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Maggie Kuhl: Hi, and welcome to an another episode of Parkinson Science POV. I'm Maggie Kuhl, the Fox Foundation's resident science translator, and I'm here with our chief scientific officers, Brian Fiske and Mark Frasier. Hi, both. Thanks for joining me again.

Mark Frasier: Hey, Maggie.

Brian Fiske: Hey Maggie. Good to hear you again.

Maggie Kuhl: It's Parkinson's awareness month, and today we are going to talk a little bit about how doctors and scientists are aware of Parkinson's disease, how to predict and measure and track Parkinson's. But before we dive into that, I just wanted to celebrate that this Parkinson's awareness month looks a lot different than the ones passed, and you both were back in the community recently, and you're looking to some opportunities to meet our friends face to face. So just wanted to hear how your trips are going or what you're looking forward to.

Brian Fiske: Yeah. In March, I was at an international conference for the first time in about two years. It was in person and actually in Spain of all places. It was really exciting to see a lot of the people we've fund and grantees and researchers in person again. Whole bodies after two years of seeing them only on Zoom calls. So you miss that sort of interaction, I think, and I only think appreciated it finally seeing everybody again, but really exciting to be back on the road and some upcoming travel, we're all getting the chance to interact with the community again, so really excited by it all.

Mark Frasier: Yeah, it feels so good, Maggie to be back out on the road. I've had a couple trips recently. And then April, I'll be talking to a lot of the community members about the progress in research, and it just makes such a difference being face to face and meeting people where they are and sharing all the exciting progress about Parkinson's research.

Maggie Kuhl: Our in person events may have been paused, but Parkinson's disease did not pause as our listeners know, and neither did the efforts to come to better treatments and cures. So why don't we just set the stage, Mark, what is it like today? Measuring PD?

Mark Frasier: Well, it's hard and it's actually very crude measurements. So typically, the way people are diagnosed is through the symptoms, tremor or slowness or stiffness. And it can be a really long journey for someone that has Parkinson's to really get a diagnosis, because Parkinson's can look like a lot of different things. And aging introduces many different complicated factors that may not be Parkinson's. And so the way it is currently done and is typically in a neurologist office, they will perform tapping tests and have individuals walk and assess their movements. And it's really up to the neurologist to make that diagnosis. And it's hard because symptoms wax and wane from day to day and even from hour to hour. And so it's often hard for a neurologist to really assess those symptoms in a 20-minute visit and formulate a diagnosis that it might be Parkinson's. So those are the main challenges.

Brian Fiske: Yeah. I was thinking about this the other day as someone who is getting older, and you think about all the doctors you go see and all the normal screenings you start to get once you pass a certain age. And one thing you don't do is go see a neurologist. And I still think that's kind of really an interesting fact that you go to your heart doctor to check your heart health. You go to your dermatologist to check your skin health. You rarely go to a neurologist to check your brain health until you have a reason to do so, like a symptom. And I think we'll maybe talk more about that today, but this idea of how do you screen for some of these things and sort of think about your risk for some of these diseases like Parkinson's and the kinds of measures that we could be thinking about. So, yeah, I think it's a real challenge today.

Maggie Kuhl: That is fascinating. We just don't have the tests, I guess, which is what we're going to talk about. But Mark, just to build on your sort of how it waxes and wanes. And crude, I think is a great word to use. We heard an anecdote from a member of our community who is very active in studies, and he said that he had three of those standard Parkinson's finger tapping walk over there and back tests in one day by three different doctors and got three different scores. So I think that really illustrates why we need better measures. So Brian, talk me through, we talked about where we are, where do we want to be and why is it so important for therapeutic development?

Brian Fiske: Yeah, no, I think this is the really important part. There's so much about Parkinson's obviously we don't know about, but more and more that we're starting to learn about. And so how do you measure that? And we've talked about the symptoms and at least some of the basic ways that doctors and neurologists will initially measure those symptoms using some of the existing scales that like you just mentioned, the finger tapping and the walking across the room. What we would, of course like to be able to do is actually measure more the underlying biology of the disease and sort of the pathology of the disease so that we can actually see what might actually be happening maybe even before some of the symptoms start showing up.

Brian Fiske: And so I think that is the direction where we're desperately looking to head and we're starting to see some exciting results that suggest that we might be getting

closer to being able to do that. So whether it's measuring, again, the pathology itself or getting measuring some of the symptoms in a more sort of objective way, I think that's kind of where we're really hoping to head and what we can talk some more about where we think are actually making progress in that regard.

Maggie Kuhl: So you said that you were just in Barcelona. Let's talk about some of the exciting news as you just pointed out. From our partners, our grantees, AC Immune and the researchers at Skåne University Hospital, and Lund University in Sweden. There's been a big announcement of an imaging tool. Can you give us the latest on that?

Brian Fiske: Sure, sure. Yeah. I think this was the big sort of highlight of the meeting. Definitely in Spain, a lot of people were packed into the conference room that day. Yeah, so this is really exciting for us. This is an area that certainly the foundation have supported and put millions of dollars towards over the years, working with a whole variety of partners, including AC Immune to develop essentially a brain scan, an imaging scan for measuring the clumped alpha-synuclein protein that exists in the brains of people with Parkinson's. And so it's been a really tough challenge and it's sort of not only technologically being able to do the imaging, but just chemically because it's a hard thing to kind of develop a compound that can go into the brain and bind to the clumped protein and then sort of show up in the imaging scan.

Brian Fiske: And so we've been hopeful because they were able to do something similar in Alzheimer's disease, which also has its own sort of version of a clump protein with protein called amyloid beta. So we assumed that we could probably do something for alpha-synuclein as well, but it's just been a really long road. So the news was exciting. This company AC Immune have developed a compound that they showed has the ability, we believe, to go in and bind two and show up on the imaging scan to detect alpha-synuclein. Now sort of the caveats here are that they were able to show the signal in people not with Parkinson's actually, but with a different disease called multiple system atrophy, which is another brain disease that also has accumulation of the alpha-synuclein protein in the brain. It's distributed differently in kind of a different type of brain cell, so that could be some of the reasons why maybe we didn't see it in the Parkinson's brains for the people who were scanned.

Brian Fiske: But the fact that we could detect what we feel pretty confidently was alpha-synuclein clumped, I think was the really big highlight and exciting sort of progress that was made. So with that sort of knowledge that it's feasible now to do, I think that the really exciting next steps are, "Okay, maybe we just need to optimize the compound further so that it can detect maybe more sensitive, have more sensitivity to detect the alpha-synuclein in the Parkinson's brain." We're also learning that maybe the shape and form of alpha-synuclein and Parkinson's might differ a little bit from a disease like multiple system atrophies. So the investigators are starting to look at that too, and maybe they need to sort of tweak the compounds characteristics, so we combine the Parkinson's version.

But the fact that again, that we were able to see it at all, I think was a really big, exciting milestone. And I think really there was a lot of excitement in the room when those results were presented.

Mark Frasier: Yeah. I think it's going to galvanize the field. You mentioned the foundation has been funding this over millions of dollars and for many years. And to have this breakthrough, I think is really just going to energize, not just the AC Immune group, but the entire field and other researchers working on this problem, because it is now shown that it's possible and feasible and it's just going to get quicker from here.

Brian Fiske: Exactly, exactly. Yeah. And we know there's some other groups out there that are moving along too with their own versions and some other partners. So I think exactly, I think once one person kind of shows that it can be done, suddenly everybody's now going to go back to their notes and say, "Okay. We started this, let's continue it." There's real promise here. Maybe more investment. People will get more interested in investing in these types of imaging approaches, and I just think it's a watershed moment.

Maggie Kuhl: Yeah. And Mark you said of the results are going to galvanize the community. I think just echoing your comment, that the foundation support was really critical in getting to this point, because for huge funders of this project and a lot of the other ones that are going on. So again you sort of called out our community fundraisers before, but just want to thank all the supporters listening on up there. And mark, I have one more question on this tracer. So we were discussing earlier, what if there was a proactive doctor appointment with the neurologist? So that's sort of predicting disease. Of course people are living with Parkinson's today. More will be diagnosed soon. How is something like a tracer going to address the different stages of Parkinson's? What would its utility be from risk to early stage to later years with Parkinson's?

Mark Frasier: Yeah, well, it'll be interesting to see what the data shows, but we know that there are changes that occur in the body and the brain before symptoms develop. And there are studies in the brain looking under a microscope that show that alpha-synuclein accumulates prior to symptoms developing. And it accumulates as the disease progresses. So you can imagine with this tracer in hand, it could be, we don't know, and we'll have to support the experiments, but it could be that this tracer actually identifies that pathological species, the accumulated alpha-synuclein in individuals that may be at risk for developing Parkinson's disease. So we can visualize that and use that as a tool to potentially intervene with a treatment or a medication earlier and potentially before symptoms develop. Also, and you asked about how this could speed therapeutic development, but even in individuals with Parkinson's disease, this tool and this biomarker is going to be really important to track progression of disease.

Mark Frasier: Not just clinical progression and how your tremor or slowness might get worse over time, but these tracers could have the ability to track how the pathology is changing over time and be used as a tool to determine whether a new

treatment and intervention is working in clinical trials. So for example, you could imagine using this tracer when someone's first enrolled in a clinical trial to understand the total alpha-synuclein levels using the brain scan. And then at the end of the trial, after 12 to 18 months and understand whether the treatment actually slowed the progression or the accumulation of alpha-synuclein or maybe eliminated it all together. So this is one of, I think, many tools that will be needed to help drug developers and researchers understand whether these medicines are actually really breaking up the clumps and treating the underlying biology that's happening in Parkinson's disease.

Brian Fiske: There's another aspect that I'm really... If this tracer to really turns out to be the tool that we think it can be research question too, that I think will be really fundamental that we could answer potentially with it as well. Whereas for years now, there's of course been this theory that the pathology, the snooping and clumping linked to Parkinson sort of spreads and kind of moves throughout the brain over the course of the disease and that sort of associates with the sort of progression of the symptoms as well. But we've never been able to test that directly, right? We've only been able to look at that kind of in a cross sectional way, when looking in tissue from brains of people who've passed away with Parkinson's and said, "Well, here's where the pathology sits in that person, and here's where the pathology sits in this other person," and sort of made inferences about that spread.

Brian Fiske: But with a tool like this, you could actually follow people living with Parkinson's and actually potentially see that spread happen. I think if we actually saw that would be such a demonstration of the truth of that potential theory that I think it really would help also establish more validity for going after that pathology with the therapeutics. And I think really just sort of increase people's confidence if that's the right approach to take. So I think that's another byproduct that this tool could really help with, is just understanding the progression of the disease itself, which I think would be really, really powerful.

Maggie Kuhl: Yeah, yeah. That information is critical. And I just want to remind too, the listeners, that currently there are 15 therapies directly targeting alpha-synuclein and its pathway already in human testing, many more to come. And because we think that this is a real hallmark pathology, sort of perhaps a more downstream effect of some of the various causes and contributors to Parkinson's disease that even treatments and trials on other targets could still benefit from alpha-synuclein tracer. But I want to go back, Mark, to something that you were talking about with the impact on therapeutic development with biomarkers.

Maggie Kuhl: Because I think that it's something we think about a lot, what is a cure? And there is, as you were saying, this sort of biological effect, are we stopping what's happening in the brain? Absolutely. But for the people who are already living with Parkinson's, you also want to have that functional impact. You're not going to get a therapy approved. Regulators are concerned with this too based only on biological change. You want to really focus on function and feeling. So measures

of the Parkinson's experience or the manifestation of Parkinson's, where are we? What sort of technologies are we using? Where do you see that going?

Mark Frasier: Yeah, it's a good point because we could change all the alpha-synuclein in the brain we want, but unless it reduces tremor and stops the slowness from happening, it really doesn't matter, right? And that's what really matters to people living with Parkinson's disease. So in parallel with developing these molecular tools to track the pathology and the biology, the foundation has supported a lot of work to use different approaches to capture the patient journey. And there's a couple of ways that this is being done. One is to ask specific questions of individuals with Parkinson's, what bothers them, what bothers them the most about their Parkinson's disease? And developing tools that can quantify the specific bothersome symptoms. So whether it's tremor or walking or balance or falls, there are ways to capture that information using both what people say in response to questionnaires or questions.

Mark Frasier: And this could be just having individuals score on a one to five basis on how much this bothers them, or it could be more technological and more sophisticated, using sensor-based approaches. And there's been a lot of progress in using wearable sensors, either smart watches or smartphones to really track the symptoms more precisely. And you can measure tremor, you can measure slowness using wearable sensors, using accelerometers, and these are still exploratory, but there's been a lot of research recently to demonstrate that these sensors actually may detect symptoms more precisely and more accurately than the neurologists do because they can be worn for 24 hours a day, and the neurologist might see them only for 20 minutes in every six months. But also because of the sensitivity of these sensors, they can really capture information that may not be obvious to the naked eye, the human eye. And so these advances are happening in parallel with some of the molecular tools that we talked about to really capture whether the... Or develop measurements to determine whether the symptoms are actually changing or not.

Brian Fiske: One of the really powerful things about also collecting information directly from people with Parkinson's I think is this, what you learn about how people with Parkinson's describe their symptoms and their daily function. And often that isn't exactly how doctors or researchers would describe it. And so I think it's really important that you really be able to talk about Parkinson's through the lens of what it means to someone with the disease and not sort of the more clinical doctor perspective on that. And we've funded some work over the years, looking at how people with Parkinson's describe say their movement symptoms versus how physicians describe it, and kind of where that overlap lies. And I think that this kind of information collection in this way, I think, is really important for, especially then defining measurements and endpoints that can be more meaningful to the experience of the person with Parkinson's.

Maggie Kuhl: That's right. We say they are the true experts on disease, yeah. And the other thing too, that influences, I think everyone wants to perform for their doctor, right?

Brian Fiske: Exactly, exactly.

Maggie Kuhl: According to my medical chart, I've never had more than one glass of wine in an evening.

Brian Fiske: I don't drink at all.

Maggie Kuhl: I think to pass the monitor, you can't lie to your watch or what's with you all the time.

Mark Frasier: It's a real phenomenon, by the way. Caregivers report that all the time that people with Parkinson's do better, walk better, walk differently in the doctor's office than at their home. And so having the ability to monitor more remotely and over a longer period of time is a really important way to understand the disease and what's happening in the wild, so to speak.

Brian Fiske: Yeah. And there's a training effect. You get better at these tests over time because you practice doing them multiple times, which is different than something like a more objective measure that isn't going to change because you've been practicing.

Maggie Kuhl: So we have talked about a brain scan, we've talked about some digital devices. We're nearing our time, but just wanted to do maybe a fast fire, what to watch, because even the depths of those areas of our portfolio are still only a chosen number of everything that the Fox Foundation is supporting and attempting to understand and measure and track and predict Parkinson's disease. So, Mark, let's start with you. What other sort of bullet points do you want people to be watching or know about?

Mark Frasier: I think there's a lot of exciting work happening in bio fluids, in things like spinal fluid and blood where researchers are uncovering differences that occur in proteins located in spinal fluid or blood. So there's one test in particular that's really generating a lot of buzz. It's kind of a seeding assay where I equate it to sort of a snowball effect where you introduce a seed in spinal fluid and this alpha-synuclein sort of propagates and becomes bigger and bigger, like a snowball rolling down the hill. And you can measure this in a test tube. And this test tube test has remarkable accuracy for detecting Parkinson's disease. And it is almost all the time negative for people without Parkinson's disease. Now, it's being deployed in people at risk to determine whether we can predict someone that might develop Parkinson's disease. So this seeding essay is really a exciting, and by the way, the foundation supported the development of this work from its early days. So it's exciting to see some of the data coming out of it.

Mark Frasier: Of course it would be better to have a blood test rather than a spinal fluid test. And there's a protein called neurofilament that can be measured in blood. It's actually a brain protein that you can measure in blood. And there's some recent data suggesting that higher levels of this neurofilament protein actually predict individuals in Parkinson's that may have cognitive impairment down the road. And so this could be a really valuable tool to identify individuals that may be at risk for developing cognitive changes, and then intervening... Using that as a tool to intervene earlier with some potential medicine. So I think bio fluid markers are an exciting area. By the way, there's an also... Just because we've been taking a lot of rapid COVID tests, there is an some early research that suggests that you could potentially use a nasal swab to detect changes in alpha-synuclein. And so this is very early, but the ability to take these tests at home has really changed in the COVID times. And so I think that could be a real possibility for Parkinson's disease down the road.

Brian Fiske: Mark, I think it's really exciting times because I think again, sort of starting again from the first discussion, what are we ultimately trying to measure? We talked about trying to measure the symptoms better than sort of the experience of Parkinson's better and how important it is to get that information directly from people with Parkinson's. As we start kind of moving deeper into the biology, you start thinking about, we want to measure the pathology. So we talked a lot about how we could measure the synuclein and clumping and the different abnormal forms of synuclein that might live in the body. And then as you go deeper there, you want to start really thinking about the sort of underlying maybe disease causes and mechanisms. And there, I think it's really exciting. There's a lot of biology coming from our understanding of the disease that we're are starting to pick up on. And just with that knowledge, we're starting to get a sense of the cellular processes that might sort of be dysfunctional or breaking down in Parkinson's and then thinking about how can you develop better measures for those?

Brian Fiske: And so there's a handful of sort of biological process that the team is investing in different ways to measure. Whether it's how our cells get rid of old protein and some of the ways we can measure that better, or how our cells make energy and how that sort of process is regulated and how we can develop measures of that process. So we can actually start to, at the end of the day, have a more precise biological kind of diagnosis of someone's Parkinson's, especially in those early days to kind of understand the trajectory they might be on. And that I think can then give us a more precise way of treating that person. And I think that's an ultimate goal here too, which is how can we kind of bring Parkinson's into more of a precision medicine sort of reality.

Maggie Kuhl: So you're not aware of Parkinson's disease, you're aware of your own Parkinson's disease?

Brian Fiske: Your own flavor of Parkinson's. Exactly.

Maggie Kuhl: Yeah, yeah. Parkinson's is a incredibly complex disease and that offers a lot of challenges as we talk about frequently. But I think we like to position it more as offering a lot of opportunity and how we can measure, track, predict, Parkinson's. So very excited about all that you both shared today. Thank you so much for joining me.

Brian Fiske: Thank you.

Mark Frasier: Thanks, Maggie.

Maggie Kuhl: And thank you all to our listeners, our generous supporters and the true experts in Parkinson's, as we said, people with PD. If you want to make a difference in what we know about Parkinson's and how we measure PD, you can join our landmark PPMI study, which is the source of a lot of the findings that Mark and Brian were outlining today. You can learn more about that at michaeljfox.org/podcast-ppmi. You'll find That link in the show notes. If you liked our conversation and you'd like to leave us a review, we'd be so grateful. Please share with your friends and engage with the rest of the foundations, robust content at michaeljfox.org. Thanks and speak with you soon.

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