



## Transcript

### Welcome and Introductions

#### ***Stephanie Paul***

**[Slide 1]** Welcome everyone and thank you so much for joining us today. **[Slide 2]** My name is Stephanie Paul, and I'm the Vice President of Development and Marketing for the American Parkinson Disease Association or APDA for short.

I am pleased to welcome you to this Web/teleconference education program designed for people with Parkinson's disease, care partners, family members, and healthcare providers. I would like to thank Medtronic for funding this important program and acknowledge their continued appreciation for the critical need to provide educational programs like this one to people impacted by Parkinson's disease.

APDA is the largest grassroots network dedicated to fighting Parkinson's disease and works tirelessly to assist the more than 1 million Americans with Parkinson's disease live the best life in the face of this chronic neurological disorder. Founded in 1961, APDA has raised and invested more than \$170 million to provide outstanding patient services and education programs, elevate public awareness about the disease, and support research designed to unlock the mysteries of Parkinson's that will ultimately put an end to this disease.

APDA distinguishes itself as the national organization working one on one with the Parkinson's community to make each day better. And now to our program.

**[Slide 3]** Our presenter today is Dr. Jill L. Ostrem, who is the Professor of Neurology and Division Chief of UCSF Movement Disorders and Neuromodulation Center at Weill Institute for Neurosciences, University of California, San Francisco.

Today we are delighted to have Dr. Ostrem share with us an overview of bettering your understanding of deep brain stimulation, DBS. After the presentation, we will open the program for questions from both telephone and Web participants. We encourage everyone on the line to complete the evaluation after the program because your feedback is instrumental in helping us plan for future educational offerings, including teleconferences like this one and other programs.

It is now my pleasure to introduce Dr. Ostrem.



## Presentation

**Jill L Ostrem, MD**

Well, good afternoon everyone. I'd like to just welcome you as well to this ABC's of DBS. I'd also like to thank the APDA for this opportunity to spend a little bit of time explaining what I know about deep brain stimulation, and we have about a half an hour, I think, and then we're going to do some questions at the end. So, I just want to welcome everyone and hope that this is going to be educational for everybody.

**[Slide 4]** I'll start with just explaining a little bit about my disclosures. I'm involved with some industry activities related to education clinical trials, and I have worked with all of the device manufacturers that make deep brain stimulation systems, so that is something to just keep in mind.

**[Slide 5]** So, here's the outline for the presentation today. I'm going to talk a little bit about what deep brain stimulation is. I'm sure many of you already have a good sense of that, but we'll talk about that in a little bit of detail just to bring people up to speed if they're not as familiar with this therapy. We'll spend considerable time on who is a candidate for deep brain stimulation, and then I'd like to bring you up to speed on what is new in the field as it relates to deep brain stimulation as it applies to Parkinson's disease.

**[Slide 6]** So, what is deep brain stimulation? This is a picture of a person who has a deep brain stimulation system implanted. This is a surgical procedure that is required to use this therapy. Deep brain stimulation involves placing DBS electrodes into a deeper structure in the brain, hence the name deep. These DBS leads are then connected to an extension lead that typically travels behind the ear, down the neck, and connects to a neurostimulator or the battery of the system underneath the chest; and this influences the way the signals are delivered up into the brain.

The system does not damage the brain; and it, instead, influences the electrical signals in different brain circuits, and we'll talk a little bit more about that in a second. So, this is a completely contained system. Everything is inside the body. There's nothing outside of the skin, and so that's helpful for people to understand if you haven't seen the system before.

**[Slide 7]** Here's a schematic, a cartoon of what the system looks like. Here is a schematic of the DBS brain lead; and the traditional brain leads that we've had to work with have four electrodes on the end of these leads, and that allows for the programmer to choose one of these electrical contacts as they think it will help the patient's symptoms. You can also use more than one, and you can change the polarity of these electrodes as is necessary for symptom control.

There are really three different parameters that are adjusted. There is the amplitude of stimulation that can be increased or decreased. There is the pulse width; these are duration of each stimulation given. And there is the rate of stimulation or the number of pulses that are offered. So, these are the parameters that the programmers who are making adjustments to the stimulator, these are what they're thinking about; and in some cases, patients can also have some symptom control adjustment of these parameters, which we'll talk about a little bit as we're going along. So that's sort of the basics of the system.



**[Slide 8]** How does deep brain stimulation work? Well, to be honest, we don't absolutely know. But here is the latest theory, the way I like to think about it.

First, you have to understand a little bit about how the brain works. The motor system in the brain has this very interesting interconnected loops. So, if you think about the surface of the brain, there's a part of the surface of the brain called the motor cortex. This has neurons that originate here. These neurons project over to these deeper structures in the brain, the basal ganglia, which, in turn, project over to this other nucleus in the brain called the thalamus, which then projects back up onto the cortex. So, there's this interconnected loop within the brain that maintains normal movement, helps us to initiate movement, and filters out unnecessary movements.

In Parkinson's disease, as you all know, you get loss of dopaminergic cells; so, we have reduction in dopaminergic input to this basal ganglia, and that sets up some abnormal signals through this system, this pathological signal. There's more synchrony within the systems; and we think deep brain stimulation, by introducing this electrical energy within these very specific areas of the circuit, helps to disrupt those signals and restore more normal movement.

**[Slide 9]** All right, shifting here to who is a candidate for DBS, so, in general, most candidates, if you look at kind of everyone that is considered for DBS, these are some of the characteristics of patients who are most likely to be candidates. So, these are people who have more moderate or advanced disease. This is not people who were just diagnosed. These are patients who've experienced levodopa responsiveness, so they take medications such as Sinemet®, and their symptoms improve.

We also see patients that are experiencing motor fluctuations. This is probably the most common thing I look for. So, patients who are getting a good response to medication, but they are experiencing a wearing off of symptom control, and they're going through the day having some periods of on time where they're doing very well but other times when they're having more off symptoms and not doing as well. And to try to even out these fluctuations, deep brain stimulation can be very beneficial.

Also, patients who have dyskinesia, this is more of a feature of more of a moderate disease state where patients when they take levodopa develop dyskinesia. So, it can limit the use of medications for these patients. DBS can be very helpful in improving dyskinesia.

Also, patients who have really already tried medications in a reasonable way, they've failed good control with the traditional medical therapies that we have for Parkinson's disease, so not using DBS as kind of the first thing we use to treat the disease.

**[Slide 10]** But there are some caveats to that. There are patients who are still good candidates, and they may have milder disease. Perhaps they have not had Parkinson's disease for as long, but they have severe rest tremor. And there are people who have severe rest tremor that are resistant to levodopa or it doesn't help enough. There's still tremor that is present. Even though they take a reasonable amount of medication, it just does not improve the tremor enough. Deep brain stimulation can really improve tremor, and so for those patients we might go ahead and think about DBS.

Also, there are patients who experience off-medication state dystonia, often presenting with foot inversion or toe curling. This can happen in the morning and before medications can kick in; and so,



we know that for these kind of patients, DBS could be considered. As well as for people who have severe dyskinesia, there are people who have a very high sensitivity to levodopa and just taking one tablet of carbidopa/levodopa 25/100, may result in dyskinesia. So, that really limits the use of medications, and in those cases, we might also consider DBS a bit earlier. And then people who just require a very high level of motor performance for their job perhaps. So, any kind of disability that is preventing their employment, we would think about offering DBS a bit early.

**[Slide 11]** Who are not good candidates for DBS, those with significant psychiatric illness. We always want to think about this carefully when considering candidacy but certainly patients who have psychosis who are actively having severe hallucinations. Sure, some people can have some mild hallucinations, often from medications that they're given from Parkinson's disease. But if someone is having severe psychosis, we would not want to think about an elective brain operation.

The same is true with depression. Patients who have severe depression, who are not well-treated, are not managed with help from healthcare providers interested in their mental health, patients who are having suicidal ideation, we would not want to think about DBS until that is better controlled and managed.

Cognitive impairment is something that is kind of debated, actually, within the field. At what point are patients not candidates for DBS if they have cognitive impairment? I would say that if patients have been diagnosed with dementia, where there's severe problems with cognitive domains where memory is involved and perhaps one other domain, this is something that is also not really recommended for DBS. We know that patients who have dementia can be, their dementia could be worse with something like DBS, just going through the surgery itself, placing of the brain leads can lead to some worsening of cognition; and that can be even more disabling for the patient. It also makes management of the system very difficult in someone who can't provide feedback or really handle kind of the complexity of this therapy. But many patients with Parkinson's disease will have some cognitive decline in their disease, and so I think this is something that needs to be carefully looked at on an individual basis.

This extends significant medical comorbidities. If you have uncontrolled diabetes or end-stage malignancy, we wouldn't think about DBS as being a great choice for these kinds of candidates, just likely resulting in more complications after the surgery and perhaps not improve quality of life. And then patients who have unrealistic goals and expectations, and I'll talk about that in a little bit because this is not a cure for Parkinson's disease, and we want to make sure that people are educated about what they can and can't do so they're not disappointed.

**[Slide 12]** This is just a little bit redundant, this slide, but thinking about who is a candidate, here are some of the things if someone is coming to our center here at UCSF and many other of the major DBS centers across the country, things that they're going to go over with you are, first, do you have Parkinson's disease? What is your history, etc.? And then they're going to make sure that you've been optimized on your medications, is there anything else we can do to help you? And from a medication standpoint, I think that's just good medicine.

Then they'd likely have you undergo what's called motor testing or on/off assessment where patients hold their medications overnight generally, at least 8 hours, sometimes 12 hours, and then come into



the clinic, have a careful motor examination. Often, we perform the Unified Parkinson's Disease Rating Scale, which gives us kind of a score of the motor burden of the disease; and then we'll have patients take their medication and see what gets better. So, this helps us quite a bit in understanding the severity of the disease that the patient is experiencing, what symptoms get better with levodopa, which is often predictive of what will improve with DBS; and it just helps us to be able to counsel the patient. It also helps us to guide what brain target we might think about using, which I'll talk about in a little bit as well. So, it's very helpful and informative in knowing how to move forward with a therapy.

Patients will also undergo neuropsychological testing to, again, assess for cognitive impairment or other mood problems. Sometimes patients are asked to have psychiatric evaluations. It's not universal just because of, I think, access to psychiatry is still sort of low, unfortunately. But sometimes this will also be part of the workup. And then everyone will have some kind of a preop brain imaging MRI to evaluate for structural issues within the brain that are important to know about before thinking about a brain operation and then also to help for planning of the actual surgical procedure itself.

**[Slide 13]** So, this is a slide which just talks about predictors of good outcome versus things that are not as likely to improve or result in a bad DBS outcome. So, here on the left you can see that if you have idiopathic Parkinson's disease, that is a predictor of a better outcome than if you have one of these more rare, atypical or Parkinson-plus syndrome. So, again, making sure you have the correct diagnosis is very important; and there are patients who have these more aggressive forms of parkinsonism that are looking for ways to be better. But if these are indeed what is the true underlying diagnosis, this is not a therapy that is actually going to help their symptoms, so very important.

We talked about levodopa responsiveness and having good on-function as a predictor of improvement. Things that I think are helpful to note on this slide kind of talked about these other, the symptoms that are not adequately controlled. But let's talk about some of these other things over here.

So, let's say you're having severe disability from your Parkinson's disease, and even during your best on time, when your medications are working, you still have balance abnormalities or gait impairment. You're not able to walk independently. You're still in a wheelchair, even when your medications are working. DBS is not likely to improve as much in terms of the outcome for patients with those kinds of clinical phenomena.

Freezing of gait is a very disabling symptom that often comes more in later stages of Parkinson's disease; and, unfortunately, we don't have great ways to treat freezing of gait with DBS, so especially when medications are working at their best, if patients still have freezing, this is something that does often not improve with DBS.

And then we talked about dementia, depression psychosis, and then as people get older, DBS seems to have a little less robust response; but how we define older age is quite variable. So, I would say in patients who are older than 75, we do think about the benefit that they are likely to obtain a little bit more thoroughly before we offer DBS.



And then there are many, many nonmotor symptoms in Parkinson's disease, right, besides just the mood and cognitive issues. But often these do not improve as much as we would like with DBS, so very important to understand.

**[Slide 14]** So here's just a list of other symptoms that often go with the disease that Parkinson's patients are experiencing. So, ask yourself in terms of my personal experience with PD, which of these symptoms am I most disabled by; and let's think about which of these symptoms are actually going to be responsive to DBS. If tremor or dyskinesia are in your top three, then that is in your favor of an even better outcome with DBS. So, think about that when you go and speak with your physicians. What is likely to improve for me and really have a good understanding of that.

**[Slide 15]** All right, so we can customize DBS now. When I first started in this field a long time ago, this wasn't so much the case; but it really is true now. It's very much of a personalized approach. We have different devices now, which I'll talk about in a little bit. But, which, I think, center by center, they may have preferences for which device they want to use. But, in general, we have single channel systems that can control one brain electrode. We have dual channel systems that can control two brain electrodes, so you could just have one generator controlling both hemispheres. And we have rechargeable batteries now which are smaller and can last up to 9 or 25 years, depending on the manufacturer.

We also have to think about does a person need two implants or could they get away with just treating one hemisphere of the brain? If you have predominantly symptoms just really on one side of the body that are disabling to you, perhaps you can just get away with half of the risk of the surgery and have just one electrode placed, at least initially. And later if you needed the other one, you could go back and place that at a later time.

There's also the DBS surgical targets that need to be decided. I mentioned to you that we have a couple of different targets. So, the subthalamic nucleus or the STN is really one of the most used targets I think in the world still today, but the globus pallidus interna or the GPi is another excellent target that can also improve symptoms, so we need to think about which target we're going to recommend.

And then we have different surgical methods now where we have awake surgery which has kind of been the gold standard way in which we've placed electrodes. But we also have more common asleep methods now, which I'll talk about a little bit more.

**[Slide 16]** So what about the STN versus the GPi, these two different brain targets where the electrodes could be placed? There's been many randomized large trials now across the United States and in Europe that have tried to figure out what is the best target that we should use for Parkinson's disease. Basically, the results in total from all of these trials suggest that both the STN and the GPi are both excellent targets to improve motor symptoms, those being tremor, bradykinesia, rigidity, wearing off, dyskinesias. So, all those things are very well-controlled and improve quality of life. But there are some differences, and if you read the literature, in general, this is what you would see.

The STN is still the most commonly used target, so most functional neurosurgeons that do this surgery are trained in placing the brain electrode into the STN. The STN can also allow for greater



medication reduction after DBS, which is important for some patients. They have side effects from medications, and so this is just one of the differences that has come up from the trials. You can sometimes reduce medications somewhat with GPi, but it is more so with the subthalamic nucleus.

GPi DBS allows for somewhat easier programming. It's a larger nucleus of the brain, and the structures surrounding it are not as nearby. So, when you're delivering electrical stimulation, you're less likely to result in stimulation problems where the electricity is moving a little bit outside of the targeted nuclei. And you also don't get as much dyskinesia from stimulation itself in the globus pallidus. So, if someone is very sensitive to levodopa, and dyskinesia is a big problem, then the GPi may be a preferred target.

And in trials we've seen less cognitive impact overall in patients treated with GPi DBS. So, there's a lot to kind of disentangle here with this comment; but, in general, if you kind of look at all the trials, patients who've been implanted with a GPi DBS seem to have a little less cognitive impairment over time.

**[Slide 17]** All right, so moving on to updates in DBS for Parkinson's disease, we'll talk a little bit about the updated FDA labeling in terms of who is a candidate for DBS under kind of the FDA's guidance. I'll talk a little bit about the new DBS manufacturers, and then I'll highlight a little bit about the DBS surgical methods that have come about in the last few years.

**[Slide 18]** So how early should we offer DBS for Parkinson's disease? I mentioned earlier that when I began my career, we were really looking at patients who were more advanced in the disease. They were having resistant symptoms to medications. They were really having a lot more disability from falls and balance and freezing of gait, and medications weren't helping patients within this kind of window of the disease.

But this did not result in as much improved outcome in the patients who were getting DBS. As I've already told you, that DBS does not help these resistant symptoms as much as medications either. So, really, thinking about when patients are entering the motor complication window, having fluctuations, that was sort of the time in which we were recommending DBS.

There are folks thinking about offering DBS even earlier, but we don't have any controlled trials to really suggest that that is the way we should be thinking about this yet. But in looking at kind of the whole disease spectrum, I think we'll be learning more and more about when this should be offered. And, of course, patients have to be comfortable with the idea of having the operation in and of itself.

**[Slide 19]** Here's an important trial that was published a few years ago now by the German EARLYSTIM Study Group. They really wanted to look at patients who had earlier motor fluctuations, not patients who'd been experiencing motor fluctuations for many, many years. And they enrolled patients in this very large trial, randomized them to either to stay on their medications for two years or to have deep brain stimulation. Here was the subthalamic nucleus.

And they followed them over two years, and they showed that the patients treated with deep brain stimulation actually had an improved quality of life, they had an improved motor outcome, they had an improved Sinemet-related complications, better on time, and, overall, just across pretty much all



measures, had better improvement. So, this led to the updated labeling that Medtronic got approval for to allow for patients who have early motor complications from levodopa, within four years or after, to be eligible for DBS.

**[Slide 20]** All right, what about the new deep brain stimulation systems? The Medtronic system has been around for 20 to 30 years now. For a long time, it was the only system we had. I mentioned that there's these different batteries—the primary cell, the single cell, and the rechargeable battery. This is the patient programmer here, the small portable gray box. And then we have the physician programmer.

There's going to be some updates to this coming. Very soon they're going to move more towards a tablet-based programmer, but this has been a very good system for us for many, many years. But now there is competition that has arrived on the scene. **[Slide 21]** We have a system now approved in the United States called the Infinity™ system, which is made by Abbott or St. Jude Medical. They got their FDA approval in 2016. It's also approved in other areas in the world. This system is a little different in that it offers a constant current energy source which probably allows for more steady state delivery of energy, which is probably overall better.

It also has an upgradeable Bluetooth wireless communication system; so, patients, when they're being programmed by the neurologist, can actually move around a little bit. So, if you're assessing gait, you can make subtle changes to the system while patients are moving, and which is a little bit better, I think, than having someone just need to be sitting in a chair, kind of tethered to the controller.

They communicate with Apple digital devices, so patients receive an iPod which helps them to interface with their systems themselves, turn it on and off, find out what the settings are, and make subtle adjustments.

They do not offer a rechargeable battery at this point, and they are not MRI-compatible at this point. So, if you get one of these systems, you cannot have a brain MRI. But they also offer a directional lead. **[Slide 22]** So, what do I mean by a directional lead? So, a directional lead has, instead of the four contacts on the end of the electrode like I showed you at the very beginning, the middle two contacts have been separated into three separate electrical sources; and they can be turned on together, all three, giving you a cylindrical energy source as we normally would use, or you could just turn on one side. And so, this allows you to steer the current of stimulation one way or another around a structure and perhaps reduce side effects from stimulation.

So, this has been pretty exciting for the field to have this new way in which to deliver energy, and we hope that it's going to allow for better targeting of symptoms with less side effects. It seems to be, we don't have a lot of trials right now looking at this formally; but we think we're going to be able to use less energy and get better symptom control. So, we'll see. It's still early, but I think the field is going to be moving in this direction with all of the companies eventually having this type of a DBS lead for us to use.

**[Slide 23]** And then, lastly, we have the Boston Scientific Vercise™ system. This is the last system to be approved in the United States in 2017. Again, it uses a constant current source of energy. And, instead, this brain electrode that they provide has eight contacts along the end of it, so it allows for a





longer span to offer stimulation across. Whether that's important or not, we don't really understand yet. But it's a new innovation.

They have a very small rechargeable battery which can last up to 25 years, so that's a huge advance in my mind. And it also, along their brain lead, they offer a more refined way in which to deliver the current. It's called fractional current delivery. So, you can now enlist, for example, 25% across this contact, 50% across this contact, and perhaps 25% across this contact. There's infinite ways in which you could fractionate the current across this lead, so it really allows for along the length of the lead to deliver stimulation in a very accurate way. It is not MRI-safe, but we think this will be changing in the near future too. We'll see.

**[Slide 24]** All right, moving on to surgical methods, we have the traditional DBS surgical method which really required patients to come to a traditional operating room, be placed into a stereotactic headframe where small burr holes are created in the skull, and then a small recording electrode, a microelectrode, would be advanced through the brain, down to the target intended for the DBS lead to go. Along the way, we can hear in the operating room the discharges from the individual neurons as you're advancing the recording lead; and this allows for confirmation of where you are in the brain, because there's no way to see where you're going during the operation.

Also, stimulation is given in the operating room to make sure that the symptoms are somewhat improved, at least as much as you can tell in that situation, and that you're not having any side effects from the stimulation. So that's sort of the traditional way that DBS has been performed.

**[Slide 25]** There are new methods. This method, called interventional MRI, was developed at UCSF using the ClearPoint® system where patients are actually asleep during this procedure under general anesthesia; and the whole operation is performed within the magnet bore of an MRI, and the DBS electrode can be visualized going down to the target in real time. So, we don't need to do any recording of neuronal activity to confirm where we're going. We can use the MRI machine to show us exactly where the electrode is placed.

**[Slide 26]** So some pros and cons often our patients are faced with. Well, which way should I have the surgery? Pros are that, at least for the newer techniques, we seem to have pretty comparable efficacy. So, patients, the outcomes from having surgery this way seem very similar to the way the surgery's been done in the past. We can record where the brain electrode ends up, and we find that it's very accurately placed. You don't require as many brain penetrations with this method because it's generally just one pass, and patients can be asleep. So, patients find this to be maybe a more comfortable way to get through the procedure.

Cons are that the technique may not be available everywhere. It's still rather new, so depending on where you live, there may not be neurosurgeons that have this kind of experience in performing this procedure in this manner. And this is complicated by just lack of access for intraoperative MRIs in some patients.

Also, some nuclei within the brain are not as well-visualized. This is maybe a little bit technical for this talk, so some folks don't find ways to really see where they're going as much as they would like. And then you just have the traditional bias of, well, we've always done it this other way; and so, we don't



really want to change. And so, a lot of people will just say we still believe in anatomical targeting. Excuse me, we still believe in physiology-based target or listening to the neuron rather than just looking at an MRI.

**[Slide 27]** I wanted to leave this slide in here for folks who are interested in knowing there are some changes to MRI scans and deep brain stimulation. The Medtronic systems now have FDA approval for full body, conditional MRI use. So, in the past, if you had a DBS system, you were not eligible for having an MRI anywhere in your body, except for your brain under very specific requirements. So, if you needed an MRI on your knee, you were not able to get one safely.

So, this is a change. They now have approval for this, but the MRI has to be done in a very specific way. It has to be done in only a 1.5 Tesla closed-bore magnet, so lots of information if you need to find out more about this. I left the Medtronic number there and some of the other qualifiers for it. It doesn't apply to some of the very old systems of the Medtronic, before the Activa™ series was released. So, if you have some of the older models, you may not be a candidate.

**[Slide 28]** All right, a little bit about the future of DBS. This is a little provocative, but if we're going to talk about updates to DBS, I think it's helpful for those on the phone to just appreciate where the field is going. We now, as I was mentioning in the beginning of the talk, understand more about these brain circuits that are controlling the movement and the body; and we would like to find a way to use changes to the signals within that system to help to automate programming of DBS someday.

So much like we have cardiac pacemakers that are listening for cardiac arrhythmias and then discharging when there's a problem, we'd like this to be the case, we think, for DBS as well because right now we're offering really continuous therapies of the brain, kind of regardless of whether you're doing certain activities or whether you've taken a medication or whether you're asleep. And so, we'd like to make the system more sophisticated and have more of an adaptive mechanism. We think that's going to be better for side effects and for also thinking about moving the technology forward beyond movement disorder applications.

So now we have systems in the brain that can actually not only just deliver stimulation to the brain but also record across the brain electrode that's in the brain. So, we can listen, and we can record what is going on, and that's helped us to move forward in the **[Slide 29]** field and think about development of these new closed-loop or adaptive stimulation systems.

So, here's a patient who has an implanted DBS system, and we're recording brain signals and they are field-filtered and analyzed by physiologists. We extract those signals. We try to understand what do those signals mean because, really until now, we didn't even have access to this kind of information.

And then we figure out if these signals are normal or not, and we can then develop algorithms to adjust stimulation settings, and so we're just starting this project across the world now to use these newer systems to decipher this physiology, and I just think it's a really exciting time to be aware of this advance in the field, and we hope it's going to give even better treatments to patients as we work through this.



**[Slide 30]** Lastly, I'll leave you with this, that we have expanding indications for DBS; and so, it's not just used in Parkinson's disease. Maybe you're aware of it being used in tremor and dystonia, but there's many other ways in which we're thinking about adjusting brain circuits in a very careful and responsible way. But we hope that we can use this technology to also help patients beyond Parkinson's disease, and I think there's a lot of hope that this is going to happen in the future.

**[Slide 31]** So with that, I'll just say a few words about the UCSF Movement Disorder team without taking too much time. But at the end of every talk, I just want to acknowledge my wonderful team here at UCSF because what I do wouldn't be possible, really, without a huge team. **[Slide 32]** So, I think I'll turn it back to you, Stephanie, now, and we can move into the Question & Answer.

### ***Stephanie Paul***

Terrific. Yes, thank you, Dr. Ostrem. This is a very detailed and informative presentation, so we appreciate that.

## **Question & Answer**

### ***Stephanie Paul***

It's now time for the Question & Answer session.

### ***Stephanie Paul***

Okay, let's get started with the questions. We have a Web question coming from Alan, and the question is, "Am I a candidate for DBS if I have a pacemaker? If I am a candidate with a pacemaker, where would you put the DBS stimulator?"

### ***Jill L. Ostrem, MD***

Hi, yes, that's a wonderful question. Certainly, patients who have pacemakers are still candidates for deep brain stimulation. Sometimes there needs to be adjustments to the way in which the system is placed. Depending on the type of cardiac pacemaker, if it's MRI-compatible or not, they might need to make adjustments to the way they do the planning or placement of the system.

But the pacemaker is generally on one side of the chest wall, right, and then the DBS neuropacemaker is on the other side. So, it's definitely completely fine to think about that.

### ***Stephanie Paul***

Okay, terrific. You talked a little bit about this, Dr. Ostrem, but a question from Wallace, and the question is, "What are the pros and cons of the three primary DBS products?"



***Jill L. Ostrem, MD***

Yes, also, I tried to cover that in my presentation, but I think the pros for Medtronic is that it's been a well-established supported therapy for a very long time. Programmers and centers are very, very comfortable with that system. They know how to use it and that it has MRI compatibility.

I think the advantages for the newer Abbott system, the Infinity system is the directional lead. That's excellent, and I think the interface for the patients through the iPad system is very nice.

And then the Boston Scientific system, right now, you know, the rechargeable battery is the smallest battery on the market. It can last up to 25 years, and so I think those are really the advantages I see.

***Stephanie Paul***

Okay, here's a question from Ruth; and the question is, "What are common difficulties?"

***Jill L. Ostrem, MD***

What are common difficulties with DBS? I think I would say that access to finding a team of people that you can work with is sometimes a big barrier. If you don't live near a major DBS center, just thinking about how is this going to be something I can access and have good follow-up. I think that's very important.

Also, I would say there's challenges around knowing when stimulation of the system has been optimized. So, I think working again with someone that is very clear and experienced with this and can help you to know when it's time to stop making changes and also to know really what is realistic in terms of what can be improved and not improved. I think we sometimes are always struggling to try to improve that last 5%, and knowing when that is, is sometimes difficult.

***Stephanie Paul***

Okay, terrific. Dr. Ostrem, I believe we have a phone caller, so if the Operator could bring the phone caller in.

***Operator***

Okay. Our first call is from Lynn from California. Please state your question; your line is now live.

***Lynn, from California***

Yes, there was a drug announced yesterday, Epidiolex from CBD. I'm wondering if there's any application for Parkinson's with that drug.

***Jill L. Ostrem, MD***

So, this is a question about a new FDA-approved drug that has CBD. Is that the question?



***Lynn, from California***

Yes

***Jill L. Ostrem, MD***

Yes, and I think that was approved, if I'm correct, for rare forms of pediatric epilepsy.

***Jill L. Ostrem, MD***

Yes, there's not been a lot of work in use of CBD, rather cannabinoids in Parkinson's disease yet. So, I think that's a hot topic, but I really can't comment specifically for Parkinson's disease.

***Stephanie Paul***

Okay, we have another Web question that comes from David; and the question is any stimulator upgrades? I have bilateral STN DBS since 2008.

***Jill L. Ostrem, MD***

So, most likely, you have a Medtronic system; and when you get a new battery, if you have a system that is a non-rechargeable DBS, then it's possible whenever that point in time is that they'll be a new version of the Medtronic neurostimulator; but I'm not sure when that's going to be.

So otherwise, I would say they are coming out with newer interfaces for their system to work with patients and have it be a little more friendly in terms of being able to view the screen and things like that. But right now, we don't have any other really newer upgrades. There's not a way to come and get a firm upgrade or something on the Medtronic system at this point.

***Stephanie Paul***

Okay, thank you. Here's a question from the Web. This comes from Sheila, and the question is, "What does data indicate the range of durations, i.e., the shortest to longest periods of time and of efficacy post-DBS to be?"

***Jill L. Ostrem, MD***

Yes, that's a great question. Often patients will say, "Well how long is this going to work for me?" And we really believe that the DBS system is likely to continue to improve control of people's tremor. If you have significant tremor, that is likely to be controlled over time.

Also, we see improvement in rigidity, really kind of long-standing. We have trials now out to at least ten years. But I anticipate it will be even longer. I mean we just haven't had the therapy around long enough to really test even beyond that in a rigorous way.

Bradykinesia or slowness of movement sometimes does advance a little bit. And we continue to see improvement in motor fluctuations and dyskinesia.



The things that don't improve with DBS, things like freezing of gait, balance impairment, cognitive impairment—those kind of symptoms as I had mentioned earlier that are not as impacted by DBS in the first place—often get worse because of disease progression; and so even though patients have a DBS system, they may feel like they're getting worse because these other symptoms are playing a bigger role in the experience of the symptoms that they're having as the disease goes on. So, it's not that the DBS is no longer working, it's just that the DBS is not responsive to those more progressive symptoms.

### ***Stephanie Paul***

Okay, terrific. Here's a question that's a little bit along those lines. This comes from Alana, and the question is, "Does DBS slow down the disease and/or restore sick and dying nerve cells affected by PD?"

### ***Jill L. Ostrem, MD***

Right, no. I would say we don't have strong evidence to suggest that there's been any disease-modifying effect of deep brain stimulation. I mean there are people that are interested in that question and are trying to study it to determine whether stimulating of the subthalamic nucleus earlier could decrease some of the firing within that nucleus and thereby change the glutamate levels and perhaps that can lead to growth factor changes that could be helpful.

But, really, the science is just all in animal models right now, and we don't have any human data to support that, so I really can't advocate for that kind of argument. But I would say that there is, in my mind, a real powerful impact of DBS in terms of just quality of life. So, we can really improve motor symptoms quite dramatically with this therapy. It's the biggest impact in the field since levodopa in my mind, but it has not been shown to be neuroprotective; and we don't have evidence for that right now.

### ***Stephanie Paul***

Okay, thank you. Here's a question from Robert. When will the battery just be part of the stimulator? Can the system be damaged by contact or falls?

### ***Jill L. Ostrem, MD***

So, the DBS system is all connected. I don't have any understanding of the system being separated into two components where you'd have the battery separate from the DBS brain lead. There may be attempts at some point to try to make a small enough battery to place within the skull, so we don't have to have that long extension lead down into the chest wall.

The system can certainly be damaged. So, if you have impact to the system, if you're in an accident, you, most likely, could injure the extension wire; and that can fracture and that can require additional surgery to repair, so that is possible.



**Stephanie Paul**

Okay, terrific. Here's a question from Shirley. "How early can one become a candidate for DBS?"

**Jill L. Ostrem, MD**

Again, we have sort of the FDA guidelines for DBS in terms of timelines, so more than four years from diagnosis with mild motor fluctuations. But, again, there are situations where patients could be candidates perhaps even earlier if you had severe medication-refractory tremor, as I mentioned, or some other symptom that we think would benefit from DBS. But very early DBS, so let's say you just cannot tolerate any medication. Let's say you get severe nausea from medication and even though if you took it, your symptoms would be better, you are so sick from just the medicines and you can't control your disease with those medicines. That might be a situation where DBS would be considered early as well.

**Stephanie Paul**

Okay, terrific. Here's a question from Paul. Are there any interactions of DBS and optical changes?

**Jill L. Ostrem, MD**

There can be. If you have a deep brain stimulation system that is targeting the globus pallidus interna, the optic tract, so the main nerve leaving the eye, going to the brain, is actually right below that nucleus. Sometimes if the stimulation parameters are not set appropriately or too near that optic tract, you can have visual interference from the system.

**Stephanie Paul**

Okay, great. Here's a question from Celina. The question is, "Is DBS reversible?"

**Jill L. Ostrem, MD**

Yes, DBS is reversible. You can turn off the system, and you can explant the system. So, it is reversible, unlike some of the therapies that were used before DBS where these same areas of the brain were targeted with thermal lesions, creating damage to structures in the brain to change the circuits that I was talking about. This is a reversible treatment, so it can become completely taken out or just turned off.

**Stephanie Paul**

Okay, terrific. Here is a question from Ann, and the question is, "Is there any difference between women and male response to DBS?"

**Jill L. Ostrem, MD**

Yes, great question. We haven't had a lot of studies in this, but there seems to be a greater risk for patients who are women and have Parkinson's disease for the development of dyskinesia. We don't



know exactly why this is, but it may be that women tend to be smaller in body weight and perhaps are given higher levels of levodopa.

So, I would say that women also tend to be a little bit smaller in general, and so I think there could be a higher risk of device erosion and things like that as their skin thins as they get older. But other than that, I really can't say there's major gender outcome differences in the major trials. And honestly though, no one has really taken a really careful deep look at this question.

***Stephanie Paul***

Okay, here's a question from Arlene, and she's asking if speech can be affected by DBS.

***Jill L. Ostrem, MD***

Speech, yes. Sure, speech is affected by Parkinson's disease first and foremost, so understanding what someone's baseline speech problems are and, again, reminding folks that DBS does not often improve speech.

But where we place the DBS electrode, especially in the subthalamic nucleus, there are nerve fibers very near there that can affect speech. And if the stimulation is not shaped in the right way, you can impact those speech fibers. So that's an important thing to understand turning off the system and seeing if the speech changes is a way to kind of assess for that. So that is something that can be one of the more common side effects of stimulation if it's not been adjusted accurately.

***Stephanie Paul***

All right, thank you. Here's a question from Robert, and the question is, "How much does DBS typically cost?"

***Jill L. Ostrem, MD***

Well DBS should be covered by insurance if you have kind of the traditional Parkinson's disease symptoms and kind of meet the Medicare guidelines. So hopefully it would be covered by your insurance. If it, for some reason, was not covered by your insurance, then you would need to consider the cost of the device itself, which could be, I think it varies, depending on what system you're using. And I think I would just not want to give a number because I wouldn't be sure it would be completely accurate everywhere. But then you'd also have to consider the cost of the operation itself and then programming visits, but by and large this is something that is covered by insurance.

***Stephanie Paul***

Okay, thank you. Here's a question from Arthur, and the question is, "Asleep DBS versus awake DBS. I am incredibly anxious about having to be awake. Is there really an option or not?"





***Jill L. Ostrem, MD***

Yes, I touched on that in my presentation, so I hope that was helpful. Yes, being asleep for DBS is an option. If you don't have access to a center that performs this surgery in the interventional MRI manner where patients are taken to the MRI suite and are under general anesthesia, if that is not an option for you, the procedure can be done in more of the traditional operating room under general anesthesia; but many people are not as comfortable with that in terms of targeting the electrode because you can't have as much information about where the lead is.

So, I think I would just encourage whoever this person that asked this question to really research which centers are offering asleep DBS, and there are many now, so with good outcomes as I had said. So, it is a true option, and I think it'll help open this therapy up for patients who have that fear of being awake for DBS.

***Stephanie Paul***

Okay, thank you. Here's a question from Gregory. How long does it take to get from contacting a DBS center to surgery?

***Jill L. Ostrem, MD***

I think that's going to vary a lot, depending on the way in which centers have set up their program; but at UCSF, there it usually requires an initial consult with the neurologist as well as the neurosurgeon to kind of understand someone's history and do a careful exam and all of that. And then there needs to be some workup, as I mentioned, meeting with the neuropsychologist, on/off testing, and an MRI, so that can take several months to just work through that. And then the surgery can be scheduled.

So, I think it really varies, and you'll see a wide variety of wait times in terms of operating availability. It could be a couple months; it could be six months.

***Stephanie Paul***

Okay, great, thank you. We have one more question, and this comes from Drema. And the question is, "Is there research ongoing for DBS to be used in regard to nonmotor symptoms?"

***Jill L. Ostrem, MD***

Yes, there is. Nonmotor symptoms is a huge problem for Parkinson's disease. It's really where we need to find better treatments, and we are thinking about where else can we place electrodes in the brain to treat some of these nonmotor symptoms. We have a clinical trial right now going on as UCSF where patients are stimulated in the cortex, in the frontal lobe to try to treat anxiety and depression or understand signals that can help us to perhaps target this.

So, the field is still very young in this question, but we are hopeful that as we understand the circuits underlying nonmotor symptoms better, fatigue, sleep, urinary frequency, all of these things that are very disabling for patients, we can find better ways to help them too.



### ***Stephanie Paul***

Terrific. Dr. Ostrem, thank you so much for all this very important information. And my thanks to everyone for participating in today's telephone and Web education program.

### **Closing Remarks**

### ***Stephanie Paul***

**[Slide 33]** I do apologize that we couldn't get to all of the wonderful questions, but if you do have a question or would like to speak with someone from our Scientific & Medical Affairs Department, I encourage you to visit our website or call 1-800-223-2732 and you can ask your questions there.

Again, I want to thank Dr. Ostrem for her presentation. I also want to emphasize to everyone on the phone that we really do appreciate your feedback and comments and want to make sure that you complete the evaluation form.

APDA is so proud to support those living with Parkinson's disease by helping them live life to the fullest every day. We do this every year by providing more than 1,700 support groups that serve more than 75,000 people with Parkinson's disease and their family members and **[Slide 34]** running 770+ exercise groups attended by more than 21,000 participants. These exercise programs help improve the symptoms in Parkinson's and lessen the impact of the disease.

We also offer educational symposia across the country on living well with the disease. These programs have been attended annually by more than 5,500 people impacted by Parkinson's. We rely on the support of the entire Parkinson's community to accomplish all of this. So, join us in the fight against Parkinson's, and to learn more about the support APDA provides across the country through our network of chapters and information and referral centers, as well as our National Research Grant Program and Centers for Advanced Research, please visit [apdaparkinson.org](http://apdaparkinson.org).

To see past webinars from our Spotlight series, please visit our website at [apdaparkinson.org/webinar](http://apdaparkinson.org/webinar). We all agree that being informed about your disease and treatment options is the best way to empower yourself and take control of your care. Have a wonderful day.