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

Dr. Soania Mathur: Hi, everyone, and thank you for joining us. I'm Dr. Soania Mathur, family physician, and a person living with Parkinson's for about 24 years. I'm co-chair here at The Michael J. Fox Foundation Patient Council, and I really have the pleasure of being your moderator today. As you may know, genes are carried in our DNA. Those units of inheritance that determine the traits that are passed down from parent to offspring. We inherit, I believe, about 3 billion pairs of genes from our mothers and fathers, and they determine the color of our eyes, how tall we may be, and then also in some instances, the risk we have in developing certain diseases in our lifetime. So today, we're going to talk about the genetics behind Parkinson's disease. We'll go over what to know if you have a Parkinson's genetic mutation or think you might. We'll cover genetics testing and the latest advancements in genetic research. We've got a lot to discuss, so let's get started.

Dr. Soania Mathur: Let me first introduce our panelists. First, I'd like to welcome Dr. Roy Alcalay. He's the chief of the movement disorders division at Tel Aviv Sourasky Medical Center and associate professor of clinical neurology at Columbia University, and his research focuses on genetics and biomarkers in Parkinson's disease. We also have with us today, Jenny Verbrugge, a genetic counselor at the Department of Medical, Molecular Genetics at the Indiana University school of medicine. She works with participants getting genetic testing done through research, including the foundation's landmark study, the Parkinson's Progression Markers Initiative, or PPMI, which we will address later. And finally, we welcome John Gilman, co-founder and CEO of the business company, Crunchbase. John doesn't have Parkinson's, but has a LRRK2 mutation, and he's also a participant in PPMI. So, welcome everybody.

Roy Alcalay: Thank you.

Jenny Verbrugge: Thank you.

Dr. Soania Mathur: It's a pleasure to have you all here. So I mentioned very briefly how genes carry information and determine what makes us, us, in many ways, but perhaps Jenny, we could start with you and you could explain it a little bit more clearly than I did. What do we know about genes, and what are some of the terminology involved when we talk about genetics?

Jenny Verbrugge: Absolutely. Yeah. So understanding genetics can sometimes get complicated. So let's walk through some terms today to kind of help shed some light, give us a little bit of background.

Dr. Soania Mathur: Right.

Jenny Verbrugge: So let's start by talking about DNA. So DNA is basically our genetic code. It's our genetic information that's in each one of our cells. A gene is a segment of DNA. It's like a set of instructions. A gene tells our body how to make a protein, and proteins have different roles in our body. Genes are inherited, so genes determine our traits and characteristics, like eye color, but genes can also determine if we may have a disease or risk for disease. A variant is basically a change in the DNA. So a change in the DNA construction is kind of like a change in the spelling of a word. A variant may or may not change the way a gene works, or the words affect the way a is made or a way a protein functions.

Jenny Verbrugge: A mutation is basically a variant in the DNA that causes a gene not to work. So in other words, a variant disrupts that process of our body making a protein, and that can lead to disease or risk for disease. So hopefully this kind of helps us give a little bit more of a background for the rest of our conversation today.

Dr. Soania Mathur: Yes. Thank you, Jenny. That's great to know, because the words can be a bit confusing. Even the differentiation between variant and mutation may not necessarily make a difference in terms of the results that you get from your genetics testing, but may actually play a role in our understanding, for sure. So, Roy, Jenny has explained us sort of some general concepts in genetics, but what do we know about genetics as it relates to Parkinson's disease specifically?

Roy Alcalay: Sure. So we've learned a lot in the last couple of decades. If you look at books talking about Parkinson's, in the 1980s or 90s, they didn't mention genetics as being a major component, and our knowledge has really exploded. So if we look at the entire DNA, there is more than 60 spots on the DNA that have been associated with increased risk for Parkinson's. Each one of them probably contributes just a tiny component of incremental risk, so when we try to look at where do we see changes that really, if one carries them, the risk is significantly higher, we identify that we basically... There is a consensus about some seven genes that mutations in which, or alterations in which would increase the risk for Parkinson's. Still, in most cases, the alterations increase the risk. They do not necessarily mean that if you have them, one would develop Parkinson's.

Dr. Soania Mathur: Right.

Roy Alcalay: So just like not all cigarette smokers will develop lung cancer, but the association is there. In some places, the association is very strong, and in some places, the association is milder, which means that some mutation carriers, but not all will develop Parkinson's. The first genes that were discovered were genes that the risk mutations that in which cause high risk for Parkinson's. And we

crudely divide those to those where the risk is high if you get a mutation from both mom and dad, and then they're called recessive, and those where it's enough to have one abnormal copy, so just mother or just father, and these are the dominant genes. So the classical dominant gene is alpha synuclein. That is abbreviated, there as SNCA, and the recessive genes that are more common are PARKN, or P-R-K-N, and PINK1, which usually we find when people with younger onset of Parkinson's gets genotypes, so people in their twenties and thirties, less likely later.

Roy Alcalay: The major change in the field of genetics that made the results more relevant to a much larger group of people are the findings that the gene LRRK2, L-R-R-K-2, and the gene, GBA, which is an abbreviation of glucocerebrosidase. Since glucocerebrosidase say... I'm going to say GBA from now on. These two genes are much more common. So combined, when we look at all these genes, these five, [inaudible 00:07:24] two more, DJ1 and VPS35, roughly 10 to 15% of people with Parkinson's, independent of their ancestry or genetic background, carry a mutation or an abnormal variant in one of those seven genes. But these numbers can be higher in selected populations. So in people of Ashkenazi Jewish ancestry, between GBA and LRRK2, around one third of those with Parkinson's carry a mutation in GBA or LRRK2. And in North African Berbers, which is people who are originally from Morocco, Tunisia, Algeria, up to 40% of the people with Parkinson's there have the LRRK2 mutation, the same mutation that is found in [inaudible 00:08:10].

Dr. Soania Mathur: So you mentioned that obviously not everyone has these mutations develops the disease. Are there numbers that you sort of have in mind, what the risk would be for someone that say has alert to a GBA mutation in terms of there risk above the general population for developing a disease?

Roy Alcalay: Sure. So ideally, to tell that, I need to genotype everyone with Parkinson's, everyone in the general population, and then give an estimation. We cannot do that. I wish we could. So what we can do is go to people with those mutations and ask about the parents, assuming that at least one of the parent carried the mutation, and then estimate the risk this way. And it's not the best way, but it's the best we have. And based on that data, roughly around, I would say, crudely 10% of those with GBA mutations will develop Parkinson's. It also depends on the GBA gene, if you have a mild mutation or severe mutation. So the numbers... But that's more or less the case. So compared to where let's say 2% of the general population at an elderly age have Parkinson's. So GBA is roughly 10%. Some mutation is seven, but there are reports on 15. And in LRRK2, again, the literature is quite inconsistent, but the best reports estimate the risk is around 30%.

Roy Alcalay: So if I need to put one number, I would say that. For PINK11 and PARKN, if you have two mutations, the risk is very high. And for alpha synuclein, the mutations are too rare, so I don't want to commit to a number.

Dr. Soania Mathur: Okay. Understandable. Speaking of LRRK2, john, could you share with us how you came to know that you're a carrier for the LRRK2 mutation?

John Gilman: Yeah. Yeah, sure thing. It was probably about eight years ago now. I work in technology, and I just got into what was then called the quantified self movement, and just learning more about my body through technology and genetic testing. And consumer genetic testing was one of the options that I sort of went down just for the path of thinking about things of how I can optimize my health and live a healthier life. And then when I got the results back, went to the section where it talked about risk factors, and that's where I saw risk for Parkinson's. I forget the exact number that was reported back then, but much higher, obviously, than average, and it showed that I had the LRRK2 mutation. And at first, I sort of didn't know what to do with that. I don't have a family history of Parkinson's disease.

John Gilman: And so first thing I did was go to Google and Google the LRRK2 mutation to try and learn more. And a after skipping over the Wikipedia page, The Michael J. Fox foundation actually had a great blog post that explained a lot about what LRRK2 is, the risks, and getting involved. And so that was how I learned more about it and my introduction to the world of Parkinson's and LRRK2 and how it fits into that puzzle. So happy to talk more about it at some point, but that's sort of how found out about my mutation/

Dr. Soania Mathur: Right. And it kind of ties into my next question, which a lot of questions in the chat are alluding to this, and also one of our pre-submitted questions. Patients that have genetic mutations, they're wondering about whether or not they should have their relatives checked for the same type of mutation. And I think all three of you might have different perspectives on how to handle this question, because it's not a clear and easy decision. What would you recommend that they do in terms of... You know you have a genetic mutation yourself, what do you sort of disclose or consider when speaking to your relatives about the mutation and whether or not they should get tested. Let's start with you, John, because you're sort of in a similar situation. How have you handled that?

John Gilman: Sure. Sure. Yeah. Definitely, my experience is that every individual has their own predisposition to genetic testing, because in some respects, you're finding out a risk factor that may not impact you for many years. And some people are of the, I would rather know camp, and some, I would not rather know.

Dr. Soania Mathur: Right.

John Gilman: And in terms of my immediate family, I know I did get the mutation from my father, because my both my parents got tested. And he currently does not have have Parkinson's, but it was sort of conversations with my brothers and other relatives. It really was very individualistic, and it was based on their preferences on what to know and what not to, what they would prefer not to know. I could just say, based on my personal experience of having found it out, and then now

being able to participate in the PPMI study, that it's been such a unique and rewarding aspect to be able to feel like I can contribute, even before having any knowledge that I would be, down the road, at risk for Parkinson's that could be part of a study that is on the path towards a cure.

Dr. Soania Mathur: Right.

John Gilman: So for myself, it's taken something that at first was sort of not great news to get and turned it into something that I can really use to help contribute towards making a difference. And that's been a really rewarding aspect of it, obviously being involved with the Fox foundation and Team Fox through all the fundraising efforts.

Dr. Soania Mathur: Yeah. I mean, that's a remarkable perspective and one that you've sort of turned, like you said, some news that you may not have been so happy to receive, but you've turned it into a positive effect, which is really admirable. Thank you for that. Dr. Alcalay, what would you advise patients that test positive for a genetic mutation?

Roy Alcalay: Advice would be a strong word. I think [inaudible 00:14:09] would go over the options and discuss the pros and cons. I think that even before, when someone wants to get tested for the mutations and they have Parkinson's, I tell them, before you get tested and get the results back, think what will you do with a positive result? Will you share with your family or not? And if you're ambivalent about sharing, maybe you don't want to get tested. So I think a lot of discussion before, because knowledge cannot be undone. On the other hand, I think that the... So it's like a-

Dr. Soania Mathur: Right.

Roy Alcalay: It's an irreversible decision to tell. On the other hand, I think that the conservative approach that was prevalent in the medical field of, "Okay, there is nothing to do with it, so let's not get tested" is archaic. People get tested without-

Roy Alcalay: How could... archaic... people get tested without us. We know that 10,000 people with Parkinson's participated in 23andMe, or at least 10,000, because that's the number of samples they contributed to a genetic study. So I think that it's better to get the results back in a protected environment of genetic counseling or a physician, than to get it by celebrating the holidays with a gift of direct-to-consumer, and get this result in front of you, that then you're now what question. And they think... John said it very accurately, this is my experience with families, is that it's very common that even within families, some decide they want to know and some decide they don't. And I think anyone that wants to know should have access to testing, but I don't have an opinion.

Dr. Soania Mathur: Right. Jenny, do you find that with the families or the people that you counsel as well, and what do you advise them in terms of disclosure to their family members and recommendations regarding screening?

Jenny Verbrugge: Yeah, absolutely. So this is a really common topic that comes up when we talk to people with genetic test results... how do I think about these results and how do they impact my family members? Should I share my test results with my family members? How should I share them? When? Who should I share them with? And we definitely do talk through this information or kind of help support people through this process... so kind of thinking about the considerations in whether they want to share their test results with their family members and then kind of how to do that in the most helpful way. And it is... definitely we advise and recognize that family members can have different reactions. Some will want to know everything possible. Others maybe are a bit more hesitant to learn about their genetic risks. So they're just like... people have different thoughts on whether genetic testing is going to be a good thing for them or not. I think family members can react in the same way.

Dr. Soania Mathur: Yeah. I agree. That's been my personal experience as well in terms of my own situation. It really depends on the family member and what their appetite for that sort of thing would be in terms of what they would do emotionally with that kind of information. So I agree. Maybe we can continue on, Jenny, to the next slide. I've often used the description that genetics loads the gun, and environment pulls the trigger, when it comes to certain diseases, like Parkinson's disease, but I think you've taken it one step further in your explanation using the Parkinson's jar model. So could you please maybe go through that with us?

Jenny Verbrugge: Yeah, absolutely. So thinking about the genetics of Parkinson's can be complicated. So sometimes during genetic counseling, we might use this visual aid to kind of think about all the complex causes of Parkinson's and how this all works, because it can get complicated. So we think about it that we all have a Parkinson's jar, right? And we know that in most cases, Parkinson's results from this complex interplay of genetic factors, environmental factors, aging... kind of all these factors together triggering the process of Parkinson's. But we start with a picture on the left of the slide... we have our Parkinson's jar in the middle... on the left side, the blue triangles would represent these factors that are not genetic... so environmental risk factors, aging, other factors. On the right side are kind of these yellow marbles or balls that represent our genetic risk factors.

Jenny Verbrugge: We likely... many of us carry genetic risk factors for Parkinson's. Some are more common and those tend to factor in smaller ways to our disease risk. And then... as like the larger marble represents maybe a genetic variant or a genetic factor that plays maybe a larger role in susceptibility or risk for Parkinson's. So then walking through the picture in the middle, we have our genetic risk factors in our jar. And then as time goes on, we gather different factors, environmental factors, in the jar. We age, we get exposed to different environmental factors

like chemicals and whatnot, and the thought is that when the jar comes to the top or fills to the top, basically that's when Parkinson's disease develops.

Jenny Verbrugge: Now, the exciting thing in a place where a lot of research is interested, is in trying to learn or trying to understand certain protective factors. So we're starting to learn there may be some protective factors that perhaps we could put on the lip of the jar and maybe make the jar get bigger. And these might be things like changes in lifestyle, like exercise and other things. But certainly this is an area of research where we really want to gather a better understanding of both our disease risk and the risk factors related to that, including genetic factors, but also the factors that may offer some degree of protection for Parkinson's.

Dr. Soania Mathur: That's actually really interesting and something I'd like to go into a little bit more detail about, but maybe just let's back up to the environmental risk factors. Either Jenny or Roy, if you could answer perhaps, what are some known environmental exposures that may increase our risk for developing Parkinson's disease, if we have that sometimes genetic predisposition to do so?

Jenny Verbrugge: Yeah. So we talk about... during our counseling sessions, we often will get questions about what are the environmental factors. And I mentioned pesticides. That's an area where there's lots of research that's linked, and associated pesticide exposure, especially those pesticides used in farming, but there's research evidence that's linked other types of chemicals, things like head injury, certain infectious factors, and we likely don't have all the answers for environmental factors that may be linked to Parkinson's. So again, that's another important area of research where I think we need... we certainly have questions that remain.

Dr. Soania Mathur: Yeah, I agree. I think I've heard of Paraquat, used in farming and pesticides, which is actually banned in a lot of countries, but not in where I am in Canada. And I don't believe in the US... as well as TCE, which is used as a solvent, I guess, for a lot of manufacturing companies and dry cleaning and that sort of thing.

MJFF: A landmark study that could change the way Parkinson's disease is diagnosed, managed and treated is recruiting participants, now. PPMI or the Parkinson’s Progression Markers Initiative needs people with, and without, Parkinson's, especially people age 16 up who have close relatives living with the disease. Take a short survey today at michaeljfox.org/PPMI to see if you're eligible. That's michaelfox.org/ppmi.

Dr. Soania Mathur: It's really interesting when you said that protective factors can make the jar taller and Dr. Ackley, could you maybe describe some of those protective factors that we have maybe some evidence that they may help minimize or reduce our risk of developing Parkinson's disease?

Roy Alcalay: Yes. So I wish I could name more than I can actually name, because it's... I wouldn't say that it's a million dollar question, because I wish it was only a million dollar question, because the question is really, when we said that in GBA LRRK2, the majority of carriers will not develop Parkinson's... people would like to know what can they do to not develop Parkinson's. So we have some evidence that exercise is protective, but again, it's protective... we know of a lot of athletes who have Parkinson's, so it's not a foolproof. Probably avoiding pesticides is a good idea. And there's probably convincing data that smoking is protective. Having said that, I'm not going to recommend anyone to smoke to protect themselves from Parkinson's so. But we do try to go into the biology. I think a lot of the research we do, and a lot is supported by The Michael J. Fox, is to compare people with mutation within and without Parkinson's, to try to understand what is different in the biology between those who developed Parkinson's and those who didn't.

Roy Alcalay: And today we don't have many more answers above what I already said, but I hope that I will be able to be more specific in the future. I'll use that opportunity to answer a question in the chat... in the chat that someone mentioned a family member, who's an identical twin, that one has Parkinson's and one not. And even though we are all... my research is genetics and it makes no sense to me that someone could be identical and not have the same biological conditions. The study from Sweden where the twin registries is very strong, showed that identical twins with Parkinson's, the risk of their identical twin of Parkinson's, is roughly 12 to 15%. These are the numbers they mentioned. So even if they're wrong, 50% of the time, and the risk is 25%, it's still so much lower than what I would've guessed coming into reading that research. So a lot of it is in the genes, but not all of it is in the genes... that's for sure.

Dr. Soania Mathur: It's very unusual. You're right. Because yes, genetics would dictate a higher number really. And then they're often raised the same way, so exposure to environmental toxins, and that sort of thing, you would think would be similar as well. So it's a very interesting question to ask John... have you made any changes in your lifestyle, or even your outlook, with the knowledge that you're a carrier for LRRK2?

John Gilman: Yeah. It's just sort of, I think, since getting involved with foundation and understanding my genetic mutation, I've just been paying attention to the research and sort of keeping a tab on those high level recommendations. So I was exercising sort of before I found out, but just continuing with that. So I wouldn't say I really have changed much, but it's just sort of... it's another aspect that I'm keeping my eye on is sort of, as research comes out, is there anything I should be changing or is there anything I should be doing? And again, I think that's another unexpected positive of getting the testing done is that being able to be so proactive and it's not like I'm waiting until later in life to start taking some of these protective measures, if information comes out, I'm able to react to it sooner. So I'm sort of eagerly waiting and sort of paying attention to all the news as it comes in. And yeah, taking that approach.

Dr. Soania Mathur: That awareness I think is really important and exercise always keeps coming up, but I think that's healthy for all of us to be doing anyway, as difficult as it might be, sometimes. Jenny, as a genetics counselor, we're talking about all this testing, you help make sort of sense of the results that people receive after they've done a genetics test. Could you start by telling us the process of taking that test and what kind of information someone can hope to gain from those results? John mentioned the increased risk of Parkinson's he found out from these test results, but what generally should people expect?

Jenny Verbrugge: Yeah, so to talk first a little bit about a genetic counselor and what our role is, because we might actually meet with somebody who's interested in genetic testing for Parkinson's. We might meet with them before they decide to have a genetic test or after they've had a genetic test. So genetic counselors basically have specialized graduate training in genetics and counseling. So we're sort of the experts in helping interpret and explain complex genetic information while also providing support to people. And our kind of aim and goal is to really empower people and their families with information and guidance, helping people understand the genetic contribution to disease, helping them understand their family history, helping them evaluate genetic testing options, helping them understand genetic test results and how they may be used.

Jenny Verbrugge: And genetic counselors may serve in different roles. So we're often a part of a healthcare team where we work in collaboration with physicians and physician specialists like neurologists, but genetic counselors also... there's a growing role of us being important members of a research team as well. So really we're there to help support people through that testing process to kind of guide them, help them understand the ins and outs, what genetic testing can tell them, what genetic testing may not be able to tell them... the limitations. Of course, there's many different genetic tests out there... so helping people understand the complexities and the nuances of genetic testing that can be there.

Dr. Soania Mathur: And is there free genetic testing available in terms of any of the options that you have listed?

Jenny Verbrugge: Yeah. So to walk through the slide a little bit, a person can access genetic testing for Parkinson's through different means. I would say probably the most common way, or at least currently right now, where people may access genetic testing for Parkinson's, is really through participating in research studies. So for example, through the Parkinson’s Progression Markers Initiativeor PPMI studies. So again, we help people through that process of learning about that genetic testing that may be available through.

Jenny Verbrugge: Learning about that genetic testing that may be available through the PPMI study and kind of understand their test results when they have them. A clinical genetic testing route is sort of the traditional way that people may get genetic tests. And right now we're not doing a whole lot of that with Parkinson's, mainly because there's some cost barriers, insurance barriers. Genetic test results don't yet change care or treatment for Parkinson's in a large way. So it's not likely that

most people's insurance, unfortunately, is going to cover the cost of it. The third option is a newer option, what we call consumer initiated genetic testing. So this is a way where, really it's more patient driven, but it's still a test that's ordered through a doctor. But a doctor is not necessarily that patient's doctor. It may be a doctor that's contracted through that genetic testing laboratory.

Jenny Verbrugge: And often there's a genetic counselor involved where initial information is gathered from the patient about medical history and family history to ensure that the more optimal genetic testing is ordered for that particular individual. And then the last option, a direct to consumer genetic test of course is quite popular. And that's a way people can get genetic testing without a healthcare provider or a doctor ordering the test. And people do that genetic testing for a number of different reasons, say to learn about their ancestry, to learn about genetic traits, or to learn about their health risks. And certainly when people get it they feel empowered and have some personal... Find the information very personally useful. But that testing also creates some challenges as well. So challenges in say maybe the scope of genetic testing may not be the best fit for that individual. Maybe it's too broad or too narrow a scope of a test. And then sometimes depending on how it's done, where it's done, direct to consumer genetic testing can sometimes create confusing results and sometimes [inaudible 00:32:34] and even unexpected information can come up.

Jenny Verbrugge: So it has its challenges, it has opened up access. And I think people really are hungry for genetic testing information. And really I would encourage anyone that's thinking about doing genetic testing, whether it's through a research study or through their doctor, really take some time to explore the ins and outs of that genetic test, what it can tell you, what it can't tell you. And then meet with someone who has expertise in Parkinson's, whether it's a doctor like Dr Alcalay or a genetic counselor, we're here to answer people's questions and kind of help them navigate through this complicated process and this list of different testing options. When we think about testing through a research study, the cost of doing genetic testing would typically be covered through a research study. The other options will have some degree of cost associated with them just depending on the test and the option.

Dr. Soania Mathur: Sure. Dr. Alcalay, when should someone with Parkinson's disease consider getting testing done? Are there certain guidelines that you look at from a clinical perspective?

Roy Alcalay: Sure. So, first of all I would say that when we talk about genetic testing, I would state the obvious that it would distinguish between people with Parkinson's where the diagnosis is already there, and then the question is to identify a gene that may have caused it to people who are without Parkinson's and they're looking to see whether they have risks or they just get tested through those mechanisms. So I think the most traditional testing happened when people... In the clinical testing happens when people have Parkinson's at a young age still at this level of family planning and they want to know if they carry something that has a risk for their offspring. And sometimes the genetic testing can be

reassuring. If they carry a mutation in a recessive gene, the risk for their kids is significantly lower.

Roy Alcalay: So that's usually when I think of when did they use clinical genetic testing, it was when people were still in the family planning stage and they wanted a counselor to be involved because the questions were beyond Parkinson's. When we talk about research studies or clinical tests for people with Parkinson's, I would say that there's three instances where I would recommend testing. And that is when I call it the kind of actionable. The first is if someone wants to participate in clinical trials, there are clinical trials that are open only for LRRK2 carriers or only for GBA carriers. If you're someone who wants to do clinical trials, you need to get tested if you want to do those studies. So that would be one instance where I think genetic testing can be helpful. Again, I would rather recommend getting the test outside of that trial to get the results in a neutral environment, but that would be one indication.

Roy Alcalay: Another indication would be when someone wants to know. People have Parkinson's, they want to know why, and if they want to know why and I have access to research testing, I will refer them to the test. So I wouldn't encourage people to get tested if they're not interested in it, but if they are, I will refer to testing. And the third instance is or the fourth instance is when people really want to know what's their disease progression like. What does the future entail? And they want to know anything they can. And if they really want to know anything they can, the genetics can help us because we know that the rate of progression of the motor symptoms, the cognitive symptoms can be different in carriers of PARK and LRRK2, in alpha synuclein or PRKN. So again, when I refer to genetic testing or offer genetic testing is really when someone wants it. The reasons why I think one would want it is either family planning, clinical trial participation, if they just want to know why they had it, or if they want me to provide them more information about the prognosis.

Dr. Soania Mathur: Right. So again, each of those are very personal decisions and everyone will have a different appetite for that knowledge as well. Yeah.

Roy Alcalay: Right. Which we did find out from studies is, and I think Jenny mentioned it, is that people have much more appetite than the physicians have appetite to serve. So I really think what we learned from 23andMe is that the physicians are too conservative and people want to know. And my perspective is that it's much better to do it in a protected environment of research, of a genetic counselor, of a physician than getting results online. But they've also learned that the conservative approach that we just didn't share results back from research studies is just not what people want. People want to know most of the time.

Dr. Soania Mathur: Yeah. Absolutely. And I think the key takeaway from this discussion that we've had is doing it in that protected environment or having the benefit of a genetic counselor taking you through it I think is really important, because the results can be confusing and misinterpreted very easily. So I think that's really important to consider your role in genetics research. And maybe, John, you can

take us through a little bit more of the motivation that you had about joining PPMI for instance. Why did you decide to join exactly?

John Gilman: Yeah. It was really in reaction to getting that news. And at that time I guess feeling a little bit of helplessness of just sort of, this is something that's not going to impact me for a number of years, but what can I do now? And when we talked about some of those lifestyle actions, there were limited, a couple, but not many. And then I learned about the PPMI study in genetic research and it just felt like such an actual way for me to sort of counter offset that helplessness and really be able to do something in the vein of finding a cure for everybody with Parkinson's, but then also selfishly for myself of if I were to over time develop symptoms.

John Gilman: So it really felt like such a natural thing to do after getting a test result like that. And yeah, as I mentioned before, it's just been a super rewarding experience to be part of that broader research study and playing a small part towards helping to find a cure and finding the underlying biomarkers for Parkinson's. So it was sort of a very clear and what has become very rewarding step for me to take after getting this result.

Dr. Soania Mathur: Right. I mean, I think-

Roy Alcalay: John, I wanted to ask you.

Dr. Soania Mathur: Go ahead.

Roy Alcalay: I wanted to ask you, because you mentioned that you did share your genetics with people and family members. Are you also encouraging people to participate in research? Or do you think it's, again, just like the genetic testing, something very personal that would fit some and not others?

John Gilman: No, I did suggest that folks would participate in research and for my siblings and parents. I think at the time they were looking for more young folks, so I sort of was in a sample set that they were looking for in the PPMI study. That wasn't the case for my parents. But I think, again, for the time commitment, it seems like you're participating in research, it could be very time committing. It's been very minimal and sort of just six months, or I forget the exact time window, but it hasn't been very time consuming. And it's just, again, been some of the most rewarding stuff that I've been able to do in the realm of helping to find these biomarkers. So yeah, I do recommend it because I think my experience has been very, very positive with it. I think that getting tested versus not testing I found is more of an individualistic choice, but once people are sort of willing to make that choice to get tested, getting involved with research is very natural next step.

Dr. Soania Mathur: I think that type of proactivity is actually very empowering, which is what you're expressing. Dr. Alcalay, can you maybe, when we're talking about participating

in genetic studies, you don't always have to have Parkinson's disease obviously to participate. Can you perhaps explain why genetics research is important even though the majority of cases of Parkinson's disease are what we call sporadic, and those individuals don't seem to have a known genetic mutation or family history of Parkinson's disease. Why are genetic studies actually important for the whole community?

Roy Alcalay: Sure. So the first of all, when we started genotyping, offering people genetic testing at no cost, including genetic counseling, we anticipated the group of the negatives to be 95. And the numbers that we really get is 85. So the people who carry mutations or variants that increase the risk for Parkinson's, it's roughly, it's at least 10%. It's roughly between 10% and 15%. And these are studies from both United States and international studies. So I think what the beauty about the genetic research nowadays and why I think we're in exciting times is that I've seen the change happen in front of my eyes, that the research was previously more observational looking at, "Oh, this gene causes Parkinson's, let's see how people with this gene Parkinson's progresses." To, "let's act on this gene, let's modify it. Let's slow it down if it works too much. or let's enhance it if it works too little. And see if we can A, slow down Parkinson's or B, prevent Parkinson's in the future in people who are carriers."

Roy Alcalay: But these genes cause Parkinson's, and a lot of focus is put in whether problems in these genes are also present in people without mutations. And they think from the genes that they mentioned, the one that is the most obvious is the alpha synuclein. So quickly after alpha synuclein was discovered, researchers found that when you look at the brains of people with Parkinson's under the microscope, the protein that you find in many of them is the alpha synuclein protein. So there are a lot, a lot of clinical trial nowadays targeting the alpha synuclein pathway, trying to reduce the production of it, trying to reduce the aggregation of it, activating the immune system against alpha synuclein.

Roy Alcalay: In alpha synuclein, the vast majority of these trials, if not all of them, are offered to people with Parkinson's independent on their genotype. So even if we develop an intervention for GBA or LRRK2, the target population that would probably benefit from it the most is the carriers. But we don't know that it can help others as well. I want to give an example from another field, but there was a very rare genetic disorder that caused a high cholesterol because of a problem in the receptor. So researchers developed the drug statins, and it was tried right in these families. And look at it today and nowadays the fraction of people with genetic mutations who use statins is minimal, right? And it's commonly prevalent, very widely used drugs, a group of drugs.

Dr. Soania Mathur: Yeah, that's a great actually example. It's just going to increase our general understanding of this disease, which may then lead to therapies, which is great. And we've mentioned PPMI several times, but PPMI is the foundation's landmark-

Dr. Soania Mathur: Yeah, several times, but PPMI is the foundation's landmark study. The Parkinson's Progression Markers Initiative, which is recruiting people with genetic changes. PPMI aims to change everything about how Parkinson's is diagnosed, treated, and potentially prevented. Thousands of volunteers with and without Parkinson's are needed. And the online part of PPMI is now open to anyone over the age of 18 and living in the United States, but there are medical centers across the globe that are recruiting participants. You can get started in the study today by clicking the "get started" button in the take action box at the, I believe it's the bottom right of your screen. And you can also learn more about PPMI by clicking the link in the resource list.

Dr. Soania Mathur: And we talked a little bit about genetics research, and maybe we can further that discussion. Dr. Alcalay, there are a number of genetic studies that are ongoing, and hopefully, as I said, increase our understanding of the enigma that this disease is. Are you hopeful that it will lead ultimately to treatments or therapies that will or change the impact that this disease has? What are some of the promising studies coming down the pipeline?

Roy Alcalay: Right. So first of all, I'm very hopeful because, otherwise, I'm in the wrong .. This is what I do for a living. If I thought that it's not the right path, I would've chosen another one. I think, really, this is it. We really don't want to offer the same of the dopamine replacement therapy in 2035. We want to be able to offer people precision medicine drugs that are tailored to their genetics. So let me just take one step back and say that the three genes on which there's most therapies are alpha-synuclein, GBA and LRRK2.

Roy Alcalay: Alpha-synuclein, is the, as I said, is the gene that mutations in which cause Parkinson's in a dominant way. So it's enough to have one bad copy or duplication of the gene, but we also know that alpha-synuclein is important in the brains of people with Parkinson's independent of mutations, and that's why there is so many clinical trials for alpha-synuclein. And those that, if they succeed, will be good for people with alpha-synuclein mutations, probably with GBA mutations, and probably with people without any mutations.

Roy Alcalay: The gene GBA that, just take a step back, if you have two mutations in the gene, GBA1, develops the disease Gaucher. So basically, mutations in the GBA gene are the link between Gaucher disease; some pronounce it "Gaucher's," and Parkinson's. Where, to get the disease Gaucher, which is a rare metabolic condition, one needs two mutations in the gene. But it's enough to have one mutation. So to be a carrier of the gene could be at an increased risk for Parkinson's.

Roy Alcalay: The advantage of the link is that Gaucher has been studied for many, many, many years. So we are now trying to take knowledge that was accumulated in the Gaucher literature, and try to apply it to Parkinson's. Specifically, Gaucher has treatments. The major problem with those treatments is that they don't get into the brain. So different pharmaceuticals are trying different compounds that will get into the brain to see whether medications or interventions that will slow

down Gaucher disease, in the periphery, in the liver and the spleen. If we bring them into the brain, will they slow down or prevent Parkinson's? So these are very exciting.

Roy Alcalay: LRRK, the K in the word LRRK is kinase, which means that it's an enzyme that adds phosphorus groups into other enzymes. Luckily for us, kinase inhibitors, drugs that block kinases are very common in the oncology world. So the pharmaceuticals are very experienced in developing inhibitors for kinases, including LRRK2.

Roy Alcalay: So, I am hopeful that be between all of these clinical trials, one of them would work. I often say that clinical trials are like frogs, you need to kiss a few until you get a prince. But when we get a prince, everything will change, right? So we need to keep trying and keep trying until we find it. And we will find it, but I think the only chance of the researchers and the pharmaceuticals and the physicians to find those interventions is if more and more people get genotype, know that they are eligible for trials, and choose to participate. I think the major holdback in a lot of these studies is that people don't know their genotype, and therefore, they don't know that they're eligible to participate, and it's so hard to recruit.

Dr. Soania Mathur: There was one question that someone submitted. They said they thought that drug trials were in the process, for those of us with LRRK2 mutations, to suppress the mutation, but they seem to have stopped. Are there new trials starting up? Do you know anything about that?

Roy Alcalay: So the information that I'm going to cite is from clinicaltrials.gov. It's a great website. One word, clinicaltrials.gov. And the two pharmaceuticals that are most advanced in recruitment of patients are Denali Therapeutics and Biogen. Biogen studies active in multiple sites, including my site in Tel Aviv. The Denali drug is an oral drug that you swallow it, and it's supposed to inhibit the enzyme. The Biogen intervention is an intervention that is injected to the spinal fluids. It's called antisense oligonucleotides. It's a genetic intervention that reduces the activity of the enzyme. The production of the gene, and then the enzyme, the reason why people are very excited about antisense oligonucleotides is that in recent years, they've been successful in other neurological disorders, specifically near the baby's form of Lou Gehrig's disease or spinal muscular atrophy. The ASOs change the course of that disease, and we are all very envious and want to replicate it in other diseases, including Parkinson's.

Dr. Soania Mathur: Mm-hmm. That's a mouthful for most people, but I think that the key is, again-

Roy Alcalay: I think the idea of the mouthful is to know that there's a lot going on, and I think people are interested, really interested, and they get genotype, then they can take a look at the trials, look for their own gene, the LRRK2. Specific question that you received, yes, there are two companies that are in the process of recruitment, yes.

Dr. Soania Mathur: Perfect. Thank you so much. There's also a question that is arisen that I think is really, really important in all aspects of research and clinical care, and that's the importance of increasing diversity in genetic studies. Can you maybe comment on why that's important?

Roy Alcalay: Sure, and then I'll start, and Jenny can-

Dr. Soania Mathur: Yeah.

Roy Alcalay: So I think that a lot of what we know about the genetics of Parkinson's comes from the Caucasian population. And there are now significant efforts, some of them by The Michael J. Fox Foundation, of course, to try to diversify the knowledge we have, and to also offer genetic counseling and testing to people of diverse backgrounds. I think, on one hand, because I think that genetic knowledge is power, you want everyone to have power and not just one genetic population. And the other is that I think that if you compare genetic groups, diverse groups, and you see the same finding in every group, it makes the finding much, much stronger. For example, the LRRK2 mutation was discovered in Spain and in Japan first, then later was discovered to be more prevalent in people of Ashkenazi Jewish ancestry or at North African Berbers. So really, diversifying the population that participates is good for everyone.

Dr. Soania Mathur: Right. And another question, I guess. We're doing some of the questions that are coming through the chat, but someone wants to know are specific mutations associated with specific symptoms?

Roy Alcalay: There are some basic things. Specific mutations, in part, come with a specific symptom of early onset, so that's a very clear phenotype that is linked to it. It's, again, as a group, not on an individual level, people with LRRK2 tend to have less cognitive changes. So there are some pieces of information like this, I don't want to start going down a list, but these are examples of links between the genetics and the clinical presentation.

Dr. Soania Mathur: Great. As we sort of wrap up our time together, I'd like to ask each of you one last question. I mean, genetics testing, again, we've discussed it several times, is a very personal decision. If you had to name one thing that someone should really consider, it's very important to consider when making that informed decision to get genetics testing, what would each of you say that most important question to ask ourselves is? I'll start with Jenny.

Jenny Verbrugge: Yeah. So, I would suggest for people thinking about genetic testing is really to take time to learn about the genetic testing, learn about what it can and can't tell you know, access genetic counselors or doctors, get your questions answered. And then, the other thing I would say is genetic testing is different than most other laboratory tests that a doctor does because when you do a genetic test, it has an impact or can have an impact on your family members. So I would say gauge your family members in your decision and in your discussion

about genetic testing. So I think those would be some of the thing I would suggest people think about.

Dr. Soania Mathur: Right. John?

John Gilman: Yeah. I mean, I guess I wish I had this foresight before I went in with genetic testing. But really, thinking about so much of genetic testing can be about the risk factors and the negatives, but on the opposite side, but if you are thinking about getting genetic testing, the positive side that can come from it, and sort of the actions that you can take. Obviously, we're talking about Parkinson's today, but genetic testing is so broad that there could be a lot of things around your health outside of Parkinson's that genetic testing could potentially help with. And I think taking that broader, long-term view of testing and why you might find out some information in the short term that you need to process. Think about the long-term benefits that you would get from testing. And, obviously, weigh that with your own personal decisions on the downsides.

Dr. Soania Mathur: Right. Dr. Alcalay?

Roy Alcalay: So if I take one sentence from each one from John and Jenny, when John said for the pro, the major pro for genetic testing is the actions you may take. If you're someone that may take action on the results, that's a good reason to do it. If that would make you participate in studies, live healthier, then definitely do it. The one caution is that knowledge cannot be undone, so think carefully and educate yourself because once you got the results back, there's no way to take it back.

Dr. Soania Mathur: I like that; knowledge can't be undone. That's a very good way of putting it. I'd like to thank everyone very kindly for joining us today. I hope your felt your time was well spent. I certainly did, and I learned a lot, and that you found the discussion informative and valuable. Thank you, Dr. Alcalay and Jenny for sharing your expertise, and John for sharing your invaluable experience. I'm very inspired by everything you had to say. I'd like to thank you for joining us.

Dr. Soania Mathur: I know there were a lot of questions that we didn't get to, and hopefully, some of what we spoke about will answer those questions. A lot of questions perhaps may be best discussed with a genetic counselor, as Jenny had described to us. But remember, those of us with Parkinson's have no real choice in our diagnosis, but how we face the challenges that this disease brings into our lives is really ours to determine, so empowering yourself by educating yourself as much as you can about this disease and attending these webinars is really going to be paramount in your outlook in terms of dealing with this disease. So, until next time, thank you very much.

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