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Announcer: Navigating Parkinson's disease can be challenging, but we're 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](http://michaeljfox.org).

Maggie Kuhl: Welcome to the newest episode of our Parkinson's Science POV Series. It's been a little over a year since the announcement of a new biomarker for Parkinson's that ushered in a new era of Parkinson's research. Since then, we've taken many critical steps forward getting us that much closer to better treatments and a cure.

I'm Maggie Kuhl, Vice President of Patient Engagement at The Michael J. Fox Foundation. And with me are our co-chief scientific officers Dr. Mark Frasier and Dr. Brian Fiske to talk about what's new with the alpha-synuclein seed amplification assay. Mark and Brian, thanks for joining me for this update.

Mark Frasier, PhD: Thanks for having us, Maggie.

Brian Fiske, PhD: Always fun.

Maggie Kuhl: Always. Mark, why don't you get us started? Like I said, it's been about a year, a bit more. Can you remind us what is the alpha-synuclein seeding amplification assay or  $\alpha$ Syn-SAA for short?

Mark Frasier, PhD: Sure. I mean, besides being a mouthful to say, the seed amplification assay is a laboratory test that has really changed the face of Parkinson's disease. Until it was developed, the only way to see one of the main hallmarks of Parkinson's disease was looking at a brain under a microscope after someone passes with Parkinson's disease. And that would visualize a protein called alpha-synuclein. And this is a protein that clumps in the brain and throughout the body of people with Parkinson's.

And what this SAA test does is for the first time, it enables researchers to measure the clumped alpha-synuclein in living people. So right now it's a spinal fluid test, so it requires a lumbar puncture to get some spinal fluid. And the test takes a drop of spinal fluid, mixes it in a test tube with some other chemicals, and enables one to see this clumping of alpha-synuclein after you shake the spinal fluid in a test tube.

And what's remarkable is that pretty much about 90 to 92% of people with Parkinson's disease test positive for this seed amplification test. So it's extremely sensitive and accurate for detecting Parkinson's disease. And what's even more intriguing is that it seems to be able to be testing positive in people prior to being diagnosed with Parkinson's disease, suggesting that it's detecting some early biological changes that are contributing to Parkinson's, but even before

symptoms develop and someone complains to their doctor with a tremor or slowness or stiffness.

So why is this big? Well, it's big because you can imagine using it to identify Parkinson's earlier, but it also enables researchers to really confirm that this alpha-synuclein is present in people that are being enrolled for clinical testing. So it's a tool that clinical trials can use to confirm and enroll people that have the biology of Parkinson's disease.

Maggie Kuhl:

Fabulous. And just to give a quick thank you to all the volunteers who contributed to research studies that helped toward this biomarker. Like you said, it's in spinal fluid right now. That required many people to have lumbar punctures and to share a lot more data and assessments. So if you have participated in research, thank you for helping us make these advances.

Brian, tell us a bit about how this biomarker is changing the definition of Parkinson's, how we think about the different types and progression and stages of this very complex, very heterogeneous met one person with Parkinson's, met one person with Parkinson's disease.

Brian Fiske, PhD:

Yeah, I think you'll often hear us use this phrase, we're now in the biological era of Parkinson's disease. And I think it's helpful probably to put that in context. What that doesn't mean is this is now the first time we realized there's an underlying biology involved in Parkinson's disease. Certainly we've known that for many years. And if anything, the early genetic studies in the late '90s were really the probably major studies that put a clear biological pin in the map, if you will, of underlying cause of the Parkinson's.

But until now, we never really had the tools to measure that biology in people. And that's I think again really with the power of the seeding amplification assay. Where that has really brought us today is into this era of now being able to assess the biology of the disease again in living people. How's that being used? I think what's really exciting right now is it gives us an opportunity to start looking at people with the symptoms of Parkinson's disease to obviously measure whether they exhibit the signal, this seeding assay signal, whether they're positive on that test or not.

And not only in people with the symptoms of Parkinson's, but we know there are other related disorders where people for years have known there is clumping of synuclein in the brain in certain neurons that might be related to degeneration in those diseases. Dementia with Lewy bodies being a good example. Where we're now starting to look more broadly at these populations of people and ask the question, biologically, do all these people share a similar biological disease and just have different clinical maybe outcomes of that disease?

And so with that concept, we're now starting to build a framework that is more almost redefining not only what Parkinson's is, but maybe what some of these other diseases are, but re-centering that definition around the idea of a shared biology. So can we use a test like the seeding assay test? And again, obviously we'd love to see it expanded and optimized and maybe moved out of the spinal

fluid, things like that, obviously to make it more practical. But with that type of measurement tool, we can start to now create a biologically centered definition of the disease.

And we're starting to see that people pick up that idea and now really start to frame, okay, in that context then, what is Parkinson's and what does its progression look like and what are the different forms that progression can take? And we're starting to see groups, including efforts led by the Parkinson's Progression Markers Initiative, to establish frameworks that can better stage the disease.

It's really important because we're finding that when you use traditional clinical definitions of disease, a good example is we tend to call people who are newly diagnosed de novo Parkinson's disease or newly diagnosed Parkinson's disease, and very often this is a very important group of people to find, especially for therapeutic trials or other types of studies because you want to try to understand the disease or intervene on the disease as early as possible.

But we're actually finding now with the biology tools that we have and this reframing of the disease staging that people in that group are actually much more heterogeneous than we appreciated. So they're not really a single simple early Parkinson's, they actually represent a range of stages of Parkinson's disease. And I think that type of concept really wasn't possible until we actually had a tool like the seeding assay to start to explore that and to really understand when Parkinson's might be beginning and what are the earliest signs.

When they're newly diagnosed, often that is driven by a lot of factors like simply the time when they finally felt their symptoms were worse enough to go to a doctor or their doctor finally was willing to accept a diagnosis of Parkinson's disease. And that can vary quite a bit. So I think these types of frameworks are really important because both taking the clinical side and the use of these biology tools that we have now, we can really start to not only again redefine Parkinson's and related synuclein disorders, but also really understand the progression in a much more detailed way.

Mark Frasier, PhD:

I kind of think about it like going to an optometrist when you're checking your eyes and you compare camera one to camera two and certain lenses increase the resolution of what you're seeing, of the letters that you're seeing. And what these tools are doing are increasing the resolution of what is happening both biologically and clinically.

And so if you look at a group of people that have been diagnosed in the last two years, you think they might be all the same if you look at their clinical symptoms. But when you combine these biological tools like SAA, you're actually seeing very distinct differences between that group that are meaningful and actually could impact ultimately research trials, but ultimately care and treatment.

Maggie Kuhl:

So update one in the last year is that we have increased the clarity of the definition of this alpha-synuclein disease perhaps beyond people who have been clinically diagnosed with Parkinson's. And we also are looking at how the stages

of that disease change over time relative to someone's symptoms or perhaps other markers. But Mark, right now the test is positive or negative.

You have this SAA positivity or you don't. And so we have made some major investments in the past year to try and get to a place where this test can tell us a bit more about the disease. Can you tell us about those investments and those projects and what we hope to learn?

Mark Frasier, PhD: Sure. And you're right, it is the beginning, but certainly far from the end and there needs to be some improvement on this test and development of others. But for the SAA right now, as you said, it's binary and so you can detect the biology or not. But what we'd love to have is a measure that's quantitative so that you could understand not just whether it's there or not, the pathology, but how much is there?

And if you intervene with the treatment, do you actually decrease the percentages and do you actually decrease this clumping of alpha-synuclein? How much do you decrease it by and what does that mean from a patient perspective? And so we are making some significance investments across different groups and universities and biotech companies, diagnostic companies that are trying to develop quantitative measurements of the seed amplification assay.

And there's been a number of different innovative creative engineering approaches to try to do that. And I'm optimistic that we'll get there. There's already been some promise so far. The other area that is really important that we've made investments in is to go beyond spinal fluid. Obviously a spinal tap is not something everyone wants. And excitingly, there have been some initial publications by single groups showing that this SAA could be used in blood and maybe even skin biopsies.

And so we're funding many different researchers to develop standardized protocols for fluids outside of spinal fluid that could be more accessible, easily obtained with the blood draw to measure SAA in those individuals. So both areas are promising. I'm hopeful that the breakthrough last year is the first of many that will just improve the SAA test and its ability to understand quantitatively and biologically where people are along the disease spectrum.

Maggie Kuhl: Yeah, Brian, as you said, many people listening can probably relate to the long road to diagnosis that they had. And imagine if there was a blood test just like cholesterol levels, for example, where you could get a more definitive answer and go from there much earlier to hopefully better outcome. You also mentioned though, Mark, that this test says positive in about 90% of people who have been diagnosed with Parkinson's disease. Brian, what about that other 10%?

Brian Fiske, PhD: Yeah, no, it's an important question. And not only that, other 10% of traditional what we call sporadic PD. But if you are someone who carries certain genetic mutations like in a gene called LRRK2, we found that only about 60% or so those individuals are positive on the seeding test, on the synuclein test, while the other 30 to 40% may not be. So it's an interesting question about what is

happening in these other individuals who clearly have symptoms of Parkinson's disease but don't seem to be positive on that test.

So one answer might be that because the test is currently yes or no, some of these individuals might actually be positive, they're just right below the detection threshold. And so if we had a more quantitative measurement tool, we might be able to pick up some of these individuals and maybe they're just slightly below the surface, if you will, of the test. But it could be that some of these individuals truly don't exhibit the same kind of alpha-synuclein pathology, alpha-synuclein clumping in the brain that other people do.

And so something else may be leading to the cell loss that causes their Parkinson's symptoms. And we know that already a little bit from, again, studies of people who've passed away with Parkinson's, including people with the genetic forms. We do occasionally see people who don't have the synuclein clumps in the brain. They have maybe other types of protein pathology, other types of hallmarks, if you will, of what's going on in their brain, even though they had the loss of the dopamine cells and had the symptoms of Parkinson's.

We already knew that this might be the case, but now this test is giving us a way to maybe see that obviously before the person passes away when they're living. So what could these people have? It could be a whole range of biological triggers and pathways that people are exploring that might contribute more to disease in these stages. A lot of people, for example, are very interested in the role of the energy producing functions in our cell, so-called mitochondria, for example, that people think might be disrupted in some forms of Parkinson's.

It might contribute also to people with the alpha-synuclein associated forms of Parkinson's, but maybe it's more robust perhaps in people with these non-synuclein associated Parkinson's disease, in which case maybe their pathway then is a little bit different. So we would need other kinds of measurement tools. And luckily, we're doing a lot of work to actually look at those types of tools. We actually just had a workshop a couple of weeks ago with research experts who are specifically trying to develop, for example, better measurement tools around the mitochondria.

So can we actually assess that cellular pathway in a more definitive way in people with Parkinson's? And so I think those tools could end up being helpful perhaps in exploring what some of these other individuals, what they have if they don't have synuclein associated Parkinson's, maybe they have mitochondrial associated Parkinson's or some other cellular pathology that might be driving their degeneration.

Maggie Kuhl:

Parkinson's is such a complex disease. I sometimes like to think of it more as an opportunity though than a challenge where there's so many ways that we may be able to stop this. And some of them may be more upstream of exactly what has started this process, but some of them may be more downstream.

And so no matter what has set you on that highway toward Parkinson's, no matter what your entry onto that on-ramp was, if we address something like

inflammation, for example, which may be a little bit more downstream, no matter what type of disease someone has, it might be effective. And so there are a number of therapies against multiple targets that are in testing, and we think that they could still work for a broad population.

And I also want to emphasize that for people who may have some of those genetic factors or even if they know their alpha-synuclein seeding amplification assay status and they are negative, right now that does not change their clinical care or their treatment that they're receiving. The therapies that we have that are approved to ease Parkinson's symptoms are still effective and recommended for people with that biology. Brian, anything else to say about that?

Brian Fiske, PhD:

Yeah. I think you're raising a really important point that would probably be helpful for people to understand, which is right now if you show up positive on the seeding amplification assay for synuclein, that doesn't actually say that your Parkinson's was caused by accumulation of alpha-synuclein in the brain causing your dopamine-producing cells to die off and giving you the symptoms of Parkinson's. It might be. And certainly good data suggests that that synuclein as a pathology may contribute to the disease directly in that way.

But all the assay is saying is that if you're positive on that test is that you have small bits of alpha-synuclein in your spinal fluid that are prone to aggregate more prominently than someone who doesn't have who's negative on that test. So that doesn't really tell you... So it's important that we not put too much mechanistic value in that test yet because we just don't have the data to really show what that is actually telling us about the particular cause of that person's Parkinson's disease.

And I think that's a really important nuanced point as people continue to understand this biomarker tool that it's not telling you what caused your Parkinson's, it's just saying that you carry a biological state, if you will, that is suggestive of a shared biology with other people who are positive on that test. But we don't really know yet what the actual cause is, and we won't really know until we obviously start testing therapies that potentially target this pathology and reduce it and maybe show some benefit.

Mark Frasier, PhD:

I was just going to jump in and say I think it highlights what you were emphasizing, Brian, which is the need for additional laboratory tests that measure both synuclein and other biological pathways. Because we don't just measure cholesterol and cardiovascular disease, we measure HDL and LDL and many other analytes that we can detect in the blood.

And that entire constellation of tests really helps us understand the status and guides treatment decisions. So that's really where the field is going. This likely will be one of many tests that inform us about the type of biology that's occurring in Parkinson's disease.

Maggie Kuhl:

You've used the word constellation that I've always enjoyed in this realm. This is where I give a plug for continued research participation. So we have answered a lot of big questions with this new test built on the foundation of contributions

from volunteers. We still have a lot of questions to answer. Like Brian said, we're going to continue testing people who may be SAA negatives.

Mark, you just said there's lots more to look at. So our PPMI or Parkinson's Progression Markers Initiative study is a great way to get involved. There's an online platform for people aged 18 or older in the US with or without Parkinson's, and some of those participants may be invited to participate at a clinical site and to contribute other samples or scans or data.

So you can get involved at [michaeljfox.org/ppmi](http://michaeljfox.org/ppmi). Brian, earlier you talked about how this definition of the synuclein disease may extend to people who are not diagnosed with Parkinson's. And Mark, there's been some really interesting recent findings around SAA positivity in people with other brain diseases. Can you talk to us about how that crossover might be?

Mark Frasier, PhD: Yeah, I think it's a really exciting area of research. And in some ways really intriguing, in some ways not that surprising. And the reason I say not that surprising is that pathologists that have looked at brains under the microscope for many years and looked at brains of people that have died with Alzheimer's disease or Parkinson's disease have always recognized and reported the existence of, in particular Alzheimer's disease, amyloid pathology, but also sometimes they have alpha-synuclein accumulation in the brains of people with Alzheimer's disease.

But what's new is that these tests, this availability of the laboratory tests that can measure the different protein clumps that form across Alzheimer's and Parkinson's disease, these tests can be used in living people, in blood and spinal fluid. And some recent data just in the last couple of months has revealed that about 30 to 40% of people with Alzheimer's disease actually test positive for the SAA. Now, does that mean that they have Parkinson's disease? No, we don't think so. We think it means that they have accumulation of alpha-synuclein in their brains.

But why is this important? Well, it's important because it turns out that people that are SAA positive, it seems like that may contribute to their cognitive impairment in addition to the amyloid status. And so you can imagine how one might want to treat someone with Alzheimer's disease that has alpha-synuclein positive tests and an amyloid positive test with treatments that target each of those individual protein clumping or protein pathologies.

And so what these tests are revealing is this overlapping pathology that occurs in the different neurodegenerative disorders, and it's leading to new insights on how one might treat and target treatment to the specific pathology that is occurring in those individuals rather than just treating cognitive impairment or movement changes, motor disorders. It's really targeting the specific biology that can now be measured through these laboratory tests.

Maggie Kuhl: That's really what we mean by the biological era.

Mark Frasier, PhD: Exactly.

Maggie Kuhl: A lot of possibility there. But Brian, there are therapies that are in testing right now for Parkinson's, including against this alpha-synuclein protein. What does this new test and everything that we've been talking about mean for therapies in development?

Brian Fiske, PhD: Yeah, no, it's a really important question. We just at a recent meeting with a number of industry representatives there, and we were talking about the new biomarker and some of the new ways of thinking about defining Parkinson's and other related diseases, again, by their biology. You could tell in the room that I think drug makers are very interested I think in, of course, the idea of a more biology-defined disease.

That certainly makes their job much easier in the sense of really picking drugs and treatments that target that biology. If you can actually measure that biology in people, of course, that's a good thing. Whether they are ready to formally adopt the seeding assay tests in their trials in the sense of using it to actually select and enrich people in their trials with that particular biology, I don't think they're quite ready yet, probably for a lot of reasons.

One, I think the data still are relatively new, even though we've been talking about it for years. I think there's still more data that's needed to really understand the implications of this new biomarker tool. It's also, again, in spinal fluid, a lot of drug sponsors there. To put that into a trial, even though we've certainly shown in PPMI that you can do it repeatedly and people are very willing to do it for research purposes, operationally, it's a bit of a high bar for a lot of trials to be able to bring a test like that into their trials if they're recruiting hundreds of people into a trial.

So obviously if we could have a blood-based biological measurement tool, something like that, that would make that easier. But even with that, there are some sponsors, especially some of the leading sponsors who are developing alpha-synuclein directed therapies, who are at least starting to use the tool often in subsets of their trial populations just I think to start to get a feel for it.

So at least a couple of companies, Biogen with their alpha-synuclein immunotherapy and Roche with their immunotherapy approach, both of them have published and reported on early biomarker results from their trials suggesting at least that much like we saw in PPMI and other cohorts, they're able to identify and detect people who are positive on this test around the same rates generally as what we're seeing in PPMI.

So at least in principle, they're able to use the tool and find these individuals. But again, they're doing this after the fact. They've already done the trial. And this is really just in a subset of people they had the samples on, they did the analysis to just double-check that they had individuals that were positive on the test. Just recently, a company Vaxxinity reported on some results of their trial of a slightly different synuclein-directed therapy.



It's more of a vaccine approach. Using the tool actually to try to see if they could actually get a response, to see if there's a response of the seeding assay signal in people who receive the vaccine. So there's some interesting data just starting to explore whether not only could this be a tool for detecting and selecting people with, again, a synuclein associated Parkinson's disease, but maybe even if it would change if you gave someone some treatments.

So again, the data are super early right now. I don't think any drug makers really full-on ready to use this test in their trials, but I think they're very hungry and eager to see the insight that tools like this bring to their clinical trial approach. Because again, I think everybody agrees certainly a more biology focused centered approach to thinking about Parkinson's is only a good thing.

Mark Frasier, PhD: I would just add, I mean, just to emphasize the point that Brian just described, all of these companies are publishing the results of their tests and their trials, I think, which doesn't always happen. And the foundation just convened this meeting that Brian referenced to bring industry together to talk with regulators about how to use the different staging and the measurement of biology and clinical trials.

So this is a really big moment, I think, that's worth some attention to acknowledge that groups are sharing data, they're publishing results, they're collaborating, all with the goal of moving the field forward faster, which doesn't always happen in pharmaceutical industry.

Brian Fiske, PhD: There's another aspect to this question, which is what does a tool like this mean for treatments that don't directly target the alpha-synuclein pathology? And certainly there are many in the therapeutic pipeline being looked at and tested today. And I think the jury's still out on that. We don't really know yet if people, again, who exhibit the positive alpha-synuclein test, whether they would also respond to these other treatments or not. My initial assumption is probably yes.

Many of these treatments I think touch a broad range of biology that I think as you were getting at earlier, Maggie, might be downstream or upstream of the synuclein pathology. And so it could still be beneficial in people whether they have the seeding assay result or not. So I think the broader implications on the pipeline are still yet to be determined as we continue to get more data on this tool.

But also, again, a call-out for all the other biomarker tools that we need to really truly I think in a future state, we'd love to have a therapeutic pipeline that's built on this clear biological, mechanistic understanding of the disease so that we're really more precisely delivering the right treatment to the right individual for the right biology.

Maggie Kuhl: So just to recap the updates that we're sharing since we found this biomarker, we are looking across clinical diagnostic lines for who is positive in this test. We are looking within the Parkinson's diagnosis community to see the people who are negative, what is going on, and even people who are positive, what else is going on because we know there's going to be a lot of factors.

We've made some big investments in trying to make this test better, more accessible, more informative, and industry and drug developers are talking about this enabled by our foundation's efforts, which is such a unique and critical role that we play in this ecosystem. So this week I got one of those fun LinkedIn anniversary reminders. So I've been at the foundation more than a decade. You two as well. I think maybe closer to two decades.

Brian Fiske, PhD: Who's counting?

Maggie Kuhl: Me. But, this is a big breakthrough. And as we've talked about, there is a lot of momentum. So at this point with what you all have seen and have invested in this field, in this realm, how are you feeling? What do you think that this really means? And I think the question that most folks ask is, how close are we to a cure and how does this change that calculation? Mark, I'll ask you to go first.

Mark Frasier, PhD: Well, I mean, it's like on a daily occurrence that I have conversations about these tools and what's next and the rapid development and optimization of these tests. So I think things are going to change very quickly. The tests are going to be improved and more scalable and widely available. I think that will impact clinical trials. It's already impacting trials that were already run and they're reanalyzing the data.

So I just think the momentum is as strong as we've ever seen, and we're going to continue to see new therapies enter the pipeline because we have these tools available. And so we're closer than ever. I hesitate to give timelines, but this is really exciting, a really exciting space that we're in. And I feel like the face of Parkinson's, but also neurodegeneration is changing week to week as new data emerge.

Maggie Kuhl: Brian?

Brian Fiske, PhD: Yeah, I'll agree with Mark on that last point in particular, because I think the excitement is not just in Parkinson's, I think we're really seeing it across the neurodegenerative space. Approvals of treatments for Alzheimer's in recent years, again, largely driven by the availability of the right kinds of measurement tools to help really assess those treatments better. Again, maybe a little bit earlier stage in that than Alzheimer's, but we're getting there.

And with a little bit of our tools now, we really think in the next few years we can really start seeing the impact of those tools in clinical trials and clinical studies. I think for me too, over the last two decades, as you said, it's been powerful to see how big questions like this don't just get easily answered by single person in a lab chipping away at midnight on the problem. It really takes big group science to do this, to answer these questions, and also big risk-takers.

The fact that the foundation stepped in 10 plus years ago to just establish something like PPMI, the Parkinson's Progression Markers Initiative, to lay the groundwork for the clinical data and the bio sample resources needed to actually once the seeding assay data started to look good enough to actually very quickly

go in and verify that in large numbers of well-characterized samples and clinically characterized samples.

We wouldn't be here, I think, if those two things hadn't come together at that moment in time. So I think, again, as a proof point really for the power of big, large, expensive, yes, but critically important efforts like PPMI and other types of cohort efforts like that that have tried to really establish the resources needed to actually answer these questions quickly. So for me, that was, I think, really powerful to see as well.

Maggie Kuhl: We will continue to share updates on this field and others in Parkinson's science through our podcast and other channels. The thing that does not go unchanged is the need for research volunteers. And so you can visit, again, [michaeljfox.org/ppmi](http://michaeljfox.org/ppmi) to learn about that study or [foxtrialfinder.org](http://foxtrialfinder.org) to find many other studies and trials that need volunteers to move science forward. We've made so much momentum and I have no doubt that we will just pick up the speed in the next years to come. Thank you, Brian, thank you, Mark, for this conversation.

Brian Fiske, PhD: Always fun.

Mark Frasier, PhD: Thanks, Maggie. So fun. Always good to chat with you.

Maggie Kuhl: And thank you for listening. If you would like to learn more about how you can speed cures, you can visit our website at [michaeljfox.org/research](http://michaeljfox.org/research). We will catch you next time.

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