Michael J Fox: This is Michael J. Fox. Thanks for listening to this podcast. Learn more about the Michael J. Fox Foundation's work and how you can help speed a cure at MichaelJFox.org.

Speaker 1: 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 MichaelJFox.org.

Maggie Kuhl: Hello and welcome to our third Thursday's webinar. I'm Maggie Kuhl, Vice President of Research Engagement at the Michael J. Fox Foundation, and it's been a while since I've been on one of these webinars and it feels a bit like coming home, used to do a lot of these. So thanks for so much for tuning in today and I'm excited to be here in addition to just the webinar at all, but also on this topic, which is a major research breakthrough, a new biomarker for Parkinson's disease. If you're joining us, you'd likely read a news article or a blog post or seen our social posts around this, and we're happy to be able to answer some questions that you may have and provide more clarity on what we think are truly momentous findings. So let's introduce our panel today with us we have Sohini Chowdhury, who is our chief program officer at the Michael J. Fox Foundation, and has started and led our PPMI study, which contributed to these findings since its early days. With her since then has been Ken Marek, our PPMI Principal Investigator is also President and Senior Scientist at the Institute for Neurodegenerative Disorders in New Haven, Connecticut. And Dr. Rachel Dolhun, a movement disorder specialist and our senior vice president for medical communications.

Hello, all I would say nice to chat with you, but we chat many times a day, so nice to spend this hour with you. So our research breakthrough is a biomarker. Let's start with what is a biomarker. Sohini, hand it over to you to orient us to this slide and this term.

Sohini Chowdhury: Thank you Maggie. And I just want to echo Maggie, it's a pleasure to be here with you all today and to share with you information about this breakthrough that we're all excited about. So let's kick it off. And the title about this is A Breakthrough and A New Biomarker for Parkinson's research. So what is a biomarker? At its simplest level, a biomarker is an objective way to measure or to track biological processes in our body. And those biological processes can provide information, valuable information about disease, risk, about a disease starting or about if you have a disease, the progression of that disease. An example that we usually like to provide that kind of highlights this is cholesterol.

Obviously there's no way for us to kind of look at our heart day in and day out and get a sense of how healthy it is or if it's in initial stages of disease, et cetera. But cholesterol is a wonderful way to be able to give us that information without having to look at the heart itself. And so in this example, cholesterol is a way to not just measure how healthy your heart is, but also to get a sense of if

there's an intervention, whether that intervention is helping your heart and addressing the disease itself.

And so when we think about biomarkers, there's lots of different use cases for biomarkers and not all biomarkers can do everything, but you usually have different biomarkers or some biomarkers can kind of address multiple things. But these biomarkers usually can help when we're thinking about Parkinson's specifically, they can help us diagnose the disease, they can help us understand how the disease is progressing in an individual. They can be very, very useful in clinical trials and they allow us to really get a sense in trials about whether a therapy is having the desired effect. So it really helps us understand the impact of a therapy in a testing paradigm. And so the biomarker that we are really going to talk about today is really looking right now as a research biomarker, a biomarker that can help us advance research for Parkinson's disease. And so I'm going to pass it on now to Rachel to tell you a little bit more about the biology around which this biomarker is centered.

Maggie Kuhl: We didn't say the name of the biomarker. So it's the alpha-synuclein seed amplification assay, which is a very long term, but maybe we'll just start as you said, Sohini with the biology with the first term there in with alpha-synuclein.

Rachel Dolhun: So as Sohini said, and Maggie said, this new test is centered around a protein called alpha-synuclein. And if you've been around Parkinson's for any amount of time, you've probably heard the word alpha-synuclein. Now this is a protein that we all have Parkinson's or not. It's a normal protein. It's concentrated throughout our cells, in our bodies, but mainly in the brain cells. And we're not a hundred percent sure exactly what it does, but it's likely responsible for communication between the brain cells in people with Parkinson's. This protein folds abnormally and clumps up. And again, to kind of set context around this, we've all been hearing a lot around Alzheimer's. Many people are familiar with Alzheimer's. Alzheimer's has a protein as well that clumps abnormally and the medications go after that protein. So when we're talking about Parkinson's in the brains of most people with Parkinson's, this protein, alpha-synuclein, clumps abnormally infrastructure is called Lewy bodies. And it affects this, we think it affects the cells function or the ability of the cell to work normally. And that's what we call the sort of pathological hallmark of Parkinson's because we see this at autopsy in the brains of most people who live with Parkinson's.

Maggie Kuhl: Thanks, Rach. So part of the activity of alpha-synuclein is, as you said, sort of the misfolding. And this pathological activity can impact the other sort of neighbor proteins. And so that is what this test is leveraging. And Ken, perhaps you could explain this phenomenon and what the seeding amplification assay uses to try and measure that alpha-synuclein activity?

Ken Marek: Sure. So you heard a moment ago from Rachel that alpha-synuclein is a normal protein, one of the important proteins in our body that has many functions which are important for our health. Unfortunately, for reasons we don't fully

understand in some people over time, as you heard, the protein starts to a function abnormally and what's called misfolds. It folds on itself and it clumps or aggregates. And when you can see those squiggly aggregates in the middle, you can imagine if they're supposed to be nice, smooth little wavy lines and now there are these big clumps sitting in the nerve cell, they can cause problems in the nerve cell and the nerve cell doesn't function properly. And that's what happens in Parkinson's disease or with another protein called amyloid and Alzheimer's disease. And what we've also learned though is that which is sort of a second stage of this problem, is this doesn't only happen within a single nerve cell, but the nerve cells talk to each other so that the abnormal synuclein in one nerve cell can be spread and spread to a neighbor.

And really that's the way that this travels around the brain. So it's both the fact that this occurs at all, but also the fact that it can spread from one cell to another, that it can result in the development and the progression of Parkinson's disease.

Let me have maybe the next slide and we can talk about how this very problem can turn into a positive if as we now have developed this biomarker, which is called the alpha-synuclein seeding amplification assay, we're going to call it SAA for short. And really this takes advantage of the fact that individuals can contribute spinal fluid. And if you have Parkinson's disease, there's sufficient synuclein in that spinal fluid sample that when you mix it up with a what's called a synuclein seed, which is just a artificially made synuclein pellet, that it will aggregate just as I mentioned in the brain where it'll, it'll that one, the bits of synuclein in the spinal fluid will cause the sample to clump together and aggregate.

And it's possible to detect that aggregation because you can put another chemical on this in this mix that lights up under fluorescence. So now we can say, okay, we can take a simple sample of spinal fluid, we can mix it with this seed, we can shake it up and we can detect the difference between those people who have Parkinson's disease and those people who do not. And that's sort of the basis of this very simple assay. Now of course, as we'll talk about in a moment, we'd love to be able to do this in something other than spinal fluid. And I think that will happen over time. But today the results are require spinal fluid sample to perform this test.

Maggie Kuhl: And so we see here on the screen that if the protein [inaudible 00:10:35] clumps, then Parkinson's disease is present, that the alpha-synuclein pathology is present. But Parkinson's is not the only disease that has that alpha-synuclein pathology. So would this test also work for similar disorders such as multiple system atrophy?

Ken Marek: So it turns out that the kind of synuclein in different diseases differs. While they all clump, they don't clump exactly in the same way. And that has an implication for how this test works. So it is possible to distinguish in between Parkinson's

disease patients and multiple system atrophy patients with this test, but multiple system atrophy patients still look a lot like normal people. So it's not perfect for that group, but the Parkinson's subjects are easily distinguishable from the other groups.

Maggie Kuhl: And Sohini, how we reached this point with this test of having the understanding and availability of this is actually a great story that I never tire of hearing because it's a little bit of detective work and ingenuity and passion from some foundation scientists. So if you wouldn't mind sharing that with us.

Sohini Chowdhury.: Absolutely, I would be happy to because you're right, it's an inspiring story and it actually really shows what we can accomplish when we really sort of focus on the opportunities and the possibilities. And so this assay was first developed, or this test was actually first developed for Prion disease, not for Parkinson's. And there was a publication about this test, the early development of this test in a scientific publication. And one of our researchers who focuses on biomarkers, she read about it and she thought to herself, "Wow, this is interesting because this has applicability for Parkinson's." And so she took that and she ran with it and she reached out to the investigator and she said, "Listen, I know you're not looking at Parkinson's, but I think you should, and we want to provide funding for you to figure out how this could be something that could be useful for Parkinson's disease and specifically for the alpha synuclein that we know exists within Parkinson's disease."

And so our research team continued to work with this investigator and his lab and helped support the ongoing development and then the improvements to this assay. And at a certain point in time we were like, "Wow, this is now, this is a pretty good test," because it had been tested in small populations and we were seeing some really interesting sort of data coming out that was saying to what Dr. Marek just shared. This assay is able to tell us with pretty high confidence who has Parkinson's. It can differentiate individuals who have Parkinson's disease from those who don't. And so we said to ourselves, "Well, but these studies are small, they're about 20 individuals or less. If we really want to understand is this a legitimate biomarker for Parkinson's disease, we need to ramp up that data."

And happily the Foundation has at its disposal the Parkinson's progression markers initiative study, which Dr. Marek leads, and many of you are familiar with it. And Maggie, if I could actually ask you to advanced to the next slide. Thank you. Many of you are familiar with the Parkinson's Progression Markers Initiative, or PPMI, as we like to call it in shorthand. And this is a study that the foundation established over a decade ago to collect information from individuals with Parkinson's disease, from individuals who do not have Parkinson's disease, and from individuals who are at risk for developing Parkinson's disease. And all of these individuals who are enrolled in PPMI have a lot of information collected on them. Clinical data, they have imaging scans, and they are incredibly giving in that they provide a lot of bio samples that can be

used exactly for the purposes that we're talking about today. And so when we really felt that this assay had gotten to a stage of development where it was exciting,

but we needed to now bust it out, so to speak. We had the assay integrated in PPMI, and actually that integration is ongoing. We're still having it tested on samples. And so actually the numbers that we have are actually higher than the ones on this slide, I think we're now at over 1500 samples that have been tested in PPMI.

But the fact remains the same, is that we were able to get access very, very quickly to samples generously provided by PPMI enrolled participants. And these participants again were unique in that they included individuals that we knew had a diagnosis of Parkinson's disease, that we knew were controlled participants did not have Parkinson's disease. And interestingly enough were individuals who do not have Parkinson's disease in that they were diagnosed, but who are at risk for Parkinson's disease. And so we were able to run that assay and generate the results. And given that large population, we were able to then say when the results came out, that they're there, that we saw in those smaller studies truly exists.

PART 1 OF 4 ENDS [00:15:04]

Maggie Kuhl: I just want to quote, so as I referenced at the top of our hour, this finding has been getting a lot of attention. And I want to quote a couple articles. One had a physician who's less involved with the study called PPMI, head and shoulders, the best resource we have in the Parkinson's disease research community. And another opinion piece said that PPMI launched in 2010, and all these people, these numbers on the screen have joined since then. And an opinion piece in Bloomberg quoted that sometimes answering big questions, like PPMI is trying to do, simply requires that kind of leap of faith of joining something or investing in something that we hope is going to have a big impact. I think the findings that we're talking about today have realized that impact. And so we really want to thank the participants, the donors, people who have signed on and took that leap of faith with us for the last 13 plus years. And now we're here sharing that we have made this discovery. So PPMI is a great resource. The people in it are true partners. And with that, Ken, perhaps we can go on and talk about how we know that this is a major breakthrough. What did the data show us among those PPMI participants?

Ken Marek: Yeah, sure. So I think, let me just add though, as what you said. It's always amazing to me the commitment of the participants in PPMI. This is a not an easy thing to do and to stick with for all these years. And I think it's entirely up to your persistence that we have these results today. So thank you for that. So as Sohini mentioned, what's important about this biomarker test is a couple of things. One is that it's accurate, it's highly accurate. In this slide you see that about 93% of individuals who had a diagnosis of Parkinson's disease, had an

abnormal assay test. So just to put that in perspective, when we look to tests of this sort, if you're above 90%, that's really very good. And it becomes likely as time goes on, becomes a usable test. Right now, a research test, but in the future, hopefully a clinical test.

Can I have the next slide, please.

So I think these next two slides I wanted to just show, go back to the beginning when Sohini described or defined a biomarker. And I guess the question is why do we need biomarkers? What's so important about them? And these next two slides illustrate that for this biomarker. The first is in individuals with Parkinson's disease. So in individuals with Parkinson's disease, this is a slide where we've tried to combine different measurements that we do in PPMI. This is a measurement on the x-axis of smell function, on the Y axis of brain imaging function. And the blue dots represent individuals who are assay positive and the open blue dots are assay negative. And what you're seeing if you look at the very top is that most of those blue dots are centered in the lower left quadrant. So those are individuals who have abnormal smell function, have abnormal dopamine imaging function, and are assay positive.

But you also see there are some people who have open dots, who looked to us as if they had Parkinson's disease, but they seem to not be assay positive. So I think this is really instructive, because those individuals probably have a different biology. They would require potentially different therapies and now we can detect who these individuals may be.

I'm sorry, if you go back to the next slide.

And we can ultimately treat them effectively. This is even more notable for individuals who have a genetic mutation with Parkinson's, like a LRRK 2 group. You see there about a third of them are SAA negative, they have a different biology. And it's only using these tools that we can understand that. So the clinical information is not adequate, doesn't tell us the difference, but these biologies tell us the difference. So this biomarker is crucial for that purpose.

Now, perhaps even more exciting is the idea that we can now use these biomarkers to identify individuals who have this synuclein problem even before symptoms arise. So this legitimately offers us the possibility that we can now intervene with medications that would prevent the onset of Parkinson's disease. This is not something we can do today, but it is something we're planning to start to test in the next two years. And you can see that for individuals who have reduced sense of smell, the majority of those people are already synuclein positive. Similarly, those who have what's called REM behavior disorder. On the other hand, those individuals who have a genetic mutation, those who are unaffected family members or people who are known to have a genetic mutation, only a small portion of them synuclein positive, but maybe those are people are ones we want to follow over time to see whether they ultimately

develop symptoms because again, this period gives us an opportunity to develop treatments that could prevent the onset of disease. The next one then, Sohini's going to focus some attention on.

Maggie Kuhl: Before we go into that, actually I wanted to ask Rachel because in her blog post she talked to [inaudible 00:22:36] who is a PPMI investigator who was involved in this analysis and he used a really great analogy to talk about how we're seeing varied results among people who have been diagnosed with Parkinson's disease. So Rach, maybe you could share that.

Rachel Dolhun: Well, this just really starts to give us a deeper window into what is exactly happening in Parkinson's, the biology of Parkinson's. So again, as everybody who lives with Parkinson's knows, the disease is very different from person to person, what symptoms there are, how those symptoms change over time, et cetera. But we've lumped everybody into the same basket. This now starts to give us a way to separate what's happening in different people and eventually to correlate those with different symptoms, different progressions, and so forth. But Un's analogy was a good one I think in the sense that if we say again, we've lumped everybody in the same basket. So if we call Parkinson's an apple, now we're starting to see maybe most of those apples, most of Parkinson's is a red apple, but some of them we're going to see are green, some maybe are red and green, maybe a fewer are yellow. And so we start to understand again more, go deeper inside the body, further than what we can now see on symptoms, on exam with watching how people change over time. And we're really starting to see exactly what is happening. The biology, you hear us say the biology a lot, but exactly what's happening in the cells inside the body of people with Parkinson's and why it's different from person to person.

Maggie Kuhl: Sohini, maybe you can pick this up as kind of was saying, turning it over to you for sort of the, so we started this talking about the promise of biomarkers. Now we have one, what are we going to do with it?

Sohini Chowdhury.: Yeah, so I think that when you think about why this is so exciting, it really has to come down with enabling more and better and faster clinical trials. And the reason I say that is because when you think about what a clinical trial is designed to do, it's designed to test whether a therapy is having an impact on an individual with a disease. So whether it's having an impact on the disease and is it safe and is it having a desired impact? Is it doing something good? Is the individual with the disease benefiting from it?

And so right now, Rachel said it beautifully, right now, up till now, we've always had to look at the symptoms and I don't need to tell individuals who have Parkinson's or individuals who know people with Parkinson's that the presentation of the disease to symptoms can change day to day. It can be affected by how you sleep, whether you have stress in your life, whatever it may be. So the fact that up until recently before we have a biomarker, your way of judging whether a therapy is having an impact is very much relegated to looking

at symptoms in the measurement of symptoms is problematic because you're not really getting a sense of whether the actual disease itself, the biology, is being impacted.

And so on one hand this is extremely exciting because you're able to bring it back down to the biology. If you have the presence of synuclein, you're able to kind of say, is there something happening? Is there something in the biology of the individual that is changing with the disease? Rachel also used that analogy of the apples, which is great because this, it holds true for trials as well. You want to make sure that when you're testing a therapy, you're testing it in the individuals that are right for that particular therapy. And so we've known for a long time that there's probably subsets of disease, people are experiencing a different journey with the disease. But again, it was made complicated by the fact that we always looked at the symptoms. But now we can say, "Well, maybe if you're having synuclein targeted therapy, it's incredibly important that everyone who is enrolled in that trial actually be SAA positive." Because we saw through the slides that Dr. Marek shared that there are individuals in our Parkinson's group that were not SAA positive. There are individuals who have genetic mutations who are not. So we would want to make sure that we are getting the right people in the trial to really understand whether the therapy's having the desired impact.

And then it also allows us to, I think this is very interesting and this is a little bit forward-thinking, but it allows us to not just think about treatments here and today, but also to think about a future of preventing the disease, and particularly the data that Dr. Marek showed about the results in individuals who have risk factors for Parkinson's. If you are able to identify individuals at risk with Parkinson's because they have that biological anchor we know exists in Parkinson's, we're able to detect alpha synuclein even if the disease is not manifesting, there are no clinical symptoms. You could theoretically, and this is actually turning into reality slowly, but you could eventually run prevention studies and see whether you can prevent the manifestation of the disease ever happening.

So there's a lot of reasons why it's so exciting. But at the end of the day, it really comes down to with a biomarker, the whole landscape of thinking about how we choose the right people for the trial, how we determine what to measure to understand whether a drug is having an impact and how we decide when to intervene. All of that changes and becomes more rigorous because it's grounded in biology. And we can measure that biology, we can detect that biology, and that's really exciting.

I do want to just add one last comment. We talk about prevention here, but I want to say that this isn't just about prevention. When you have a biomarker, it allows us to be able to run more trials focusing on different sort of approaches to the disease, and to have a better sense of confidence about whether we can get a right readout, that benefits the entire Parkinson's community. It benefits

people who have Parkinson's now, because even if you may not be in the trial population, if you have that biological anchor, you can profit from that potential therapy. And I think that's the big message here is that this can really benefit everybody with Parkinson's disease because it allows us to run more trials because they're cheaper, they can happen faster, and we can have more confidence in the accuracy of the results and how those results in that small trial population can be then leveraged and applied to the broader Parkinson patient community.

Maggie Kuhl: Thank you for making that note. I was going to ask that question. I know it's something we've got today in our Q& A box and have heard over the last week as we've been sharing this, what does this mean for people who already have Parkinson's disease? And I think you said it

That there are a lot of therapies and there is a lot of hope on the horizon and this sort of lifts all boats for all. I want to ask a couple other follow up questions. You referenced nucleon therapies and we have gotten the question, are there therapies in trials to de-clump or prevent the aggregation of alpha synuclein? So Ken, there are, the answer is yes, many. So maybe you could give us a little bit more on that.

PART 2 OF 4 ENDS [00:30:04]

Ken Marek: Yes, part of the excitement is that there is a very robust pipeline of drugs that are waiting to be tested in Parkinson's disease. And if we, as Sohini points out, what we want to do is test them in the smartest way, in the most efficient way possible. And so this biomarker will really help to enable that and will, I think, benefit both people who are at risk and people who have disease.

But there are a number of different strategies to try to prevent the clumping of synuclein and well, actually both the clumping and the spread of synuclein. Some of these have been tested in small trials already and continue to be making their way through the drug development process. There are synuclein antibodies that are akin to a amyloid antibodies that have recently been approved as a drug for Parkinson's disease, for Alzheimer's disease.

Another strategy really addresses the different ways to prevent the clumping of synuclein from occurring in maybe pills or other approaches. There may be other genetic approaches that are being used. So there are a lot of different options that are being developed and will be tested. As I would say again, that one of the real key needs, in order to make these tests move forward effectively, is to have relevant biomarkers to give everyone the confidence that these drugs are being tested in the right people and so that we can make decisions based on the results of these clinical trials. So this biomarker and clinical drug availability for testing go hand-in-hand. And happily, this is a very robust moment for these types of drugs.

Maggie Kuhl: And I want to make the point that people have asked about synuclein targeting therapies, there are a lot there. But the biology of Parkinson's is so complex that even if a drug's target is not directly alpha synuclein, if it's another pathway, or another modifier, there could be real utility to this test for advancing a swath of the therapies that are already or close to trials.

So we don't mean to give the impression that this test will only work for the number of therapies that we position as targeting alpha synuclein directly. This will likely have broader application.

Ken Marek: Yes, I would agree with you entirely. And this sort of speaks to the other issue I think we wanted to raise, which, this is just the beginning of a story. Now that we can begin to understand who has this synuclein pathology, we can also understand and identify other biomarkers that are going to sort of modify synuclein. And I think that's where I think many of these other drugs that may be targeting the immune system or the other parts of this, the mitochondrial system in cells, they are likely also going to be benefited by having this test available to select the subjects who would be enrolled in those studies as well.

Rachel Dolhun: I would also just add Maggie, that I think what is also exciting is that it allows us now to look deeper in studies like PPMI in individuals who are SAA negative but are presenting with Parkinson's disease, the features of Parkinson's disease. And to better understand that biology, or those biologies if they're multiple, so that we can really start to get a handle on the different biologies inherent in what we call Parkinson's disease now, the symptoms that are part of this Parkinson's, the part of the umbrella of Parkinson's disease, and to understand those journeys and to figure out how to best treat those individuals.

So you begin to actually really move forward and make tangible an idea of a personalized medicine approach where your biology of the disease you have is really informing the way your treatment should be oriented. And I think that's extremely exciting because we've seen how a personalized approach in oncology, for example, how effective that can be in really improving the impact of treatments when they're really targeting the right biology. And in the case of oncology, of the right type of cancer or biological process, biology underpinning the tumors that an individual will have, for example.

Maggie Kuhl: Yes. So we are not putting the green or the yellow apples back on the shelf for [inaudible 00:35:35] by any means.

Rachel Dolhun: No.

Maggie Kuhl: We are equal opportunity apple enthusiasts, love a granny smith. Okay Rachel, so we have gotten the question, we've talked a lot about the research impact of this test. Very deep research impact, clinical impact. If you have Parkinson's today, if you have a risk factor, a family member with Parkinson's, there is a test

available that does the seating amplification assay. What do you tell people who fall into those camps about that test and if they should pursue?

Rachel Dolhun: So first I'll say we've appropriately so been focusing on the research aspect of this because it's a research breakthrough. It's ready, as you've heard from Ken, Sohini, and Maggie, this is ready for research. It's being used in research and it has huge and widespread implications for how we do our trials, how the trials run and on and on.

Clinically, it's a little bit different. I will say right now it has the potential to really make huge changes in how we diagnose and how we care for people with Parkinson's. But when we think about it as it exists today, so let's take a step back and just remind everyone again, I'm sure most people know and have experienced how Parkinson's is diagnosed today. And that's through an examination by your Parkinson's doctor, a movement disorder specialist, who watches you walk, move your hands like this, see how quickly and how big you're making movements.

And that's how we make the diagnosis. We look for the motor symptoms: slowness, tremors, stiffness, maybe some walking changes. That's how we are able to and how we've been able to diagnose the disease. And as you heard Sohini mention earlier, how we also track changes in our clinical trials. So you can see how it's the best we have and we use it as ideally as we can, but how this can have some implications for how quickly trials can move and also how confident we can be in the results.

So when we think about this clinically today, for somebody who's living with Parkinson's, this is a tool that, or somebody who's concerned about Parkinson's, maybe has early symptoms of Parkinson's, this is a tool that can really help support your doctor's diagnosis. In a sense, it's a complimentary piece of information. It doesn't by itself tell us yes or no, you have Parkinson's, it tells us yes or no, your alpha synuclein protein is abnormal at the time of the test.

And again, I don't know that we said this out loud, but just to reinforce that point, it's a yes/no test right now. Future of it is, we hopefully will be able to measure exact numbers, follow that over time. But right now it's, at the time of the test, do you have the abnormal protein or do you not?

So now, if we take some of these scenarios, Maggie, that you pointed out, if I'm living with Parkinson's and I've been diagnosed, I trust my doctor, I'm confident in the diagnosis, I'm responding to the medication. I have the classic symptoms of Parkinson's. This test may not have significant implications for your care or how things would, what we'd be able to tell you about your Parkinson's today. So again, for some people, it may offer that extra piece of data, that sort of tangible piece of information to hold onto to support your doctor's diagnosis.

But it may or may not be necessary. Somebody who's a little bit earlier on in their journey to diagnosis, maybe there's some symptoms there that are mild and we're not quite exactly sure or we can't a hundred percent say it Parkinson's, maybe this could help us, again in the context of your doctor's examination, your medical history and discussion with a Parkinson's doctor for people who maybe have a risk factor.

So Ken mentioned smell loss, acting out your dreams. These, in some people, are some of the earliest indicators of Parkinson's. Meaning that in some people who have these symptoms, they may go on years or even decades later to develop Parkinson's. We've also seen in the study, as Ken pointed out through the data, that a lot of people who have these early signs or these early potential indicators do have a positive SAA, positive alpha synuclein spinal fluid test.

The decision whether to get this test, if you have smell loss, if you act out your dreams, even if you're worried because you have a family history of Parkinson's. Really an individual and very personal decision, something that you should talk with a movement disorder specialist about. Mainly to get the information and the context about what can this and can't this tell me. What will we do with the information?

I didn't say that out loud, but when we think about tests as doctors, or even as patients undergoing tests, we want to know what are we going to do with the information? Is it worth the time and the energy and the potential risks of the test, et cetera. And so when you think about whether or not to pursue this test, again in conjunction with your movement disorder specialist and after discussion, it's really about what is this information going to do for you? Is it going to help you feel empowered, knowing more about yourself, maybe potentially joining a clinical trial? Or does it have the possibility of making you more concerned and worried about what your future may hold?

So it really goes down to this is, as you said, this test is available but it comes down to individual, personal, case-by-case basis. And it's really important to think about talking to a movement disorder specialist, seeing a Parkinson's doctor before you'd consider pursuing this test, so you get all of the information, going in fully informed and aware of what the test can and can't tell you and what you do with that information.

Maggie Kuhl: I know we're getting a lot of questions about how you access the test and how much it costs and where you have it. So we'll just say the test is called Syntap, S-Y-N-T-A-P. You can talk to your doctor about it. You can look it up more online. There are a lot of nuances of cost and process, et cetera. So you'll have to explore for yourself what that would mean to engage with the test. But the information is available through some of our communications around this and through the test's website.

Rachel Dolhun: And I can say too on that, again, talk to your doctor. It does, as we've talked about, it does require a spinal tap or a lumbar puncture, which means that we are taking spinal fluid out. It's a relatively common and benign procedure, but not without risk. So the test itself can be, for some people, fairly invasive. It's not yet covered by insurance. So something, too, to think about cost. Talk to your doctor, talk to the company that runs the test, your insurer, so that you know about potential costs before pursuing.

Maggie Kuhl: So maybe that leads us to our last slide here to what's next. I think we've already discussed some of the hopes to move this out of spinal fluid, but also I think right now, as you said Rachel, the test is positive or negative. And especially for our audience who are living with Parkinson's today, our aims to make it more quantitative or have more data points rather than a binary yes/no could potentially have impacts. So Ken, maybe you could tell us about future hopes for, as you said, this is the start of the story. What's the rest?

Ken Marek: Yeah, there are a number of plans and opportunities to gather more information. I think everyone is probably, is realizing from our discussion so far, is that we need more information. This is really exciting. But we need to learn more about how best to take advantage of this test as we continue to accelerate the therapeutics for trials and Parkinson's disease.

So one important way would be to be able to measure the how, or determine whether that the amount of the synuclein in the test can be measured and whether that correlates with the severity of the illness. So this is something that is not yet available, but are hopeful it will be possible to quantify this outcome in the relatively near future. What is relative? It's hard to know, but probably maybe a couple of years it will take. In the meantime, the yes/no test is still quite valuable. But this would, of course, be an area which is going to make it much more desirable.

As we already discussed, it would be much easier to take advantage of this if it didn't require spinal fluid. So if it was available in blood, or skin biopsies, or nasal swabs, or saliva, all of those are also being tested and there's reason to believe that it's very likely that as time goes on, it will be possible to take advantage of this test using one of these other body fluids than spinal fluid. I think there are lots of other questions about this which are really going to be important

... in both helping us to understand and define the early stage of Parkinson's disease and how Parkinson's disease progresses.

And that's really the key to this. And in so many ways, this will help us to be able to effectively test therapies for Parkinson's disease. But for an example, we would like to know when do people first start to get synuclein in their brain? Is it in their fifties? Is it in their sixties? Why is it that some people may have

synuclein in their brain and never have any problems at all and others will develop Parkinson's disease?

So now we can begin to really address these issues more directly. And then this is really going to lead us to opportunities for new therapies and speed the therapies that are already being tested today.

PART 3 OF 4 ENDS [00:45:04]

Maggie Kuhl: So I just want to wind down and transition to our Q and A period by saying that these findings were possible because of PPMI. You can join PPMI. Nearly everyone in the United States can join PPMI in some way, shape or form, as can many people outside of the US. I saw on the Q and A list, a lot of people who are with us who have been in PPMI for years, a decade or more. Thank you. Please join them.

We are looking for people especially who have been recently diagnosed with Parkinson's in the last two years, or with that REM sleep behavior disorder that Ken described. Also, anyone who is age 60 or older without Parkinson's for that smell loss category, we're screening for that. So please visit our website. There's a link on your screen. Share broadly, share often.

All right, let's get to Q and A. So we had a couple come through beforehand and now our team's going to be sort of sending me a couple from our current chat, but I wanted to start with something that I think we have covered in our time together, but I also think is worth just asking very pointedly. So we got the question Sohini, I'll direct this one to you. Will this help us develop a cure for Parkinson's disease?

Sohini Chowdhury.: So the short answer is yes, it will, because this, it's the first time that we are able to go past the symptoms of the disease and go to the underlying biology of the disease. In and of itself, it is a huge advance, but what it allows us now to do is to understand this biological anchor, this test vis-a-vis other aspects of the disease we know, and to begin to peel the layers of the onion back and really understand what it is we're dealing with in the individual who's presenting with the disease.

And to Ken's point, going earlier and earlier, people who may not have the disease but may go on to develop the disease. So what this allows us to basically do is start to focus on the disease itself and not the clinical symptoms. And that is a huge change. It also allows us to start to target, to target our therapies to the right individuals.

And that matters a lot because we talked, both Ken and Rachel mentioned some of the successes that we've seen in Alzheimer's. I don't know how many people are aware that in the eighties and nineties, what we found out retrospectively as we developed biomarkers for Alzheimer's is that up to 30% of individuals in

some of those early Alzheimer's trials did not have the biology that is associated with Alzheimer's disease. And that's a pretty high percentage.

And what that means is that the results that came out of those trials were probably really significantly affected and impacted. And so it gives you a sense of why biology matters and the ability to measure the biology matters, because it allows us to actually go to the right individuals with the right therapy at the right time point. And that essentially means that we are that much closer to a cure because we're able to now focus on the disease itself and not solely the clinical manifestations of the disease.

Maggie Kuhl: Thank you. Okay. Next question for Ken. We talked about multiple system atrophies specifically. We got a number of questions around Lewy body dementia and other Parkinsonisms and the ability of this test to either diagnose or differentiate between those.

Ken Marek: Yeah, that's a great question and I think it's one of the true advantages of focusing on biology, is that some of these different syndromes that are defined by their clinical features kind of come together. And so we know and have known for many years of course, that people with Lew body dementia also have synuclein in their brain, the same kind of synuclein. And indeed they are positive on this test, there's no doubt.

So now we can begin to think about yet another question I posed a few questions earlier, which is that why is it that some people who have a positive on this test and have synuclein seem to have predominantly cognitive problems early on, and some people have motor problems early on?

That's an important question that we can now address directly and really develop, again, much more targeted kinds of treatments for each of these types of symptoms moving forward. But I think, so this enables us to refocus our thinking to understand these types of diseases based on their biology. And it turns out that the underlying pathology of between at least Parkinson's disease and Lewy body dementia or diffuse Lewy body disease is the same. And that has really important implications as we move forward and think about how we're going to develop therapies for these problems.

Maggie Kuhl: A similar differentiation question. So again, I know we talked about this, but some of these points I think are just so worth repeating. So someone had commented, am I right then that this test does not have utility for people with a LRRK2 or GBA mutation in Parkinson's? And I think the answer's going to be no. But I would like you to say in your own words why that might be the case.

Ken Marek: No, I would say absolutely yes, it has-

Maggie Kuhl: Yes, it will have, yeah. It's sort of a double negative, so I didn't mean to confuse you.

Ken Marek: So I think it has important implications for individuals who have a gene mutation. I think certainly for individuals with Parkinson's diseases, it's particularly important because we've learned that maybe particularly with LRRK2, that there are people who are SF positive, people who are SF negative. We need to understand that so we can figure out the best way in the future to treat both of those individuals and to understand the biology that contributes to those both of those individuals.

For individuals who are at risk, who simply have a mutation but have no symptoms, I think we go back to what Rachel said. I think that's a much more difficult decision and a personal decision as to whether one wants to gather additional information at this time to add to your knowledge base about your own biology and your family's biology. But I think that for today, that that's really a decision of that sort. But we hope that in the not too distant future, there might be legitimate therapies that could be initiated during that at-risk period that might make it more valuable to have this type of test at that time.

Maggie Kuhl: Okay. I'm going to put you on the spot, Rachel, and ask what I think is assigned this least favorite question, but it's usually the one that we get from the patient community, which is when do we think this might be more of a widespread test or accepted practice we can talk about in research and in clinical care?

Rachel Dolhun: Yeah. Well again, I think it's ready for research and we will start to see it immediately become more widely utilized when people are joining trials. Again, back to what we've talked about extensively here, especially for the trials that are testing therapies against alpha synuclein.

But in general clinically, we want to make sure that we've got the data, that we've got utility for the test, that it's informing our decision making. So as Ken said, we've got questions, we need more data. So as we build that more data, you will start to see it as more of a general practice. And it also, again, at the same time, we may start to see some shifting in how we think about diagnosing Parkinson's.

So in tandem, this may help help move us into that future of how do we diagnose Parkinson's and how do we separate the clinical care Sohini was mentioning in the future where we get more to this personalized medicine where we're looking at all this data and saying, 'This drug maybe is the best one for you because you have the positive test. This one's maybe the best for you because you have a negative test." And so as we move forward to understanding more and developing more targeted therapies, we will get to that more personalized precision type medicine.

Maggie Kuhl: In our last couple minutes, Ken, I wanted to perhaps just give you the floor for some last words. As we've said, PPMI launched in 2010. We had this vision of this need and a roadmap to get there. And it seems like we have hit a significant milestone in that effort and in our overall effort to develop new treatments and

cures for Parkinson's. So what does it feel like? What are you thinking and feeling over these last few weeks? What do you want to share with the Parkinson's community with us today?

Ken Marek: Well, thank you for that opportunity. I think you're absolutely right. This is really a moment to stand back and take notice and say, we have really as a community accomplished something that's really important. Certainly PPMI was established more than a dozen years ago with the idea that we might identify tools like this, biomarkers like this that could really, really be paradigm shifts in our ability to define Parkinson's disease and ultimately develop therapies for Parkinson's disease.

And it's, now we have one. And that is only because we were absolutely ready, having had many on this call being participants for years contributing spinal fluid for years, going to see their physicians for years. And this is a tough task, but I think it's what's required in order to really move forward.

And also, of course, I have to single out the Fox Foundation for its vision in initiating PPMI a dozen years ago. Now we look back and we think, oh, well, of course that would've been something we would've done. But when we started, that was not the case. And it was not the case that we said, oh yeah, we should collect spinal fluid in everybody. And honestly, all of the physicians who were at the site said, "That's never going to happen." And we learned that if we explain this to participants carefully and effectively, of course it would happen because people wanted to move forward and find better biomarkers and of course, better treatments.

So it's a very exciting moment. I'm very grateful, especially to the participants in PPMI and their continued participation. Your job is not over yet, and I think we're just at the start of what is going to be a really, very much accelerated process to develop new research and new therapies. So thank you.

Maggie Kuhl: Thank you, Ken. Yes. The job's not over. We need to capitalize in this momentum. So please join us if you haven't already in PPMI and thank you for joining us today.

So thank you again. Thank you to our panel and yeah, toward the next breakthrough.

Speaker 1: Did you enjoy this podcast? Share it with a friend or leave a review on iTunes. It helps listeners like you find and support our mission. Learn more about the Michael J. Fox foundation at michaeljfox.org. Thanks for listening.

Michael J Fox: This is Michael J. Fox. Thanks for listening to this podcast. Learn more about the Michael J. Fox Foundation's work and how you can help speed a cure at michaeljfox.org.

PART 4 OF 4 ENDS [00:59:15]