

Section 1 of 4 [00:00:00 - 00:15:04]

- Speaker 1: 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](http://michaeljfox.org).
- Speaker 2: Welcome to a recap of our latest Third Thursday Webinar. Hear directly from expert panelists as they discuss Parkinson's research and answer your questions about living with the disease. Join us live next time by registering for an upcoming webinar at [michaeljfox.org](http://michaeljfox.org).
- Maggie Kuhl: Hello, and welcome to our Third Thursdays Webinar. I'm your moderator today, Maggie Kuhl. I am Vice President of Research Engagement at the Michael J. Fox Foundation. Thank you for tuning in with us. Today, we'll be talking about genetics and an exciting new approach to therapies, gene therapy, which you might have heard a little bit about. And after our next hour, you'll know hopefully a lot more.
- With me today are our four esteemed panelists. Sorry, I'm looking at three boxes. First, we have Dr. Christine Klein, who is Professor of Neurogenetics and Neurology, and Director of the Institute of Neurogenetics at the University of Lubeck, and University Hospital Schleswig-Holstein in Germany. And when you think Parkinson's genetics, you think Dr. Klein, so we are thrilled that she is here today for this topic. Thanks for joining us.
- Christine Klein: I'm thrilled to be here. Good afternoon, everyone.
- Maggie Kuhl: Great. Thank you, Dr. Klein. Okay. And with us, also from the Michael J. Fox Foundation, is Dr. Bradford Casey. He is Senior Associate Director of Research Programs at our foundation, and an expert in genomics and how our genes are translated into cellular function. So Bradford, thanks for being with us as well.
- Bradford Casey: Thanks for having me.
- Maggie Kuhl: And Rich and Pola Sussman. They live in New Jersey. They're joining us today. And Pola was diagnosed with Parkinson's disease in 2017. She carries a GBA mutation, which we'll talk a little bit about today. And both Rich and Pola are extreme advocates of research participation and learning everything you can about the disease, and taking an active role in pursuing treatments not only for Pola herself, but the Parkinson's community overall. So thank you, Rich and Pola, for being with us as well.
- Pola Sussman: It's our pleasure. And anything we can do to help, we're there.
- Maggie Kuhl: All right. So with that ... Gene therapies. Something that you might have heard of in the news, gene therapies are growing in application across diseases. Some notable approvals from the Food and Drug Administration include gene therapies for spinal muscular atrophy. Just earlier this month, there was another approval for severe hemophilia. And now, Parkinson's disease is in this vein of looking at gene therapies

as a way to target many dysfunctions that we see with Parkinson's.

To understand how gene therapies work, we have to have a bit of a foundation on what is a gene, gene mutations, and how genes play roles in what happens in our cells. So we're going to talk about that a little bit. And then we'll talk more about the different kinds of therapies that are currently in testing in this therapeutic approach, and what you should consider if you were to potentially be eligible to join those studies.

As always, we are not endorsing one therapeutic approach over another. We are hoping to inform you of this new frontier in therapies, and hope that you share our optimism that more approaches and more targets means more shots on goal and more likelihood of success to manage Parkinson's, and to slow and stop its progression. So with that, I'm going to move us in, and hand it over to Dr. Klein to start our foundation of what are genes and how do they work?

Christine Klein: Yes. So first of all, thank you very much. So as you heard, I'm here in Germany, so it's already 6:00 here in the afternoon. But I got a lot of my training in the US, in genetics, at Boston University. And I also trained in Toronto, so I'm very closely connected to North America. And thank you very much for having me.

So what are genes? I think we all have a good understanding what genes are, but let's just briefly review this, and especially with a view towards gene therapy. So a gene is basically the core unit of inheritance. So basically we carry, in each of our cells of our body, all of our genetic information, the genetic code. So we have that in every single little skin cell. Even in our hair, everywhere, and of course in the brain as well.

And the important thing, of course, is that these genes are passed on from parents to their offspring. And we typically have two parents, so we get half of our genes from the mother and half of the genes from the father. And they then contain all this information that determine our physical and also our biological traits. And we all know that, right? When we have children or when we look at our parents, we're sometimes thinking, "Oh, I'm so similar here. Sometimes, I'm very different." And so that's all about the genes that are either transmitted the way they are, or sometimes they change.

And what the genes do ... There's a little detour. So it's not directly from gene to protein, but there is one step in between. But eventually, the genes code. It's like a code. They code for specific proteins, and they serve very different purposes within the body. So they can be, for example, part of our bones or part of our brain, but they can also be very active little enzymes, for example, that facilitate certain processes in the body. And we have a lot of those. An estimated 20,000 to 25,000 genes we each carry, always in duplicate. One from the mother and one from the father.

Maggie Kuhl: Great. Thank you. So Bradford, maybe you could talk to us a little bit more about

proteins and the role that those play. Dr. Klein, as you said, they do a lot of things. They're part of a lot of our ... Not only makeup, but also function. So Bradford, that might be a good next step in our foundation.

Bradford Casey: Yeah, absolutely. So it's important to think about our body as, really, a collection of cells. And so those cells contain a lot of different things, but proteins are largely the structure of that. And the genes, as Christine mentioned, are really how we build those different proteins. That's a catalog of every protein, every enzyme, a lot of the structural pieces that we might need to make.

And so there are different classes of proteins, and each of those is very different. And those vary between the cells and tissues of our body. You can imagine, for example, that we have very complex structures. We have rigid bones. We have contractile muscles that let us do things. Then we have, of course, our nervous system. And we need a lot of different proteins and different amounts of those proteins to make sure that we can achieve that diversity throughout our bodies. And so making sure that we have a clean map of that, making sure that all those different basic building blocks of the cell, and of our bodies more broadly, is a key piece of understanding the importance of genetics and thinking through how those changes affect us down the road.

Maggie Kuhl: So as we know, though, in Parkinson's, a lot of the machinery goes wrong and sometimes the factories themselves are responsible. So I wanted to bring our conversation to gene mutations, some of the things that we know that are different in the genes of people who have Parkinson's disease. I do want to state, we're not going to get very deep into personal genetics. Of course, the Parkinson's community has many questions about heritability, and the varied genes that we have identified that play a role in Parkinson's.

We have a lot of educational content on our website that talks specifically about different genes. There is a link in the resource list about genetic testing, and how to consider and pursue that. But for this discussion today, we want to base it on those basics, so that we can talk about how gene therapies might be applied to genetic mutations. So Dr. Klein, could you illuminate more on gene mutations?

Christine Klein: Absolutely. It's a pleasure. So a gene mutation, as you can see here, is a change in the gene. And really, mutation is derived from the Latin word, as you may know, *mutari*, which means literally to change. And of course, a change in genes we have to have, because we only, if you will, have these 20, 25,000 genes. And yet, we are so different from one another. And of course, we have so many different tasks for these genes. So it is clear that genes will have some variation and variability. And this variability is our personal fingerprint. So we each have our own genetic makeup, and that is always different. And even in identical twins, you can find some ... Few changes. And some of them actually come on later in life. That's also possible, and so change in a gene.

And that raises the important question. If you go down below, you will read that

researchers have found many gene mutations that raise the risk of Parkinson's disease. That is very true. They have even found mutations that, I think we can say, cause Parkinson's disease. So they really are the cause of Parkinson's disease. So we can relate one specific gene or even one specific mutation to a specific form of Parkinson's disease, even in an individual patient.

However, it's also true, and this is I think why it is so carefully phrased here, that this risk or this cause is not like a dichotomous concept. So it's not a black and white situation, where either you have a cause or you just have an increased risk. Rather, I think it's a continuum. So there are some rare genes that are related to Parkinson's disease where you have one mutation ... Just to give you an example, the first gene that was found for Parkinson's disease is called alpha-synuclein. You may be familiar with this particular gene, which actually, also, is very well-known in conjunction with the Lewy bodies that individuals with Parkinson's disease tend to have in their brain, and they are made up of alpha-synuclein.

So if you have alpha-synuclein ... We talked before that you have one gene from the mother, one gene from the father. It can also happen that you have an extra copy. So if you have one too many, or even two too many, this can result in Parkinson's. Just to give you one relatively simple example of the first gene that was found related to Parkinson's. However, there's also this risk. And that's very conceivable, if you think about all these 25,000 genes, and the rest of our genome. There are, of course, many, many, many variables and variations across different people. And it's very conceivable that it's not always just one that causes the disease, but sometimes many have to come together. Or others, some, can modify what one causal mutation does.

So it's a relatively complex scenario, and this is why I don't like to see it as black and white. And that's the last thing I'll say. Sometimes it's very difficult for us in genetics to really determine whether a change or a mutation that is found is actually causal, so with a very high probability will cause and result in Parkinson's, or is just a risk factor that may or may not cause the disease, or may be something totally benign that may be relatively rare. So maybe we haven't found it before, but when you look closely, you'll find it in other people as well, and maybe it doesn't even matter.

So this determination and interpretation is extremely important but also challenging. And so these changes can, of course, impact the protein. Remember, the protein is the final step. Of course, if you have a mutation, this may result in a change in the protein. And we heard this already from Maggie, so when you want to learn more on genetic testing opportunities and options, you can please use the link that's indicated here.

Maggie Kuhl:

So it sounds like we have a strong base of knowledge around some of the genetic mutations that are linked to Parkinson's disease. None of them are an absolute cause of Parkinson's. There is a continuum. And we do know, though, that when something does go awry and it causes Parkinson's, there's an impact on the

proteins downstream of those. And what I take from these conversations is that it's so helpful to learn about genetics, because it teaches us so much more about the disease and this cascade of things that can go wrong, sometimes even in people who don't start with that mutation, but just other factors impact the same pathway, and you end up with that same dysfunction.

So we've established genes and proteins and these building blocks of how we function. Sometimes, things go wrong with mutations and lead to disease, but that's a very valuable thing to know because it teaches us about disease and, as we'll discuss more, it may teach us how to intervene and stop it. So I want to turn the discussion over to you, Pola and Rich, and talk about your own Parkinson's journey, and your discovery of your GBA mutation, and just reflect on all that Dr. Klein and Dr. Casey have shared with us thus far.

**Pola Sussman:** Okay. So as somebody already mentioned, I was diagnosed with PD in the fall of '17. In the fall of '18, my husband suggested that I be genetically tested, partly because my dad had PD, and there are other members of our family a little further out than me that had PD also. So I had the genetic testing done, which was the easiest thing in the world to do. You just spit into a test tube. Figure I can do that. I was found to have the GBA mutation. And then my brother decided he would also test. He has the same genetic mutation that I do, the same GBA, but he does not have PD. So as Dr. Klein noted, it's not a guarantee that you have or don't have it.

His two children tested. They have the same genetic mutation, but they do not have PD. And only one of my three children has decided to have the testing, and she does not have the same mutation. I kind of figured that if I did have some genetic link, potentially, to Parkinson's, it might be something easier for me to focus on looking for cures that deal with the GBA end of it. I'm not a scientist, but that was my thought.

**Rich Sussman:** I have taken on the role of trying to learn as much as I can about PD with a GBA mutation, and to share anything positive, optimistic with Pola. And there's quite a lot to be optimistic about. We know that the particular mutation that Pola has is on the mild end of the scale. That's good to know. Not all mutations are the same. We've also learned from resources like this and other Fox resources, and speaking to researchers, that many Parkinson's researchers believe that the effects of Pola's mutation are kind of the root cause of her Parkinson's. And if you could address that, then you have a really good chance of being able to slow down or halt the progression.

**Section 1 of 4** [00:00:00 - 00:15:04]

**Section 2 of 4** [00:15:00 - 00:30:04]

**Rich Sussman:** And you have a really good chance of being able to slow down or halt of progression. And there are many different approaches that are currently in clinical trials or about to enter clinical trials or soon thereafter will enter clinical trials, so we believe we have reasons to be very optimistic.

Maggie Kuhl: We share that optimism with you, Rich, and we just want to emphasize, too, genetic testing is such a personal decision. It varies individual. As you shared, some of your children have chosen to be tested and others have not, so it's something to certainly talk with your physician and your family about, but there are resources to help you have those conversations. Genetic counselors can be a very valuable partner even before the test in helping to understand what you may or may not learn and what that might mean for you.

But I did want to turn to you, Bradford, Dr. Casey, because we often hear people are genetically tested and they receive a negative result from the panel that this test uses, the genes that this test tests for, then they think, "I don't have a genetic link to Parkinson's." And actually we are learning so much about Parkinson's genetics constantly, that there's still a lot to discover. And so if you're watching right now and you're thinking, "Well, I've been tested for GBA and I know I don't carry that," what would you say to those listeners? There's still a lot to learn out there.

Bradford Casey: Yeah, that's a great question, Maggie. I'm so glad you asked. So you're right. It's important to remember that genetic testing takes a lot of different forms, and those tests are constantly evolving as our understanding of the disease evolves. So, for example, within GBA, we know that there's a number of different GBA mutations and variants, changes that may not lead specifically or be tied to disease. And we know that there is a spectrum of risk there.

And so as we learn more and more about the disease, we're also testing for more of those variants and trying to add those to the different testing technologies and get those into the hands of clinicians and patients. And that may tell patients more about their risk. There may be tests that you think were run because you had one genetic test years ago, but in fact, the test has changed over the years to encompass more spots.

And you can think of that more broadly in disease. We're always learning so much. This is a field that has changed so rapidly just in the last few years that the number of tests that are run even by the same clinician using the same essential tests and billing would actually encompass a lot more knowledge about your genetics. And so it's really important to remember that part's changing.

It's also important to think again about that spectrum of risk. I often tell people that if you think about your DNA as the cookbook of all the different proteins that your body needs to make, again those proteins, those are the final dishes. And so there is a wide range of severity. You can imagine if you're doing some baking, for example, doubling the amount of vanilla in a batch of cookies isn't going to be a deal killer.

But if you forget the baking powder or something like that, you could end up with something that doesn't really look like what you're hoping for. And so it's just the same with our genetic code. There is a wide range. We really want to be mindful

about just thinking about that severity, thinking about how it may affect different patients and allow us to learn more, again, about how those changes translate to actual human disease.

So I think that, again, it's just important to remember that there is that diversity, things are always changing, and it's important to understand that not all genetic testing is the same. And that's part of the reason that we encourage people to really dig in to what may be available to you. Research testing is different, for example, than general clinical testing. And we're running a lot of different studies that run a wide range so that we can help improve that understanding and ultimately make sure that we're bringing that knowledge back to the research community so we can develop treatments around it.

Maggie Kuhl: Yes, development of treatments is certainly the goal. So why don't we pivot back to our topic about gene therapies and we hopefully have laid some strong foundation of genes and proteins and gene mutations, and now going back to how we might intervene and use this approach and use this machinery, this framework, to stop, slow, potentially prevent disease. So we have a couple bullets and a basic, "What is gene therapy here?" primer. And Dr. Klein, I might ask you to introduce this topic.

Christine Klein: Yes, very happy to do so. So when we try to understand gene therapy, I think the basic building block is really that gene therapy modifies a person's genes with the aim, obviously, to treat or to cure a disease or to modify its course. So that's the idea to definitely make it better. However, what is very important to note, and we've talked a lot about now mutations, and you may think, "Well, these mutations, they're interesting, but they're very rare." And for example, I had genetic testing done and nobody found any mutation.

As Dr. Casey also just said, it may depend on various things, on the technique or just on the fact that nothing is to be found. And so it's important to note that gene therapy could have and can have two potential targets. So it can be the idea to correct or to replace, for example, a faulty gene that doesn't work properly because it has a mutation, but it can also potentially be for people without PD-linked mutations with the forms that we call idiopathic PD, so where we do not find any mutation.

And why is that? And that was already alluded to previously, and maybe I should also give you one number that was just recently presented at the World Parkinson Congress and there were two very large studies. One is the PD GENERation study that some of you may have participated in. It took place or takes place in the U.S. mainly. The other one being the ROPAD study, also with branches in the U.S. Together, they analyzed more than 25,000 patients with PD. And they found almost the same, although they were very independently done, they found the almost exact same results. And that is between 14 and 15% of all of the patients tested within these studies carry a mutation in a known PD gene, I should say, because as Dr. Casey said, there may be others as well that we still haven't found.



That's also possible. And so this is 15%, so you could either say, "15%, that's not a lot. There's 85% out there that don't have it." But you could also say, "It's 15% and it's definitely worth investigating." Then further because, as we heard, we understand these forms better, and we have also learned from these genetic forms that are, as I mentioned before, they are linked to the forms that do not have the monogenic or the genetic causes because there are very similar mechanisms that underlie the disease.

So this is the hope that the gene therapy may not only work for patients with identified mutations, but that it could also potentially be targeting later, probably as a second step, people that don't have such mutations. And what is also important to note as a final comment, I suppose, is that these gene therapies, they're really novel and this is really just in the research realm at this stage. And so, therefore, they're only available in clinical trials and you cannot just go to your local neurologist and say, "I want the gene therapy done." That's just not yet available, and we still have a lot more to do in this field. It's the most experimental therapy I can, probably, it's fair to say, that we currently are developing for PD.

Maggie Kuhl: Thank you. So maybe we could take all of those segments or one by one and go a little bit deeper in. So, Bradford, why don't I ask you, how does a gene therapy actually work? What exactly are you doing with a gene therapy?

Bradford Casey: Thanks, Maggie. Yeah, let me answer that question, but let me start just a little earlier than that by thinking just a little bit how we get to therapy more broadly because I think that's really informative here. So if we think about conventional pharmaceuticals, whether that's something that comes in a bottle at your doctor's office or in a bottle of pills that you can rattle in your hand, developing those really relied on identifying these specific chemicals or molecules that can really change the conditions inside of our bodies to help improve our health and prevent symptoms and prevent the progression of those symptoms and ultimately reduce harm.

And that's happened throughout medical history. That's happened all the way from happy accidents, understanding the medical effects of certain plants and foods, all the way to really sophisticated, more contemporary approaches where they, for example, grow lots of cells in dishes, for example, and try to treat them with things just to help test on specific effects.

That's been very effective, for example, in the cancer field where you can test certain molecules. And so each of those requires this very specific testing approach. And so, throughout history, we really wanted to find a more targeted way to get at modifying the things that we really think are going wrong in a disease, in this instance Parkinson's. And so that technology has really come just very recently, as Dr. Klein said, in the form of this gene therapy. And it's really an exciting and emerging area. And so that's where we get to how it specifically works to answer your specific question.



So if you think about, again, all those genes, we know a lot about them. We know about how they work and not only in disease, how they may go wrong, but also a lot more about how they may work just to keep us healthy. Again, how to help our cells grow, divide, our bodies stay and maintain everything that they need. And we call those molecular or biochemical pathways. Just how everything works together. You can think of it as if all the proteins are gears, this is how they come together as a clock. And so understanding that mechanism helps us to understand, "Well, if X is broken, then how do we get around that? Is there something that we can do? Can we turn that gear faster? Can we get a bigger gear or a better gear?"

And so gene therapy allows us to do that by introducing those genes, those modified versions of a gear, back into the cells of the body. And so it's a really exciting approach because it lets us really take a very rational, very thoughtful hypothesis-driven way of going back to develop those medications and not have to rely on, "Do we have a chemical that does it? Can we find something? Where do we look for it?"

And instead, you're actually introducing that into the body. So there's a couple different ways we can do it. I'm happy to go into the details. I want to be mindful of time here. But, again, the core technology is really again about introducing that into the body in a way that your body can take that gene, can use it just like the genes that exist inside, even the ones that may be broken, to try to improve the health of that patient.

Maggie Kuhl: So, as you said, we can fix what went wrong, but we can also perhaps work on the full product or do something else that would, even if this isn't working the way it should, we can make up for it with other things or we can try to improve the product. Or to use your analogy, if there's a little bit too much salt, maybe you add in a little bit more sugar or something to even it out.

So Rich and Pola, you, Pola, you considered a gene therapy and then with COVID and some other contra contributors, you are not currently enrolled in the study, but you did speak with your physician about enrolling in a gene therapy trial. And so I would love to hear from you, what was that education curve like for you, and how did your physician explain this approach and its potential in impacting your Parkinson's disease?

Pola Sussman: Okay. Well, I have an excellent movement specialist who's very into research and finding the best things for his patients. He suggested, because I had the genetic testing, that I consider a gene therapy trial. He was actually one of the centers for one of these genetic therapy trials, I should say. As you mentioned, it got shut down for COVID. And then the center that he's in, temporarily I guess, dropped out of the study. I don't know if they're going to come back in or out. I'm not currently enrolled in the study, but I would absolutely consider going back in if that's possible. I figured that instead of waiting for my PD to progress, if I could get some help along the gene therapy lines, why not?

Maggie Kuhl: You said knowing that cause and being able to approach that specifically was really appealing-

Pola Sussman: Yes.

Maggie Kuhl: ...for you, knowing it was a GBA and that this gene therapy would potentially introduce a working GBA team.

Pola Sussman: Exactly.

Maggie Kuhl: So we discussed that some of these, they're only available in clinical trials. And I wanted to point to a slide that all our attendees should be able to access in the resource list, which has a listing of there are currently two active recruiting trials and one that is active, but not recruiting anymore. They are following the participants and analyzing that data. And if you happen to be in those studies, thank you for your contributions to that science.

But you can learn more about where they're recruiting and how to get in touch with those studies more through that link in the resource list. But I wanted to advance us to the next slide, and it actually builds on the second point from the last one, which is that these are not just for people with known PD mutations. And we've talked about this a little bit, but maybe we could talk about if you are not fixing what goes wrong, if you're not in that 15% that, as you said, Dr. Klein, has been identified to a Parkinson's linked mutation, Dr. Casey, maybe you could tell us for that 85%, what exactly would you be doing with the gene therapy? What are some of the targets or the strategies that are in testing?

Bradford Casey: Sure, yeah, those are very important questions. So it's definitely important to think about the overall significance, which as you mentioned, Maggie, is not limited to people who may have one of these very specific mutations. We think that that is an early place where we're going to learn a lot. And those are many of the current gene therapy approaches that have been considered both in Parkinson's and in other disorders are focused on those specific genetic mutations because we know a little bit more about that mechanism that may be broken, and it's a little clearer where we want to target.

But we know a lot of things about Parkinson's, and one of them is that, again, as Dr. Klein mentioned, only about 15, maybe 20% of people have an identifiable risk that's tied to one specific mechanism. And yet, we have a lot of Parkinson's patients out there. And those patients have a lot of the same symptoms, they have a lot of the same progression in their disease, and they have a lot of the same features if you look at it on a chemical or molecular level. So-

Section 2 of 4 [00:15:00 - 00:30:04]

Section 3 of 4 [00:30:00 - 00:45:04]

Bradford Casey: If you look at it on a chemical or molecular level. So we know that there's a lot more in common than just that mutation itself. So we think that, again, these gene

therapies may allow us to intervene in some of those mechanisms. And even though people may not have a specific mutation, it may also support the broader system. And so as was mentioned, some of these therapies are really targeted around those specific mutations and may be improving something very specific. GBA1 again, which I know we've discussed here today, is one of those. We know the function of that protein, which encodes an enzyme. And so by changing how that is working, we think that that may improve it. But it's not just for people that have that specific mutation or a GBA mutation overall. We think that the GBA pathway is important for patients that don't have that mutation, for Parkinson's patients that don't have that mutation.

And so we think that by kind of restoring function in that pathway or improving its ability to work, that we may see other people have major improvements in their symptoms. It may help prevent additional damage, for example. And so it's just really important to remember that we all rely on those systems. Again, as I always point out to people, people will say like, "Well, I have the GBA gene, for example, or the LRRK2 gene," but we all do. We all have that plus the synuclein gene and many others. And so again, there's a lot more that's in common even if you don't have that mutation. And making sure that we're restoring the health of that system more broadly is a broader goal of gene therapy. So there's other approaches in addition to just the more PD gene, if you will, targeted approaches. And those include things like neurotrophic factors.

So these are proteins that our body uses. They're signaling proteins essentially that help our body understand that they need to grow, for example, or stop growing. And so the thought there is that by enhancing the activity of those pathways in our bodies, we may be able to support the survival of neurons that may remain, things like that. And that's not tied to a specific mutation. We think that that's tied more to the hallmark loss of those neurons in Parkinson's patients. And so there's a lot of hope that that can help prevent that damage, perhaps even reverse some of it in some ways. And so it's just really important again to remember that there's different types of gene therapies, but ultimately they're all targeted at trying to restore the health of the system more broadly. And understanding both those targeted ones, those gene specific ones, but then also the system-wide ones is really where we see the merit of gene therapy more as an overall approach.

Maggie Kuhl: Dr. Klein, would those other strategies have application if you knew, knew [inaudible 00:32:39], that your Parkinson's was not from a genetic source? I think we talked to a lot of people who say, "I worked at a metal processing facility," or "I worked in agriculture," or "I am a veteran and I was exposed to Agent Orange," or another environmental factor that similar to genetics, we know there are some very strong links there to Parkinson's cause. And so if you fall into that camp, would some of these other alternative gene therapy approaches work for you?

Christine Klein: Yeah, that's an excellent question. Thank you very much for asking it. I would say yes, and I think I really like the baking analogy. So when it comes to risk and the environment, when we talk about the environment, we're mostly talking about

risk. Maybe I have to take one step back. So when it comes to analyzing our genome, we're very good now so we can analyze our entire genome in less than a day and we'll get the results. So this is really amazing. And this is a development that's relatively recent over the last decade or so. When it comes to the environment, we're not that good. So typically we have certain ideas and we have certain... And this includes pesticides for example. So we know, and there is a lot of data there that pesticide exposure can increase the risk, but we have no evidence, at least in the doses that are typically used in agriculture that this would cause PD.

And again, I think taking again one step back and thinking about this likelihood. So if you think about the risk of developing PD for anybody that's born today. So healthy baby, what's the risk of developing PD in a lifetime? It's way less than 1%. So if we then double the risk, for example, which sounds scary or even triple the risk, which sounds very scary, but then the lifetime risk by, for example, having been exposed to a particular environmental factor, that sounds very scary. But when you really think it through, you'll end up with a risk that's still less than two, 3% lifetime risk. So I think that's a very important consideration that we don't get too scared in that kind of scenario and don't blame too much on these environmental factors. Plus there's another problem that we don't have with the genes. We are born with the genes.

The genes can be modified throughout our lives. That is important. We haven't talked about that. And it's not today's topic, but we call it epigenetics. So there are changes throughout our lifetime. However, it does connect to the environment because we are thinking that at least some of these changes are actually conferred by environmental factors. So there is a link there, but what makes it so difficult? We have no way, unlike in the genome, to study the entire environmental, if I may use that term, we can't do that. And not only that, but we may be interested in the environmental factors that we were exposed to like 30 years ago, 40 years ago, maybe since birth or maybe even already during pregnancy. And we have hardly any way of doing this. So this is just, I think to put this into perspective, we have very, very bad tools at the moment to study the environment compared to genetics. I think that's important to understand and not to jump to conclusions where we don't have a good scientific or technical even basis for. But I didn't answer your [inaudible 00:36:12]-

Maggie Kuhl: You talk about [inaudible 00:36:11]-

Christine Klein: [inaudible 00:36:13].

Maggie Kuhl: We can tell you very-

Christine Klein: Yeah I'm sorry.

Maggie Kuhl: ... passionate about this.

Christine Klein: But that is quick. I said at the beginning, yes, I think it's just like with the genetic risk

factors, you don't have to have a specific mutation. I think Dr. Casey explained this very well. So there are all these supporting factors that could also be enhanced by gene therapy. And one of the approaches actually does exactly this. And so I think this would be as helpful to somebody who has more of an environmental risk as to someone who has more of a genetic risk. In fact, and I don't want to complicate things, but I would not even be surprised, and this is now at least 10 years into the future, but if we might even at some point consider even combinations. So for example, I think it could make a lot of sense if we have somebody with a mutation to try and correct that or do something specific against that mutation with gene therapy.

And on top of that, provide these growth factors, for example, to help those neurons that are still there because by the time somebody develops the first signs of Parkinson's already a lot of cells have passed away. They're already gone. So I think it might be very, very clever and smart to actually potentially even combine these two different strategies. And while I think it's somewhat easier or maybe easier for us to understand how to tackle a monogenic or genetic condition, I think the others, the non-genetic or non monogenic ones, I think can definitely benefit also from gene therapy. I would predict that. We don't have that data yet, but that will be my prediction.

Maggie Kuhl: Yeah. So protecting brain cells, even if you know and fix the cause of Parkinson's could be beneficial. And you used the term growth factor. I don't think we've introduced that into this discussion yet, but that's, as Dr. Casey was saying, to sort of protect the cells and help them survive. And I just have one other question. If my genes are changing over time, why am I more and more like my mother? Can you answer that? No. Okay, we're moving on.

Our last slide before we go to Q&A is that considering a gene therapy trial. So all trials have risks and benefits. And so as I think Dr. Casey, you alluded earlier, this is a really new approach for us in Parkinson's disease, and with that comes a lot of unknowns. So I'm actually going to start with Pola and Rich you, and hear a little bit again when you were considering this therapy, what were some of the discussions that you were having yourselves and with your physician and your family to talk about? Okay, it's a little bit invasive and we can talk about that, but it's also a one-time thing. There's items on both sides of the list. So maybe you could run us through that.

Pola Sussman: Okay. So I'll start, but Rich will pick up because he only feeds me positive news. I want to dig my head in the sand if there's negative stuff. So I'm a big baby, and I wanted to know if I did participate in this genetic therapy trial, how would they do it? What would be the side effects? Do they have any idea what those side effects might be? Is this a one and done, et cetera, et cetera. Rich?

Rich Sussman: Okay. So the big benefit is that there's a logical scientific reason behind why the gene therapy would greatly slow down or halt the progression of Pola's PD. So that's a huge positive. The one and done was concerned to be a huge positive.

Obviously the way that it's implemented does involve a neurosurgeon. So there are risks associated with the procedure. The way that it's done does involve introducing a non replicating virus into the brain. And sometimes people can get an immune response to that, which has to be treated.

Pola Sussman: But they are developing other ways.

Rich Sussman: Oh, absolutely.

Pola Sussman: That's not a done deal.

Rich Sussman: Absolutely. We were looking at doing this right when COVID was hitting and as part of this, you'd have to be taking some immunosuppressants. So that was a risk given COVID, and of course, one and done is the real positive, but this stays with you forever. So we're looking for this over the next 40, 50, 60 years. And obviously there isn't any long-term track record as to what this might look like over that kind of time period. But again, the underlying rationale was there and very attracted to have a one and done kind of approach.

Pola Sussman: And quite frankly, I'd be happy... If I do not have any expectations that it would reverse or cure my Parkinson's at this point. But if it could halt the progression, I'd be okay with that.

Maggie Kuhl: Dr. Casey, anything to add around the sort of current state of where we are with these trials as it pertains to understanding if they're safe and if they work?

Bradford Casey: Sure. Again, this is really an area of very active development, and it's important to understand that it's not just in Parkinson's disease. Gene therapy has been a real priority for the field more broadly to try to understand a lot of different things. But as Rich mentioned, there is something that is specific about Parkinson's, which is that one of the key things about gene therapy is that is often going to be delivered where we think it is needed most in this case, in the brain of patients. And so there is a need to involve a neurosurgeon in that procedure. And while this is done really with very high level safety concerns in mind, there is a risk there. As we have seen this field emerge and progress, we've seen a lot of differences. And the technologies, again, have improved over time in terms of getting things where they need to be, trying to find ways to make sure that they are safe in the first place, that they can be tested ahead of time.

This has been tested in what's called preclinical systems, which includes a lot of different things. But so by the time it gets to a human trial, a lot of effort has really been made to make sure that things are as safe as they can be before we have patients involved in that equation at all. I think one thing that's really important to recognize is that we fundamentally don't know just what can happen for some of these things, but again, a lot of the early strategies in gene therapy are again focused on trying to support the mechanisms that the body is already using. So for example, in the GBA example that we discussed, that's about introducing a healthy

copy of that gene essentially into the body. So it's not as foreign as we might think. You're really borrowing a healthy copy from what we know more broadly than just starting from scratch, for example.

So while it is experimental, there's a lot of thought and consideration that goes into finding the most safe and reliable strategy that we can come up with that that is going to help the most people more broadly. And that's the ultimate goal of everyone that's working on these therapies across the board. The other piece that I want to talk about is in term of those benefits, the goal, of course is to have kind of a one and done solution, but because we don't know the lifetime of how these treatments may work, there may be a need for people to go back. That may provide an opportunity for, again, these types of cocktail approaches where we may have more than one gene therapy approach.

And at the end of the day, we also don't know that this is going to completely remove people's need to have other treatments, including things like Levodopa support, potentially DBS in some cases, all of these different things that we're already using for Parkinson's patients more broadly. So it's important to remember that this, like anything is a complex decision. You really need to talk to your care provider and movement disorder specialist about what's best for you and whether you're a good candidate for it and think about that very deeply.

Maggie Kuhl:

Okay. I just want to underscore that a lot of safety work has been done before it makes it to humans. There are ethical review boards that are looking at the data from the models and the protocol and schedule to try to balance those benefits and reduce the risk as much as possible, and protect the very generous research partners volunteering for these studies. So I have some other questions on this topic that folks from the audience have asked, but that's a good segue then to our Q&A session. So before we do that, I am obligated by my own love of the study and just our foundation priorities to mention our PPMI study, which is the source of a lot of data and findings around not only genetics, but as we were discussing this interplay with-

**Section 3 of 4** [00:30:00 - 00:45:04]

**Section 4 of 4** [00:45:00 - 00:59:24]

Maggie Kuhl:

Not only genetics, but as we were discussing, this interplay with different genes and proteins, and what goes wrong in Parkinson's. And how we might better diagnose and intervene even before the onset of symptoms. So if you have not already engaged anyone age 18 or older can participate in PPMI, then please visit that website and join the study that is already changing everything. Now as I said, we already have some great questions from our audience, and we will spend the next 12 to 13 minutes going through some of what our audience is wondering about. So, Dr. Klein, I'm going to sort of build on the conversation we were just having about this sort of healthy gene, and putting in something that we feel pretty confident about. So one question that we got was, how do you know that there won't be an unknown change? That your body might react differently, or I don't know. Everything from all suddenly become a blonde, to who knows what would



happen from changing your genes? It sounds a little scary. Maybe you can address that.

Christine Klein: Yes. So, thank you for this important question. And I could totally understand that this really would come up within this topic, and is something to wonder and maybe also to worry about. And so first of all, and this we heard already, gene therapy needs to get there where it's needed, and that is the brain. So there could be, and that's probably something that I would consider one of the more likely events to happen potentially, although we have measures against this as well. Could be that your immune system, for example, recognizes something, and there may be a small immune response or something like this. But this all as we heard, will be carefully monitored, and also prevented as much as possible. But I guess your question is not really that, but rather what is it the genetics that are being introduced.

And again, I think building on what was just said by Maggie is really important. And I think we have to understand a little bit more just one step of the biology, because the genes, that can be two different... broadly speaking, two different scenarios. Either, you can be lacking a gene because it's mutated. Or you can even lose a copy, that's also possible. Or you can have too much function of a gene or gene product of the actual protein. And those are obviously two very different scenarios, right? And you would also devise different types of gene therapy. And that I think is probably a lot less scary to begin with, if you're missing a certain gene, and you're just replacing exactly what is missing. And we can really determine very exactly by genetic testing what is missing and how big that piece is.

So if you really just replace it, then I think I would not see too much of a risk there. If you have the opposite situation where you have too much function or too much of a gene, which I mentioned before with the alpha-Synuclein, you want to turn that down. But then same applies to some extent to if you're missing something, it's a very fine balance as you may imagine. So one of the potential risks lies, and that needs to be again, carefully monitored and kept at a very, very tight balance. You don't want to have too much, and you don't want to have too little. So that's important. And that is something where, again, theoretically there are risks, for example, that you are silencing something too much, or that you are increasing some function too much. So that is also possible, that you would turn into something different or a different person, or that genes would have a mind of their own, or travel somewhere or something. That is not something that would...

So the technique around this, and I'm sure everyone has good knowledge, of course, the immunization that we had against COVID is not a gene therapy. But I think we all learned a lot about general biological principles, and again, those never change your genome. So I think that's true for the gene therapy approaches too, broadly speaking.

Maggie Kuhl: Dr. Casey, next question to you. We've talked a lot about gene therapy as a means to slow, stop, prevent overall disease progression. Is there any application for specific symptoms, pain, autonomic dysfunction, cognitive impairment that we

know are unfortunately part of the slew of experiences one has with Parkinson's disease?

Bradford Casey: Yeah, it's a great question. So at present, the current therapies, the current gene therapies that are in trials are not targeted towards those specific symptoms. In the future, I would imagine that we will see that, but I think that it will depend on identifying again, whether those are specific genes or mutations in those genes, or just a better understanding of the biology of those specific symptoms, identifying those targets that then can be pursued using gene therapy. So we don't have any in trials yet, but that's definitely an area of interest as are more general strategies to modify the course of the disease.

Maggie Kuhl: And I know your team and others at the foundation are really fixated on better understanding the circuitry and the molecular issues that lead to different subtypes or kinds of disease and symptoms. So thank you for that work. Hopefully, that will lead us down that path. Switching gears a bit, Dr. Klein, deep brain stimulation and gene therapy, some of the ones that are active exclude people who have had DBS from their trials. Is that more of a testing thing, or would the therapies have application for people who have DBS?

Christine Klein: It's a very, very good question. Admittedly, I'm not a DBS expert, but just from my general knowledge, I would say for the trials, obviously people for trials. And this is as we mentioned, is one of the most experimental treatments for PD that we currently have. So one would probably at this stage, select people with the least of potentially interfering other therapies or changes in the brain. And obviously, sticking in an electrode changes things. So, just because also the numbers of individuals that go into such a trial are relatively small, it is very... And we want to see the effects, right? We don't want to muddy the waters by introducing too many different variables that then make it very difficult for us to disentangle what is the effect of the gene therapy, and what may have been something else.

So I think at this stage, it's probably likely and probably also a wise decision to select a patient population as homogeneous as possible, and with as little interference as possible. But I think in the future, I do not think that those should exclude each other. In fact, oh, as one already has the electrodes in a place where we want potentially gene therapy also to act. Maybe there could even be... But now I'm wildly speculating. Maybe there could even be, in the future, it could be even an advantage in a way. But like I said, this is really a speculation.

Maggie Kuhl: I think we can tell from this conversation why you're so prolific in this field. Because you're always thinking 10 steps ahead. Here we are, but what if we could do this? And-

Christine Klein: Yeah, but we don't-

Maggie Kuhl: It's gotten us very [inaudible 00:52:42].

- Christine Klein: ... and unrealistic expectations, I think that's not fair either. So we can be, I think, excited, and work hard towards this. But I think we also should stress that it's still early days.
- Maggie Kuhl: But it's a good comment on the fact that we talked about risks and benefits. And one of the potential impacts of choosing any therapy approved like DBS, or something experimental like gene therapy, means that it might impact what other sort of studies you can be involved in. And Rich and Pola, as you are both in so many observational and therapeutic studies, maybe you could just talk about how you see your position in the research ecosystem, and how you think about, if I do this, I might not be able to do that. And how you weigh all of the different opportunities that you're presented with to contribute in that way.
- Pola Sussman: That was actually a huge factor in my deciding to enroll in that particular gene therapy trial that I started with, because it was very clearly explained that they need to understand if they did this gene therapy on me, what were the things that would then happen in the future to my body and my Parkinson's, that they could attribute completely to that therapy program and not to some other medicines or trials or whatever that I had had. We do research trials because the more data that scientists, and researchers, and doctors have, the better they will be equipped to help find a cure for PD.
- Rich Sussman: And if I could just add some to that. Pola obviously participates at someone with PD with a GBA mutation. I participate as someone who is a control, and Pola's brother who has a mutation, but no PD, is of extreme interest to researchers. So if family members are thinking about should we get genetically tested? I would say that if they have an inclination to help the research, they absolutely should. Because that's just a huge need, and it just makes us feel better participating in research. We feel like we're potentially part of the solution.
- Maggie Kuhl: Well, you certainly are. We're getting close to the end of our hour, and that's such a nice sentiment to end on. Certainly, as I started our discussion, our goal was to talk about this emerging therapeutic approach, and share information and motivations that you have, so that people feel more equipped when hopefully these opportunities are presented to them as well, or when they're discussing any research opportunity. Because as you said, Pola, more data is the only way, more information is the way that we're going to learn more about, as we've covered today, the many variations of Parkinson's disease that exist, and the many ways that we may stop it. So Dr. Casey and then Dr. Klein, I would love to perhaps just hear some parting words from you about just the overall schema of therapeutic development, gene therapy or otherwise, and how you're feeling on the Parkinson's research programs overall.
- Bradford Casey: Absolutely. So for one, I mean I am really both inspired and enabled to do the type of research that we work on here at the foundation because of people like Pola and Rich, right? We do really need a participation by people not just that have Parkinson's, but also that don't. And that's the kind of participation that really

enables us to make those key discoveries and actually drive things forward. I'm really optimistic right now about not only gene therapy, but other strategies that are in process. But I think more broadly, thinking through the impact of genetics, and how genetics can help inform all these different treatment developments is really... I think that we are just really on the cusp of some really big discoveries. And that's largely due to the contributions of people not just here in the US, but around the world. And so that's one thing I'm really excited about right now. And in fact, I get to work with Dr. Klein on a project that's very focused on that, and helping to make sure that our understanding and our treatment strategies are designed around that more diverse community.

Christine Klein: Thank you. That's wonderful. And because it was exactly what I wanted to mention. And of course, I can only echo what Dr. Casey just said. But being from outside the US, I think... and this needs to be said here as well, the Michael J. Fox Foundation does an absolutely amazing job of being global. And you said it's a global disease, and we are all working together. We're part of this PPM study, that was the PPMI study that was just mentioned. We just had a visit here from the Michael J. Fox Foundation, and we had a patient also at this event, who very similar to you Pola and Rich, expressed similar sentiments. And I was very touched by this because it is a global phenomenon, and I think we have to work all together. We have to work together at the patients and the persons with Parkinson's disease, the caregivers, the therapists. Of course, the clinicians, the doctors, the researchers, and also of course the funders.

And I think this is a great example. So we're here all together, and only together we can solve this. And as Dr. Casey just said, I think the prospects are really promising. Like I said, I want to be somewhat modest because we have seen also other things that did not work as well as we had hoped. So let's be a little bit careful. But I think things are moving in the right direction. We are all working together on this, and that's the key to success to do this together. And I'm grateful for being able to participate a little bit in this, and for having been here today. And yeah, it was just wonderful to also read your questions and interact. Thank you for that.

Maggie Kuhl: Yes, thank you all, Pola, Rich, Christine, Bradford for being with us. And all of you who are watching, thank you for giving us your time. We hope that you found it beneficial, and that you'll engage with research opportunities with the foundation further. Thank you and have a great rest of your day.

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Section 4 of 4 [00:45:00 - 00:59:24]

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