

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](http://michaeljfox.org).

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

Maggie Kuhl: Hi, and thank you for tuning into our Parkinson's Science POV podcast. I'm Maggie Kuhl, Vice President of Research Engagement at the Michael J. Fox Foundation, and I'm here with my friends and our Chief Scientific Officers, Dr. Mark Frasier and Dr. Brian Fiske. Nice to be back on the mic with you.

Dr. Mark Frasier: Hey, Maggie. How's it going?

Maggie Kuhl: Good.

Dr. Brian Fiske: Nice to see you again.

Maggie Kuhl: Yeah, and it's been a while. Summer 2022 is the last time that we recorded, and we've been busy since then. I should have said, "Thank you for listening to the award-winning Parkinson's Science POV podcast," because we won the Silver and the Listener's Choice, which I think we should take real big pride in, from the Signal Awards in the Science and Education Podcast Limited Series category. So yeah, thank you all for your listener support, and thank you Mark and Brian for producing such an award-winning cast here with me.

Dr. Brian Fiske: It's all credit to you and your great question asking.

Maggie Kuhl: Well, I'm not going to be asking the questions on this one actually because we went to the people for this episode. So science begets a lot of questions. So this is a special ask us anything episode of Parkinson's Science POV, where we gathered questions from social media and from our in-person events and our online events and called down to try and capture some categories or things that really rose to the top that a lot of people were asking about.

And a lot of questions came in around something that we talked about around this time last year. So in 2022, April, we talked, Mark, about this biomarker that was sort of on the horizon. And I have a little transcript here of you talking about this thing called a seeding assay, and it's really exciting to see some of the data coming out of it. So that was last year. Flash forward to April, May 2023 and a big paper came out, huge announcement around a biomarker breakthrough. So what's the last year been like for you in that sense?

Dr. Mark Frasier:

Oh, it's really been exciting, Maggie. It's not often that, as a scientist, you get to see new data every week that is positive and looks good. Oftentimes, there's frustration, and the world of science is a lot of disappointing experiments.

But the last year, and especially in the last six months, it's been really exciting because there have been results from the seeding assay pretty much on a weekly basis as PPMI samples are sent to be tested on the seeding assay, and results are returned pretty much every week. One of our investigators said it was like a new Netflix series being dropped every week, and the data were emerging, and they were just looking more and more exciting. And the results really confirmed what we suspected last year, and then some, which is the seeding assay has really high diagnostic accuracy for being positive in people with Parkinson's disease. It's an objective measure that is consistent with the diagnosis of Parkinson's disease.

But then interestingly, it also seems to detect this synuclein seeding in people at risk for developing Parkinson's disease. So it suggests that one might be able to identify people before the symptoms of Parkinson's disease emerge, the movement, the tremor, and ultimately, potentially intervene with therapeutics at an earlier stage.

So it's just been an exciting time. The publication came out recently, and there's been a lot of positive feedback from the research and the patient community.

Maggie Kuhl:

That's right. So if you would like to learn more about that biomarker breakthrough, there are blog posts and webinars and other podcasts, all accessible on our website, michaeljfox.org. But some people have been following the news and had some questions. So Mark, I'm going to kick off our ask us anything with some of the questions that we got around this alpha-synuclein seeding amplification assay, which is the first comparing it to a similar finding, or potentially, you tell us, in another brain disease called Huntington's. So the question was received over social from @murphyslaw1987, so thank you for your question. "We've known about the Huntington's disease gene mutation/biomarker since 1993, but this discovery has yet to lead to an effective intervention against the disease. Do we know if things will be different with this biomarker for Parkinson's?" How would you answer that, Mark?

Dr. Mark Frasier:

It's a great question, and I think it's a reminder to everyone, but especially scientists, that we have to be realistic in our expectations and how fast the research will develop. I think it's important to clarify the difference between the discovery of a gene or the identification of a gene and the identification of a biomarker. So in Parkinson's disease, the alpha-synuclein gene was identified in 1997, I think, and there's been a lot of progress since the identification of this gene, and the evidence for the role of alpha-synuclein in Parkinson's has just increased over that time period.

But that's the gene. That's the change in DNA. What we were talking about last year, and just now, is this marker, this objective marker that's different than DNA. It's actually right now in spinal fluid. It's a spinal fluid test that indicates whether someone might have this biology, this clumped synuclein associated with Parkinson's disease.

So there is a difference between the identification of a gene and the identification of this objective marker. But be that as it may, the question still stands, what does this really mean? How fast will things progress in terms of new treatments for Parkinson's disease? And I think the really exciting part about this finding is that there's sort of two streams of science that were progressing in parallel, and they're converging pretty much at the same time. That is, there were already treatments underway in clinical testing to test whether breaking up alpha-synuclein clumps in the brain or reducing alpha-synuclein levels in the body could actually be useful and treat and slow or stop the progression of Parkinson's disease. So those treatments were already marching through clinical trials. Some of them are in mid-stage. Some are moving to late stage clinical trials.

While in parallel, this other stream of science was developing with the objective biomarkers, the biomarker tests. And so this new seeding assay discovery and report is really a just in time test that can be used for these clinical trials that are testing new therapeutics targeting alpha-synuclein. And we're already seeing that impact at the moment where clinical trials are integrating the seeding assay into their trials as ways to identify people that are truly positive that have this alpha-synuclein changed that would then identify individuals that might respond to this treatment.

So the exciting part is that there's really these trials and these new interventions that are developing alongside the biomarker that, I think, will really accelerate the progress. It's not as if we need to wait for new treatments to emerge at once now that this biomarker has been identified and reported on.

Dr. Brian Fiske:

I think this question about how long should it take from a basic discovery until you have treatments is certainly a really important one and one that many, many people ask. And it says a lot too about where the initial discovery comes from. So when it's a gene that points to a biology, we kind of understand and know then that timeline might be very quick.

But in many cases, that gene points to a biology that we don't know very well yet, and we then have to, it's sort of the first step really, and you have to then really understand that biology better. And we've seen that with, in Parkinson's, of course, with the original mutation in the alpha-synuclein gene, which was, you're correct, Mark, it was 1997, where researchers first found that, discovered that gene mutation.

But there have been other genes too, where the biology was equally more or less understood, and people have had to sort of use that information as their starting point. So I think, we obviously would like to go faster, but sometimes there's often a lot of initial steps you have to take around that initial discovery before you can really figure out how to target it with a treatment or how to measure it with a biomarker.

Maggie Kuhl: Well, we jumped right in, didn't we? That was sort of heavy-

Dr. Brian Fiske: That was a good starting question. That was a hard one.

Maggie Kuhl: A heavy kickoff. Yeah.

Dr. Mark Frasier: Sorry for the long answer to the short question.

Maggie Kuhl: Well, it-

Dr. Mark Frasier: There was a in there.

Maggie Kuhl: It was exactly, it was a longer question, and it just goes to show how informed and engaged our community is, for sure.

So another question we got on a webinar that we did around this topic was, "Can the test differentiate between Parkinson's and other diseases? There are other so-called synucleinopathies that have alpha-synuclein pathology as well, multiple system atrophy. There are other diseases that look like Parkinson's, like progressive supranuclear palsy, but might have other proteins at play. How can this test help us say this is PD versus something else?"

Dr. Mark Frasier: Right. It's a really important need to have this differential diagnostic test. And the SAA right now seems to differentiate people with MSA, multiple systems atrophy, and Parkinson's disease. Although I would say that's very early in development because both MSA and Parkinson's disease are positive on the SAA. But if you look at the data in more detail, you seem to distinguish a different pattern in the people with MSA than Parkinson's disease. But researchers, and in particular the group that developed this test, this company called Amprion, are really working hard to make it more reliable to have this differential diagnosis. So currently, I think it's very much in the research setting, but I'm optimistic that the test will be able to identify differences between these Parkinson-isms, these Parkinson-like disorders and Parkinson's disease.

Dr. Brian Fiske: Yeah, and my guess is the test will never be used in isolation by itself to do that. There are other signs and features that you could use in addition to the outcome of this particular test that would help you make that diagnosis more accurate.

Dr. Mark Frasier: It's a good point that these tests are not removing the need for neurologists. The clinical signs and symptoms are still very important and critical to making these diagnoses and having the conversations with people that are experiencing them.

Maggie Kuhl: Absolutely, more tools in their toolbox.

Another question, last question on this topic is, "How is this different, this test that we are discussing, which is a test from spinal fluid?" You said it was from Amprion. It's called the SYNTap test. From what people may have heard of the Syn-One skin biopsy test?

Dr. Mark Frasier: Yes. So another good question, and can clearly be confusing

Because one is called, "Syn-One" and the other is, "SYNTap." But in parallel with this, the seeding assay, SYNTap discovery and observation, the skin biopsy work was also moving, and there were recent reports last month at a neurology conference that this available skin biopsy, which actually takes tissue samples, skin samples, from three different regions, the neck, the back of the leg, and the ankle, and that test sends the samples to a central laboratory and measures alpha synuclein, abnormal alpha synuclein, just using a dye. And using this dye, you can see abnormal alpha synuclein under a microscope, and a pathologist looks at it under the microscope and essentially makes a determination whether it's abnormal or normal. And the recent results reported that this skin biopsy shows similar diagnostic accuracy, alongside of clinical symptoms, for detecting people with Parkinson's disease.

So it's a skin biopsy, it's read by a central pathologist, it's not spinal fluid. It's also not seeding. It's important to clarify that this method that the skin biopsy uses is this staining method, where you can highlight alpha synuclein and you see it under a microscope. So there's two different methods, both similar type of accuracy, from what we can tell. And at the highest level, these are both really useful objective tools to help neurologists and researchers identify individuals with this abnormal alpha alpha synuclein biology that occurs with Parkinson's disease.

PART 1 OF 4 ENDS [00:13:04]

Dr. Brian Fiske: It's exciting, actually also, too, just to see that you're seeing more of these types of approaches now coming to this level of advance and use in the community. Just 'cause I think a few years ago, we had nothing really out there like this, and now, I think, whether these are the end all be all measurements that are going to be used in future healthcare, I think it's too early to say, but certainly they are good starting points. And we'll see more innovation happening as people figure out how to turn these into simpler tests, maybe get them out of spinal fluid and maybe we move to blood, other types of approaches. And I think that's really

where the excitement is because we're just starting the journey, I think, at this point, and this isn't the end of the journey.

Dr. Mark Frasier: Yeah. As you know, Brian, the foundation has been funding this biomarker research since the beginning, since the foundation started over 20 years ago. And so, we've been after these tests for a long time, and it's really exciting to see the progress. And I agree that now that there's been a couple of breakthroughs, I think the innovation will really happen quickly, and we're going to see lots of new tests, lots of more precise tests, more sensitive tests, in better tissues, like blood, develop very rapidly, so it's exciting.

Maggie Kuhl: So it sounds like people are going to have a lot to choose from on the test side. Right now, there are a lot of different treatments already available, while as we were discussing, we're urgently working toward many more, and ones that will stop disease. But today, people do have some options in how to treat and manage their Parkinson's disease. So Brian, I wanted to turn to you and talk more about treatments that are already available or potentially close to availability. The first one, can deep brain stimulation be turned off or removed? So maybe you could first just give us a quick primer, remind everyone what DBS is, and then answer, could it be turned off or removed?

Dr. Brian Fiske: Right. So DBS stands for, "Deep Brain Stimulation." So it's basically a surgical way of implanting, deep into your brain, hence the "Deep" part, electrodes that are then hooked up to a stimulator, and usually, currently, the stimulator is implanted just around your collar bone, and this provides a stimulation to a part of the brain that is impacted by Parkinson's disease. And we don't know exactly how the mechanism of the stimulation necessarily works, but we know it seems to help reset that circuit a little bit, helps with some of mostly the movement problems of Parkinson's disease.

So it's a treatment that's available, I think the first version was approved in the late 90s, and there's been iterations from a number of companies that have been approved over the years, and they keep optimizing the approaches as well. But what is great about DBS is it's a great, certainly, option for people as they're progressing with their Parkinson's, and they may be taking lots of medication to try to deal with their motor symptoms, they may be having some complications from taking those therapies, and this can sometimes be an option then for some people to get DBS surgery to put in these electrodes, and then that helps manage their symptoms a bit better. They don't to go off all their medications necessarily, but maybe they can reduce some of the medications they're taking, and the DBS can take up some of the burden of addressing those symptoms.

So can it be turned off or removed? Because it's an electrical device, yes, it can be turned off, so you can turn off the stimulator. That isn't always necessarily a good thing. Obviously, if you're getting benefit from DBS and you turn it off, you will no longer get that benefit, but it can be turned off. Can it be removed? Certainly surgically it can, and certainly in some cases it might have to be

removed for some medical reason. So it does have that reversibility, if you will, in that you can turn it off or remove it completely if needed.

It differs from, interestingly, some other approaches out there, around the time early before DBS was really offered, there were some surgical approaches where people could go in and actually remove essentially what they call, "Lesion," a small part of the brain, that could also address some of these similar types of issues that people deal with, and help with some of the movement problems that people were struggling with when they'd been on medication for a while. And this lesioning approach has largely been replaced then with deep brain stimulation over the years.

More recently though, there's some other approaches, something called, "Focused Ultrasound," which you may have heard of as well, that allows you to also go in and lesion a part of the brain, but you can do it without having to actually open up the skull, so they can use focused ultrasound waves to do this lesioning approach. And that's also been approved for Parkinson's in the last several years. And so, that can offer as another surgical option for people who either aren't good candidates for, or don't want to get, deep brain stimulation. Unlike DBS though, focused ultrasound, you can't turn off. Once you lesion that part of the brain, it's lesioned and you can't remove that lesion or turn the lesion off, so that's the big difference between DBS and focused ultrasound.

But these are options, particularly for later stages of the disease, when, again, people are maybe taking too many medications throughout the day and having some of these complications, and it gives them a yet another therapeutic option for addressing their symptoms.

Maggie Kuhl:

So those surgical interventions and the medications that you were referencing target the dopamine system, that's where most of the movement symptoms, we believe, arise from, the degeneration of the cells that make this brain chemical, this neurotransmitter, dopamine. One of the questions we received from MIV Agents, "Can dopaminergic cells be regenerated or replaced?" Presumably to avoid or restore movement, avoid those issues.

Dr. Brian Fiske:

No, this is a great question and one that's been, I think, around for a while. People have, very early on when I think people understood that at least the main movement challenges in Parkinson's were related to the cells in the brain that make dopamine, there was always this idea of, can you replace those cells? Can you give people back those dopamine cells? In the early days, there were some efforts to use tissue transplantation for that. So they could essentially replace dopamine cells with tissue, that was used to replace those dopamine cells. Those were a little messy, those early days. They showed some benefits in some people, some people did not get benefits from those early attempts to do tissue transplantation, and some people had some side effects as well. So those initial attempts to use tissue, I think, were largely abandoned after a few attempts with some clinical trials.

Where people got really excited though was when in, again, the late 90s, early 2000s, stem cells were discovered, if you will. People knew they existed, but to be able to isolate them and manipulate them, a lot of those early discoveries were happening in the early 2000s. And that offered suddenly an opportunity where maybe we could actually use stem cells to create new dopamine cells, in the case of Parkinson's. Parkinson's certainly wasn't the only disease where people were excited about stem cells, but for us at least, the idea that you could make dopamine cells from stem cells was an early exciting advance. And the idea then of taking those cells and transplanting them into someone with Parkinson's became a really important idea for the field, so there was a lot of work on that idea.

A lot of the initial work had to do with how do you actually coax these cells to become dopamine cells that actually could function like dopamine cells in the brain? And so, there was a lot of work, actually, the Michael J. Fox Foundation put a lot of money and effort in those early days to develop the recipes for how you can turn stem cells into dopamine cells. And some of them, the initial laboratory work that was needed to understand, can you then put them into a brain of a laboratory model and actually see if it can actually function like it should?

But now, we're seeing, actually, these move into clinical testing. And so, there's actually a number of companies and groups now that are actually doing transplants with stem cell-derived dopamine cells in Parkinson's disease. And that's really exciting to see because we now really, I think, have an opportunity to test whether this cell replacement idea might really actually have benefits for Parkinson's disease. Now, if you ask experts today, many will say that the benefits you might see with this type of approach might be similar to what you might see with deep brain stimulation and some other approaches like that. So it's quite possible that simply replacing the dopamine cells is isn't going to be a cure for the disease, you're not completely growing back your brain. But they could potentially offer some benefits that could be yet another surgical option for people with Parkinson's disease, especially, perhaps, maybe at later stages of the disease. So it's exciting to see some of those advances.

Thinking back to the first question in this question, I think they both hit on an interesting theme, which is, what do you do, especially at the later stages of Parkinson's disease, when the brain, you've lost some cells, you've lost some function, and how do you give that back? And I think when you see these options, like DBS, potentially with the cell replacement approaches, you're seeing the advances, I think, that we're trying to make, which is literally about how do you give someone with Parkinson's back that function that they need, especially at those later stages?

And I'm excited to see these new approaches tried. I think there's even in the probably a little bit further future, could you actually convince the brain to repair itself? And there actually is some reasonable work that's happening out



there with the idea of can you actually replace lost cells by coaxing the brain to replace those cells directly, versus you needing to transplant them? And so, a lot of that work is still in very early stage in the laboratory, but it's exciting to see that we might have some even further advances in this idea of restoring and repairing the brain in people with Parkinson's disease.

Maggie Kuhl:

Fascinating. Well, I have three young kids and can't coax them to do anything, so perhaps there's some lesson in there for me about coaxing your brain. Amazing. Also, I just want to give a plug for these more care relevant topics, like deep brain stimulation, stem cells is a question we get asked a lot about. We have an Ask the MD series with very educational videos and guides

and a lot of helpful content that can help evaluate different options or consider what's out there and give you scripts or questions to ask and discuss with your loved ones and your physicians. So please check that out if you haven't already. That series touches a lot on this topic from our next question, which is: why does exercise improve balance? I think we hear a lot about how exercise is a great treatment, exercise, great medicine, and it can slow symptoms and make you feel better for lots of different reasons. But we do hear it especially referenced with balance. And so I think this is an interesting question about what exactly is happening either with the body or the brain that improves balance when you exercise.

PART 2 OF 4 ENDS [00:26:04]

Dr. Brian Fiske:

This is a good one. I'll caveat and say I'm not an expert in the physiology of balance circuits in the brain, but I think exercise, as you said, provides a lot of different types of benefits from just the strengthening, it improves your mood, does a lot of things, maybe helps you even sleep better if you're exercising aggressively and getting tired. So there's a lot of probably ways that it could ultimately help someone with Parkinson's disease.

I think for balance, it's such a complicated system. It involves obviously your muscles and the coordination of your muscles to be able to maintain balance along with the parts within your ear that are about detecting balance and where your head is in space and things like that. I think things like this can help people compensate, and I think that's probably a big part of this, which is by exercising, by challenging your body and your brain to maintain certain kinds of movement, being able to stand better, more solidly on the ground when you're doing certain kinds of exercises, I think these just ultimately can help train your brain. 'Cause your brain's a pretty plastic, malleable thing.

It's always adjusting itself based on new experiences. And so I think if you, in the context of exercise, by simply doing that consistently, I think you can improve things like balance and your ability to walk and things like that just by, again, retraining your brain on how to compensate for maybe the things that you've lost in Parkinson's disease. It's not always easy, and certainly it's something you

have to keep up and consistently do, but I do think there's some good benefits that can come from these types of approaches.

Dr. Mark Frasier: Yeah, I was going to say something similar. It's about practice, and you hear about Tai chi or boxing being really helpful for things like balance in Parkinson's disease. And it's really just practicing and training, as Brian said; training that neuromuscular connection and strengthening the connections to really be able to improve your balance. And so the more you do it, to the extent can, I think it will improve things like balance because you're strengthening those connections, you're practicing doing the exercise, and it will apply to real life when balance and falling might be a challenge.

Dr. Brian Fiske: Yeah. And we get a lot of questions about exercise. There's a lot of different venues, and I think people are looking for that one prescription. "Tell me what I need to do to do the best exercise and how many minutes a day do I need to do it?" And I think the real answer to that is do the types of exercises that you'll keep doing over time and that you actually enjoy and that you can do safely without the fear of falling or anything else like that. It's important just to make sure you're maintaining movement and keeping yourself. Getting out of the chair and doing physical exercise, I think, is just a general good rule of thumb for all of us, not even just those with Parkinson's.

Maggie Kuhl: Our last category is biology and patient experience. Everything that we've talked about, we've learned from studying the human experience, the biological experience of Parkinson's disease. So Mark, I'm going to toss this first question in this category to you, which is: we hear a lot about the microbiome in our gut. How would learnings about the Parkinson's microbiome actually impact treatments or care?

Dr. Mark Frasier: This is a really hot area of science in general, not just neurology but especially neurology. And it's a new area because there's so much we don't know about the microbiome. But what we do know as it relates to Parkinson's disease, it's fairly well-established that there are different bugs and a different makeup of bugs in the gut of someone with Parkinson's disease compared to someone without. Now, why is that? There could be a number of reasons. There are certainly changes to the gastrointestinal function. There's delayed gastric emptying in Parkinson's disease. Some people have constipation, so this could contribute to changes in microbiome.

Obviously what you eat and the environment really influences it. So we know there's a role for gut health and a connection between the gut and the brain, and we know there are slight differences between people with Parkinson's and their microbiome and people without. But there's a lot that we really need to understand. And what a quote, unquote "normal" microbiome is, I think that's still up for some debate.

However, there are some therapeutic avenues that are being pursued for Parkinson's and other disorders that try to bring back a balance of the microbiome in Parkinson's disease. And these are in very early testing, maybe early safety studies, but the idea is could you rebalance the gut microbiome and would that result in better brain health and ultimately better improve Parkinson's symptoms? And we have a lot of work to test that question and that hypothesis, but there is a lot of ongoing activity in this space.

Maggie Kuhl:

No softballs today. Sorry, our community is just too good. Brian, let's see if this one stumps you. Is it true that too few hours of sleep during a lifetime can increase the probability of getting Parkinson's?

Dr. Brian Fiske:

Yeah, no, this is a great question and actually timely because there's been a lot of discussion, I think, in the last few years about the role of sleep and sleep impairment as a risk factor for brain health diseases. And certainly we live in a time when all of us probably sit up at night in bed with our phones in our hand and bright light screens shining into our eyes and wonder why then we wake up feeling groggy the next day. So I think this idea of sleep and its role in healthy aging, I think, is an important one.

So is it true that too few hours of sleep can be a risk factor for Parkinson's? I will admit I don't know the data around that very well, but I do know there have been suggestive reports in Alzheimer's disease that would suggest that reduced hours of sleep might be associated with higher risks for diseases like Alzheimer's.

Why that's the case though, I don't think people really fully know. There's a lot about sleep, just as a basic physiological process, that we don't understand, like why do we sleep, and why do we need sleep, and why can you not stay awake if you try to stay awake more than 24, 36 hours? You basically start falling asleep whether you want to or not. And so what's the drive, main force that is making that happen?

And so there's some ideas out there, and one idea is actually that sleep is really important for allowing your brain to clear out all the garbage, to get rid of the toxins and the brain and clear out all the detritus of essentially a functioning brain and what it produces over the course of a day. And that is a powerful idea when you think about brain health and that maybe if you don't get enough of that good downtime where your body can clear out that junk, that over time that could be damaging to your brain and ultimately lead to impairments over time that could lead to accumulation of toxins that could ultimately harm parts of your brain and lead to age-related neurodegenerative disorders.

No one's really directly shown that yet in Parkinson's, so we can't say yes indeed that that is the cause of Parkinson's disease, but it certainly could be one hypothesis worth digging into more. We do know sleep is certainly an outcome and maybe an early symptom of Parkinson's disease. You may have heard us

talk before about REM behavior sleep disorder, which is a disorder of a sleeping disorder that happens early on in people with Parkinson's where they lose their ability to keep their muscles still while they're dreaming. Now, that's probably less about sleep and more about muscle control. So whether that is the same thing as a sleep impairment, I guess, is a different question. But I do think there clearly is an impact in Parkinson's on our ability to sleep, and it's quite possible that there could be impairments over time if you're not getting enough sleep that could be contributing to Parkinson's in the process over time.

So anyway, lot of research that probably still needs to happen. I was actually at a conference last fall that brought together a bunch of different groups, including from other brain disorders. And we spent a lot of time talking about the potential role of sleep as a contributing factor to these diseases as well as a symptom and an outcome of these diseases, and how do you even think about treating that as a problem?

We just learned, I think, how complex this sleep process is and even that there are different types of sleep. The normal sleep we think of every night is different from the sleep you might be dealing with, the tiredness and the fatigue you deal with during when you're sick or you have a disease, could be a very different process. So I think it's, again, it's a very complicated biology around sleep. But that being said, I think good quality sleep is generally good for all of us and probably something that we need to be taking closer looks at, including thinking about light hygiene and how do you deal with light as a risk factor for disease when we're all exposed to devices now that can never be turned off fully and are always in our face. And how do we deal with that as a population?

Dr. Mark Frasier: Maggie, some have argued that sleep should be added to the list of vital signs including body temperature, heart rate, blood pressure, oxygen rate, et cetera. And it's clear that this role of sleep clearing out the toxins is very intriguing, and you could certainly argue that sleep should be an essential vital sign that is reflective of general health, not just brain health. So it's really interesting.

Maggie Kuhl: Some of these might be helpful in establishing those associations because a lot of these wearables and such are tracking sleep. So now that we have these big data sets, and if people go on to develop Parkinson's or other diseases and you can look back and I'm sure many other contributing factors but, like you said, if sleep or lack of it is one of them.

With all this data too, we are able to look at early signs of Parkinson's. Right now, as we were discussing before, diagnostics are done by a physician, there are tests that are emerging, but how do you know even how early you can give those tests to measure biology? A user, I like this username, @perfectlyhappy2306, has asked us, "Is there a specific list of early signs, and are they different between men and women?" which is a very interesting coda there?" Mark?

Dr. Mark Frasier: Well, there are early signs, and it's not consistent across everyone that it eventually develops Parkinson's disease, but things like REM sleep behavior disorder that is this disorder where people act out their dreams, that's certainly an early sign. Olfactory deficits or smell loss, that people lose their sense of smell, that often occurs prior to developing some of the motor symptoms

Although there are many things like COVID that can cause smell loss, so it's not specific to Parkinson's disease.

Interestingly, there are some reports that there can be some depression linked to Parkinson's disease before some of the motor symptoms, so mood changes. Then a neurologist once told me the most common early sign is shoulder pain, which I think is associated with the rigidity and stiffness that occurs. But many people just think it's getting old or arthritis. But that's, I think, an early sign as well.

PART 3 OF 4 ENDS [00:39:04]

Dr. Brian Fiske: Yeah.

Maggie Kuhl: Yeah, we've heard that a lot. People thinking it's like a tennis injury or something and going to see an orthopedist. Then they have a very long journey to Parkinson's disease. Sorry, Brian, you were going to say?

Dr. Brian Fiske: No, I was going to, yeah, say I think one of the things that these early signs tells us too is how early on we tend to not recognize these as Parkinson's early symptoms. They get recognized as other things. Like you said, you have pain in the shoulder, and you go to the doctor. You think you just need physical therapy. Or you're not sleeping so well, so you go to a sleep clinic. Or your smell function doesn't seem so well, so you just assume that someone hit you in the nose or something like that. So these things don't get recognized as early signs of age-related neurodegenerative disorders like Parkinson's.

Harkening back to our earlier discussion about the new biomarker discovery and the benefits of something like that is that you could imagine a day where someone comes in with some of these types of early signs. Instead of getting sort of told the usual, "Oh, don't worry about it, it must just be an injury," you actually get maybe one of these tests. They can sort of rule out whether there's something more serious going on that might be predictive of you being at the early stages of something like Parkinson's disease. So I think these early signs become really important for helping to kind of combine with those new biomarker measurements that we talked about as a way to really kind of get a hopefully an earlier, faster hint of what might be happening in your body.

Maggie Kuhl: That's the aim of our PPMI study, which is where a lot of the data from the new biomarker tests came from. Which is recruiting people with some of those clinical factors that we feel confident about like RBD, REM Sleep Behavior

Disorder or smell loss to help us understand what is the profile or profiles more likely of early Parkinson's. Who should, as you were saying, sort of have that test and learn more about their biology. So you can learn more about that study on our website as well, [michaeljfox.org/ppmi](http://michaeljfox.org/ppmi).

So that wraps up our audience submitted questions. But our producer, Namesha, and I thought it might be fun to put you two on the spot for a little lightning round.

Dr. Brian Fiske: Ut-oh.

Maggie Kuhl: Just to get to know you a little bit better. What are you doing when you're not trying to end Parkinson's disease? I had said earlier that some of them were straightforward, and that was not the case. So this time I'm going to require that your answers are straightforward. This is lightning, not long thunderstorm round. Okay. Mark, what is your favorite Michael J. Fox movie?

Dr. Mark Frasier: Yeah, most people say Back to the Future. But I had a VHS recording of Teen Wolf growing up that I watched a lot and used to know every line to it. So I would have to go with Teen Wolf. That was a great movie, kind of a cult classic.

Dr. Brian Fiske: That's a good one. That's a good one. I'm still a Back to the Future fan though. But I agree with you, Teen Wolf was a good one as well.

Maggie Kuhl: Yeah, and if you haven't seen Michael's new movie Still, it's a great film overall. But it's also a really fun compilation of a lot of sort of highlights from across his career, so check that out. Brian, what is the best book you have read?

Dr. Brian Fiske: I read one not so long ago that I really liked. It wasn't a particularly new book, but one I'd been meaning to read called The Gene: An Intimate History. It's by Siddhartha Mukherjee. What I liked about it, it was sort of a history of essentially the discovery of genetics all the way from the [inaudible 00:43:31]-

Maggie Kuhl: Mark's holding it up. You can't see if you're listening.

Dr. Brian Fiske: Oh, there we go. Mark, yeah.

Maggie Kuhl: His home office.

Dr. Mark Frasier: I've got a copy.

Dr. Brian Fiske: It's a great story because it just talks about the history of science basically, and in this case centered on genetics. But just talks about how these little moments of discovery become so powerful and amplifying about our understanding of the world around us. We're seeing this obviously, I think, in the Parkinson's field now with some of these newer discoveries coming out. How every new discovery opens the door for letting you enter the next room, which is where

the next discovery comes from. Anyway, so it was a really well-written book and a great history on genetics if you're interested in it. But that was probably one of the better books I've read in the last couple of weeks.

Dr. Mark Frasier: I agree. It was a good one. It's not just science, but also history of science, which is really fun.

Maggie Kuhl: Yeah, I think I saw he just had a new one called Cell, right?

Dr. Brian Fiske: Oh, yeah. It's all about how the cell works.

Maggie Kuhl: Yeah, so the sequel. Gene the sequel, yeah. So yes, check those out. So you two have both worked here at Fox for a long time. Mark, how many MJFF office spaces have you worked in? You can count that home office where you just picked up that gene book as one if you'd like.

Dr. Mark Frasier: I think three. Well then, sorry, four if you include my home office, which I've been working out of a lot since COVID, so four.

Maggie Kuhl: Brian, how about you? Four as well?

Dr. Brian Fiske: Well, I guess it would be five if it's the original, well not the original, but close to the original space. Then, yeah, so one, two, three. Yeah, I would say so four actual offices and then partly now my home office as well.

Maggie Kuhl: Okay. Brian, what is a technology or product that has gone the way of the wind and is not available anymore that you really miss?

Dr. Brian Fiske: You know what I kind of miss? I would have to say this is a hard question because there's a lot of advances, and all the advances certainly make your life easier. But I kind of miss the simplicity of old style TV watching, when you had to know what time your show was on and you had to go watch it that evening. None of this on demand streaming, a way of watching TV today. Just because one, it probably kept us from watching too much TV maybe? We actually had to do other things when something wasn't on that we wanted to watch. But it also, I don't know, there was a shared sort of cultural moment that everybody had, which sometimes they still capture, I think, in streaming when they release the shows one at a time.

Maggie Kuhl: I think they called that appointment television where you had to schedule, I will be watching the Sopranos finale or whatever it was.

Dr. Brian Fiske: Exactly. I don't know, there was something about that. Again, I obviously still love being able to stream whatever I want late at night, but there's still something I miss about that old school TV watching.

Maggie Kuhl: Mark, how about you? VHS, so you can't watch that Teen Wolf tape anymore?

Dr. Mark Frasier: Yeah, I loved watching VHS recordings. I actually was going to say listening to the radio to hear your school announced for snow days and the joy of sitting in bed listening to the radio. If you missed your school, you'd have to wait another 20 minutes or half hour until they announced them again. But there was something so exciting about hearing your school called during snow days. That just doesn't happen anymore with email and text threads.

Dr. Brian Fiske: Yeah, I grew up in Texas, so the idea of snow days wasn't something that resonated with me. Although occasionally, we had ice storms.

Maggie Kuhl: Did you have like sand storms or something?

Dr. Brian Fiske: Ice storms occasionally.

Maggie Kuhl: Ice storms, okay. Tornadoes? Yeah.

Dr. Brian Fiske: But yeah, very rarely would we ever have school canceled because of snow, for sure.

Maggie Kuhl: Amazing. Well, snow or ice or sandstorms are not canceling our pursuit of a Parkinson's cure. So thank you for taking the time to answer some of our audience questions and my fun get-to-know-you ones at the end and for keeping it short. Thank you all for listening to another episode of our Parkinson's Science POV podcast. You can learn more about our PPMI study, our educational content, and all the other things that we covered during this chat at our website, [michaeljfox.org](http://michaeljfox.org). If you like our podcasts, please share it with friends and family. Until next time, thanks for listening.

Announcer: 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](http://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](http://michaeljfox.org).

PART 4 OF 4 ENDS [00:48:32]