

Soania Mathur:	00:02	<p>Thank you every one for joining us. I'm Dr. Soania Mathur, co-chair of The Michael J. Fox Foundation Patient Council and I have the pleasure of being your moderator today. As you know, the field of medical research continues to advance and the area of Parkinson's disease is no exception to that. In today's webinar, we're going to review the progresses made in 2018. Throughout the hour, you're able to submit questions via the Q&A box which you should see in the middle of your screen. Submit your questions there and we'll do our best to get to as many as we can. Most of them we'll probably tackle toward the end of our time together but some of you have already submitted some questions, so I'll try and weave them in as we go along.</p> <p>Also, we're providing slides from today's webinar for download. You should see a box called "resource list" on your screen just below the Q&A box. Click on the link there and the document will open up in another window. You can save or print from that window.</p> <p>So let's get started. Joining me today is Dr. Andrew Siderowf. He is director of the Parkinson's Disease and Movement Disorder Center, chief of the Movement Disorders Division at University of Pennsylvania and the co-principal investigator of the Parkinson's Progression Markers Initiative. Welcome, Dr. Siderowf.</p>
Andrew Siderowf:	01:10	Thank you. Nice to be here.
Soania Mathur:	01:13	Dr. Todd Sherer is the CEO of The Michael J. Fox Foundation, formally trained as a neuroscientist, who directs the organization's research strategy and is responsible for the Foundation's overall scientific and fundraising direction. Hi, Todd.
Todd Sherer:	01:27	Hi. Glad to be part of this.
Soania Mathur:	01:32	Glad to have you both here. So what will be covering? Our exceptional panelists today will look at progress this year, what it means to the patient community and how the science has advanced in a number of areas. Developing new treatments to manage symptoms of Parkinson's, what's new in the market, as well as those treatments that are getting closer to the pharmacy shelves and therapies to slow down or stop Parkinson's, which we call modifying therapies. Biomarkers that are being developed to not only diagnose Parkinson's but to track the progression of the disease, something I really believe is revolutionary. Also, looking ahead to what we can expect in

2019. We've got a lot to cover over the next hour, so let's get started.

We're going to start by looking at what we call symptomatic therapies. There are a number of things that I'm struck by, looking at this slide, having followed the direction of research over the past couple of decades. One of the biggest changes I've witnessed is the change in focus from the motor symptoms of this disease which were really the focus at one time, not only the monitoring of these symptoms, but also their significant impact on quality of life for the patients.

Andrew, I'm wondering if you could maybe take us through the first couple of treatments, one that's already been approved and the other two which are hopefully close to landing in the hands of clinicians and patients. Those are directed toward the very frustrating built in problem of "off" periods. So how will these new drugs help and how long before patients can begin to use them?

Andrew Siderowf: 02:55

So regarding Xeomin, which is botulinum toxin A. It's actually effectively the same ingredient that's in the brand Botox and it's just another brand of the same toxin. Right now we have two botulinum toxins that are available for excessive drooling. One is botulinum toxin strain A, which is either Dysport, Xeomin or Botox are the three brands that are available in the U.S. There's Myobloc, which is botulinum toxin B, which is the other main strain that's available for drooling. The big advantage here is that Xeomin was specifically approved by the FDA for drooling, which means that it's likely to be covered by most insurers, especially Medicare. So it will be another option for patients who, for whatever reason, haven't done well on other brands of botulinum toxin. I think you'd expect the efficacy to be similar to what could be seen with the other brands of Botox specifically, but there may be advantages in terms of availability and also if a patient's had a reaction to one of the other brands, they might not have a reaction to Xeomin because the other constituents are a little different.

Regarding the inhaled carbidopa levodopa and the thin film apomorphine, my understanding is these are both well along in the FDA review process and I'm hopeful that we'll see them for patients even as early as sometime in the next year. I don't think either of them, as far as I know and correct me if I'm wrong Todd, are actually fully approved right now but they're close to being approved and the FDA has been reviewing them. I think that obviously these "off" episodes are disabling for patients with Parkinson's disease who have had the disease for

a long time. They can prevent people from wanting to go out because they're afraid they'll go "off" and not be able to get back to wherever they were. The inhaled carbidopa levodopa is a totally novel mechanism that is absorbed through the lungs. The thin film apomorphine is sort of a tape that you put under your tongue and it's absorbed directly through the mucous membranes, very similar to the other forms of apomorphine that are available now but I think that they will both offer new delivery systems for existing drugs and will be useful for patients.

Soania Mathur: 05:37 That's incredible because the "off" symptoms particularly can really isolate patients so it would be really great for patients' life. There are also a number of therapies in various stages of clinical trials and it's probably easiest to group them in terms of those directed toward motor symptoms and those being developed to treat non-motor symptoms. In the motor symptoms group actually a number are listed on the slide. Motor symptoms of course are the hallmark of this disease and represent significant progressive disability. One of the first ones is glutamate therapy. Andrew, could you tell me what glutamate therapy is and how it works?

Andrew Siderowf: 06:14 Yeah. I mean, most people who have had Parkinson's are familiar with the idea that a brain chemical called dopamine is really at the heart of why people with Parkinson's have trouble with movement, but it's really only part of the story. And, while dopamine and dopamine replacement remains probably the mainstay for treatment of motor symptoms with Parkinson's disease, other neurotransmitters are definitely important too and glutamate is a good example of this. Glutamate is the most prevalent excitatory neurotransmitter in the brain and it's ubiquitous. It's also important in regulating dopaminergic activity in normal function and in Parkinson's disease. There have been attempts at glutamatergic therapy. The idea of glutamatergic therapy in Parkinson's is that it would regulate medications like levodopa so that they work better. You'd have better "on" time without dyskinesia and that would be the place where these drugs would fit in, sort of people who are already on levodopa. It would make the levodopa work smoother and better in terms of better "on" time and "on" time without dyskinesia.

An example of glutamatergic therapy that's available now is Amantadine. Amantadine, maybe people feel, does both of these things, but there's still an unmet need to do these things better. So there are new glutamatergic agents which modulate glutamate transmission and the hope is that they'll work in

combination with levodopa and dopaminergic replacement therapy to give people with Parkinson's better quality of life.

- Soania Mathur: 08:14 And how far away are these from the patient's hands I guess?
- Andrew Siderowf: 08:19 I think that we'll see clinical trials very soon. In fact, I think there are probably clinical trials in phase II that a small number of subjects can participate in now. I think we're probably looking at 18 months at the best for seeing these more widely in clinic, maybe even a bit longer. There's a bit of a longer time horizon for these therapies than for the other ones. So I think you'll see clinical trials more and more. Todd, what do you think? I would think we're two years off at least.
- Todd Sherer: 08:54 Yeah. This is Todd. Just to add, I would say the new therapies being spoken about here that are closest are the ones listed under the with FDA reviewed. These have already completed their clinical trials and are just now at the stage of presenting the data for approval. The glutamate therapies, which are more experimental at this point, as Andrew mentioned, are entering the clinical testing phases, probably the earlier stages. Luckily, in some ways, since these treatments are looking for more acute benefit of the people with Parkinson's, they can progress more quickly through clinical trials but it still takes time to recruit the patients and assess the outcomes. So those are definitely more delayed. I would say a couple of years behind the ones that are now up for the approval, assuming that they all are showing success.
- Soania Mathur: 09:52 One drug's been around for years and years, decades, is levodopa. It's listed here that they're offering new levodopa formulations. Could you tell me a little bit more about that, Andrew?
- Andrew Siderowf: 10:07 Sure. I think actually one of the main themes that we've really in the last few years is new formulations of levodopa with medications that are approved now like Rytary and Duopa, and I think that we're going to be seeing even new versions. There's a new delayed release form of levodopa which is being tested in Israel mostly, which looks like it could be promising. Sort of an in between Rytary and regular levodopa in terms of its duration of action. The novelty of it is that the pill sort of deploys like an accordion in your stomach and releases the levodopa very slowly once you swallow it. Then I guess we talked about the inhaled carbidopa levodopa. There's also a levodopa pump which is being tested. The problem with levodopa has never been that it didn't work well. It's always been that you have "on/off" after a while, so these new delivery systems are really

aimed at smoothing the “ons” and the “offs” out. Unfortunately, even though it's an old drug it still needs to be tested and go through the FDA so there's still a time lag there but I think that these will, when they do reach the market, will help patients.

Soania Mathur: 11:31

Well that's exciting, actually, because you're right, levodopa does work but it's the ups and downs, the “ons” and “offs”, that are most bothersome. Next are the non-motor symptoms. A list of non-motor symptoms is a long and diverse one. It affects almost every bodily system. We know from patient surveys that they are, in large part, more bothersome and impact quality of life even more than motor symptoms. Todd, could you fill us in on the non-motor symptoms that are being targeted and how soon these may come to market?

Todd Sherer: 11:58

Yeah, this is actually, I think, a very exciting area where the scientific community and research community is catching up with the patient community and the patients have been expressing the impact of these symptoms for many years and now we're actually seeing the research moving in this direction and making progress. So there are clinical trials underway now that are looking to target some of the non-motor symptoms within Parkinson's disease, such as cognitive dysfunction, some of the neuro-behavioral challenges people might have like anxiety or other psychological symptoms and also the digestive symptoms like constipation.

There's really two approaches that are being used to develop treatments in this area. One is focused on what we would call repurposing or repositioning of existing medications, so testing drugs that we already know can treat anxiety for example or digestive problems and see how they work in the context of Parkinson's disease. So these are medications that are already available and then now see if we can test them to show whether they have effectiveness on these symptoms within Parkinson's.

The other area where this is really getting a lot of interest is looking to develop new medications based on increased understanding of what might be the underlying causes of these symptoms in Parkinson's and see if we could develop treatments to address that aspect of these symptoms as well. But this is, I think, a very promising area because there's much greater interest and activity in developing treatments against these non-motor symptoms. I think it's a great example of where the patient voice and the community, the Parkinson's community, voice of highlighting the impact of these symptoms

has now directly lead to changes in direction in the research area.

Soania Mathur: 14:03 Yes, absolutely. Absolutely true. I think the patient voice and the patient community have spoken about the impact of these symptoms on quality of life and the research community has listened, which is fantastic. That last one brings up the use of technology, something that impacts all aspects of life and medicine also benefits from those advances. Todd, can you explain what technology or virtual therapies are being proposed?

Todd Sherer: 14:28 Yeah so this is a really interesting new area which is trying to leverage technology actually as a therapeutic. We've talked a lot about using technologies in the past webinars for tracking the disease. Could we use wearable sensors or smart watches to really try to understand the disease better, but in this case these are actually now trying to look at ways to use technology or leverage technology to expand availability of treatments or develop new treatments. Some of the trials that are going on, one for example is using video conferencing or sort of voice video interactions to apply behavioral therapy to people. So one of the trials that we're involved in is looking at treating depression, which there are pharmacological or drug-based treatments for depression, but there's also behavioral therapy that is used to treat a symptom like depression. In this case, what they're experimenting with is to see how effective could that behavioral therapy be for patients if it's done through a video conferencing type of system, which would allow greater access to more patients than the current approach for this type of therapy.

So very exciting. There's great data already that the neurological exam can be conducted using what we'd call telemedicine, virtual assessment afar. So this would be a real way to bring the therapy to the patients rather than make it difficult for patients to access this type of therapy.

Soania Mathur: 16:10 Absolutely, especially those with mobility issues or those that may not be in that kind of environment where they have access to good healthcare, so that's great. This next slide lists a couple very interesting areas of research. The first, stems cells, have a bit of tumultuous history and have had some complications in the past. Todd, have the newer technologies overcome some of the initial limitations? I guess what were they initially and could you describe where we're at now with this area of research?

Todd Sherer:

16:42

Sure. This has always been a very exciting area of research, particularly for Parkinson's disease, really based on the concept that we know that many of the symptoms of Parkinson's disease are due to the specific loss of cells in the brain of people with the disease, particularly those cells that make dopamine. And there's always been the promise of using stem cells to be able to develop and replace those dopamine cells that are lost in the disease. So the general concept would be that you could grow the stem cells in a laboratory using various molecular techniques, convert those stem cells into dopamine producing cells and then transplant those dopamine producing cells back into the brain of someone with Parkinson's to replace the cells that have been lost in the disease. So that concept is still the approach that's being tried to be developed with stem cells.

One of the challenges historically that we've found in the research in this area is that when we grow the cells in the laboratory, we can very much control the environment in which those cells are grown and can make, particularly from embryonic stem cells, very, very robust numbers of dopamine producing cells. However in the past when those cells were then transplanted into the animals to sort of look at how they would integrate into the brain and form, they would lose their, what we'd call, lose their phenotype. This means they revert back to the stem cell phenotype and no longer have a very robust production of dopamine, which is what you'd want for this to be a therapeutic. So with that challenge, the investigators in this field sort of went back to basics, back to the techniques on how to grow the stem cells, how to design them to be dopamine producing cells.

And there have been a number of advances that have moved this field forward. One is improvements in the ability to engineer the stems cells into dopamine cells and also an advance where, not only can we use embryonic stem cells, there's now a new technology that's called induced pluripotent stem cells and in this case what can be done is taking a skin cell or a blood cell from an adult and using techniques to convert that back into a stem cells and then make that stem cell into a dopamine producing cell. So both to these approaches are now moving forward and with improved technology there's now been pretty significant success in transplanting these cells into animal models of the disease and the cells maintaining their phenotype, meaning that in those animal models they're still able to produce dopamine at levels that would be beneficial.

So based on those discoveries there's now a few groups, one you may have seen in the news recently in Japan, and some

coming up soon in the United States that are moving forward with stem cell treatment into clinical trials. And again the goal here would be to take this engineered stem cells, transplant them into the brain of someone with the disease and hope that those cells now make enough dopamine to revert some of the and hope that those cells now make enough dopamine to revert some of the symptoms. But there's been a long, as you mentioned, a long path here, but right now, I just think a lot of the early roadblocks have been overcome, and now we're back into clinical testing.

Soania Mathur: 20:17 Todd, would you say that that's an example of certain precision medicine, or personalized medicine, in that when you say that you can take a blood cell or a skin cell, you're talking about from the person you're going to treat with the cell to help with rejection or is that in general?

Todd Sherer: 20:33 Yeah, I think that's one of the possibilities with this, so it could be personalized in that you could, in fact, take the cells from the same person that you would do the transplant back in with. I think the other way that this technology is really being used in a kind of personalized way is that you also can take, let's say you took a blood cell from a patient and then converted it back to a stem cell and made it into different types of brain cells. You also now could understand and test medications, potential medications, against the biology that's happening in that individual because you've taken the cells from the person with the disease.

That's also being used now as a drug development tool because we still are challenged in Parkinson's disease compared to a disease like cancer where we can't take the biopsy of the diseased part of the body because no one would recommend brain biopsy to anybody, so we have to come up with surrogate ways to understand the biology that's happening in the disease and the stem cell technology in addition to being a therapy itself has the potential to really explode the science around the understanding of Parkinson's disease.

Soania Mathur: 21:57 That's really impactful. Andrew, I just wanted to ask you about stem cells. Have any of your patients come in with questions about the medical tourism that exists around stem cell therapy where they make promises of successful treatment and often a cure? What do you advise them?

Andrew Siderowf: 22:15 Often, I get a question about stem cells and, specifically, this idea of medical tourism maybe once every other week, very often. It's on people's minds, for sure. I'm very conservative

about the advice that I give patients. I think that there's a real risk for unscrupulous operators doing this sort of thing. As Todd mentioned, there's a very reputable clinical trial going on in Japan right now and I think is working in other countries as well. I really discourage people from going to studies that are being done in universities that don't like to go about them in advance.

I think it's very reasonable for my patients to get a consent form and bring it back so I have a look at it if they're interested, but going some place where somebody's going to inject stem cells back into your vein, for example, where we certainly don't think they would work. You really need to be injected into the brain where they're more likely to connect, these sorts of things. Patients are hopeful that this sort of thing will work, and I think that there's a real risk there. I think that reputable scientists, reputable universities, talk to your doctor about it. I wouldn't just go and sign up without checking a lot first.

Soania Mathur: 23:43 You know, I agree. I think you're right. I think sometimes people pray upon the desperation of some patients and, certainly, stem cells sound like an exciting area of research, but it doesn't sound like we're quite there yet. The next on this slide is gene therapy. From what I understand, gene therapy is using genes in the treatment and providing genetic instructions they'll need to change their fate. Is that correct, Todd, and how does this actually work and how far along are we in this field?

Todd Sherer: 24:12 Yeah, that's a good explanation. Basically, the gene therapy approach is to use different molecular techniques to get the cells within the brain to make the therapy that you're interested in. Rather than inject the therapy or make it into a drug, what you do in this case is, using different molecular techniques, you actually get the brain itself to generate the therapeutic molecule that you're hoping to produce. It's a very innovative type of approach, and Parkinson's disease is actually one of the diseases that's pretty far ahead in gene therapy in that there are a very handful of clinical trials that are ongoing.

Particularly the ones that are furthest along are looking at ways to get the brain to make more dopamine using the gene therapy, so you would have a surgical procedure, a one-time kind of injection of the different molecular machines, and then it has to be demonstrated in animals. After the fact, that brain that gets exposed to this is able to make more dopamine. It's a very exciting approach because it's incredibly innovative from a molecular science perspective, and the idea then is that the brain becomes the source of the therapy.

Soania Mathur: 25:52 The injection actually happens into the brain, though, into the area.

Todd Sherer: 25:56 That's right. I mean, in Parkinson's, it does. In other diseases, it happens wherever you're looking to make the therapy be developed. It allows a very localized, with the exception of the surgical procedure, after the fact, it's a very localized then production of the therapy. One of the things that gene therapy has allowed holistically is sort of a redefinition of the different types of science and biology you could target as a therapy because there could be certain therapies that you really can't have being exposed to the entire body because of side effects.

If you can use something like gene therapy where you get a very targeted production of that therapy, you could have the benefit without some of the systemic side effects, so it's a very exciting new area and is really showing a lot of potential. There's at least one Parkinson's trial that is in pretty late stage development that we should be getting results within the next year on how beneficial it's been for Parkinson's.

There have been trials in the past using gene therapy in Parkinson's, particularly to try to develop treatments for what are called neurotropic factors. These are proteins that can help brain cells to survive and behave appropriately. There's a lot of at least safety data in Parkinson's. Those trials were not successful from a clinical perspective, but there's a lot of safety data showing that injecting this molecular machinery for gene therapy into the brains of people with Parkinson's has not shown any adverse effects in past trials, so there's a lot of potential for expanding the types of therapies that could be developed using gene therapy.

Soania Mathur: 27:54 It seems like these biological therapies are really exciting. We have to keep an eye on them, for sure. The next slide shows us those therapies that are currently in clinical trials that are directed toward slowing or stopping the progression of Parkinson's disease, what we call disease-modifying trials.

Looking at the slide makes me hopeful because there are a fair number of potential treatments and trials at this time, and they seem to be directed toward a variety of targets and outcomes, some toward alpha-synuclein, which we hear some clinical trials are working with those certain genetic mutations. Even though these mutations are found in a small percentage of Parkinson's patients, we'll learn how these results may help the global Parkinson's community.

Let's start with the top one, repurposed drugs, which I believe, Todd, you explained already, but they're drugs that have already been approved and used for other medical conditions, such as blood pressure, diabetes or cancer and now are being investigated for use in Parkinson's disease. Andrew, I see there are eight treatments in Phase II and one which must be getting closer because it's in Phase III. Could you tell us, generally, what types of drugs these are?

Andrew Siderowf: 29:00

Repurposed drugs, there's a range of them. Some are diabetes drugs. In fact, a number of them are, so that's definitely been an area. The one that's got the most attention, to my mind, is one called exenatide, which was originally developed for diabetes and now is being repurposed for Parkinson's disease. There's one called ambroxol, which is developed actually to clear mucus, as it turns out, but has an effect on reducing the amount of glucocerebrosidase, which is a molecule that is involved in Parkinson's pathology, especially in people that are carriers of the GBA mutation.

I think the one that's farthest along is probably nilotinib, which is a cancer drug which acts through a pathway which, coincidentally, is implicated in Parkinson's disease. There was a small, single center trial that looked promising. It came out of Georgetown about two years ago, and there's a large multicenter effort underway now to try to replicate the effects that we're seeing in Georgetown. Whether it pans out or not, I think, is an open question, but these are just three examples.

I think, obviously, the question about whether repurposed drugs work in terms of do they help people with Parkinson's reduce their symptoms or still a progression, that is an unanswered question, and we really don't know that at all. That's why they're being tested. The nice thing about repurposed drugs is, we do have some information about whether they're safe because they've been used in other indications.

Sometimes, in thousands of patients, we do have a good sense of what the dose range which is safe is, so it's a little easier to go ahead and use these drugs with confidence in trials knowing that we don't know if they work or not, but we do know probably that the doses we're going to try won't cause harm. That's where we are with repurposed drugs.

Soania Mathur: 31:13

Andrew or Todd, you can jump in, too. Why do these drugs actually have to go through clinical trials at all if they're already approved and are used for other illnesses?

Todd Sherer:

31:22

I'll just jump in on that.

I think there's really two things that are hoping to be accomplished from these trials, which are both the efficacy and the safety. While certain drugs might be available, we actually always still need to be careful to know how safe they are, what doses could be used in people with Parkinson's. An example of one of the drugs that Andrew mentioned is a cancer drug, so there's a different safety profile for cancer drugs than there may be for a drug that people have to take chronically in a long-term disease like Parkinson's.

It could be that a certain drug is approved and has been developed for young people, pediatric drugs, and just because it's available in young people doesn't mean that we automatically know that it's safe at the same doses in people in the demographic of Parkinson's disease. I think that always has to be still looked at. It's a very important aspect that, just because a drug is available doesn't mean it has been thoroughly tested for its safety in people with Parkinson's disease. Given that, we still want to make sure that every drug that people take have risk/benefits.

There's really no drugs that are available that have no safety issues. You also want to confirm and understand the efficacy. Does the drug actually work for people with Parkinson's disease? So that's the other aspect of these trials, and at what dose do we need to give the drug in order for it to work because it could be that the drug's available, but it's only being given at a very low dose. And, in order to get a benefit for Parkinson's, we're not even able to give people the drug at the dose that is required.

They can move quickly into clinical trials because we really don't have to do these types of drugs. We don't have to do a lot of the basic preclinical safety because that's usually been accomplished already, but we still need to do the clinical testing to make sure we understand that the benefits outweigh the risks of any of these drugs.

Soania Mathur:

33:42

That makes good sense.

Andrew Siderowf:

33:42

I agree. I didn't mean to represent that these drugs were safe. I just meant that some of the very early phase safety testing is done, and you can move into the middle phase trials sooner. I would also say that I have patients who are taking, for example, Isradipine, just as a prescription, or Coenzyme Q10 is a great example, probably very, very widely used and probably not

much of a toxicity footprint, but we really don't know whether these drugs work or not.

Any time you take something effectively for no reason, it's probably not a good idea. I, generally in my practice, don't encourage people to use these drugs sort of in a speculative way, hoping that they might work because I think that the clinical trials need to be done first.

Soania Mathur: 34:31 Right. I guess unless they have a clinical condition that requires them, and then maybe that would be a reason.

Todd Sherer: 34:45 If you already have a reason to be taking the drug, right?

Andrew Siderowf: 34:48 Exactly.

Todd Sherer: 34:50 Wouldn't stop it.

Soania Mathur: 34:51 Wouldn't stop, right? One thing I've noticed, which would not have been the case when I started this journey over 20 years ago, and even 10 years ago, is the targets that we're looking at. They likely have been skewed toward dopamine replacements, but not the pathology of disease itself. Trials directed toward alpha-synuclein are an example of how things have changed. Andrew, could you please explain, in general terms, what aspect of alpha-synuclein treatments are directed toward and what they hope to accomplish and maybe a little bit about alpha-synuclein in general?

Andrew Siderowf: 35:21 Sure. I'm always impressed that my patients know about alpha-synuclein, and I think that patients always knew about dopamine, but now they know about alpha-synuclein, too. Alpha-synuclein is a protein that occurs normally in the brain, and we don't know exactly what it does actually. Its normal function is not known, but what is known is that, in Parkinson's disease, it's probably the main protein involved in Parkinson's pathology, so it's the main component of Lewy bodies, which are almost always seen in degenerating neurons in patients with Parkinson's disease.

It's also known that, in relatively rare families that have mutations in the alpha-synuclein gene, and sometimes even cases where they have genetic mutations, lead them to have extra copies of the alpha-synuclein gene that those genetic mutations are very likely to produce Parkinson's disease. These two lines of evidence that alpha-synuclein is almost always seen in pathology specimens from Parkinson's disease and that

mutations in the gene often cause Parkinson's disease in families where there are mutations have been two really strong pieces of evidence that alpha-synuclein is at the heart of what causes Parkinson's disease.

Generally, it's thought that there's too much alpha-synuclein. And, when there's too much, it always, what we call, misfolds, which means that it changes from its normal shape to an abnormal shape. This can't be eliminated from cells and builds up and effectively forms, I call it, brain garbage inside the cells. The cells can't function and ultimately leads the cell to dysfunction and death.

Just to summarize, synuclein is central to Parkinson's pathology and probably too much synuclein and too much misfolded synuclein that can't be removed from cells is really at the core of why cells become dysfunctional and die with Parkinson's. Leading into that, the main thrust of alpha-synuclein therapy is directed at trying to reduce the amount of alpha-synuclein and remove the existing sort of misfolded, aggregated synuclein from the cells, so that they can function better and survive better.

Soania Mathur: 38:01 The seven trials they say right now are under clinical evaluation, are those sort of directed at different points in the alpha-synuclein story? Are some drugs toward clearing the garbage? Are others directed toward it not forming in the first place?

Andrew Siderowf: 38:18 Yeah, absolutely. There are agents that are meant to prevent the synuclein from aggregating in the first place. Absolutely, yeah. There are agents that are meant to prevent the synuclein from aggregating in the first place. Aggregating just means building up into clumps where it's sort of hard to get rid of it. There are several large trials, maybe three or four big pharma efforts, that are directed at removing the already existing alpha-synuclein using, what we call, passive immunotherapy, which is basically antibody infusions, antibodies that have been specifically developed to target alpha-synuclein and then, in this way, harness the immune system to remove the extra misfolded alpha-synuclein. In addition to this, there's actually an alpha-synuclein vaccine, which is being tested in an earlier stage. The idea there is to get the body to develop its own antibodies against alpha-synuclein and use native antibodies to remove the alpha-synuclein, but this immunotherapy, either through vaccination or through IVIG immunoglobulin infusions, is probably the main way that people are thinking about removing alpha-synuclein. It's really very similar to the efforts to remove

the amyloid plaques using antibodies that are being tested now in Alzheimer's disease.

Soania Mathur: 39:40 Right, so all sorts of approaches to the one problem, which seems to be alpha-synuclein. Next, on the slide are the studies and the treatments directed toward specific genetic mutations that can lead to Parkinson's disease. Todd, could you please first explain why we're studying genetic mutations that are sort of only in a small percentage of people with Parkinson's disease and what we can discover in these trials that can be generalized to the broader patient community.

Todd Sherer: 40:08 When you mention what's changed the most, kind of in the last 10 to 15 years in Parkinson's, it really has been the role of an appreciation of the role of genetics in disease. That has led to the discovery of the specific genetic changes in genes, like GBA and LRRK2, as causal factors in percentages of Parkinson's disease. And as you mentioned, it's not that LRRK2 or GBA are found in a majority of cases of Parkinson's, it's a small, less than 10 percent of all the cases of Parkinson's that may be caused by these genes. What is really exciting about this is in trying to really develop truly transformative treatments, the best things that we could target, is what is the underlying cause, the underlying trigger of the entire process of the disease. If we could figure out a way to target that trigger and cause, and intervene on it, we have the potential to stop the process, stop the biological process that's leading to the disease and leading to the progression of the disease.

So, that's why there's such great interest in looking at genes like GBA and LRRK2, because they are very specific indicators of what might be causing cells to degenerate in Parkinson's disease. So, there's two things that are exciting about this, and one, just to go back to a question you asked before about personalized medicine. This is an area where you really are getting to the concept of personalized medicine, where companies are developing specific drugs to correct the deficit in these genes, and the trials that are being run currently are looking for individuals with Parkinson's disease who carry those genetic changes.

So, you're really targeting very specifically an individual who has a known biology that has changed, and then intervene on that biology. This is much more akin to what's being done now in diseases like cancer, where they really understand molecularly what's happening to that individual, and then try to use therapies very specifically engineered against that molecular change.

So, that's one very exciting concept and aspect. We've even seen that they've reached the clinic and are moving ahead, is also exciting. The other point is the point that you were making, which is, as we've uncovered these changes that are leading to these limited number of cases in Parkinson's, what we're finding is that as we go back to the laboratory and study the impact of these genetic changes, we're understanding that the same biology, the same molecular pathways, may be involved in a much larger percentage of Parkinson's patients than we first thought. So, while other individuals may not have the same genetic mutation, it seems that the same impact on the biology is being found in a broader number of Parkinson's patients, meaning that these therapies that are being developed initially to target the more limited populations of individuals with the genetic mutation, may really have the potential to impact the broader Parkinson's population.

- Soania Mathur: 43:34 Right.
- Todd Sherer: 43:35 It really shows how these may seem like limited or nuance genetic discoveries, are really impacting the entire field, with a great potential for the entire Parkinson's population.
- Soania Mathur: 43:49 Well, it certainly sounds like that. It sounds like it's expanding our knowledge of this disease and that the pathology then, our understanding of that disease can then be generalized to everybody and benefit everyone, so that's really exciting. The next slide addresses an area I'm really excited about, and that's finding a mark for this disease, because I think if we can discover a test to accurately diagnose and track Parkinson's, it will, in my opinion, revolutionize how we do research, and ultimately how we manage patient care. The Parkinson's Progression Markers Initiative is a landmark study that the Foundation has taken on, and Andrew, I know you've been intimately involved with it. Can you just describe what the term biomarker mean, what we're looking for, and what areas may be targeted for measurement? And also how PPMI has evolved over the past, I guess, more than five years, and what was learned?
- Andrew Siderowf: 44:43 Yeah, sure. So, that's a few things. So, to start out with, a biomarker is some objectively measured characteristic, and that means something that usually comes out of a lab, like your glucose level in your blood, would be an example of a biomarker, but so would an MRI scan of your brain. It's usually a test that's objectively measured, as contrasted to something that your doctor might examine in a physical exam in the office, or something, a symptom that you might report. So, it usually

has to do with some kind of machine or technology producing the results. It's usually quantitative, and it's usually, for that reason it's said to be objective, because it's free of the human factor, as much as possible. Although, you know, there's always a little bit of human factor.

And biomarkers can be used in a range of ways for a better diagnosis. Does the person have Parkinson's, or not, for example, or is it due to something else? For a prognosis, you might get a test when you get diagnosed, and it could give you an idea of whether you have a mild case or a more severe case. And also for tracking progression, and the last thing biomarkers can be used for among, I think the main things, is for looking for a response to therapy. So, this happens all the time. You get a blood test to make sure that your diabetes medicine is working, for example, or you have your blood pressure checked, which is actually a biomarker to make sure that your blood pressure medicine is working.

But, it would be really terrific in the case of these new drugs that are targeted against GBA or LRRK2, for example, or synuclein. If we could have a biomarker that could tell us almost immediately whether the drug was going to work or not in an individual person, this would greatly accelerate the development of drugs, because you wouldn't have to wait years to know whether you're on the right track or not, which is the case now.

And so, it would accelerate drug development, and so switching gears to PPMI, the real goal of PPMI is to find biomarkers that will accelerate drug development in just the way I was talking about a minute ago. And PPMI is, I think, I've been lucky enough to be involved in it recently. And actually as a side investigator from the beginning, and I'm always impressed that when you hear people outside of the Parkinson's community, they talk about PPMI as being a landmark study, and I think that it really has that external status. It's been going on, I think, since 2011, now, and it's scheduled to go all the way through 2023, now, and I guess that could always be extended.

So, it's a very long duration study. It involves, I think, almost 1000 participants, now, if you count or maybe, actually more. I think it's just over 1000 participants when you count the various cohorts, and it started out with about 400 Parkinson's patients, and about 200 healthy age matched controls, and it's been expanded. The main expansion, really, has been in the area of genetics, where there's been an additional 600 subjects that were added that had either genetically determined forms of

Parkinson's due to LRRK2, GBA or alpha-synuclein. And also, a relatively similar number of people who carry these genes, but were unaffected by Parkinson's when they were enrolled, and obviously, they're at risk.

And I think that we've learned. We're learning new things from PPMI all the time. There are literally hundreds of publications that have used PPMI data that are in the medical literature, and more all the time. The number grows exponentially, year by year. And drug companies are using PPMI data to plan their trials. A number of different biomarkers are being stored in the context of PPMI ranging from improved dopaminergic imaging, better ways to use existing dopaminergic imaging like DaTscan, CFS based biomarkers, and also really high tech things, like gene profiling, gene expression. Now the latest thing is to look at the use of sensors to measure people's movements, like wearable sensors, you can use to measure people's tremors, and walking speed, and so forth as they go about their daily activities at home. Hopefully to get a better sense of how people with Parkinson's, really function when they're in their normal environment.

So, PPMI is sprawling, longstanding, and it's contributing in ways we expected, and also in ways we didn't expect.

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| Soania Mathur: | 49:48 | I think also, PPMI is sort of an example of the collaboration that the Foundation pursues, as well as the sharing of information, because it has been used by so many people all over the world, the data that's been collected. |
| Andrew Siderowf: | 50:07 | I think the thing that people may not realize is that, almost all PPMI data is available to the public in real-time, like almost as it's collected. |
| Soania Mathur: | 50:18 | Wow. |
| Andrew Siderowf: | 50:18 | I've lost track of how many times the data's been downloaded, but it's hundreds of thousands, if not millions of times. |
| Soania Mathur: | 50:27 | Wow. And so, this leads us into our last area of discussion, looking ahead to the upcoming year. Andrew, building on what you just discussed with PPMI, could you tell us how this mission will help us in areas, not only early diagnosis, but development of preventive therapies. Because if diagnosing it early in someone, is there a follow up that we have in place, or will it help us develop that follow up? |

Andrew Siderowf: 50:52 Yeah, so that's a really good question, and this is something I think the field is struggling with a little bit, but definitely an emerging concept. The general feeling that an ounce of prevention is worth a pound of cure, in general this is true for Parkinson's disease, just like it's true for virtually all medical conditions. So, if it were possible to identify people who had Parkinson's at the very beginning of the disease, rather than waiting until the symptoms are full blown, they come to the doctor, and able to use a therapy like an anti-synuclein, antibody, if they worked, or the drug is targeted, in one of these personalized medicine approaches. So, that these drugs would work better if they were started earlier.

And so, this is a theme that is emerging, I think, because we don't have the therapies in place yet, to really test it, but across neurodegeneration, among Alzheimer's experts, and Parkinson's experts, I think there's a strong feeling that earlier therapy would work better, when there's more dopamine or neurologic neurons that are still healthy and could be saved. And so this leads to the question, how can we find people early as possible in the course of diagnosis? And there's two main approaches.

One is that it's people usually, and I think people on the phone would probably agree to this, but they wait maybe six months, a year, two years before they get diagnosed. This can certainly be improved, and there's research going on now that looks at how mild early signs that are detectable in a clinic could be picked and then a correct diagnosis could be made sooner.

And then the other thing, which is quite novel really, is that probably the injury to the dopamine neuron, starts three, five, ten years before any symptoms are apparent, and this would really be the ideal time to step in and short circuit the disease process before it really takes hold.

Soania Mathur: 52:58 Right, right.

Andrew Siderowf: 52:58 New research is looking at ways to do this, and this is something I think you'll hear a lot more about the next few years.

Soania Mathur: 53:04 Excellent. Next, we're looking at environmental lifestyle factors. It's been said in the case of chronic illnesses, genetic loads done, and environment pulled the trigger. Todd, do you agree with this analogy? And what work in this area can we look forward to in the next year?

Todd Sherer: 53:18 Yeah, so really what we're looking at now in the role of environment is really two fold. One is exactly what you said, which is, clearly not all cases of Parkinson's are explained by genetics, and even when there are different people that have the same genetics, they both don't line up with Parkinson's. So, there is some interplay between the environment and genetics. We're looking at things that might be in the environment that could lead to a causal factor for Parkinson's, things like pesticides, other exposures that when you think about things like prevention, there could even be things in the advocacy realm that could be done to try to get some of these chemicals out of the environment.

The other thing that we're looking at, though, when you think about environment and lifestyle, is that not all treatments have to be drugs that go through the FDA process. We're going to use our Fox Insight platform, which is a way to reach thousands and thousands of people with Parkinson's, to try to understand better, what are people doing behaviorally with their lifestyle that could be impacting the disease. Or even, can we uncover new repositioned drugs that are being looked at in other disease indications that could be beneficial to Parkinson's.

Many people, for example, may have just seen this paper that came out recently that looked at the appendix and removal of the appendix, and the impact that might have in Parkinson's. So, it's really to try to do a more holistic look at some of these lifestyle, other factors, that maybe are things we could do something about more quickly than having to push things all the way through the FDA pipeline.

Soania Mathur: 55:01 Right. And lastly, Todd, what's coming down the pipeline, specifically in terms of new therapies? Which studies are wrapping up what? What are expecting from those studies?

Todd Sherer: 55:09 I think the most exciting thing we're looking for early in the year, we mentioned and we started this discussion today with these drugs that are up for FDA approval, and we should find that out in the first quarter of the year. And a number of the other symptomatic trials will be reporting results in the beginning, or first half of 2019. And we should be, by the end of next year, learning about some of those synuclein trials that Andrew mentioned, and what came out of those.

We'll also continue to see really significant investment from the pharmaceutical industry in this area, and we started the year by hearing that Pfizer was pulling out some of their resources from neuroscience, and we end the year now knowing that they've

invested along with others, into a new company to keep moving the Parkinson's program forward. So, in general, we still see a lot of momentum in this area, and obviously we want things to move as fast as possible so we can get these results.

Soania Mathur: 56:11 And, we talked about so much today, so much information. If I had to pin you both down to what the most important advance in PD research will be in 2019, what you're most hopeful about for the upcoming year, what would you say, Andrew and Todd?

Andrew Siderowf: 56:31 I would, well, it's sort of a wish list I suppose, but the two things that I would single out are, we'll get some inkling of positive results from alpha-synuclein antibodies. It may be at the very end of the year, or maybe the very beginning of next year, but I think that would be really exciting, and that's something I'm looking forward to. And then, the other thing that I think is always, and you mentioned it early on, is where they will have an alpha-synuclein PET tracer at some point, and that would be a tremendous advance if that were to happen. So, those are things that I'm hoping for the most.

Soania Mathur: 57:09 Thank you. And, Todd?

Todd Sherer: 57:13 I'll put mine in the similar two categories I just mentioned. One: I'm very excited and hopeful that at least one if not both of the new therapies we mentioned, will not only be approved, but be able to reach patients and effect their lives. It's a lot of research that went behind those, so it'll be very exciting to see the tail end of that, and then the actual outcome. And then, I'm very excited to hear about the trial results of these genetically based treatments, LRRK2 and GBAs, because I think if those are successful, we'll set a new standard for how we could really develop transformative treatments for the disease that are targeting the actual triggers of the disease process.

Soania Mathur: 57:57 Excellent. On your screen now, you'll see a number of initiatives. Fox Insight, Fox Trial finder, Team Fox, and these are all ways that you all who are listening, can get involved and help advance the science, help us get closer to our end goal. Thank you, everyone, for joining us today, and thank you Dr. Andrew Siderowf and Dr. Todd Sherer for sharing your expertise.

We'll be sending a link to the webinar on-demand to listen again or share as you like, and mark your calendars for our next webinar on December 20, where we'll play a webinar on sleeping well with Parkinson's, and we'll have staff behind the scenes to answer your questions live.

One last thought. Being hopeful about the future is an important way of coping with a chronic illness like Parkinson's disease, but I think it's also important to ground that hope in science as well. And it is my hope that you are even more optimistic after our time together, because as you have heard, it is indeed a very exciting time in Parkinson's research, in our search for better treatments and that illusive cure, but until next time, be well. Thank you very much.