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MJFF: Navigating Parkinson's disease can be challenging, but we are here to help. Welcome to the Michael J. Fox Foundation podcast tune in as we discuss what you should know today about Parkinson's research, living well with the disease, and the foundation's mission to speed a cure. Free resources like this podcast are always available at michaeljfox.org work.

Maggie Kuhl: Welcome to our latest episode of the Parkinson's Science POV podcast, where we break down what's happening in Parkinson's research and how the Michael J. Fox Foundation is advancing new treatments. I'm Maggie Kuhl, vice president of research communications. Today, we're going to talk about a topic that we hear a lot about from our Parkinson's community. Gait and balance issues, freezing, falls, shuffling, posture issues. These are some of the most troublesome and really impact quality of life. And can frankly be pretty dangerous. Joining me today is Mark Frasier, our chief scientific officer, and instead of our other CSO, Brian Fiske, who is currently stretching his gait while hiking the Grand Canyon, we have with us Dr. Katie Kopil, who is our senior vice president of clinical research. Katie, thanks for joining us.

Katie Kopil: I'm excited. This is fun and a topic that's so important to the community and a great area of focus for the Foundation. So excited to share some updates.

Maggie Kuhl: Yeah.

Mark Frasier: Hey, Maggie, how's it going?

Maggie Kuhl: So Mark, why don't you kick us off and just sort of frame the issue for us, what gait and balance challenges do people with Parkinson's face and why is it so difficult to treat them?

Mark Frasier: Sure. So, I mean, studies show probably about 80%, if not higher of people with Parkinson's experience challenge with gait and balance and ultimately falls. And this is just a huge unmet need, as you said, I mean, falls can lead to hospitalizations, broken bones, really, really difficult things to deal with. And the challenge with gait and balance and treating falls and Parkinson's is that it happens, typically, balance issues, they can occur early, but the falls really develop as the disease progresses. And we know Parkinson's is a progressive disorder, and there are a lot of other things that are happening as Parkinson's progresses. So there could be cognitive changes. There could be mood changes, other non-motor symptoms along with the typical tremor issues. And so really understanding why the freezing of gait is occurring when all of these other challenges are happening with Parkinson's disease is a big problem.

Mark Frasier: So teasing that out scientifically and understanding what goes wrong in the brain when someone freezes is really hard. There's also very little that we understand, our understanding of the brain and how freezing of gait occurs and what goes wrong, what circuits go wrong in the brain is limited. And so there's a lot of studies that are doing neuro imaging approaches to really understand why someone freezes, what causes someone to freeze, what causes someone to not freeze and overcome that freeze to reduce the falling. And so just the neuroscience behind it, I think is challenging. And then the last issue is that the current medicines, typical, the dopaminergic medicines like levodopa or Sinemet and some of the other medicines available really don't treat gait and balance. They do a pretty good job with movement and tremor, but they really don't treat or improve someone's balance.

Mark Frasier: So that's a big challenge. I guess the last thing I would say is one of the things that we're learning and we learned from this workshop that we held, is that there's a lot of variability in the types of challenges that people have with gait and balance. So some have just slower steps. Some people have more variable steps where they might have a long step then a short step. And so the variability may cause falls to occur. And then there is a subset of individuals that just have freezing when they're walking and understanding this sort of variability, even within Parkinson's disease, is a big challenge. There are some projects that are going on to address that challenge, but it turns out that this sort of gait and balance as a category actually can be very personal and personalized depending on the person and their experience and journey with Parkinson's disease.

Maggie Kuhl: So it sounds like, as you said, there's a lot of issues, different types of issues that people could face and potentially a lot of contributors to those issues. I just want to make sure that our audience is coming along with us on this conversation. We said the word freezing a lot and freezing of gait. Can you quickly define what that means? What the experience is like for someone?

Mark Frasier: Sure. Well, people will be walking along and then a lot of times their feet will feel like they're stuck in cement and they cannot continue to walk. And so that's what we call freezing where you'll see perhaps the feet are moving just a little bit, but they really feel like they cannot lift their foot to make a next step. And it's a big problem because as you may imagine that could lead to balance issues and then falling.

Maggie Kuhl: Okay. Thanks for that quick clarification. So, as we said, a lot of different types of issues, and it seems like it would take a lot of different types of approaches to prevent or ease these issues. So Katie, can you bring us through some of the therapies and testing to prevent or ease all of these gait and balance challenges?

Katie Kopil: Yes. There's an exciting pipeline trying to tackle this really complicated challenge. And I just think about before going into the therapies, the ease with which I walk and I take for granted how natural and organic it is, but there's a reason it takes humans a year to learn how to walk. It's a very complicated,

coordinated process. And I have young kids who fall all of the time. It's easy for them. They bounce back, but it's a really nuanced, complex system of brain functions that need to coordinate walking. And this is why we are interested in funding so many different types of therapies that could help address this really complicated system. So some of the work that's ongoing includes drug development and the Fox Foundation is supporting a pharmaceutical company, Takeda, that's developing a new drug that's aimed at improving balance that we also think might help with attention and focus and cognition, because this is all linked into good gait, good walking and preventing of falls.

Katie Kopil: There's also non-drug type of interventions that are being developed, like music therapy to help increase awareness of the beat of the music and try to provide some regularity and stepping. And what Mark talked about with cadence and length of the stride. There's also a lot of important work that we'd like to build on in the physical therapy space that we know provides benefit. But for anyone that has tried to access physical therapy, you might at most get it once a week, if you're lucky, you may only get it once a month and it doesn't last forever. And so a lot of the new technologies that are being developed, virtual reality, devices that could provide sort of a metronome or personalized ticker that helps you maintain a positive gait, other noninvasive approaches are largely aimed at making physical therapy more accessible, something that people could partner on with their physical therapists and be able to use at home and in the community more routinely.

Katie Kopil: So the Fox Foundation is taking a very holistic approach at trying to invest in treatments that may help adjust neuropharmacology and treatments that augment physical therapy. In parallel, we're working with a lot of important researchers to better understand why gait disturbances occur and progress in Parkinson's overall, so that we have smarter insights into how this complex process of walking and balance works so that we could fuel future therapeutic development.

Mark Frasier: Can I add to that? I think it is just to emphasize this notion, this concept of activating someone through technology. So there are walkers or canes that exist that have a laser attached to them. And one of the common solutions that neurologists use in the clinic when someone's freezing is to either step in front of them to try to get the individual to take a step. But these lasers, if you point to a spot on the floor, are really good at sort of reactivating the brain and engaging the circuit so that the person can then take a step towards the spot on the floor, if you shine a laser on the floor. And so there's a number of different technologies that either exist now or in development that are really pretty nifty solutions to this complex challenge where they can sort of reset the circuit so that when someone is freezing and feels like they are standing in cement can kind of get out of that and take a quick step and continue with their walking. So it's an exciting area.

Katie Kopil: Agreed. And I remember now many, many years ago, talking with a neurologist whose dad had Parkinson's and she said she would put tape in his house. So that

would help him visually overcome this freezing of gait, but that is limited to your house. And with these technologies, people can be out in the community, they can be out in their neighborhood. They can enjoy time with family in locations that are not at home. And I think that's a really important advance.

Maggie Kuhl: That is amazing though. Can we just take a second to reflect on how the brain works that you telling yourself, walk, take a step, foot, pick up and move forward, cannot work, but seeing a light or a piece of tape or hearing a specific sound can somehow trick your brain into thinking, okay, now, now I will do this. What is going on in there that that happens? I don't know if you can answer, that's sort of a big question, but...

Katie Kopil: No, it's not possible. And this is why I love neuroscience and the brain is who you are, and we need to use the brain to figure out how it works, but it is really complicated. I think we are good at seeing how humans work at a whole person level. And we are very good at understanding how different brain cells function and then this level of neuro circuitry and how different brain systems coordinate together is an important frontier that is yet to be unlocked. And is part of that interest in understanding how do you go from a cell function to a human function? There's a lot of missing pieces that we need to unlock.

Mark Frasier: You know, but one thing we do know, Katie, you mentioned this when you talked about the pharmaceutical trial that we're funding. We know that people with Parkinson's have challenge with executive function, which is sort of multitasking and planning multiple things, executing multiple things at once. And it turns out, at least the research is suggesting, that in Parkinson's, gait is kind of related to attention and multitasking. So if someone is challenged to walk and chew gum and a couple of other tasks at the same time, it becomes really hard for someone with Parkinson's disease. So I think one of the things that these lasers are queuing does is sort of focus their attention on walking. Whereas people without Parkinson's, I think just do it out of habit, but you really have to focus and pay attention. And this role, this kind of what we're understanding about the role of attention and related to walking and gait, I think is a really exciting area. And that's where I think some of these solutions and treatments are being derived from.

Maggie Kuhl: Makes me think if you've been something like mindfulness and stress reduction, and some of the other things that we think about for Parkinson's would help this. Well, just to recap, it sounds like we are looking at the biochemistry and looking at some solutions to what we already know, and also trying to explore what we don't know and find out more about what's happening in the brain, but also exploring in the meantime, some sort of life hacks, if you will, to not need to know exactly what's happening, but how, as you said, Katie, the human form operates and how we can address that. So gait on the cellular level and the person level. So this was discussed at the workshop that you hosted in June, Katie, the therapies in development and how to advance those, but also how to prevent a lot of these issues. And that really comes down to prediction and having the right measures to say, yes, this person is at risk of having gait or

balance issues. So why don't you tell us a little bit about the state of the science there?

Katie Kopil: One of the things that is most critical to that vision, Maggie, this idea of preventing falls or preventing worsening of gait or balance issues is really better measurements. And this is important, different people, as Mark alluded to, will have gait issues for different reasons. And so one of the opportunities, especially with advanced digital health technologies, is to be able to measure gait, not just in the clinic, but in more natural environments like people's homes and neighborhoods. And there's been a lot of interesting advances trying to marry that digital health technology more real time, 24 hours a day type monitoring a movement to what we understand is meaningful to patients and connected to gait. That requires a lot of math, much more complex math than I'm capable of doing, but advances in machine learning, AI, algorithm development is helping better understand and measure gait based on objective, wearable devices and helping connect that to what gait looks like in the human form, predicting falls, and also seeing who might be more at risk for worsening of gait versus those individuals who may not end up having problems with that aspect of Parkinson's.

Mark Frasier: Yeah, I would, I was just going to pick up on that. I mean, you could imagine a scenario where someone's using one of these devices, a wearable or something in their home that's monitoring their gait passively and picking up on changes that might predict maybe not freezing at that time, but down the road. And using that information as an intervention strategy that might signal to the neurologist, Hey, we have to intervene or do some physical therapy or start thinking about some other options to really prevent these falls from occurring. So I think measuring gait changes that may not be freezing right away, but they may lead to something that could look like freezing, I think would be a really useful tool in the toolbox of a doctor to help care for their people living with Parkinson's disease.

Mark Frasier: The other thing I think is sort of maybe a little bit farther down the field, but I think there is research suggesting that individuals that are at risk for developing Parkinson's, so people that might have genetic mutation associated with Parkinson's, but have not been diagnosed with Parkinson's actually have subtle gait changes, right? Using these digital technologies, researchers can measure them. And so that suggests that while I said the falls might occur, the freezing might occur later in illness, the subtle gait changes can be detected very early. And so I think that's a really exciting opportunity to really measure some of these subtle gait changes. And again, identify individuals that might be right for intervention strategies or treatment.

Maggie Kuhl: That's happening in our landmark Parkinson's Progression Markers Initiative study. Is it not?

Mark Frasier: Yeah, so that the data I see I mentioned came out of the Parkinson's Progression Marker Initiative study the PPMI study. And now we are funding a larger study

to sort of verify that data and expand on it in individuals living with Parkinson's that have been diagnosed to really understand some of these gait changes that occur early.

Maggie Kuhl: And that PPMI study is still recruiting people at risk for Parkinson's and those recently diagnosed. So I'll do a quick plug. If you're interested in learning more, you can visit michaeljfox.org/podcast-ppmi, because everything that we've been discussing about learning more about the human form of gait challenges and Parkinson's disease and Parkinson's risk, as we were just saying comes from human volunteers. So if you would like to join us in PPMI, please reach out. Back to the measures. Katie, we were chatting before we pressed record here, and you were saying something interesting about how it's really hard to measure gait and balance in a clinic setting, that sort of white coat syndrome we all have of doing our best in the doctor's office. Can you describe why that challenge exists and how we're trying to overcome it?

Katie Kopil: Beyond human nature, why there's performative, trying to show up as your best self at the doctor, I can't say more, but I can say that it's certainly true in Parkinson's disease and it's seemingly particularly true for more advanced gait issues, including freezing of gait. Many clinical research studies that are aiming to try to see if treatments provide benefit or relief for freezing of gait actually have a hard time measuring efficacy in a laboratory or a clinical setting because many people despite freezing frequently at home will not do it in a clinic setting without having some sort of trigger. Walking through a doorway or being forced to turn very quickly, which is not to say, the normal lived experience of Parkinson's disease.

Katie Kopil: So the ability to take measures and measurement tools home with you as a research participant or a person that wants to be empowered to monitor their own disease and be a smarter advocate in their own healthcare allows for more realistic and naturalistic and accurate tracking of issues with gait, which I think is going to not just transform research, but also has the opportunity, as Mark said, to transform the way the Parkinson's is treated today.

Maggie Kuhl: So Katie, we've sort of used the workshop that you hosted as our organizing principal today and what went on there. Anything else from that meeting that you would like to share with the audience? What were your major takeaways walking out of that room full of experts?

Katie Kopil: It was an exciting day and that I would emphasize also our experts included people living with Parkinson's disease. And I want people that are interested in getting more involved with the Foundation and with research to know that your perspective is equally, if not more, valuable than many people that have initials after their name, because you live with Parkinson's, whether you have a diagnosis or have a family member with it 24/7. So this group of experts, researchers, clinicians, drug developers, engineers, physical therapists, and patients talked about how do we measure gait? How do we better understand why gait disturbances occur in Parkinson's? And then how do we treat them?

One of the themes that kept coming up that was quite interesting is this idea of a personalized medicine. Different individuals have underlying neuro circuitry or constellation of symptoms that create different types of gait issues for different individuals.

Katie Kopil: This idea of being able to measure gait in individual people relates to wanting to not just look at a population level, but really understand what gait issues that our individuals having and then be able to treat those specific issues and that a one size fits all approach would be a dream. We would love to see that sort of umbrella solution for treating gait issues. But what we understand right now and what solutions we have today, suggest that different people will benefit from different types of therapies. And so the more we can build solutions and treatments that work for individuals that can be personalized to the gait disturbances that people are experiencing, the greater impact we can have today on people living with Parkinson's.

Maggie Kuhl: And Mark, what can people do today if they are living with Parkinson's and these gait issues, what strategies or maybe life hacks, as we said, would you recommend to people who struggle with walking, freezing and falls?

Mark Frasier: Well, I would talk to other people living with Parkinson's because as Katie said, they're really the experts and I've seen a lot of innovative life hacks when talking to people with Parkinson's that I would never have thought of. So I think sharing their information and asking others that are experiencing these challenges is useful. I think things like the walkers or canes that have lasers on them, those exist. I think those are very useful. Participating in research, I think often is very fulfilling and actually provides individuals a sense that they're doing something about their Parkinson's disease. That also, incidentally, I think, often connects them to individuals, doctors, caring for a lot of people with Parkinson's that may have certain tips for them, but also it sometimes connects them to other individuals, other people living with Parkinson's. So I think it just increases your network of people you can rely on and ask for advice. I should also mention the Fox Foundation Buddy Network. That is a good way to find individuals that are living with similar symptoms and ask their opinions on what works for them. I think that's also a good opportunity.

Maggie Kuhl: Great. And I'll add one more from my list, something Katie called out earlier as I'm the daughter of a physical therapist. So I'll always give a plug to PT and exercise as helping with gait and balance. So something that absolutely can help prevent or offset the impact of that symptom. So, well, thank you so much for joining us. Katie, don't tell Brian, but you are an amazing guest and we're sure to have you back.

Katie Kopil: Thanks, Maggie, for inviting me. This was great opportunity to share some of the work that I do at the Fox Foundation, with the community that makes it all possible.

Maggie Kuhl: And Mark, always nice chatting with you.

Mark Frasier: Thanks Maggie. And thanks so much, Katie. I can't wait to have you back.

Maggie Kuhl: And thank you to you all, our listeners, who your generous support and your research participation, make the advances in Parkinson's research and the efforts of our Foundation possible. For more resources on gait and balance issues, as well as the many other aspects of living with Parkinson's disease, visit our website, michaeljfox.org, and stay tuned for our next episode. Thanks for listening.

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