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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.

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Katie Kopil: Hi, and welcome to the Michael J. Fox Foundation Webinar. I'm Katie Kopil, senior vice president of clinical research at the Fox Foundation, and I'm also the moderator of today's webinar. We've got a lot to discuss, so we'll get started. In this webinar, we have a panel who will answer your questions about imaging and Parkinson's disease. Now I'd like to introduce today's panelists.

Here today we have Dr. Madeleine Sharp. Dr. Sharp is a neurologist specializing in movement disorders. She's an assistant professor of Neurology and Neurosurgery at McGill University in Montreal. One of her areas of research is MRI-derived biomarkers of Parkinson's disease. Thank you for joining us. Then we also are joined by Peter DiBiaso, a member of the Fox Foundation's Patient Council. Peter was diagnosed with early-onset Parkinson's at 49.

He works in clinical development with a strategic focus on leading global operations, supporting optimization of biopharmaceutical research and investigator relationships. He's coming at this conversation from two angles as well. Let's get started and we'll set the stage by a little introduction to Brain Imaging 101. We'll talk about the different types of imaging tools and how they're used in Parkinson's.

This is the 101 level, and then we'll go to the experts for our 102 level in a minute. At the very basic level, we can start maybe Dr. Sharp with you, how is Parkinson's diagnosed today? I know it's primarily clinically, but how do you think about imaging tools that could also help diagnose PD?

Madeleine Sharp, MD: Yeah. Parkinson's disease remains a clinical diagnosis, which means that you have to see a physician, typically a neurologist or a movement disorder neurologist, who examines you for the signs and symptoms of Parkinson's disease. And asks you a lot of questions to eliminate other things that may cause signs and symptoms similar to those of Parkinson's disease.

In order to make the diagnosis of Parkinson's disease, it's not necessary to actually undergo imaging, but imaging can be helpful in certain circumstances, and it can be extra helpful in the research setting. There's, of course, differences in the tools that we use when we're evaluating patients in the clinical setting versus the research setting.

On this slide here, there's a picture of an MRI scanner, so that's magnetic resonance imaging. There's also a picture of, I don't know here actually if it's a PET scanner or a SPECT scanner, but those two have a lot of similarities more than they have differences. Maybe the thing to say here is with brain imaging, there are different things that we can measure about the brain.

One is the structure of the brain, so the shape of it, the size of it. With a higher resolution imaging like we are able to do now with MRI imaging, which many of you are probably familiar with or have had, we can also take a look at the deeper structures of the brain, which are those that are of interest in Parkinson's disease. In particular, the areas of the brain that produce dopamine, which is what leads to some of the symptoms in Parkinson's disease.

That's really for looking at the structure. Shape, size and different features about the shape and the size that can be of utility. PET and SPECT imaging are quite different in that they are really more interested in the function of the brain. There's a number of different types of PET and SPECT imaging, and we'll go into some of the details later, in particular for DaTscan, which some of you might be familiar with.

That's a type of SPECT imaging that's interested in looking at the dopamine-producing neurons. When we measure function in the brains of people with Parkinson's disease, it's that we're trying to get a sense of the effects of the degeneration. That's the loss of neurons, which is what Parkinson's disease causes, to see what effects that's having on the brain. Is it causing a reduction in the amount of dopamine that's being released?

Is it causing a reduction in the amount of neurons that are still available to release that dopamine? Is it causing a reduction in the pattern of glucose utilization around the brain, which is a signal that the brain is not functioning like it used to? Those are really for a measure of function of the brain. These are variably used in clinical evaluation at the time of diagnosis or for tracking things about the disease, especially in the context of research. But I think we'll have the opportunity to go back to each of these.

Katie Kopil: Perfect. Maybe diving in more deeply and using a focus on perhaps one of the types of imaging techniques that people might be more familiar with.

Dr. Sharp, can you talk about how you use MRI in your care to help with a diagnosis of PD in particular?

Madeleine Sharp, MD: Yeah. I would say that in the clinical setting, MRI comes up sometimes at the time of diagnosis, but it's actually the exception rather than the rule that we would obtain an MRI in someone that we're evaluating for Parkinson's disease. Again, back to this idea that Parkinson's disease is a clinical diagnosis. The reason actually for not using MRI in the diagnosis, is that especially in the early

stages of the disease, there's really not much to be seen on the MRI of people with Parkinson's disease.

We don't see really evident changes to structure, to the size or to the shape of the brain. Certainly, those changes are not really visible with the types of MRIs that are used in the clinical setting, which can be different than research MRI, where they have essentially fancier techniques to be able to measure some of these deeper things in the brain. In the clinical setting, what I'm most used to using MRI for is if I'm uncertain about the diagnosis of Parkinson's disease, and I want to eliminate the possibility that there's an alternate to diagnosis.

Some of those alternate diagnoses sometimes have some features that can be visible on MRI. But no matter the case, it is rare that MRI ever gives you a definitive answer about any of these things. It's really an extra tool to provide a little bit of extra information. The specific cases in which I use it most often, are if we are evaluating someone who has Parkinsonism. Parkinsonism is just a description of the symptoms that are similar to those of Parkinson's disease.

The changes to the gait, the changes to the appearance of tremor and that sort of thing. Other diseases also cause Parkinsonism. In particular, some that can have some imaging findings on MRI are progressive supranuclear palsy, so PSP, some of you may be familiar, or multiple systems atrophy, MSA. Again, MRI cannot make a diagnosis of those other conditions, but it can give you clues that you should maybe be considering an alternative to the diagnosis of Parkinson's disease.

But I think for most of us, if we're confident about the diagnosis of Parkinson's disease based on the symptoms that the individual describes and based on our findings on our physical exam, we would not proceed to MRI for the additional information that it provides. Sometimes it is the case that we might be considering that something like a stroke or a brain tumor could be in a location of the brain that could cause symptoms similar to those of Parkinson's disease. But again, that's really the exception rather than the rule.

Katie Kopil: An individual in the audience said that they were recently diagnosed with Parkinson's. They're seeing a movement disorder specialist who ordered a brain and cervical MRI, but only the cervical MRI was approved and the brain MRI was not.

Do you think it's sufficient or is it something to push for? What do you think from your clinical perspective, in terms of the types of confidence you'd like to have in diagnosing someone?

Madeleine Sharp, MD: I guess it's worth saying that we all practice in different settings. In the setting where I am, access to MRI is maybe not as easy as it is in other settings. For part of that reason too, things are more often or less often included in our standard workup. I think as neurologists, we all have curiosity to see the brain.

If I could, I would get an MRI in everyone because I just like to look at the pictures, but that's not a good enough reason to necessarily justify it. To the individual who's asking about this, I think that the best way to address this is to speak to the neurologist and see were they actually concerned about anything, and did they have a specific reason for requesting the MRI?

If they did, then they would probably be able to justify that. If not, then I think you can be reassured that it wasn't really necessary, because again, it's not part of the clinical evaluation that is required to make the diagnosis of Parkinson's disease.

Katie Kopil: Thank you. Maybe Peter, bringing you into the conversation, as a person living with Parkinson's and an advocate in many different settings but including a healthcare setting, do you have any advice on folks that are facing this challenge?

Peter DiBiaso: Sure. I'll firstly thank the Fox Foundation for providing me the opportunity to share some of my insights with the rest of the group. I've been very fortunate that I've had great medical care and great follow-up, but I was actually early diagnosis of Parkinson's disease about nine years ago. But prior to going forward with any additional tests, I first worked with a neurologist, which led to an opportunity to work with a moving disorder specialist.

It was at that time that they suggested that a DaTscan, and we've talked about that earlier in today's discussions, but a DaTscan would be used for that. I was very unfamiliar with that at the time, but following some research, I very quickly learned that this is one more way of narrowing down the diagnosis. Again, to be clear, as we all regrettably know, there's no definitive diagnosis for Parkinson's disease, although we're getting quite close.

But I think what this really did was enabled me to look at nice, pretty pictures. But once you actually go through and complete the DaTscan, you have the ability to really look at a very high-contrast picture of a healthy brain and brain where you're having maybe some difficulties with dopamine uptake, so the ability to use and generate dopamine. Again, after seeing that, that gave me a little more confidence.

But yet again, going back to some of the earlier concerns, it was quite frankly stated that the results of it were suggestive of Parkinsonian symptoms. Which isn't exactly telling someone that was newly diagnosed, but I think you can make your own conclusion when you're looking at some of these pictures. Again, there's still some challenges in how we use and interpret this.

There's also practical challenges to that scan with regards to the variation of what insurance companies will cover. Then there's really the fundamental concern that some people don't necessarily like, whether it's an MRI or a DaTscan or others, going through the procedure in this big machinery. But I

think it's really gained a lot of acceptance in the last few years. Now they'll let you bring your own music in and relax you and other ways to address that.

Again, it's not a cure all or one size fits all, but it's another tool that we as researchers that we as patients can look at, rely on and use as this broader management of Parkinson's disease.

Katie Kopil: Thank you. Maybe pinging off the idea of researchers use these tools, Dr. Sharp, maybe you could address some of them. You had referenced the tools that are available for research are maybe more powerful or different approaches that are used in care.

Someone had asked about that difference, how it would be different in a research study. For example, the Parkinson's Progression Markers Initiative study, they're a volunteer there and they've had that done, an MRI done in research versus care. What would you expect to be the big differences?

Madeleine Sharp, MD: Well, I guess there's a few. I guess one of the reason we would consider something still in research, is that it's not yet definitively proven to be helpful for measuring something that tells us anything more about the patient and about Parkinson's disease. For instance, there are many things that people are trying to measure in the brains of people with Parkinson's disease.

One is to look at the part of the brain where dopamine neurons reside, and to see if we could get a really high resolution. A good, fine-grained measurement of how many neurons have been lost in order to get a sense of the stage of the disease. There's a number of different techniques that are being evaluated for this.

But none have been shown to be, I guess, reliable enough to be able to yet be used in a clinical setting to say to someone, "Oh, I see that you have X percent reduction in your dopamine neurons. Therefore, that means this about your Parkinson's disease or that gives me this confidence about your Parkinson's disease." We're still quite a ways from that and so that's why these other tools are considered research.

It has less to do with, let's say, the machine that is used, like the MRI scanner that is used to obtain the images. But there are some differences there in terms of the kind of resolution of images that is obtainable, but it has more to do with the types of analyses that are then done on those images that are acquired and what information can be derived from those analyses. To the individual, the experience of the MRI is similar. It's just the way we can then analyze it.

Katie Kopil: Is there maybe one comment on the most exciting MRI research you're doing right now? What are you looking forward to?

Madeleine Sharp, MD: I think the most exciting, and I think some of the most important stuff is figuring out how we can standardize some of these measurements. For instance, taking a study like PPMI, which is an incredible feat because it's a study that takes place in multiple, different centers. We have a sense that measuring someone's blood pressure, we know enough about how to measure blood pressure.

Blood pressure cuffs have been around long enough that we can reliably assume that blood pressure measurement by X individual in X state with X machine will be similar to the blood pressure measured in another state by a different machine. But we're still not 100% certain about A, how to ensure that MRI measurements are comparable across different MRI scanners.

B, we're not yet certain about how reliable the analyses done on MRIs, on MRI imaging data can be reproduced in a certain way. It's a lot about making sure that we have confidence in the measurements that we're actually obtaining from these things. There are a lot of efforts underway to improving the reliability of those measurements. In large part, thanks to studies like PPMI or thanks to PPMI in particular, because so much data was acquired.

So many people have been scanned in so many different settings, which allows us to advance on that. It allows us to also compare results from PPMI to results in other studies to get a sense of how reproducible some of these things are. It's really about, I think, advancing our confidence in the measurements of what we're measuring.

Katie Kopil: Fantastic. We'll come back to research participation in a little bit. Maybe moving on to another type of technique, imaging technique for nuclear medicine, which we talked about briefly in the Brain Imaging 101.

There is PET and SPECT, and this is a type of nuclear medicine imaging. Dr. Sharp, maybe at the highest level, you can talk about some of the differences between these techniques compared to MRI.

Madeleine Sharp, MD: Yeah. I think here we're coming back to this idea that this measures function rather than just structure, like shape and size. I see here in the first sentence it says, "Imaging techniques that provide metabolic and functional information." The metabolic piece is about how much energy is being used in different parts of the brain, which can be interesting.

Because you can see patterns of early changes to a metabolic function, as in some regions either using less energy or more energy. You can imagine using more energy if you are starting to have some loss of neurons, and then you need to compensate by using more energy so you might pick that up very early. The converse is also true. If you have fewer neurons, you're using less energy.

That's a technique to measure the metabolic function of the brain. Then the other functional piece of the brain, which also relates to this availability of

radiotracers, so tracers that can be seen on the images and that bind to particular things basically in the brain that are of interest. For instance, we'll be talking about DaTscan, so that's imaging. I don't know if Dr. Seibyl is now on the call yet.

Katie Kopil: Welcome, John.

John Seibyl: Oh, wonderful.

Katie Kopil: Well, maybe we'll use this as an opportunity to bring you into the conversation. I'll start by just introducing our friend, Dr. John Seibyl, who's a clinician and a researcher. He's board certified in psychiatry and nuclear medicine, what we're talking about right now.

He helped co-found the Institute for Neurodegenerative Diseases, which is a nonprofit, an independent clinical imaging research facility in New Haven, Connecticut. In New Haven, he's also an adjunct professor at the Yale School of Medicine. He also joins Peter in the shared experience of living with Parkinson's, so wearing a couple hats today.

John, do you want to jump in and talk about your thoughts on opportunities and key differences for PET and SPECT?

John Seibyl: Sure, yeah. PET and SPECT are, as you heard earlier, tools for imaging of the brain. They both basically work the same way that you inject a small amount of a radioactive tracer. In the case of DaTscan, that's actually radioactive cocaine, believe it or not. It's a molecule very similar to cocaine. The difference between cocaine and the radiopharmaceutical DaTscan, is that DaTscan lasts longer.

Cocaine gets broken down very quickly in the body, but for imaging, you need time for the material to get up into the brain, to bind to where it binds to and then to undergo radioactive decay. You get a 3D picture out of that. That's a common technique used in nuclear medicine. PET imaging is similar to that. You inject a radiotracer, a radioactive-labeled medication at a very low dose.

It binds to some specific target, whether it's a protein or something called a dopamine transporter, which gives you a proxy measure of the cell integrity. As was pointed out earlier, we can't measure exactly how many nerve cells are there and how many have died, but this gives a proxy measure of it. SPECT is short for single-proton emission computed tomography. PET is dual proton.

That is, it undergoes different radioactive decay scheme. It has a little different physics of detection, but it works very similar. All these devices are rings that it's like taking a picture of an automobile from all different angles. If you get enough pictures, you can create a 3D view of the automobile.

The difference is between taking a lot of pictures of a solid object and these nuclear medicine and MRI techniques, is that you can get a 3D picture where you can actually look inside the brain. You get these very powerful images, which give you a sense of how many nerve cells are present, how severe the patient is relative to other patients.

One advantage of PET and SPECT is that you can get a number, a quantitative number and then you can track that over time, which is helpful for seeing how people are doing. In particular, as we think about moving ahead with new treatments that may slow down the progression of the disease, if we were ever so lucky to have those.

I think we're getting there. That having a good, objective tool that can measure the integrity of where the medicines work is very important.

Katie Kopil: That's helpful. You were talking about trying to build one of those pictures. Let's go to that now and show an example of what one of these looks like for DaTscans.

John Seibyl: It doesn't look like much. It looks like scrambled eggs. On the left, you see a healthy person who has what are called normal dopamine transporters. This is a DaTscan or an Ioflupane. SPECT scan is the generic term. You see a area that's yellow and white, and at the top it's like a round ball, and then there's a little tail that comes off. It looks like a comma or a kidney bean, and that's a normal person.

The scan on the right is a patient with idiopathic Parkinson's disease, and you can see that it looks very different. Instead of seeing the comma, you see little periods, little punctate marks, and there's differences between the left side and the right side. You can see the right side is actually the patient's left. On our left side of that patient's image, we see a more intense uptake.

There's more yellow and white than on the right side, which is more dull. What this shows you is that the process of changes in the brain can be evidenced very easily with these techniques, because there's such high amounts of signal where the dopamine transporters are. When you lose them, you get a hole there. You don't take up that tracer.

We have some techniques that we developed over now 30 years where we can quantitate these images and have a reasonable sense of what can happen over time in patients, and how fast these changes occur on the scans, that sort of thing.

Katie Kopil: That's really helpful. Well, you can see here, and this was mentioned earlier that in clinical care in the US, DaTscan is FDA approved to help diagnose PD. Peter, you talked a little bit about your experience.

There's a comment in the chat and maybe you could respond to this in terms of your own journey. Someone indicated that their DaTscan result came back as consistent with Parkinsonism, but it didn't have any definite answer.

Is that similar to your experience? Based on what you know now, how would you interpret that type of read?

Peter DiBiaso: Yeah, it really was. Thanks, Katie. I think for me, it was very much a personal journey and like a lot of people, when I first learned of my diagnosis or potential diagnosis, I was very adamant that it must be a mistake. It wasn't due for anything, that it must be something else. I don't believe the results. How can this be happening? All the fear, guilt, concern, anger that one goes through with getting a potential diagnosis like that.

But that said, once some time had progressed, I was able to look at the different ways to do that, whether it's a physical test, whether it's some of the work that we've talked about with other diagnoses and other triggers. But in this case, the DaTscan, it sounds like the question was more related to what happens if that's negative? Does that mean I'm out of the clear?

Best I can tell and I'd welcome John or others to weigh in, but one of the challenges is it's not definitive. There's always situations where not necessarily a false positive or a false negative, but there are areas where it's not telling the whole story. As we like to focus on the work leading up to Parkinson's disease, it's a disease that requires many different quivers, if you will.

Many different arrows to look and help to diagnose it. That really is not, again, definitive. It's fairly highly suggestive of the conditions we've talked about, but it is important to recognize going into these, that it's not a perfect science. Very, very good for what it does, but Parkinson's is a very complicated disease. All you have to do is look at some of the continued progress that we're making that I know we'll touch on later today.

But the continued progress we made is not just relying on one indicator, not just relying on one procedure, but as part of the journey that we're all focused on.

Katie Kopil: From a clinician perspective, Dr. Sharp, there've been a few different questions that have come in. Should people have, if they've already had a DaTscan, is there value in having it again for care versus for research? Is it recommended?

I know the practices in Canada are slightly different than the US or elsewhere in the world. But would it be recommended even if you've been diagnosed with Parkinson's for several years, do you see the value there from a clinical care perspective versus what can go separately on the research side?

Madeleine Sharp, MD: Yeah. I think from a clinical care perspective, it's useful, especially if you're considering alternate diagnoses and only some alternate diagnoses. If there's a

strong confidence about the diagnosis of Parkinson's disease, especially in the case of someone who's had Parkinson's for many years, who's been taking medications like Sinemet or levodopa, and is responding well to those medications.

No one is calling in question the diagnosis of Parkinson's disease, I don't think that that's a situation where a DaTscan is required. Maybe back to one of the earlier questions about this description consistent with Parkinsonism. That's a good example of how DaTscan is helpful to measure the fact that there's a reduction in the dopamine-producing neurons.

But Parkinson's disease is not the only thing that can cause a reduction in dopamine-producing neurons, or the appearance of a reduction in dopamine-producing neurons. That's why it all depends on the clinical reason for ordering a DaTscan. For instance, one of the common situations where it can be helpful is if you're considering someone who has just a tremor.

You are debating between a diagnosis like essential tremor where we don't think that the dopamine neurons are involved, versus Parkinson's disease where we do know that they are involved. There, the description of Parkinsonism on the report for the DaTscan and the picture showing you that there's a reduction in those neurons or rather in the uptake of the radiotracer, would give you confidence that you're facing a diagnosis of Parkinson's disease and not of essential tremor.

But for some of these other Parkinsonism disorders, it's not necessarily helpful. Back to your actual question, which is it helpful for tracking the disease in the clinical setting? No, I would say no. I think what's helpful for tracking the disease is really how someone is doing, what symptoms are evolving. How they're responding to the medication because all the decisions that we make in the clinical setting are about controlling the symptoms.

In order to do that, we measure the symptoms of that individual that's sitting with us in the office. We make recommendations, changes to medications, suggestions of therapy and all that kind of thing in response to those symptoms. Seeing the images would not help you make those clinical, therapeutic decisions in any way.

Katie Kopil: Thank you. Maybe then shifting into the research setting, Dr. Seibyl, I know that you're part of the leadership team for the PPMI study. You're getting lots of repeat DaTscans on volunteers in that study.

Can you tell us what is the purpose of DaTscan and longitudinal or repeated measures of DaTscan in a research study, and where do you hope this is going to be in the future?

John Seibyl: First of all, I agree with my co-panelists that there's a difference between research and clinical applications with the use of DaTscan imaging. That's very important. One resonance that I have with Peter in particular, as I'm a patient, I've noticed that sometimes patients will get a DaTscan when they're very early in their disease course. When they see the scan, it's very meaningful to them because they can see something that's actually physically changed.

It's easy to compare as you can see on the screen still, which in a healthy subject, and that undisclosed the fact that they have the disease. I went through the same thing, I denied it. I said, "I'm the researcher, not the researchee. This can't be happening." I went through all sorts of things. Finally, I came to the conclusion that the universe has a sense of humor, but so do I and get on with it.

But with regard to the research applications, we are very interested in tracking the progression of Parkinson's disease. We know that it happens quite variably between patients. It happens variably within the course of a patient's clinical experience of Parkinson's disease. We're looking for biomarkers or ways that we can track objectively the changes. It's very hard in Parkinson's disease for several reasons, because first of all, it progresses very slowly.

Also, the medications are pretty reasonably effective. When you get to a point where you can't really ethically wash out a person from their medications, it's hard to use a clinical measure to track changes over time. Because there may be a little medication side effects or something where the imaging is unaffected by the dopamine replacement medications that people are on. You can use this as a measure.

The problem is that there's enough variability within the test from a quantitative perspective, that you can't use it on an individual very easily. We are doing these large studies with populations of patients, who are getting scans on a yearly or depending upon the particular protocol they're in. We have this wonderful now 12-year resource of scans, several thousand scans, that is like a fine wine becoming better with age, because it's complete and it's really just a remarkable dataset.

We've learned a number of things. We've learned that the change in the rate of DaTscan is about 11% to 13% a year. That number that we get goes down to about 11% to 13% a year. But we also know that healthy people have reductions in their DaTscan, about 6% per decade. So much slower, but everyone's losing these targets in the brain. But in a pathologic case of Parkinson's disease, it's much faster and much more asymmetric.

We have to correct our data to make sure that someone who is a certain age is compared to an appropriate comparison. I think that we've learned some ways to make these numbers a little tighter and less variable. We're looking at other

tracers as well that involve PET for interrogating this target in the brain for assessing these punitive markers of dopamine neurons.

As well as tracers that look for others things like the protein that's involved called alpha-synuclein, which is a very important biomarker, because it's one of the major reasons that we get symptoms from Parkinson's disease. I would say that both of these changes in the dopamine system and in the protein, happen many years before patients start to get motor symptoms, start to get tremor, or rigidity or gait problems, many, many years.

There's a great opportunity here from a research perspective, we can figure out who those folks are. We can get them on, get a test to confirm their diagnosis even before they have motor symptoms. You get them on a treatment that may actually prevent the manifestation of subsequent motor problems. This is just a heads-turning possibility. We've got a long way to go, but it's certainly where we're working towards in getting these objective markers of changes in the brains of patients like myself with Parkinson's disease.

Katie Kopil: John, I want to tease out just one small bit of what I think you referred to here, is that you can see these changes in DaT before there are enough clinical symptoms that someone is diagnosed.

How do you see the role of DaTscan now in a research setting helping better understand risk for Parkinson's disease?

John Seibyl: It's just a good question, and really we're working on the algorithms now. We can't just have people go to the shopping mall and get their local DaTscan screening test, although you get colonoscopies every so often and those are pretty invasive, but it just doesn't make sense because the test is too expensive. What you do is you look for common syndromes that may be predictive of people who are going to have a change on their scan.

There are two in particular that have risen to the top. One is a sleep disturbance, where a patient when they're sleeping will act out their dreams and may tussle in bed, and hit their bed partner and kick them out of bed and all that stuff. It's called REM behavioral disorder. That seems to predict a change early on in patients who are going to develop either Parkinson's disease or maybe Lewy body dementia.

It's not specific, but it does enrich the number of abnormal scans in taking all comers in recent studies, about 30% of people who have this syndrome, will go on to develop changes in the brain on a dopamine transporter scan. The other change that is seen, which is a little bit easier to test, is a loss of smell. Sense of smell is changed in Parkinson's disease, as it is in Alzheimer's disease and other neurodegenerative disorders.

It's not specific, but we've done studies where we've sent scratch-and-sniff smell tests out to around the world, some 5,000 in one study. People would test their sense of smell at home and send us back the scorecard, and we'd rank them. Invite about the lowest 10th percentile back to New Haven, Connecticut for an all-expense paid vacation to have a brain scan. That study revealed again that it's not perfect.

Most of the people who have the abnormal sense of smell don't have a change in their scan, but about 25% will have enough of a change that we track them over time, and they do develop Parkinson's disease in this cohort. Now, it depends upon what your cutoff for bad smell, and you have to correct for the fact that women smell better than men.

Katie Kopil: Everyone knows that, John. Not in a research setting, just a regular setting.

John Seibyl: In many ways. Yes, in many ways. We're looking at these algorithms or these ways to figure out who these people are.

It'd be great if when I developed my Parkinson's disease about 11 years ago, if five years before that I had a test that showed there was an abnormality.

There was something to give me that would slow it down, but we're not there. But that's the vision and the dream, at least my dream.

Katie Kopil: Thank you. We can spend just a moment on PET imaging and John already referenced a protein of interest, alpha-synuclein, that we think might be something that could be measured in the future by PET imaging.

Dr. Sharp, can you talk about how PET imaging has changed therapeutic development for Alzheimer's field? What do you think might be on the horizon for PET imaging in the Parkinson's field?

Madeleine Sharp, MD: Yeah. I think this comes back to being able to use the imaging test to be able to definitively say that what we're seeing is Parkinson's disease versus something else that can have a similar pattern to Parkinson's disease. As we were saying before, the loss of dopamine neurons could theoretically be caused by things other than Parkinson's disease.

But the accumulation of certain proteins that are known to be at the root cause of Parkinson's disease, so namely the synuclein that Dr. Seibyl was mentioning earlier. That's something that we know to be specific, so clearly indicative of Parkinson's disease. That's ultimately what we want to search for in the brain.

In the field of Alzheimer's disease, it is possible right now to measure the accumulation of amyloid, which is the abnormal protein that accumulates in Alzheimer's disease. That's been quite helpful, especially in the research setting.

Now transitioning into the clinical setting, because it means that as Dr. Seibyl... Maybe let's take a step back.

With the vision that Dr. Seibyl has, I think is the vision, the hope that all of us have, like researchers, clinicians and patients alike. That we are able to long before the disease actually manifests with symptoms, we can definitively diagnose that someone is at risk of it. That we would have a treatment to be able to slow or prevent any further accumulation of abnormalities in the brain.

In order to get there, we need to have clinical trials where it's possible to test drugs that could actually have that slowing down of disease effects. In order to be able to support those clinical trials, we need something that we can measure to prove this drug is actually having its intended effect, and it's reducing the burden of disease in the brain.

In people who are not yet manifesting the disease, that means that by definition, they don't have symptoms. There's nothing that you can measure as a neurologist to prove that they're not progressing. But so if we had a test that could prove to us and that we could use to track whether the disease is progressing in the brain, slowing down or not appearing at all.

Then we would be able to prove that drug A is effective versus drug B or whatever, which would advance us to this vision of the future that we have. That's where something that can actually identify this abnormal protein, which is the defining feature of Parkinson's disease, so that synuclein would be helpful. There's certainly been some developments.

I think one of the challenges in Parkinson's disease compared to Alzheimer's disease, which explains why in the field of Alzheimer's disease, they already have such a PET imaging tracer and we don't, is that there's less of this protein that accumulates in the brain. There's less of this abnormal confirmation of this protein that accumulates in the brain.

Where it accumulates in the brain is actually inside the cells, inside the neurons, which makes it harder to also be able to image it as opposed to outside of the cells. But there's been some really interesting progress, especially in the last year. A few studies that have indicated that there's certainly a lot of hope to be had that we're getting closer and closer to developing we call them these PET radiotracers.

That could be sensitive enough to actually pick up on this abnormal protein in the brains of people who have synuclein. The other tricky piece, maybe just to add because it's not such a simple story. Parkinson's disease has this abnormal protein, but other diseases too, namely multiple systems atrophy, which manifest a bit different than Parkinson's disease.

There's still some work to be done to be able to develop these tracers, such that they really tell us exactly the information that we're looking for. But I think there's really a lot of reason to be very hopeful that we're well on our way towards achieving that goal.

Katie Kopil: I think the hope is what continues to fuel the folks at the Fox Foundation and our partners, who have been on a quest to help support development of α-synuclein tracer since our inception. The protein alpha-synuclein, who if you've tuned into these webinars before, I'm sure you're all familiar with that term. It's the protein that clumps and misfolds in the disease.

The Fox Foundation has been focused on trying to develop these types of tools to image alpha-synuclein in the brain. We're not afraid of a bit of hard work and the challenge, and that we're going to continue to track that aggressively. Indeed, maybe now several years ago back in 2016, we announced a $2 million alpha-synuclein imaging prize that would be awarded to the first team to achieve successful selective imaging of alpha-synuclein in the brain.

You could imagine we have one of those giant-sized checks that come with some balloons. We're excited to share in 2020, the Ken Griffin Alpha-Synuclein Imaging Competition awarded three teams $8.5 million in funding to help accelerate work in this area. This past year, a team from Merck was awarded a $1.5 million prize for having made the most progress with their synuclein tracer.

The team is planning to use its tool in people with Parkinson's this upcoming year to test it. I think there's a lot of exciting progress, Dr. Sharp, as you've talked about, and it's on the horizon for the field.

John Seibyl: One thing I might add, Katie, augmenting Dr. Sharp's comments, there is a way to detect alpha-synuclein. It's a cerebral spinal fluid test, and that test has been very popular recently. There's been a lot of research and excitement about it. It does involve a lumbar puncture, but it looks like it is specific between the Parkinson's type of alpha-synuclein and the MSA type of alpha-synuclein.

The Parkinson's type is associated with nerve cells, neurons, whereas MSA is associated with these helper cells called glial. They're like supporting the neurons. It has a little different structure, and so you can actually tell them apart with this test. The problem with the test is that it doesn't give you a quantitative number, so you can't track people right now anyway over time.

It does involve a lumbar puncture, which is a little invasive for some folks, although it's a pretty common procedure. Many of you who are in PPMI, I've just undergone that. It doesn't give information about the region of the brain that the changes are occurring. There's some complementarity between the PET imaging and the blood test for alpha-synuclein side.

I think like all biomarkers, this complementarity is important because we're going to make the best use of these tools in whatever way that we can.

Katie Kopil: This alpha-synuclein seed amplification test or the spinal fluid test to measure alpha-synuclein in living people, has been something that the Fox Foundation has been shouting from the rooftops as a major breakthrough.

This breakthrough is really possible thanks to thousands of volunteers who participated in the Parkinson's Progression Markers Initiative study. Peter, what would you say is the role of study participants in research and helping advance these types of breakthroughs?

Peter DiBiaso: First of all, I think it's an acknowledgement that there's selfless focus and devotion to this really is amazing. I've been in industry for 25 plus years and I've never seen a more coalesced charge, if you will, an endorsement of all the work that could be done. That being said, I think we can do more. It's probably the number one reason that research sometimes lags and slows down a little bit.

Suffice to say that the patient is waiting, and I'm one of those patients, so I'm just as eager as anyone to get that process through. There's also some opportunity in terms of healthy controls with caregivers or non-diagnosed patients. Often I hear from folks that aren't a caregiver or someone that's taking care of someone with Parkinson's disease, and it's often said, "What can I do? What can I do?"

Well, you don't have to look any further than any of the hundreds and hundreds of ongoing clinical studies that are being featured. Again, I think a real step forward is embracing an opportunity to be a subject participant, really being a research hero. It really does provide that reinforcement to the caregivers. All of us are doing absolutely whatever we possibly can to promote the benefits of research.

And more importantly, to really dig down and look at Parkinson's disease and just how much difference we've really made. If you haven't seen some of the research over the last six months, it's really quite amazing. The advancements that we've made is no short of miraculous, and I don't use that slogan blindly. We're really excited to see the progress, but there's still a lot more to be done.

Katie Kopil: With your call to action and the need for more people to raise their hand and participate in research, I just wanted to highlight that the foundation's landmark study is still recruiting volunteers for PPMI. PPMI follows participants and collects data over time. This information helps researchers and drug developers better understand Parkinson's.

I think this is a really exciting opportunity and a critical need for developing better treatments, including paving pathways to preventing the disease in the future. Now coming back to the panel and topics and making sure we leave

some dedicated time for additional questions at the end. There have been some questions about getting the scan and what does it take to go through this?

It can be stressful because people have to stay still in a confined space. You're sliding into this doughnut with a loud banging sound, or you have an injection of a radioactive tracer. Peter, maybe you could start by talking about any concerns you had when getting an imaging test and if you had them, what were they? Was there anything you did to make yourself more comfortable?

Peter DiBiaso: Nuclear medicine is a wonderful field, but to the layperson, it's a little bit intimidating in terms of how to understand that. When it's purposely that I'm getting an injection of radioactive fluid into my body, suffice to say I did question that a little bit and wanted to do some more research on my own. But it's well-served and it's really been an advancement that's really been in place for decades.

It really is very effective, as Dr. Seibyl was alluding to earlier with some of the work that we've seen there. That being said, it's still a challenge in terms of these procedures. As I briefly referenced earlier, it's not always necessarily something that is comfortable for people. But there are strategies and you see some great recommendations here or there, here on the screen in front of you. But there's some great opportunities, I think, in terms of that.

It didn't bother me because I was really clear and my questions were made. I think the MRI technicians are phenomenal about making sure that you're comfortable. They're talking you through every single move that they make in terms of that. I think it's very comforting to hear the perspective of the physician and the MRI tech that's really walking step-by-step the expectations, what can be done, what they're going to hear, what they're going to feel.

It really helps put the patient at ease. Then certainly having a caregiver with you for that moral support can't be underlooked. But again, I think it is potentially uncomfortable for people, but I think with some education and with some follow up from the neurologist, this movement disorder specialist and others, it really helps to assuage a lot of those concerns.

Katie Kopil: Thank you, Peter. I'll highlight that this list of tips was not just generated by the panelists here or folks at the Fox Foundation. This was crowdsourced from people living with Parkinson's and the Fox Foundation's online community.

These are suggestions that came directly from the community. Dr. Sharp, anything you'd say about risks from imaging or are there risks and what are they? How do you advise your patients?

Madeleine Sharp, MD: The risks are from, for instance, in the case of, well, depending on the type of imaging, from radiation exposure or from the injection of the contrast agent, or

from the discomfort of having to lie through this procedure and potentially be somewhat uncomfortable.

The risks are considered to be really minimal. In the terms of exposure, they're not considered to be significantly more than what is expected from everyday exposures. We consider them to be very safe tests. I think the limitation remains just access.

Katie Kopil: Okay. Maybe we'll now move to the final Q&A session starting with one, and maybe I'd like a couple perspectives here from the panelists.

When would it be useful to have the spinal fluid test that was suggested on alpha-synuclein versus something like a DaTscan or MRI? Maybe Dr. Sharp, we can start with you with your clinical perspective.

Madeleine Sharp, MD: Yeah. Again, in the clinical setting, we would do things that are recognized definitively clinically as being helpful. That's the case for DaTscan, for added support towards the diagnosis of Parkinson's disease and eliminating alternatives. The CSF test for alpha-synuclein is something that is currently, well, at least as far as I'm aware, at least in my surroundings, something that is done in the research setting and not part of the clinical diagnosis.

It will really have value for in the way that DaTscan was used in PPMI because PPMI was interested and continues to be interested in identifying people who were very, very, very early or before the manifestation of symptoms. Where you need some added confirmation of the diagnosis, that's where the CSF could be helpful. But in the clinical setting, that's not part of the diagnostic workup yet.

Katie Kopil: Thank you. Peter, what are your thoughts as a person that's curious and living with PD, what would you say about a spinal fluid test, DaTscan? How you think about those two different types of tests?

Peter DiBiaso: I think from a pure risk standpoint and concern, I think the easiest opportunity for me was really the brain scan. As Dr. Seibyl alluded to earlier, it does come up with some really cool pictures, and it's very fascinating seeing your brain sliced and diced and visualized, so I think at that regard. I think the spinal tap, I think spinal work is again, intimidating.

But I've been fortunate, maybe unfortunate enough, to actually take that procedure, for that procedure as well. Despite my concerns and fear going into it, the physician was phenomenal and it was less than a flu shot in terms of pinprick. There's always the risk of any jot, and you think about all the terrible things that can happen if you miss, but it was amazing in terms of how easy that was.

Again, just another tool that we can use as researchers and as patients and as advocates to better understand, and there'll be many more on the way.

Katie Kopil: Thanks. John, anything you'd add from a research perspective? The alpha-synuclein seed amplification test, DaTscan, both where do you see there-

John Seibyl: First of all, this is a game changer for clinical research trials. In a lot of ways, it's going to standardize how we approach the diagnosis of Parkinson's disease. It's going to be based on biomarkers. We believe the presence of alpha-synuclein in the cerebral spinal fluid and maybe a blood test will be developed. We're hoping that the case, there's some skin biopsies and other ways to get it, but they're not quite as good as the lumbar puncture, CSF to sample.

Dopamine transport imaging, which is important because it shows you the changes in where the action is, where many of the symptoms that patients have are resulting from changes in those circuits in the brain. Between these two biomarkers, there's been initiative to redefine how we think of Parkinson's diagnosis based on the biology, instead of based on a cluster of clinical symptoms. This happens in all areas of medicine.

Once you get a better understanding of the pathology, you define the disease based on the pathology, not on which doctor discovered the clinical syndrome in the 1800s. We're moving along here, and I think that's very exciting. We will have a very different approach to standardizing how we do clinical trials with treatments. I think the other part about developing these redefined ways for diagnosing Parkinson's and staging the changes over time, is that it gives caregivers and patients a little sense of what's important to them.

In some cases, neurologists will look at symptoms of various sorts, and they may be irrelevant to the patient. But by looking at functional measures, measures that actually impact your life, like for me, it's tremor. Trying to click on a mouse in an accurate fashion is a problem, that may not be a problem for someone who doesn't do the work that I do. Having functional measures that impact the patient are really important.

The FDA likes that too, because it means that you're looking at relevant effects of the disease and relevant things that you could prevent from happening or look to get better. I think from a research perspective, these imaging and other biomarkers are going to be critically important to help us develop the drugs. Then I think they'll translate in some form or fashion into the real world, where the actual care patients takes place.

Either to make sure that the diagnosis is made more accurately or diagnosis is made earlier, or that we have a way to track changes over time and determine whether medication is working or not. If it's not working, maybe there's a different one that the patient may respond to. There's a lot of... I see a rosy future. I've been more excited now than I have been in years, over the changes that have happened in the past year. It's a very heady time, if you'll excuse the pun.

Katie Kopil: You're sending us into the new year with a lot of hope. There is really rapid progress. I've been at the Fox Foundation for 10 years, less time in Parkinson's than our panelists, but I agree there's a lot to be optimistic about with the speed of progress.

To close us out, last comment from Dr. Sharp. Could you take us through the big important takeaway? Where is PD imaging today and what does the community need to know about imaging in Parkinson's?

Madeleine Sharp, MD: I think the big takeaway is that there's a lot in the pipeline. I think we already use imaging in ways that are useful clinically and useful for research, and I think we'll be able to get a lot more out of it. What's really exciting about the imaging piece, in addition to some of these other tests that we've been talking about, like the test from the lumbar puncture or maybe from blood sometime soon.

Is that it allows us to actually look at the organ, the brain that is affected by the disease and that is causing the symptoms. I think that's why there continues to be so much interest in finding ways that we can optimally use the images that we can capture from MRI, PET or SPECT. I think the takeaway is really that there's a lot in the research pipeline for measurements that will be useful in research, and eventually for our patients in the clinical setting too.

Katie Kopil: Fantastic. Dr. Sharp, Dr. Seibyl, Peter, thank you for joining us today.

Thank you to the audience for tuning in, and we'll look forward to seeing you back here next year. Thanks all.

John Seibyl: My pleasure. Thank you.

Madeleine Sharp, MD: Thank you.

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