from our audience, Bradford or Aditya, you can answer this one. Does the risk of developing Parkinson's change depending on which gene or specific genetic variant a person inherits, of the genes that we know about?

Aditya Boddu: Yes. So if I may begin on this one, so there are some fully penetrant or completely penetrant high-risk genes that we say, but these are really rare. They're only seen in certain kindreds or certain clusters of families across the world. The more common gene variants are the GBA and the LRRK2 that we've discussing that confer not a large size effect, but probably a moderate or an intermediate size effect. So yes, it very much depends on what gene is affected and also what kind of gene variant you have that you inherit. So it depends on those factors. And in addition, one of the things the GP2 study showed was several smaller gene risk variants across the genome, what we call polymorphisms, that background which can again influence the gene variant that you have. So it's really that milieu and also the gene variant that you have, which depends if somebody expresses the disease, if that helps answer the question.

Dr Soania Mathur: It's complicated, is really the answer. Bradford, is inherited Parkinson's different from sporadic Parkinson's in symptoms, age onset or progression? Or maybe Aditya can answer that.

Bradford Casey: So I would say that we do know a little bit about that. We know, for example, that people with Parkin mutations may have an earlier onset. They may have a somewhat different progression trajectory within the disease than, for example, LRRK2 or GBA. But I would highlight that, again, this is a very heterogeneous disease and many people never go on to develop the disease with any of these mutations. Other people may be diagnosed quite early but not progress. So I would say that while there are some common trends, it's more important to remember that it is heterogeneous. So one person's experience with a genetic variant and with Parkinson's disease, it may look very different from others. And again, this is an area where I always encourage people to talk to their physician, especially a movement disorder specialist who really understands some of those subtleties and can help people make decisions about their own lifestyle.

Aditya Boddu: And to just stack onto this, so for instance, LRRK2 Parkinson's in most cases is really something which is not clearly distinguishable from sporadic Parkinson's disease, for instance. These are patients who have typical levodopa responsive symptoms with a slow progression and all the clinical motor features of the disease. So in some instances, it can be very difficult to piece apart if this is sporadic or genetic Parkinson's disease, because as we've seen, sometimes you may not even have that family history even though you have a LRRK2 variant, because not everybody with the variant develops that disease.

Dr Soania Mathur: Do other variants have different symptoms in presentation or progression?

Aditya Boddu: That is a good question, and basically you're talking about the phenotype of the disease. I'm not quite sure if there really are huge variations in the clinical phenotype, but it does influence your risk based on the penetrance of the variant of the gene that you have.

Dr Soania Mathur: Bradford, are treatments being developed specifically for people with genetic forms of Parkinson's, including gene therapy, CRISPR, or other gene-targeted approaches, someone wants to know?

Bradford Casey: Yeah, so we talked about that a bit earlier. There are definitely people developing therapeutics for all of these variants that we've mentioned, basically. The reason for that is that they're really good starting points. Again, understanding that underlying biology that's associated with these variants can tell us a little bit more about how we might be able to target them. And when I say that, what I mean is that if we have a variant that, for example, leads to a protein that's overactive in the body or doesn't work properly, then that might tell us the direction that we need to make those changes. So there are different targeted therapies in development, but again, it's important to remember that we ultimately are looking for therapeutics that are going to be beneficial to all patients. And so we are always trying to keep an eye out for approaches that are really going to help us understand and help us treat every patient regardless of whether or not they carry specific variants.

Dr Soania Mathur: Aditya, does the risk change depending on the number of family members you have with the disease? So not just one, but several, say, within your extended family.

Aditya Boddu: So when you think about it, if there is a family with several individuals affected across multiple generations, then it probably also tells you about the pattern of inheritance. You may be seeing something with what is called an autosomal dominant inheritance, which means you need just one copy of the gene to manifest the disease. In such a case, you would suspect a high risk gene.

Dr Soania Mathur: And this ties into the question, Bradford, for you, because you said that having a parent with PD increases the PD risk approximately twofold. Audience member wants to know, is the increase in risk the same if the parent has PD but does not carry any known genetic risk factors?

Bradford Casey: It's a really interesting question. So what I would tell people is that, generally speaking, the numbers suggest that yes, you still have an elevated risk just from having a first-generation relative that has Parkinson's, regardless of whether you know that specific genetic risk factor. There are a couple of interesting reasons for that. I'll be really brief, but just say it's possible that they have a genetic risk factor that just hasn't been discovered yet. So this is part of the reason that we really want to include people like that in research studies so that we can better understand it. In addition to that, there may be other factors, again, things like environmental factors or other things. And so we are not really sure about the specific mechanisms for some people, but it's important to remember that in addition to the handful of genes that are very commonly tested for, there are many, many others that are currently under investigation. So we're learning a lot about things in this space right now.

Dr Soania Mathur: Another audience member wants to know, can you address the gender issues, please? It seems that there are more men developing Parkinson's than women. Does the Y chromosome matter?

Aditya Boddu: That's a very good question, and I feel one I'm afraid I left out when we were talking about all the possible contributors to Parkinson's disease. PD seems to be more common in men compared to women. So sex does have an influence on possibly Parkinson's disease. One thought is whether estrogen could possibly influence this whole biological network that gets disrupted when one has Parkinson's disease. But the other thing is also that in general, unfortunately, women have been underrepresented in a lot of studies related to Parkinson's disease, and particularly the experiences of women with Parkinson's seems to be very different from men. I'm not entirely sure if it has something to do with the Y chromosome though, as the question asks. But yes, an individual's sex definitely seems to at least have a contributory effect to the risk of Parkinson's.

Dr Soania Mathur: Thank you so much. I think that's probably as much time as we have for Q&A, and I hope this conversation has helped make the relationship between genetics and Parkinson's a little clearer, and also helped illustrate why this research is so important. We're learning more about the biology of Parkinson's every day, and genetics is giving researchers new ways to understand why Parkinson's develops, why it can look so different from one person to another, and how we might eventually develop treatments that are much more precisely targeted. But none of that progress happens without people willing to participate, ask questions, share their experiences, and contribute to research. So thank you to everyone in our

audience for your interest, your questions, and your commitment to advancing Parkinson's research, and a very special thank you to our panelists, Bradford, Aditya, and Susan for sharing your time, expertise, and perspectives with us today.

And I hope you found today's discussion informative, useful, and most importantly, hopeful about where Parkinson's research is headed. Thank you, everyone. Have a wonderful day, and until next time.

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