Hello everyone and welcome to today's Third Thursday Webinar. I'm Dave Iverson, the contributing editor at The Michael J. Fox Foundation and the moderator for today's webinar and this series of Third Thursday Webinars. As you know, throughout the year we pick a different topic each month that has to do with Parkinson's research and living with Parkinson's disease. This is something we've done for a number of years now, which is to end the year by doing a year in review. Looking at the latest developments in Parkinson's research that have occurred, in this case, 2017. Talking about their significance both for the patient community, but for scientific inquiry as well. As always, you'll be able to submit your questions throughout the hour. You'll see that little Q&A box in the middle of the screen. So, just type in your questions there and we'll do our best to get to them over the course of the hour, taking most of the questions toward the end of our webinar today in the last fifteen, twenty minutes or so. But, we'll sprinkle them in throughout the hour, so do be sending them to us.

Also, you'll be able to download the slides from today's webinar in the resource list box you see on the screen. You can click on the link there and then that will open up in a new window and you'll be able to save it or print it from there. All right, let's take a look at what we're going to be focusing on in our webinar today.

We're going to talk about the number of therapies that are now in clinical trials that may slow or stop Parkinson's disease. This is a huge, real shift in the way in which research has advanced in recent years. We're going to talk about where we are with the therapies that we hope, may eventually prove to slow or stop the disease.

Then we'll move on and talk about medications that are, either have been approved or are close to being approved that will do, hopefully, a better job of managing particular Parkinson's symptoms. Then we're going to kind of widen things out a little bit and talk about where we are as far as what we've learned about Parkinson's disease overall. Are we getting closer to sort of being able to put this puzzle together? And then we'll also talk some about new developments and innovations in deep brain stimulation surgery in particular.

Okay, here's who's going to be joining us throughout our hour today. Doug DuMond joins us. Doug is the former managing director of ING Clarion real estate. He was diagnosed with Parkinson's four years ago, in 2013 and has been very active in the Parkinson's disease broader community. First with the Parkinson's Action Network and is now a member of the public policy council for The Michael J. Fox Foundation. Doug, thanks so much for being part of our conversation today.

Thank you Dave. It's good to be here.

It's good to have you.

Joining us as well is Dr. Andrew Siderowf. Dr. Siderowf is the director of the
Andrew Siderowf: Thanks Dave, again. Pleasure to be here.

Dave: Thanks. Thanks for joining us.

And Todd Sherer joins us. Dr. Sherer is the CEO of The Michael J. Fox Foundation and brings to that position a long career in research as well as leadership in the Foundation. Todd, always a pleasure to have you join us. Thank you.

Todd Sherer: Thanks Dave. I look forward to the discussion today.

Dave: All right, let's dig right in. And we're putting up this first slide now on the screen which has to do with the therapies that we hope may slow or stop Parkinson's disease that are now in clinical trials. Either in phase I, II or III. We'll talk a little bit about what those distinctions mean. And we see up on the screen, everything from strategies to stop the buildup of alpha-synuclein, the sticky protein that goes wrong in Parkinson's or that causes problems in Parkinson's in a variety of other strategies, both genetic opportunities as well as some drugs that have also, have been approved for other things. But, we think they also play a role, perhaps, in halting Parkinson's.

Todd, before we dig in to this, what I'm struck by when I see this screen is if you add up all the numbers there, the four at the top means there are four particular trials having to do with one approach to stopping alpha-synuclein. Two others that might approach alpha-synuclein and so forth and so on. You total them up and there are 12 therapies that are now in clinical trial and it's striking to me. You and I have done these conversations at the end of the year for a number of years now and this wouldn't have been the case if we had put up a slide like this a half a dozen years ago. Just to start us out Todd, give us your sense of what that indicates in terms of what's changing in the field of research.

Todd: Yeah, so I think the diversity and breadth of this pipeline certainly reflects a great momentum that we're seeing in Parkinson's disease research and in the drug development pipeline. What's particularly exciting here is the buildup of a lot of basic research and knowledge of what might be causing Parkinson's, what might be causing the progression of Parkinson's and now seeing the translation of some of that knowledge into potential new therapies. So what's exciting about a number of these approaches that are now being explored in the clinic is that they really are targeting the underlying pathophysiology, pathobiology of what might be responsible for Parkinson's. The idea of really trying to get at that underlying, biological process that's leading to the disease and impacting the progression and intervening in that progress, I think is extremely exciting. I think one of the other things that's important to know and to be encouraged by, is the diversity of scientific hypotheses that are being explored.
So we certainly are not in a situation where all our eggs are in one basket. And we have multiple hypotheses being moved forward in parallel, which of course just gives us a greater chance of success in the end from one or multiple of these approaches.

Dave:
[00:06:30]
And as we look at the diversity here, I think part of what I hear you saying Todd, is that this is also testimony to the way in which basic research, so called bench research in the laboratory, now has evolved to the point where it's translated into something that actually might play a role in halting disease progression. Just to ask you, Todd, if you would, to clarify this terminology. Because sometimes we talk about disease modification versus symptomatic treatment and it can get a little confusing sometimes about what [the difference] actually is. But, as I understand what you're saying, you're really talking about really getting to the basics of how the disease works and somehow interfering with that or stopping that so that it doesn't advance in such a way and therefore get at the real, the root cause of the disease. Or the root way in which the disease moves forward. Is that right?

Todd:
[00:07:00]
Yeah, that's correct and I think just to kind of add a little bit more to that. It's not only sort of basic science, it's really the basic understanding of what might be happening in the disease. Some of that research does in fact come from studies of people with Parkinson's to understand genetic factors, other changes that might be happening in people with Parkinson's. Taking those observations then back into the laboratory to understand more of the scientific mechanisms, the cell biology, the biochemistry. And now that's being converted into these potential therapies.

[00:08:00]
And I do think you're right. Sometimes we, in the scientific community, get overly concerned with defining, "Is this a disease modifying approach? Is it a symptomatic approach?" All of these approaches have the goal of improving the symptoms and trajectory of Parkinson's. Some of that depends on the timeline, how quickly you see that effect in someone with Parkinson's. In this case, what we're really talking about is the target, the science, the biology, that these therapies are going after. And to just reiterate what you've pointed out, is that in the case, the projects on this slide, these therapies are really trying to go and address underlying biology, underlying biological changes that are impacting the disease. Rather than simply replacing the dopamine for example that's lost as a consequence of the disease.

Dave:
[00:09:00]
Exactly. And Andrew Siderowf, let's begin walking our way through some of these. And if you could, just talk us through a little bit generally about where we are with halting the progress of the alpha-synuclein that clumps up in the brain and we think causes damage. We see six different trials now that are going on in that area. That's in and of itself encouraging. I know you've worked on some of these. Without necessarily taking us too deep into the science, can you just sketch out for us what it is that these approaches dare and what their overall goal may be.

Andrew:
[00:09:30]
Oh sure Dave. So, I think probably everybody in the audience knows, but just in case. alpha-synuclein is the bad protein in Parkinson's disease and a lot of scientific
inquiry recently is focused on the idea that when alpha synuclein, which has a normal function in brain cells, but under disease condition, it can clump up and form aggregates. And what these aggregates collect inside of dopaminergic neurons in particular –

Andrew: ...collect inside of dopaminergic neurons in particular and lead to cell dysfunction, ultimately, cell death. So aggregation of alpha-synuclein is probably at the core of what causes Parkinson's Disease. And so it's not surprising that the majority of the treatments we see on this list are designed at attacking alpha-synuclein in one way or another. Just as a couple of examples, the AFFiRiS project that you see on the top is actually a vaccine, which tricks your own body's immune system into removing alpha-synuclein. And then the Biogen and Roche project you see down below are also treatments that use the immune system, more or less, they are infusions of alpha-synuclein antibodies, which will allow the immune system again to remove excess alpha-synuclein from the body. And some of the other treatments you see on the list also reduce alpha-synuclein aggregation. So the general concept here is that accumulation and aggregation into clumps of alpha-synuclein is really the core of what causes Parkinson's and if you could remove it, or cause it to stop clumping up, then you could reverse the progression of the disease. And so that's what these alpha-synuclein therapies are aimed at.

Do you want me to go on and talk about the –

Dave: And of course from the patient's point of view –

So let me just ask you some follow up on that part Andrew, and that is I think from the patient community of course, and family community, we're all eager to know, "When will we know something?" And these have gone through the preliminary Phase I and into Phase II, so we know so far that they're safe right? We know that these are things that we don't think are going to be problematic from a safety standpoint. How much – can you just kind of sketch out what it is we still need to know, and when we might know about it as far as whether or not some of these approaches might actually work?

Andrew: Yeah. So we'd all like to have this information next month/the month after. Unfortunately it is going to take longer than that. And just for example the Biogen and Roche trials, which are the furthest along, are really probably not going to read out until 2019. So we're going to have to wait awhile. Also, these are Phase II trials, and probably the definitive studies are going even be later than that, although they'll probably be accelerated to some extent if the Phase II studies look promising. But we're still, you know, two years at least, away from seeing these drugs in the clinic. I think we'll get some preliminary evidence about whether this is a fruitful avenue of therapeutics probably at the very end of next year.

Dave: Well that in itself is encouraging.

Andrew: Yeah but there's definitely a lag between the results showing up in a scientific journal, leading to a sense that something's going to work and the FDA really being
confident that it's okay to let a company market a drug like this.

[00:13:30] Dave: Right. I think as you say we are all eager for that day. On the other hand it is just interesting that we can foresee when that day might happen as opposed to it just being some imaginary outcome that is not advancing in a way that these are. We'll come back to take more of people's questions about this, but let's keep moving forward and Todd hand it back to you to just describe briefly what's going on with the next two, which are both having to do with genetic mutations, which can lead to Parkinson's disease. And this is quite new that we actually now are testing something that might provide some sort of fix for those particular mutations. Describe where we are with this.

[00:14:00] Todd: Yeah this is a very interesting new direction for Parkinson's, and I think one that is a culmination of a number of years of research. We've known for many years that there's great variability in the cases of Parkinson's disease, meaning that some people might have young-onset Parkinson's compared to others, some people have a different symptomology than others and there's quite a lot of variability as we know in terms of the clinical symptoms, clinical progression, that people can have in the disease.

[00:15:00] And we really haven't known much about what can be some of the scientific or biological underpinnings of that variability. And what's been uncovered over the last decade or so are some of these genetic factors including alpha-synuclein but in this case we're listing GBA and LRRK2, where we've uncovered that mutations in these genes can increase the risk of getting Parkinson's disease. In the broad population, these mutations are not very common, so for LRRK2 for example it could be between two to five percent of all Parkinson's patients. What this approach is starting to do now is to pull us more in the direction that fields like oncology or cancer has gone to, where you really can start to more subset of the population of the disease based on some genetic factors or other biological factors, and then develop therapies that can very specifically target that biology that's impacting that subset of the patient population.

[00:16:00] And that's what's happening now in GBA and LRRK2 where these particular approaches, in the first phase of their evaluation, are really targeting individuals with Parkinson's disease, but individuals with Parkinson's disease who happen to have the mutations in these particular genes. So this is a very new direction and you may have heard of the concept of personalized medicine, where you target the therapy specifically to the right patient at the right stage of their disease, and in this case, genetics is one of those driving factors for how to target the individuals who may be benefiting from these therapies.

[00:17:00] One point, just to raise, is that you may think and say, "Well, if I don't have the LRRK2 mutation or I don't have the GBA mutation, should I particularly care about these therapies?" And one of the things that we've learned in other diseases, and we're learning in Parkinson's, is that these genetic mutations really serve as a foothold for advancing therapies in the disease and what we are uncovering is that
there is evidence that other broader aspects of the population of the disease could, in fact, benefit from these therapies. But when we do the studies this way, in terms of selecting the individuals with the mutations, it gives us the greatest chance of success in really understanding the potential benefit of this type of therapy.

Dave:

So it sounds like this could be a kind of double win, in the sense that it could provide, as you suggest, a personalized approach to deal with a particular kind of Parkinson’s, just like in breast cancer, there might be a particular approach, which works with some kinds of breast cancer and not another. On the other hand, it sounds like you're also saying that there are enough similarities that we can learn from this and some of what we might learn, that could fix a particular mutation, might tell us something about what's going on more broadly in the disease and be applicable to the rest of the population. Is that right? So it kind of hits at both.

Todd:

Yeah, that's correct. And I think one of the other things we've learned, where I'm very optimistic and enthusiastic about this much more rigorous and personalized approach is that it's a very high bar to hope that an individual therapy could have the ability to slow the progression of Parkinson's disease across the entire population of Parkinson's, given that we understand the variability in the disease. So by having this diversity of approaches with a solid foundation in the science, it gives us a great opportunity to move these all in parallel and really start to tease out and identify the patient populations that have the greatest chances of benefiting from each other these individual therapeutic approaches.

Dave:

Great. Andrew, let’s go back to you on the next three that we're approaching, which are very different approaches, that are all drugs that have been approved for different conditions: Isradipine for blood pressure, Inosine is something that boosts urate levels, Nilotinib is a cancer drug, they've all had other purposes but we think they may play a role in Parkinson's as well. Is what Todd's suggesting about, once we were just talking about true cure as well, that we might learn that one makes sense. Isradipine works for one set of people with Parkinson's, Inosine another, is that sort of also applicable to this idea?

Andrew:

So I think, to a certain extent, it is, but it's not the primary purpose of these trials. They really are looking at a cross-section of Parkinson's patients and they're comparing whether people who get treated have less progression over time than people who don't, and then as a secondary analysis of these trials, the investigators will certainly –

Andrew:

... secondary analysis of these trials that investigators will certainly look at whether they're certain sub-types of patients that do better than others. I think that this is the examples of GBA and LRRK2 are really great examples of the way personalized medicine is coming to Parkinson's disease and these are more about therapies that are potentially applicable for everyone. One trial is really targeted at people who have a specifically low level of urate and the idea is to raise the level of urate. It's not including people that have normal urate so, this is a bit of a tailored approach.
But the other two are more traditional in their approach where they're looking at people with early, recently diagnosed, there's Isradipine at least. Early, recently diagnosed Parkinson's is seeing if the progression is slowed and Nilotinib is over a cross section of Parkinson patients, looking at whether both motor and cognitive features actually of Parkinson's are slowed by the treatment.

Dave: Andrew, these, particularly the Isradipine and Adenosine, are quite far along, so we'll learn something fairly soon in about whether or not those particular approaches are efficacious. Can you briefly describe perhaps with Nilotinib, which is less far along, that got a lot of attention a year or so ago. It's a cancer drug and that in and of itself it's sort of hard to get your head around. How could a cancer drug play a role in Parkinson's? You just fill us in a little bit more about where we are with that?

Andrew: Sure. So, Nilotinib, like you said is a drug that's approved and on the market for cancer and investigators at Georgetown University discovered last year, or they reported last year that they saw improvements in the clinical symptoms of people with Parkinson's in their clinic, when they were treated with Nilotinib and these where in parallel to studies that were going on in their laboratories showing improvements in features that are lab markers of the Parkinson's in the laboratory animals and this obviously led to a lot of excitement about Nilotinib and Novel Mechanism of Action for treating Parkinson's.

I think that the thing that's exciting now is that Georgetown is going back and doing their own study to try and confirm their results and then The Michael J. Fox Foundation in collaboration with the Parkinson's study group is doing an independent study to try to confirm whether Nilotinib is good for people with Parkinson's disease. I think that Georgetown has been a pioneer in this area and in conjunction with that we'd have independent group testing whether this drug is effective.

But one quick thing about this is that there's safety data that already exists for these drugs so the pathway to getting the patients is faster.

Dave: Right. That's a big plus of these so-called repurposed therapies –

Andrew: These Isradipine and Inosine have good safety profiles and Nilotinib obviously has more safety issues because it's a chemo-therapeutic drug but it's not as toxic as you might think of ... it's not the way you normally think of cancer treatment in toxicity there.

Dave: And let me ask just one more question about this to and then we'll move on to our next slide and involve Doug [Dumond 00:23:48] in our conversation about new symptomatic approaches. One of the things that can happen when a drug is already on the market, like the blood pressure drug, Isradipine, is there can be eagerness in the patient community that say, "Well if that works, it's already been approved for something else, why don't I just start taking it now?" Yet there are concerns about that and that part of why we need to go even though that temptation is
understandable, describe for us why it's important to still go through this sort of more rigorous scientific process?

Todd: While Andrew mentioned we have a great knowledge of these drugs, sort of the safety issues because they've been in use in many, many people. We also know that whenever we see a commercial for a drug, the last half of the commercial lists all the side effects of every medication. No, drug comes without any potential safety liabilities and in many cases the drugs may never have been given to Parkinson's patients. So, there's other drugs that people are taking with Parkinson's, there's other aspects of the Parkinson's disease that we have to really assess the safety aspects of these drugs, even though they're available.

We always want to make sure we have enough evidence that the benefit of taking a drug outweighs any of the potential side effects and there could be unexpected interactions with some of the Parkinson's medications that people are taking. I think this scientific and data based, data driven approach is always the best mechanism. Now it could be that for some individuals there's a reason they should be taking some of these other medications because of other illnesses that they have and I think it's worth discussing, obviously with both your Parkinson's doctor and other doctors whether it makes sense to use some of these medicines.

Dave: Okay. With that, let's push on and talk about some more specific therapies that have to do with specific symptoms in Parkinson's but again if you've questions about any of these approaches that we've been discussing, do send in your questions and we'll circle back to that. Let's talk now about some new treatments that have been approved or will soon be approved, we think will tackle specific symptoms and let me bring Doug DuMond into our conversation again. Doug was diagnosed with Parkinson's four years ago and has undergone deep brain stimulation as a way of contending with some of the symptoms that he was facing.

So we're going to do this a bit out of order Doug and talk about this third bullet point that we see on the screen now, which are some new developments in deep brain stimulation that are going into effect now but before we describe those, tell us something about your own experience with DBS. The symptoms that you were struggling with before you had that procedure and then what happened from your point of view, after you had a deep brain stimulation procedure.

Doug: Sure, I was diagnosed in October 2013 and for a period of time the medications seemed to work very effectively. I was initially on Mirapex and Azilect and then went on then went on the Sinemet regimen. Beginning in 2017, I began to experience severe "off" episodes. So, when I was "on" I felt like I could practically run a marathon or bike ten miles, but then I would be running errands in a grocery store and all of a sudden freeze. It was a very discomforting feeling and made it hard to operate day to day. My symptoms where stiffness, not so much tremors, sleep disorder and fatigue and it exasperated itself in the last year, that I felt like I wanted to do something fairly drastic or momentous.
Since I've had the DBS surgery – I just actually finished it six weeks ago – I've had two programming sessions since and it was divided into three surgeries and since then my symptoms have almost gone away. I have no more stiffness, no more dyskinesia, no more sleep problems, no more motor fluctuations, no more down time. It really, for me, hasn’t been a small miracle or a big miracle, it’s been life changing. One of the things about the technology that I think has made a difference is the ability for the practitioner with the new technology, to target specific areas of the brain. The technology is often referred to as Multi-Segment Directional Leads in the Brain Stimulation.

The other unique thing about it is it has a smart phone, I'm not sure I'm using the right term, but we're all familiar with apple products, it could be another product but it has a smart phone application. So when you go in for programming it's done on an iPad and all the various touch points, there's like 4,000 different settings that they can do under this new Multi-Stim approach, the Multi-Directional Lead approach and it's done initially on an iPad and then you're given an iTouch, which looks like ...

Doug: An iPad, and then you're given an iTouch, which looks like an iPhone, to take with you. The iPhone is programmed in a way that allows you to work within ranges so you don't turn yourself into young Frankenstein, which there's a risk of if you have too much electrical stimulation. It can generate significant dyskinesia and other problems. So they have you work within a range and, during the first period of time, you go back every two weeks. And then you graduate to every quarter. And then you graduate to once or twice a year.

But to give an example of the preciseness of where they're able to target, I was in the office and I've developed some pretty severe dyskinesia in the left leg. The doctor or the nurse practitioner went to touch point 4B and adjusted it to 2.2. All of a sudden, the dyskinesia went away. It was just amazing from that standpoint. A lot of the symptoms that are listed, ongoing treatment, motor symptoms, motor fluctuations on and off, dyskinesia, I'm not sure about dementia, but, constipation, depression, anxiety and sleep disorders have been successfully addressed with this procedure.

I would just add, it's a little bit like a combination of physics and calculus when they're going through this process. It's simply amazing, in terms of their ability to program the stimulation with multi-directional leads. Dave, is that helpful?

Dave: Yeah. Thank you, Doug. Very helpful, Doug. Thank you. And it's obviously great to hear how well this approach is working for you. Andrew, if you could comment further on this being a conflict, perhaps another example of the way in which Parkinson's treatments are being more personalized, more tailored to the particular individuals, whether that's for specific symptoms or whether or not someone is more troubled by one symptom than another. It sounds like from Doug's description, that with deep brain stimulation in particular, which has been effective for a long time, we're now refining it further so that it can be more
personalized. Is that what you’re seeing in the field from your point of view?

Andrew: I think that I absolutely agree with you. I think that this is a great example of making the therapy more tailored to individual patients. First we had pallidotomy, which was just a hole in the brain, and everybody got the same thing. It was once really a literally a one size fits all solution. And then there were the traditional DBS, which had four contacts and was programmable and was somewhat flexible, certainly more flexible than the old surgery deals, reasoning surgeries were. And now we’re seeing a real explosion, I think, in terms of the ability to program very flexibly the DBS machines. And I think that it allows to shape the DBS contacts in a way, which is very adapted to individual patients then, I think that we’re all going to see more of it.

Andrew: One of the things I’m excited about too is the smartphone and the iPad interfaces because I think that they'll make it much easier for doctors to visualize the therapy and also potentially for patients to have a little bit more control over their own treatment in a way, which is a little more intuitive for them. I think these are all nice advances.

Dave: And well obviously, DBS is not necessarily for everyone and we should express that, that it makes sense for some and perhaps not for others. One thing that's also changing and Doug you're an example of this is, it's seeing now sometimes offered to people much earlier on in these disease course that used to be, as I understand it, something that was worked on well into your once Parkinson’s experience. Now it seems like it's being brought out ... Its availability is offered up sooner. A, is that right? And B, why is that, that we're now thinking, well let's get to this sooner rather than later?

Andrew: I agree with you. I can really speak mostly to my own practice, and a little bit to the broader practice, I suppose. I definitely find that I offered DBS to especially younger patients like Doug earlier on. I feel like it's something that term types of Parkinson's patients are going to want to access at some point during their course of their disease. And that a lot of the risk is really upfront risk associated with the surgery and the benefits begin after you had this procedure and then they accrue overtime. So for the right patient, you obviously have to talk to your own doctor about whether this was something that apply to you or not. I think that sometimes earlier does make sense.

Andrew: And I think there's also been some reports that are suggesting that earlier DBS does offer clinical benefits over medical therapy alone. I also think that because we had experience obviously new technologies that are being prosper on DBS, I was just talking about that, but the concept has been around for well over a decade now, probably about two I think. So I think that doctors are just getting more comfortable with it and so that they feel more comfortable using it earlier in the course of disease in some patients, not all. A young patient who's having medicine side effects is a great candidate for earlier rather than later DBS.

Dave: And we got a lot on this slide that we need to cover some other ground but we are
getting a couple of other questions about DBS that are coming in. So let's see about those and then we'll move on to some other symptomatic approaches. But one individual wanting to know whether or not you're continuing to take medication even though you've had the deep brain stimulation procedure. It's often a benefit that you could at least reduce the number of drugs that you're taking. What's that experience been like for you?

Doug: Yeah. I'm still continuing but I reduced it by almost two-thirds, the amount of medication that I'm taking. I'm still taking Azilect and I'm taking carbidopa-levodopa. I was getting to the point where I'm just taking three carbidopa-levodopa, three or four times a day, or four or five times a day. Now, I'm just taking one, three times a day. My understanding is, you still need to take it because you're not generating enough of the natural dopamine. But the DBS smooths the peaks and valleys. I wake up in the morning and I feel fine. I used to be in bed and my wife would bring me my medication and it would take 20 minutes until it's good. Now I feel good. But you do have to continue to take the medication but if it's successful at a vastly reduced rate, which also results in less side effects, longer term such as a dyskinesia.

Dave: Okay. Thank you Doug. We'll come back if we have time and address some other issues about DBS but we do have lots on our screen here. So we want to make sure we touch on those. We're getting a number of questions about stem cells and we see on our slide here under trials where there are ongoing treatments and testing of stem cell therapies. Stem cells used to have a kind of roller coaster ride overtime with its possibilities for Parkinson's. Times were more optimistic. Times never left though. Give us a kind of a snapshot of where we are now and what you think may still be promising about that approach.

Todd: Yeah. I think stem cells is also a pretty broad category so I just want to break it down a little bit. We talk about trials and approaches is different types that have been looked at. I think one of the original pushes for stem cells had to do with the concept of looking at whether stem cells could be made into dopamine producing brain cells. And then those cells could be transplanted back into the brain of someone with Parkinson's since we know that at least many of the motor symptoms of Parkinson's are due to the loss of those dopamine producing cells. That avenue of research has been ongoing for many years. And as you mentioned, has had sort of peaks and valleys. At this point, we are fortunate that I believe this area is getting more of an upswing and having a lot of momentum. The concept is that you could take either human embryonic stem cells and make those into dopamine producing brain cells. Or another technology that has been developed more recently, which is called induced flora potent stem cells. This is where you could take a blood sample or skin sample from an adult.

Todd: You could take a blood sample or skin sample from an adult, convert that back into a stem cell and then use those cells to make dopamine-producing cells. Both of those approaches have been successful over the years to make large
numbers of dopamine producing cells in the laboratory, but upon transplant of putting those in the brains of animal models of the disease, we had some issues in sort of the survival and dopamine production of those cells during the transplant.

Those challenges have recently been overcome and now there are a few groups that are now gearing up to do the first clinical trials of these embryonic stem cells derived dopamine cells or the IPS (induced pluripotent stem cell) derived cells. It does involve brain surgery in terms of implanting the cells back into the brain. The hope of these studies would be that the brain would start producing greater amounts of dopamine under natural physiological conditions.

That area has, while it kind of had some challenges, is now kind of on an upswing and I'd anticipate these trials happening probably within the next year because I know they're being planned.

Other things you may have heard about in terms of stem cells are where people, some researchers are just injecting more, not differentiating, meaning that the cells have not been converted into dopamine producing cells, so injecting stem cells either peripherally or directly into the brain. Those I believe have less sort of scientific basis. There was one report this year that was done overseas that did not have positive outcome in terms of improving the symptoms of Parkinson’s.

There is another interesting approach that's in an early stage study, which is using healthy blood in more of a transfusion type of approach. There's some evidence from animals that if you put young blood into an older animal, the animal can kind of appear younger, have some of the features of being younger. An approach like this is actually being tested in a trial at Stanford with more of a transfusion type of approach in an unknown biology, does seem, at least in animal models, to be of quite interest so at an early stage trial happening there. It's sort of a stem cell-like type of approach.

Dave: As someone who’s driving down actually to the Stanford campus later today and being the age that I am, that sounds incredibly promising. Maybe I'll just stop by and see what's comfortable.

Todd: I'll give you some of mine, Dave, as a youngster.

Dave: Let's touch on a couple of other things on this slide. Doug was talking about how problematic being "off" is, when your medications aren't working. Before Doug had the DBS procedure. Trying to solve that problem has been something that researchers have focused on for some time. We see interestingly up on the slide here that ... We've been tantalizingly close, I think, to a couple of new approaches being through for some time. One is the idea of inhaled levodopa. Sort of like an asthma inhaler. The other being something that you could slip under your tongue. A little sublingual strip that would give you something called apomorphine that used to be just injectable.
Do these seem promising to you as approaches because we hope that they will be available soon? It's really helping us solve that prenatally difficult problem to solve of someone being “off” rather than “on.”

Todd: Yeah, so good question. I think that both of these approaches have sort of been in the works for a while, especially the inhaled levodopa. I think people had high hopes for it and we haven't seen it yet, but we may still. I think, let's keep our eyes on that. We have in the last couple of years, I think, very fortuitously seen some new delivery systems for levodopa, the extended relief levodopa by Rytary, which really works quite nicely. Then the levodopa internal infusion. These are examples of approved alternate approaches to delivering levodopa. Then in terms of apomorphine, I think that there is the apomorphine injection and the apomorphine pumps that are used in Europe and I think we'll probably see an apomorphine pump in the United States fairly soon, actually.

Then just to cover some of the other medications that are on this slide. Safinamide and the extended release Amantadine because that would be okay. I think these are just examples of how the pipeline does move forward all the time and these are new drugs that are available this year for patients with Parkinson's disease in place of Safinamide. It's for “off” episodes and the case of Amantadine, it's for levodopa induced dyskinesias. Also, may potentially have an effect on “off” time, so this is just example of drugs that are approved that are continuing to give patients more options as we continue to wait for the disease modifying therapies we talked about earlier.

Dave: One other area here. Doug, let me ask you this question. I think anyone who lives with Parkinson's disease or is a family member with someone with Parkinson's disease, knows in time, that while we focus initially on the motor symptoms and problems like stiffness and tremor and rigidity, sometimes what can be just as problematic or even more are things that aren't motor symptoms. Whether that's worries about whether or not you're losing some of your cognitive abilities or concerns or feeling depression or anxiety or the sleep disorders you mentioned, Doug.

Can you just, from a patient point of view, tell us a little bit about your experience, if that's relevant for you, and your worries about that and then I'd like to bring us up to date on what's going on to approach some of those more, I think, difficult, sometimes symptoms to live with when you have Parkinson's. Have those been issues for you at all, Doug? Those concerns? Those sort of more emotional, cognitive kind of things?

Doug: Yeah, yeah. They have. Clearly you have depression or anxiety related to what's unknown in terms of the progression of the disease and the burden that's going to put on your caretaker and the stress on the family.

Also, the financial aspects of somebody who develops Parkinson's. Many people who develop Parkinson's, before they're diagnoses worked their way through it and continue to work until they can't keep up anymore. Then they're diagnosed and
sometimes they are diagnosed after their disability has been ... they're eligible for disability.

That's always a concern is putting the diagnosis and getting the benefits that people deserve because a good amount of anxiety is putting food on the table and still being able to educate your kids, particularly when your early diagnosis. That played a big role in both the depression and anxiety and sleep disorder, the worry that you have for your loved ones.

In my case, kids that still needed to be educated for college and a caregiver, from my stand point.

Dave: Doug, thank you, and Todd, I want to ask if there are sort of things that are maybe promising dealing in terms of depression or some of those issues. This also brings up something that I know you can comment on, which is part of what the Foundation is focusing right now. It's also just gathering more experience and more information rather, about the lived experience of Parkinson's through something called Fox Insight, because part of what we're learning is what Doug just described. That we want to do a better job, I think, of understanding the reality of living with Parkinson's and then matching up our research efforts to try to provide assistance in those areas. Talk about that please, a little bit, and then maybe give us a quick update on where we are in finding some solutions.

Todd: I think this is a really important conversation. I really appreciate Doug for sharing that experience because these aspects of Parkinson's historically have not been greatly appreciated both by the medical community and the research community while people with Parkinson's have known about them and been aware about them this whole time.

I think one of the goals we have in a project like Fox Insight is to really try to get access to this expert information that people with Parkinson's have on the challenges, limitations of current medications, some of the unanticipated side effects of current treatments. What are the aspects of the disease that are having the most significant impact on their lives, their wellbeing, so that we can make sure that the research is targeting and measuring.

Todd: We could make sure that the research is targeting and measuring those aspects. We've talked a lot so far in this webinar about looking at the effectiveness of new medications. Well you want to really be able to judge the effectiveness of those new medications against what the unmet needs and aspects of the disease that are most significantly impacting someone with the disease are. So I think this communication and interaction between the research community, the medical community, and people with Parkinson's and the families is critical. Fox insight is a web-based platform to really enable that communication to happen for people with the disease, to really provide that information in real time that could be used by the research community.

In terms of some areas of advances, there is research going on in these areas that
we've just talked about and focus a lot on trying to develop treatments that are not predominately targeting the dopamine system. As we know that many of the symptoms that are currently going untreated, are untreated because they are not responding to the various dopamine treatments. Therefore, we mentioned on the slide here some new drug approvals that are targeting other mechanisms in the brain to look at some of the motor symptoms. Not in 2017, but in 2016 there was an approval of a drug that targeted some of the hallucinations and other psychological symptoms that some people with Parkinson's can have. So that's now available. This is really, as we list here, an area of pretty active research in terms of trying to develop new treatments.

Not all the treatments for these symptoms have to be pharmacological. Particularly with sleep and depression, anxiety there are exercise based therapies, physical therapy and activities. Maybe Andrew could talk a little bit about that, that can have benefit. We have a study we're funding, which is to do telephone based psychotherapy for depression. So it doesn't only have to be a pharmacological treatment or a drug pill to treat some of these symptoms but it's an area of research we need certainly to learn a lot more about what the underlying biology is that impacts some of these symptoms.

Just to wrap up my comments here it's one of the reasons why I'm excited about the array of treatments we talked about targeting the underlying biology such as alpha-synuclein or LRRK2 because we do believe that, that biology is broad in terms of its impact on the symptoms. That alpha-synuclein pathology is probably not only limited to the motor symptoms and these broad array of symptoms. So if we have a treatment that really targets that underlying puzzle factors of the disease it could have a broader impact not only on motor symptoms but some of these non-motor and currently untreated symptoms.

Dave: Perhaps even halt the development of some of those problems before they even begin.

I'm going to put our last slide up which is kind of about our broader understanding of Parkinson's and allow people a moment to kind of look at these and we'll get some last comments on them but because time is short I also want to make sure we get to couple of questions that people have raised. And Todd just mentioned exercise, but a few people have sent in questions about exercise. Andrew ... I don't know if maybe you can comment on that a little bit. There seems to be just this growing body of evidence of how important exercise is in terms of not only managing symptoms but perhaps also even slowing how quickly the disease advances. I read something yesterday that sort of seem to make the point that exercise, particularly vigorous exercise, is important. Give us a quick snapshot of what we're knowing ... What we've learned, so far, about its value.

Andrew: I recommend exercise for all of my patients. A lot of people are older and have other problems like arthritis and it's hard for them to exercise. So I think it's important to do whatever you can. There are definitely studies that show that vigorous exercise may have particular benefits a few times a week and they even
have improvements in physiological measurements in brain function and not just in your stamina and other things you associate with exercise.

But this is still, I think, an open question and it's not confirmed that vigorous exercise specifically is good for the Parkinson's brain. I think the big message here is that any exercise is better than no exercise at all. And I always tell people they should at least get out and have a good walk three times a week for a half hour. You know, try and get up a little bit of a sweat if you can.

There are studies that show that certain kinds of exercise like Tai Chi may be good. Probably just cause it really tackles the problems that people have with stiffness, loss of flexibility, and balance problems that are so typical with Parkinson's.

The last point I would make about this is that we have a physical therapist that we work closely with in our practice. I think even if people don't think that they need physical therapy per se, I think going to have a visit with either a physical therapist or a personal trainer and really having a program that's tailored to you and your physical abilities, having somebody who's keeping an eye on you, making you stick with it, is a really good way to ingrain good physical habits.

Dave: As we approach the end of our hour I'm going to ask you to do something, which is difficult, but I know you can. Which is to summarize if you can the slide that we have up now about our sort of growing understanding of Parkinson's and perhaps the way, sort of, these things are beginning to fit together. That we're learning more about genetic risk. We're learning about, perhaps, the linkage between certain kinds of Parkinson's and how those different kinds of Parkinson's might progress over time and that there are these different understandings in the sense of Parkinson's. We're learning more about how to identify what's going on in the brain with more sophisticated scanning. Give us, kind of, your sense of what that picture looks like. And I guess ... Are we really making significant strides in beginning to fill in that picture so there aren't quite so many dark corners.

Todd: Yeah, I mean, I think this goes back, and I'll try to be quick, goes back to the discussion we had in kind of talking about the new generation of therapies that are being tested that are really based on an increased knowledge of the disease and a lot of this work really starts with very rigorous systematic evaluation and study of people with Parkinson's disease. There's a large initiative the Foundation has been leading over a number of years called the Parkinson's Progression Markers Initiative. Which has really been feeding the field, fueling the field with very significant data around clinical aspects of Parkinson's; genetic, biological, looking at brain scans because we have to get some kind of window into what's happening in the brain of the people with Parkinson's. And out of that kind of research comes new direction for therapies, developing therapies against novel biology that could be impacting the disease. But one thing we haven't talked a lot about which is equally important is coming up with better ways to do these trials more quickly.

One of the reasons why it's exciting is trials with select individuals in those trials who have the greatest chance of having benefit is you could probably do the trial...
with less individuals because you'll have less variability. So smaller trials with more robust outcomes so we can really test a lot of these treatments earlier and more quickly and not have to continue to talk about the longer time frames that we currently face like Andrew was mentioning for some of the synuclein therapies.

So all of that goal of new therapies, new directions, as well as new and better ways to actually test these come out of the need to have a greater understanding of what's really happening in the disease and how can we measure it in a better way.

Dave: It's such an interesting point because you think of a phrase like “improvements in trial design” and it doesn't sound that interesting or that significant but if you think about it in the way you just framed it, if we're able to do our trials in a smarter way and more focused way, focusing on people who have a particular kind of Parkinson's and a drug that may work for them we can speed up this process and advance the ball forward much quicker. Andrew Siderowf, a last word from you and then I'll give the last word to you Doug. But Andrew as you look at this big picture, sum up for us where you think we are at the end of 2017. Where you hope we may be a year from now when we have this conversation once again.

Andrew: I guess I would finish up where we started we saw ... How many was it? Twelve different disease-modifying treatments in clinical trials right now and I think that's really remarkable. I think when you couple that with a really deeper understanding about patho-mechanisms for Parkinson's disease ranging from progression of synuclein aggregation to genetic deficits we've really never been in a better position to identify disease modifying treatments. And I think it's going to take longer than we wish it did but I that I've never been more optimistic about disease modification than I am now.

Dave: Great, thank you. Doug a last word from you from the patient perspective about sort of your hopes about where this can go and perhaps also the importance of people like you and like me of being engaged in this process so that we make sure that the patients are participating in research and also making sure scientists like Andrew and Todd know what the patient experience is.

Doug: Absolutely Dave. I guess the key point I would make is that there's an individual life's approach ... there should be an individual life approach to every Parkinson's patient. And whether that's physical therapy, whether that's medicine, or in my case DBS. One of the things they put me through was extensive psycho-neurological testing and that included “on” and “off” testing; on medication, off medication. Because, of that and what they learned from that, they learned that it would make a difference. And as I said, DBS, or somebody said isn't for everyone, I think don’t assume it's the answer for you unless you go through the consultation and testing. I went to doctors at four different major centers in New York and Boston before I made the decision to go forward. So I'm glad I could contribute as a patient and I look forward to continuing to do so based on my experience.

Dave: Doug, thank you and that's a great last thought. I think that we all have a
responsibility to participate in our own treatment course because it not only, of course, matters to us most but we're really, as Michael J. Fox likes to say, "The solution is also in us." We can't get there unless we participate. Thanks all very much. Thanks to Doug DuMond, to Andrew Siderowf, and to Todd Sherer for their participation in our webinar today. We have up on the screen how you can watch previous webinars. We'll also be sending a link to this webinar so that if you want to listen to it again or if you want to share it with others you'll be able to do so.

That wraps up our Third Thursday Webinar series for 2017. We will rejoin you in just a month in January of 2018 and we look forward to another year of these discussions about the latest in Parkinson's disease research. Thank you for joining us, I'm Dave Iverson.