Michael J. Fox:

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Narrator:

Welcome to a recap of our latest third Thursday webinar. Hear directly from expert panelists as they discuss Parkinson's research and answer your questions about living with the disease. Join us live next time by registering for an upcoming webinar at michaeljfox.org.

Maggie Kuhl:

Thank you for joining us today. I'm Maggie Kuhl, Vice President of Patient Engagement at the Michael J. Fox Foundation, and I'll be your moderator today. I have done this webinar many years, and it's always one of my favorites. This is our year-in-review talking about all the exciting research that's happened in 2024. We have a lot to share with you, so we're glad that you joined us today. Today, with me are three CMOs. First we have Dr. Maurizio Facheris, who is currently Chief Medical Officer at Vanqua, but for a long time was here on staff with us at the Michael J. Fox Foundation as one of our research scientists. Maurizio, thanks for this reunion on a snowy Chicago morning.

Maurizio Facheris:

Yeah. Yes, good morning, good afternoon, everybody, wherever you are in the world. Thank you for having me. Very excited to be part of this panel and to talk about exciting things for 2024.

Maggie Kuhl:

Someone on our panel who has not yet worked for the Michael J. Fox Foundation but is actually joining us from our offices today because he's there for a meeting is the Chief Medical Officer at the Institute for Neurodegenerative Disorders and a Movement Disorder Specialist at the University of Pennsylvania, Dr. Tom Tropea. Tom, thanks for joining us.

Thomas Tropea:

Of course. Thank you and nice to see everybody and happy to be here.

Maggie Kuhl:

Our other CMO, Chief Mission Officer, Todd Sherer of the Michael J. Fox Foundation. Todd, thanks for sharing your deep well of knowledge and foundation strategy with our attendees today.

Todd Sherer:

Thanks, Maggie. I look forward to the webinar. I just want to start by thanking Maurizio and Tom for donating their time to share their expertise with the community.

Maggie Kuhl:

Well, let's jump in and start with some big news this year. The Food and Drug Administration in the United States approved two new drugs for Parkinson's disease. These are both to help with motor symptoms and motor fluctuations. The first is Crexont and the second is Vyalev. Maurizio, between Fox Foundation and Vanqua, you worked at Abbvie on Vyalev for nine years, and so you're really familiar with that therapy and this space in general, so maybe you could share with our attendees a little bit more about these therapies and what they can do for patients living with PD today.

Maurizio Facheris:

Yeah, absolutely. As you mentioned, those are both medications, so very exciting. Very exciting, because again, we are adding onto options and therapies for people living with Parkinson's disease. Those two medications specifically are helping people with the later, more advanced stage of Parkinson's. I think everybody understands that Parkinson's has several phases and one where symptoms are becoming a little bit more naughty and resistant to medications, this is where we have motor fluctuations. Both these medications are helping patients to improve those motor fluctuations, reduce those motor fluctuations, improving the time on, so when there's no symptoms, reducing the time off when symptoms are reappearing, for example, so those hours of off time are reduced. Or potentially also reducing the time of dyskinesias, which is when symptoms are, that medication seems to work over and giving some of those annoying fluctuations instead of this dyskinesias.

The good news is that both medication had been approved. One is an oral, a tablet is a pill, specifically made to have granules of levodopa, which we know it's the main drug that helps symptoms of Parkinson's. Those granules are releasing levodopa quickly. Some others are pellets that release levodopa more slowly, so over time. The good news, the novelty about this medication, this is Crexont, that it's coded. Specifically coded to prevent the degradation of this medication in the stomach and goes directly into the intestine where this medication is absorbed. It's improving the time that this medication stays in circulation and therefore increasing the time of levodopa in blood and dopamine in the brain, so they can keep a more stable concentration of dopamine and reducing those fluctuations.

Now, as Maggie mentioned, I work on Vyalev. What is Vyalev? It's novel compared to this, a little different compared to Crexont. Vyalev is a drug device combination product. It's an infusion of foslevodopa and foscarbidopa that goes under the skin through a small infusion set that is attached to a portable pump. The difference is that rather than using that by mouth, so still taking that pills, et cetera, it gives a consistent, predictable continuous infusion of foslevodopa, which is transformed in the blood directly into levodopa, and again, we are back into the standard approach of controlling symptom for Parkinson's disease.

The good news is that it is bypassing the stomach completely. Any concerns about absorption or if you have problems swallowing or in general or even overnight, you can maintain that concentration of the drug overnight rather than waking up and taking pills. This is actually a big advantage and both studies that demonstrated an improvement in motor fluctuations, I would say that Vyalev has that add-on on the nighttime symptoms, the 24-hour infusion. Overall though, I think what is important to remind everybody here is that we are just increasing options, so giving more opportunities to patient from choosing what they think is best for them, for their quality of life, for the lifestyle, et cetera. Very, very exciting thus far.

Maggie Kuhl:

That's actually where I was going to go next. Tom, you treat people with Parkinson's in your clinic, how do you help the patients navigate the tools in the toolbox and select which therapy is right for them at the right time?

Thomas Tropea:

Well, this is always a conversation with the patient, with their family members and making decisions around the right treatment is so, so individualized. Not everyone is best-suited for one particular therapy. I want to highlight something actually that Dr. Facheris brought up, which is that these are options in our arsenal to expand how we can treat people with Parkinson's and how we can target the symptoms maybe by reducing the number of pills that you have to take during a single day, or frankly, maybe by not taking pills and instead using an infusion therapy. There is a really big advance in the field now to have an option that is a non-oral or non-pill form of levodopa that can be given in a subcutaneous under the skin

infusion, not necessitating a procedure essentially to deliver that medication. These are really big advances and all of that contributes to our conversation with patients.

There are some people that will be interested in taking a pill 2, 3, 4 times a day and that's great and we can support people in doing that. There may be people who are interested more in using infusion therapies or other therapies. These are just new options that we have. It's usually early on in meeting with new patients that I will offer education around all these different options that they have, and maybe that's not right at the first visit, but it could become an important consideration at the second visit, the follow-up visits, maybe even years and years later.

Maggie Kuhl:

Dr. Todd Sherer, many people on the call, everyone on the call knows that Parkinson's is much more than the motor or movement symptoms that come with the disease, and so there are more than 100 other treatments and testing, many for other symptoms of Parkinson's such as cognition, depression, swallowing issues. Can you talk to us about where the pipeline is today and any movement we've seen in the last year toward treating other aspects of PD?

Todd Sherer:

Sure. Yeah. I think this is where the optimism on the momentum in the field really comes to play. As Maurizio and Tom were just talking about, two new drugs have made it all the way across the goal line. Now, they'll be available in 2025 for patients, and it's not that common that that would happen, so that's a great achievement. What we want to see is more options and more opportunities and you could see that now we have quite a vast development pipeline of new therapies that are making their way all the way through various stages of clinical development and treatment options or clinical trial options.

A couple of things I also wanted to highlight is that not all of these are drugs. They mentioned the drug device combination, but we still have innovations happening with deep brain stimulation, which is another type of surgical procedure that's used for people with Parkinson's. The availability and the vast impact of that therapy is improving based on some of the research that's being done. There's stem cell therapies and cell replacement therapies that are moving through clinical development. Gene therapy is also another, genetic-based therapies are all being part of this pipeline. There's quite a lot of activity and it's really great to see a lot of the underlying science that we've been learning about over the last decade or so now being converted into potential new therapies for people with Parkinson's.

Maggie Kuhl:

Great. What I'm taking away is there's a lot of different approaches, be it drugs or surgical interventions or even exercise interventions for a lot of different aspects of Parkinson's that also address the different journey with PD, the different time points that one may be walking post their diagnosis. I'll also maybe give a plug here that all of these treatments cannot move forward in testing and toward approval and use in clinical care without research participants. If you are interested in joining trials, then you can visit our Fox Trial Finder tool, which will help match you to the hundreds of recruiting studies looking for volunteers to help test their hypotheses.

I want to move on now, and Todd, you pointed out how much of this pie chart is around progression and targeting the underlying biology. Our hope would be that there would be therapies that would stop or ease many aspects of the disease by really addressing what is the root cause of the many symptoms of Parkinson's. We're going to talk about targets and give a little bit of a 101 to help move us into the next part of our conversation, because just like the therapies that, Maurizio, you shared with us work on the dopamine system, we have many other targets that drugs are addressing to try and stop PDs. Maybe you can just give us more of a primer on what is a target when we talk about that.

Maurizio Facheris:

Sure. I'll try my best, because there are several targets. Potentially, a gene or the byproduct of a gene, which is a protein or a pathway like a series of protein and enzymes involved in a process in our cells in the brain or somewhere else in the body. I would say that maybe we can recollect as a common denominator to one protein that we are very interested about, which is alpha-synuclein. We all know that alpha-synuclein accumulates and this protein clumps in the brain, and we don't know if it does it as a way to prevent this accumulation or as cause. We really started learning about this accumulation in the brain, in the cells, in the dopaminergic cells, the cells that produce dopamine, and we heard before how dopamine is important. But now, alpha-synuclein clumps in this dopaminergic cell and eventually the cells die.

When we say, "What is the target? Why are we interested in these targets?", is that we know that there are several ways why there's potential alpha-synuclein clumps. It could be because the organelles in the cells are not doing the job of cleaning this rubbish. The trash alpha-synuclein that is free and soluble in the cells, there is these organelles that can clean up but they don't do the job very well. Or maybe there is another protein or a gene that is involved in producing too much of this protein. We can target the gene by say, "Okay. Well, shut down a little bit, try to avoid this overproduction of this toxic protein." There are several processes that can be put in place to address the baseline problem, and all of those processes that are focusing on one of those underlying problems are targets.

Why this is important? It is because if you understand what a target is or you actually figure out what a target is, not necessarily what it does, but what it is, you can develop potential medications that go and interact on that target and interact by, as I said before, maybe preventing too much formation of a protein or cutting that protein up and helping the cleaning up or activating the enzyme that helps cleaning the protein. I might just make an example, but once you identify what target is, you can act on it by either mechanism, as we said, pharmaceuticals, so creating molecules that interact with those targets or by using devices, as Todd mentioned, DBS uses electricity to modulate some of those neurons, and that's the way, it's another a way to target. Or you can use even non non-therapeutic or non-device approaches that are stimulating or producing other protein in the brain or the chemicals in the brain that help with maintaining the balance of the brain.

I'm talking about, we always say that at the Fox Foundation, exercise. Exercise is something that we always know it seems not a therapeutic, but it does work. It does by increasing level of endorphins and something like that. Maybe those molecules are interacting with those targets and making some benefits physically into our brain. This is, again, a big answer and I know maybe sometimes create more confusion, but the take home message is that when you identify a target, you can find something that can work on that target, modulate that target, and eventually help with the pathology of the disease, in this case, Parkinson's.

Maggie Kuhl:

Yes, and really, it differs. Sometimes you have to increase the target activity, sometimes you have to decrease, sometimes you have to cancel out, sometimes you have to replace, and so a lot of our work goes to study exactly how we would modulate. Todd, I want to go to you next because Parkinson's is such a complex disease. We've uncovered so many targets, but a lot of our understanding of Parkinson's comes from studies from individuals from European descent. We, over the last couple of years and again in 2024, really added to this bank of knowledge around the disease biology from populations who have been underrepresented in research. What is the value of that? What is the Foundation doing to try and fill those gaps?

Todd Sherer:

I think that one of the keys and we're learning about Parkinson's is that there's not going to be one target or one biology that is at play in every individual with the disease or even at every stage of the journey of the disease, so some of this biology could be at play at risk of developing the early stages of the disease and different biology may come at play as the disease is progressing. There's going to be a need to really understand which biology is taking place and which subpopulation of individuals with the disease and also at what stage of disease. To really understand this and learn this, we need to study a vast population of people with Parkinson's that have diverse backgrounds, both different genetic backgrounds, different environmental exposure backgrounds to really understand and fine tune what could be the causes of Parkinson's and what biology may be at play in the different populations.

As Maggie was saying, historically there's been a narrow slice of the population of people with Parkinson's that has been studied mostly from North America and Western Europe. The foundation took on a big effort with our partners from the ASAP initiative and NIH to launch a more worldwide study that's called the Global Parkinson's Genetic Program, GP2, and they're now, in that study, integrating and working with patients and clinicians throughout the entire world, Africa and Asia and Latin America, as well as North America, South America and Europe. What we're really uncovering is that there's some very clear commonalities in the cause of Parkinson's and the underlying biology in Parkinson's across these populations, but there are some more population-specific genetic findings and other biology. It's really important, again, to do this in order to develop therapies that will treat the biggest population, the vast majority of people with Parkinson's to know what really is the biology we need to target and which are the right patients that would benefit from those types of therapies, so we can design the best trials with the best chance of success.

Maggie Kuhl:

Absolutely. Some of the targets that we've already identified may have broader application and we may uncover some new ones. Tom, Dr. Tropea, we see on the slide a couple of the targets, the pathways, proteins that we have identified and profiled to play major roles in Parkinson's disease. Maybe you could just quickly cover some of those.

Thomas Tropea:

Sure. I'd like to sort of tie together what Dr. Sherer and Dr. Facheris basically mentioned, which is essentially understanding more about the biology helps us to understand what are targets for drug development. We've done a lot of this over the years and recently, I think people on this call have probably seen, that there are drugs and development that drugs and clinical trials that target specific pathways. These are rooted in years and years of biology and understanding targets for potential therapies. Clinical trials ongoing right now and in the past couple of years have targeted individuals carrying a variant or a change in a specific gene and in particular the LARP-II gene or the GBA gene. But it's also important to understand that while we use targets as a way to approach, say enrollment in a trial, it does not necessarily mean that those drugs may not be relevant outside of individuals carrying changes in those specific genes.

Again, we understand the targets so we can develop therapies. Understanding more about the biology helps us to understand if targeting that therapy is relevant even outside of say a group carrying a change in one of those genes. It's important to understand that, and we have some really interesting studies ongoing, clinical trials, as well of drugs and development targeting gene pathways, targeting alpha-synuclein, the protein most associated with Parkinson's disease symptoms, as well as inflammation. I think in the next bunch of years, we're going to see a lot of interesting results from those studies. It'll help us to understand, again, more about the biology and how those targets relate to individuals versus Parkinson's disease much more broadly.

Todd Sherer:

Maggie, just one thing I also wanted to add on this. One of the things that's very important and exciting about targeting this underlying biology is that these are the processes that we believe are involved in the onset and progression of Parkinson's. The hope here is that by interfering in these key biological pathways, you may actually be able to interfere in the actual disease process and progression itself. It's different than some of the therapies that we've talked about that just came across the FDA goal line that are managing and mitigating some of the symptoms of the disease. With all the advances in understanding the underlying biological pathways and targets of the disease, there's the hope and the design of these trials to really be trying to target the disease itself, the actual nuggets of the disease that are leading to the symptom development and progression.

Maggie Kuhl:

Absolutely. Maurizio, anything to add? I know that you're working in this space particularly.

Maurizio Facheris:

Yeah. Two things that I wanted to add. One is to close the circle to what Todd mentioned. Even the symptomatic therapies, that is all we have right now for Parkinson's disease started by focusing on a target. We initially realized long ago that what was happening in Parkinson's was this reduction of dopamine and here we are. We couldn't give dopamine directly because it doesn't get into the brain, but we were able to give levodopa and that was the start of therapy. Levodopa-based therapies that we know are the cornerstone of symptomatic therapy from 1967 on, so more than 50 years now of levodopa-available therapies, but that started with a target.

Speaking of those targets that are now of interest because they can really slow down or the hypothesis, the goal is to slow down the progression of disease and/or even potentially stop the progression of disease making the disorder from progressive to chronic, just keeping as it is or maybe preventing it in the future. It is focusing on those mechanisms that seems to be the underlying reason for the degeneration of those neurons.

I give you an example and I want to close returning to what Dr. Tropea said before, which is there are targets like the GBA and as you said, I'm interested in that. It's only approximately 10% of the population with Parkinson's disease had a mutation on the GBA, and that GBA gene encodes for a protein that is in the lysosome, which is one of the organelles that cleans up, as I said before, the toxic proteins. But what we learned is that everybody in Parkinson's, the majority of patients with Parkinson's disease, has a reduction of that protein that cleans up the toxin proteins, that cleans up alpha-synuclein. And so, you don't have to have a mutation to potentially have that reduction in the GKs, that's the enzyme that encodes via GBA. Again, the importance of understanding the targets or finding targets is because you can learn the biology underneath the progression of the disease and you can target those targets potentially via pharmacology. For us, absolutely very interesting because open opportunities would truly slow down or stopping the progression of disease, which is the goal that we all have.

Maggie Kuhl:

Yeah. I like to think of it as sort of like a GPS or a map. If you can put in a starting origin and end destination of Parkinson's, it might show you the roads to get there, but other people might get on that same road just from different entry points, different on ramps. As you said, if you treat the disease pathology that's on that road, if you came from one spot with a GBA gene variant or another spot with exposure to agent orange or other things that we know send you toward Parkinson's, if you're treating something a little bit more downstream, it might have efficacy in different causal populations.

Maurizio Facheris:

Right. And as Don said before, it might not necessarily be a single approach. We, obviously, for developers, you need to focus out one thing at a time, but I believe it in the future will be a combination of all those strategies. That's why we now want to put all the eggs in single basket. We are truly focusing on multiple approaches because potentially it's a combination of all of that, targeting all of that then will bring us to the conclusion.

Maggie Kuhl:

Yes. We have more than 100 targets that have already been named in Parkinson's disease. We are not stopping the pursuit of new targets or we are working very hard to nominate which targets we think play a really big role and put our resources toward moving those closer to drug development. Now is time, I'm going to make a small callout because research like this that we're talking about at the foundation is made possible by our community. Giving Tuesday is coming up, so we encourage you to think about giving to the foundation and all gifts made before or on December 3 will be matched up to $4 million. You can double your impact and any gift is a double investment in our biggest, boldest initiatives to close in on the cure.

There's a take action box on your screen that I'll direct you to. While I'm doing my commercials, I'll go back to my previous one as well because, as we've talked about, there's so many targets, there's so many therapies, a lot of trials were in development. They recruited volunteers, they followed volunteers, we're now getting the readouts and that means that a lot of them are going to be starting and moving toward this next phase, which is really exciting. It means that they need a lot of volunteers. I know my team, which works on recruitment, has a lot of calls with companies who are throwing out numbers like, "We just need 400 people with Parkinson's."

There's multiple studies coming down the line, and so, if you are interested in helping us move closer to a cure in that way, again, Fox Trial Finder is a great way or you can keep an eye on the Fox Foundation communications, because we'll be sure to let you know when some of those big trials start opening. Want to move us forward in our conversation to how we can get the right drugs to the right people at the right times as we have been talking about and really, as quickly as possible, assess are these the right therapies that are doing the things that we want to on the targets and having the right impacts on disease and how you all really feel day-to-day? For that, we have had some breakthroughs in biomarkers over the last year or so. Tom, I'm going to start with you, and again, go back to our one-on-one. What is the biomarker? Why are they so important?

Thomas Tropea:

Biomarkers can take many forms. A biomarker itself is something that's measurable from some fluid or process throughout the body that we can access and measure. That's really broad. That's not actually all that helpful. But you can think of it as maybe like a protein that we could measure, say from the blood or the spinal fluid, or a biomarker in a really broad sense could be say even maybe an imaging marker that's a little bit expanding, but a biomarker traditionally is, but it could be an imaging marker of a process that's going on in someone's body.

It's basically an external measure of an internal process. You can think of that it's really helpful for us to have effective, easily-measured biomarkers because it allows us to understand more, again, about the biology of what's going on in someone's body, but it can also be an indicator of a ongoing process. We may be able to measure these, say proteins or whatever we're going to measure over time and see how things change or may be affected by an intervention or a drug or therapy that we use. Maggie has alluded to some really big breakthroughs in biomarkers this year. I don't know if you want to talk about that more.

Maggie Kuhl:

Yeah, please go ahead. Tell us about what's happened.

Thomas Tropea:

Absolutely. This year, I hope everyone has seen some of the excitement around our ability to measure and detect the pathological protein, alpha-synuclein, from samples provided from spinal fluid, as well as from other tissues around the body. This is really a breakthrough. In the past, we have relied predominantly on a diagnosis that is justified by symptoms, clinical symptoms and signs that we see in the office. We've moved from our ability to do an exam and give a diagnosis maybe with some imaging to detect the biology of Parkinson's disease.

Rather than clinical symptomology, we've moved to our ability, we've advanced in our ability to do biology. Has so many implications for what we can do from studying the biology, studying drugs in development, but also, I think it has a big impact on how people can define their own disease and their own symptoms. It can be helpful to know with more clarity why you have, say tremor or changes in your walking speed and things like that, that are beyond just the clinical diagnosis that we've relied on for so many years. There's a lot of impact from this big breakthrough.

Maggie Kuhl:

I'm going to just define quickly because we've been using the term biology of PD law and we got in the Q&A, what does that mean? And I think your definition of biomarker, which is I'm going to apply perhaps even more broadly to disease, an internal process. Like you said, there's the clinical experience, there's that you have tremor or that you have depression or your memory and thinking issues. But then, there's actually what is happening inside that is causing those manifestations, and so that is what we mean by biology of disease. When we're talking about what targets are at play or what changes you can measure like we're talking about now. Wanted to level set for that. But Todd, as Tom was saying, we had this biomarker breakthrough with our PPMI study and now, we can detect this disease biology and living people with the disease. Then, this year, we had this letter from the Food and Drug Administration that really endorsed this biomarker. Can you tell us about that milestone and why that is important?

Todd Sherer:

Yeah. I just want to add a little bit about the biomarker. First, for the FDA support, this is really the FDA encouraging the use of this biomarker and further studies utilizing the biomarker to help better inform how clinical trials can be done in Parkinson's in the future. I think that's a key step, because we want to have trials designed that have the best chance for success. Having the best tools so that we can, again, design the trials, so that if we have a therapy that works, we actually can detect that it's working. One of the most things also about the biomarker is that right now, this alpha-synuclein test is just a yes-no test. It just tells you whether you have the presence of the synuclein or not. It doesn't tell you how much is there. It also relies on a spinal tap or it's measured in CSF, cerebral spinal fluid.

The foundation, it also has quite a robust effort now to improve this biomarker, both to make it quantitative, which means rather than yes-no, it actually gives you a number readout, so that we could see, for example, does it change over time in an individual? And importantly, if a therapy comes in, does it reduce the presence of the synuclein, which would indicate to us that it's positively impacting the biology of the disease? And also, to see if it could be moved to a more easily obtainable biological samples, particularly with a lot of effort to see if we could develop the measure in blood, which could be then done at a much broader scale in the population. This is an incredibly important advance because it allows us right now to better design clinical trials using the biomarker and also opens the door for much more robust study of the disease and improvements in the biomarkers going forward.

Maggie Kuhl:

Great. Maurizio, maybe you can build on that from the industry angle, how do drug developers and study sponsors, trial sponsors think about biomarkers and their use?

Maurizio Facheris:

I give examples, how do you diagnose diabetes? We know that diabetes is a chronic disorder that can cause clogging in the arteries, can give neuropathy, you can have several disorders, but it's easy to detect, because you do a blood test and you have glucose, sugar in blood and you know if it's high or too low, you can actually adjust that and you create therapies based on that marker moving in the blood, so you can control if your therapy is working well or not. As Tom mentioned earlier, so far, even with the medications that we have available, you can say it's working or not working because it's based on symptoms. It's something very easily to assess. You are shaking or you are rigid, you take levodopa or you take another medication that is working for symptoms and the symptoms disappear for that period of time or now for a longer period of time because we learn about new medications. But point A is, you can immediately know if this medication is working.

Now, when we are moving towards disease-modifying therapies, so something that really is focusing on slowing the progression, well, unfortunately, if we don't have something to measure, as Tom mentioned, biomarker is something that we can measure whether it is in blood, in the spinal fluid, an imaging marker, a digital marker, something that you can move, like something that you can measure physically. As a drug developer, you only rely on clinical symptoms. If we are working towards slowing the progression of disease, we are going very early in Parkinson's just after diagnosis or potentially even before diagnosis. If we need to rely only on symptoms, the risk is that it's going to take 5, 6, 7 years to notice a difference, and that is, one, very costly, and I don't think patients are actually really willing to wait that long.

That's the sense of urgency that we all share. We, as drug developer, physician because they see patients, the foundation has been a mission of this. We have a sense of urgency. Finding a biomarker is a way for us to detect, as Todd mentioned, if the medication that we are testing on that biological background in the biological basis is working on clean the alpha-synuclein that we heard or other potential mechanics, is that working by looking at those measurable things in blood, spinal fluid, imaging, et cetera. If we can, we need a lot of data unfortunately. That's another thing. Before we can use an marker to define whether something is working, we need a lot of data to make that marker qualifiable to say, "Okay, yes. If we see a reduction of alpha synuclein, then it's actually targeting the biology underneath Parkinson's and potentially the medication works."

There are several markers. We heard, there are several biomarkers. You can use biomarkers to reach the population, meaning diagnostic marker. Then you say, "Oh, then that patient truly has Parkinson's and it's not multiple system atrophy. It's not another disorder. You help narrowing down the population and there are markers for progression, which is the most important ... Well, it's not the most important, but very important thing for drug development, because if we need to rely only on clinical, as I said, it will take very long and it will be very expensive. It will take a lot of people, not only 400 people as Maggie mentioned before, it will take thousands. But if we can have a reliable marker, then we can reduce the sample size and actually come up with a result sooner and with more precision. This is why it's very important for drug developer to have a reliable biomarker,

Maggie Kuhl:

Much faster, higher likelihood of success. Parkinson's is such a complex disease. We've talked about so many things that go wrong biologically, internal processes. Obviously, again, people experience so many different symptoms and rates of progression and it means that there's a lot of room for opportunity, places that we could stop the disease. But it also means that we need a lot of people to help us learn about all these different subtypes and experiences. Again, like Maurizio, you said we need a lot of data, we need a lot of people to participate in studies to help us learn because you are the experts. I think actually Michael was just in the news doing some interviews and such and he was saying, "If there's a room full of scientists and there's one person with Parkinson's disease, they are the expert on the disease," and so we need you experts to help us understand all of the different intricacies and how we can stop Parkinson's for every person living with PD and at risk for PD.

I really like to save a lot of room for questions on this webinar each year. I'm going to move us forward. We could not talk about news in 2024 without talking about the passage of the National Plan to End Parkinson's Act. Todd, if you could just give us a brief overview of what this is, what this means for people living with Parkinson's and research and where we are currently in our next steps.

Todd Sherer:

Yeah. I think first, most importantly, the goal of this plan is to keep in mind and remember that the United States government plays a critical role in both the support of research but also the care of people with Parkinson's disease. We can't do this alone in terms of moving forward the development of new treatments for Parkinson's. We really want to get more strategic and focus attention from the federal government in the United States. That was the goal of this legislation, the National Plan to End Parkinson's Act, which was passed by Congress and then signed into law this summer. It focuses the attention of the US government to develop a National Parkinson's project, something they'd done some years ago for Alzheimer's disease. The result of the Alzheimer's Disease Act and subsequent plan led to, not only an increased amount of funding and attention at the federal government for Alzheimer's disease, it developed a more coordinated plan across the research enterprise up through drug approvals and into the clinical care and delivery of care to people with Alzheimer's.

Where we are right now? For the Parkinson's plan, as I mentioned, it was passed this summer. Now, as the next step, the US Department of Health and Human Services would be charged over the next period of time to develop a holistic coordinated plan for the National Parkinson's Project, which is an initiative to both prevent, treat and cure Parkinson's disease. It's a great opportunity for us to get more involvement and more focus from the federal government to join this fight in a more holistic way to improve the lives of people with Parkinson's disease.

Maggie Kuhl:

We're asking a lot of the attendees on this call, but we have a lot to do and we go much farther together. As Todd said, there's a lot to be done and you can be updated on what's happening with the national plan and help us advocate for the support and the policies that it hopes to enact by visiting our website as well. With that, let's turn to some of the questions from the audience. The first that I wanted to talk to is actually go back to our first topic in these new therapies. Maurizio, I'll toss this to you. Some people may be aware that with long-term levodopa use or advanced disease, people experience dyskinesia, uncontrolled movements. Do these new therapies help address that side effect at all?

Maurizio Facheris:

Short answer, yes. Both medications are aiming to reduce motor complications. When I say complications, it's fluctuations, so changes in on and off, unpredictable, as well as dyskinesia. The reason for this is because dyskinesia is not necessarily a problem of long use of levodopa, but it's just when after degeneration of the neuron, sensitivity of the receptor, et cetera, when you take a lot of levodopa, that causes those potentially unwanted movements. By keeping the concentration of levodopa stable in blood and therefore trying to keep the concentration of dopamine stable in the brain, you can prevent those peaks that cause dyskinesia and those drops that cause the off symptoms.

All-in-all, it is a way to keep that symptom control as stable as possible during the day and potentially during the night in the case, for example of Bialive. This is something that is addressing the dyskinesias. Can we say they will prevent from developing dyskinesia in the future? We don't know. We haven't done any study that shows that people who start with Parkinson's and maybe start taking those medications will not develop dyskinesia. That's something that we haven't studied. We don't have an idea yet, but again, those medications are indicated for people who have a little bit more advanced stages of Parkinson's, so we haven't addressed that.

Maggie Kuhl:

Well, I guess we will see. It's just came to market, and so people will be taking it over the next couple of years and, again, the true experts in the experience. Todd, I'm going to turn to you for our next question, which is, what new research has happened this year in our understanding of the gastrointestinal tracts connection to Parkinson's? Perhaps also I'll throw microbiome in there if that's not the same thing in your mind.

Todd Sherer:

Yeah. This has been a real area of interest, not just in Parkinson's but in neurodegenerative and neurological diseases broadly, which is the interaction between the digestive system and the brain, what they call the gut-brain axis. In Parkinson's, it's particularly of interest, because there's some data that suggests that early symptoms of Parkinson's may actually begin in the digestive system. We talked about some of the advances with alpha-synuclein and the importance of alpha-synuclein in Parkinson's. It is actually found that there are alpha-synuclein pathology in the nervous system that controls the digestive system, so it's not only found in the brain.

There's been a lot of effort and interest around what you're calling the microbiome. Microbiome is, we are both an animal itself and we are an environment, so there are bacteria that live within our body and in different parts of our body, and one main area is within the digestive system. The microbiome is actually the bacterial makeup of your digestive system, and each individual has a different microbiome based on their diet and their genetics and other factors. There have been some studies that have indicated that the particular makeup of the microbiome may be different in people with Parkinson's disease than those without Parkinson's suggesting perhaps that there's some involvement of that microbiome in the disease.

I think it is interesting because, for most cases of Parkinson's, we say that the cause of Parkinson's is the interaction of your genetics and your environment. And if you think in your body of some of the places where this happens are both areas that there are early symptoms of the disease. One is in the olfactory system, so in your smell, which is where some of the environment is getting exposure to your body. The other is what we're talking about now, which is in the digestive system, which is also a nexus of where environmental factors could interact with the host. You're the host. You're the genetics of the host, which is you. I think this is an area of interest. There's a lot of research to still determine exactly the role in the cause of Parkinson's. But certainly, digestive symptoms are important features of Parkinson's and a lot of work is being done to also try to figure out how to mitigate those symptoms as well.

Maggie Kuhl:

Yes. Like Maurizio gave a plug around exercise, I think diet is one where we know it does good things and there doesn't necessarily need to be a lot of research on exactly which diet is best. We have a great guide on our website from our on-staff movement disorder specialist. We encourage you to check that out. A healthy diet, Mediterranean, fruits, vegetables, healthy grains, healthy fats, et cetera based, there's some nice outlines in there to help manage life with PD. Todd, you touched on where I was going to go next, but I'm going to turn it over to Tom, Dr. Tropea. We had a couple of questions on factors that could help us identify Parkinson's very early on. Todd had talked a little bit about smell loss and the PPMI study that we support, but again, you're one of the leaders of, is really leading the charge and understanding the relationship to smell loss early in disease. Can you tell us perhaps what we're learning and maybe what some of our attendees can do to help us learn more?

Thomas Tropea:

Sure. Smell loss is, of course, I think one of the biggest expanding area for us to collect samples from individuals and data from individuals prior to the onset of say, tremor or what we traditionally call Parkinson's symptoms. But even years before that, people who later on go on to develop tremor and

Parkinson's symptoms, constipation is very, very common. In fact, anxiety and depression are very, very common, but these are so non-specific and they can happen to a lot of people who don't end up going on to develop a neurodegenerative, Parkinson's, Alzheimer's disease or something else.

One of the best study at this point is actually the link between the loss of sense of smell or decrease in sense of smell and the later development of Parkinson's disease. Now, of course, it's not in everybody that develops Parkinson's symptoms that has a loss of sense of smell, but there is a strong relationship between the loss of sense of smell and the development of what we keep calling the pathological protein or alpha-synuclein.

It's now becoming one of the best studied areas. In the PPMI study and in efforts around the PPMI study, we are expanding how people can go about getting smell testing. There are efforts led by the Fox Foundation to expand access to smell tests. This has been both very helpful for us to understand more about what it means to have loss of sense of smell, but also, for reaching back out and saying, "Hey, we found this finding in you, would you be interested in coming in and doing more work with us?" That more work may look like participating in a study or it may be completing some questionnaires. It serves a whole bunch of purposes for us. It's expanding what we know about the disease, but it also helps to address what has come up a number of times, which is that we have this need for participants in studies at all different levels.

Maggie Kuhl:

On that theme of maybe early risk detection or understanding some of the underlying factors that led to disease, we got a question about genetic testing. We've talked a lot about genetic targets. How can individuals, either with Parkinson's or concerns family members, get genetically tested for some of these genes that we have identified to be linked to Parkinson's? Tom, you usually counsel your patients in any way, but of course, others jump in as well.

Thomas Tropea:

Yeah, of course. I'm happy to take this one, and I've spoken in it in a number of different forums around access to genetic testing. There is no one way that we can offer genetic studies and frankly, genetic counseling to everybody. Not only with Parkinson's disease, but actually more broadly and across all different fields of medicine. Although genetic counselors do tend to provide a large amount of counseling prior to doing testing, there really is this mismatch between the need and the supply for neurogenetic services. There is no one way to go about getting access to testing. There are large centralized programs for people that have a diagnosis of Parkinson's disease, and I would encourage you to seek out those opportunities. They do provide counseling and access to testing, but there are also programs that exist where you can initiate your own testing. You can discuss it with your physician, your neurologist, or your primary care doctor about how to access genetic services.

That may be through a local genetic counselor, a neurogeneticist or a medical geneticist, someone with training in how to conduct neurogenetic services. Or it may be through one of these centralized processes, sign on and participate in a research study or expanded access program from one of the companies that provides genetic testing. There are opportunities to do this in the clinical realm, meaning just for your medical care, there are opportunities to do this in research. All right.

There really is no one way to do this, and I would encourage you to talk with your primary care doctor, your neurologist, and you talk about different ways that you can do that if you are interested in pursuing testing or counseling. One of the most important things is prior to pursuing testing is actually talking with someone that is informed that can explain what it is that you might learn about testing, what you won't learn about testing and how, if they're interested, what your family members may be able to access as well. I hope that's helpful. It's actually a really amorphous. It's a very complicated field right now, but there's a lot of effort going into trying, increasing access to testing for anyone who's interested.

Maggie Kuhl:

Well, we're coming up on our hour. We got so many questions on so many different topics. Everything from artificial intelligence to non-motor symptoms, to what phase two and three trials are coming. We wish we could cover everything in so much more detail. Of course, in this webinar series, in our podcasts, on our blog, we tried to go much deeper on a lot of those topics. If we weren't able to answer your question or you didn't get all that you were looking for today, please visit our website and hopefully, you can get more or tell us where you're still lacking and we'll put it on our agenda for next year. I want to end with a little bit of around the room. This is a look back at 2024. I want to now look ahead to 2025. What are you most looking forward to or hoping or see in your crystal ball that this is going to be the year? What should people be looking for, waiting for partnering on to make a reality? Todd, why don't I start with you?

Todd Sherer:

Yeah. There's a couple of things I'm looking forward to. One, I think we're going to have more advances with these biomarker tests, which I think are going to really then accelerate our therapeutic development in trials. There's also some very important trials around alpha-synuclein and other targets that we'll be getting the results from this upcoming year. I think we have a chance for another very exciting year next year with the momentum continuing to build forward for Parkinson's.

Maggie Kuhl:

Maurizio, what does 2025 hold?

Maurizio Facheris:

Well, I'll second the biomarker sentiment that Todd just expressed. I'm really hopeful both because of the clinical trials as we mentioned, so that the help that can provide to clinical trials, but also optimistic that we will find a way to improve that quantitative measure of alpha-synuclein, both in the spinal fluid, as well and in a different matrix, like potentially something easier to collect than through a lumbar puncture spinal tab. That, I am very, very optimistic, very, very positive.

The second is, I think, among the targets that we mentioned, truly, I do believe that GBA, and I know I'm biased, but GBA has been one of the highest interest in the last few years. There's been several clinical studies ongoing. Some of those did not provide the results that they hoped for, but they really shed a lot of light on understanding where we need to target. Again, not only what to target about where, how. It's not by moving this molecule, it's not by moving this enzyme, it's actually activating the enzyme directly where it matters. Working towards that I think is going to be very interesting in the next couple of years, but specifically next year for us to understand how we can improve the activity of that enzyme that cleans up alpha-synuclein in the cells. This is my spin for now.

Maggie Kuhl:

Tom, the last word is yours.

Thomas Tropea:

Oh, wow. I get the last. That's great. I'll be very quick. I think, in the next year, we are going to continue to refine what we believe to be the biology of Parkinson's by expanding our biomarkers, but also improving those biomarkers and using those in a foundational way rather than an alternate diagnosis. That's what I'm most excited about this coming year.

Maggie Kuhl:

Well, thank the three of you for joining us and thank you who are tuning in for giving us your time today. We hope you found it helpful and informative. Thank you one more time and have a great day.

Narrator:

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