

every victory counts ®

# Davis Phinney Foundation Presents a Virtual Deep Brain Stimulation Panel April 22, 2020

### Melani Dizon (00:02:05):

I'm going to turn this over to Dr. Soania Mather. She is a member of our board of directors. She's been living with Parkinson's for over 20 years and she's a former family physician. She has a lot to offer this and we're so excited to have her. She's our absolute favorite moderator, so welcome Soania, take it away.

## Dr. Soania Mathur (<u>00:02:24</u>):

Thank you, Mel for that introduction. Good afternoon everyone. Thank you for joining us today for our virtual deep brain stimulation forum As Mel mentioned, my name is Dr. Soania Mathur and I am a member of the board of directors for the Davis Phinney Foundation and I had the great pleasure of being your moderator today. As I'm sure we're all aware there really is no current cure for Parkinson's disease. Instead we depend on treatments to help control our symptoms and optimize our quality of life. What these symptoms consist of really varies from person to person because we are truly unique in terms of our symptoms, our course of disease, our prognosis and how we respond to certain treatments. in conjunction with medications, surgical options including deep brain stimulation can help manage our Parkinson's symptoms. This procedure is an excellent option but it's of course not appropriate for everybody. Our panelists today will discuss what this procedure is all about, who should consider this treatment and when, and what some may expect after the surgery. We'll also try to address any misunderstandings or myths about DBS and what the future holds for this technology to help examine this topic in detail is a wonderful panel of experts that we've invited today. I would first like to welcome Dr. Helen Brontë-Stewart. Dr. Brontë-Stewart is a professor in the departments of science and neurosurgery at Stanford school of medicine. Welcome. We also have Dr. Kelly Foote with us today. Dr. Foote is one of a very select few neurosurgeons who has a fellowship training in both movement disorder neurology and movement disorder neurosurgery. He currently works at the university of Florida health. Welcome. We also have the privilege of having Dr Aaron Haug who works as a movement disorder specialist at Blue Sky Neurology in Colorado and he has interests that include DBS and Botulinum toxin for the treatment of neurological disorders. Welcome Dr. Haug. We also have Dr. Francisco Ponce, who's a neurosurgeon with subspecialty training and stereotactic. (Sound Dropped)

#### Dr. Soania Mathur (00:04:41)

It's nice to have you here as well, Dr Ponce. We're also very fortunate to be joined by representatives from two of the companies that make DBS devices. Lisa Johanek is a technical

fellow, medical and scientific affairs scientist at Medtronic. Welcome Lisa. And Steven Carcieri, I hope I said that properly, is a fellow research scientist for the research and advanced concept team at Boston scientific. Welcome Steven. And finally, I'm pleased to welcome fellow patient Marty Acevedo, a patient living with a diagnosis of Parkinson's disease since 2010 who underwent DBS in 2016 as part of her management. Welcome Marty. It's a true privilege to have all of you here with us today to really explore the topic of DBS, over the next, I guess hour or more. I thought it might be helpful to take our listeners on a journey. The journey a patient kind of takes from the time a decision is made to consider DBS, through the procedure itself and the workup that comes ahead of time, and then what comes afterwards. Along with our expert physicians, Marty I hope that you'll also be able to kind of humanize it and give us patient's perspective from your own experience. So, let's start with first defining what we're talking about. Dr. Brontë-Stewart, could you help us understand what exactly DBS or deep brain stimulation is?

#### Dr. Helen Brontë-Stewart (00:06:11):

So one of the ways I like to talk about deep brain stimulation is as a brain pacemaker. So, we all know what a cardiac pacemaker is, and it is a very effective way of correcting abnormal rhythms in the heart. And you can regard deep brain stimulation as a brain pacemaker, which helps us restore normal rhythms in the brain.

### Dr. Soania Mathur (00:06:36):

Great, Dr. Haug, when do you sort of begin to think of DBS as a potential treatment for your patients? At what kind of stage do you start thinking that you'll head down that path?

## Dr. Aaron Haug (00:06:50):

That's a great question and it's really changed a lot in the last five or 10 years. 10 years ago I think DBS was often thought of as kind of a last ditch effort for people that had very advanced symptoms of Parkinson's. And a few years ago even the FDA changed the label of DBS to say that it could be considered as soon as four or five years into diagnosis. As soon as there started to be complications for medications. So, for people that have prominent motor symptoms: tremors, stiffness, slowness, I will start talking about it from as early as the first visit as potentially something that may be on the table for them within the coming few years.

#### Dr. Soania Mathur (00:07:34):

Marty, when did you first hear about DBS as being a potential option for you in your treatment? When did your medical team sort of first recommend it to you?

#### Marty Acevedo (00:07:43):

When they were having trouble with managing my medication which was causing significant dyskinesia. So, it was about six months before I had the surgery. So, in 2015.

## Dr. Soania Mathur (<u>00:07:57</u>):

2015. And what did you think at that time? What was your sort of reaction to being told that surgery would be an option for you?

## Marty Acevedo (00:08:07):

I was pretty surprised, but quickly did some research, did my job finding out what it would mean for me and, bought in right away and started the different types of testing with the therapies and other things.

#### Dr. Soania Mathur (00:08:23):

Right. Well we'll get to that testing. I think that's an important part of the puzzle. Dr Haug, what symptoms does DBS help? When you say you're looking at your patients, like what symptoms in particular is it beneficial for?

## Dr. Aaron Haug (00:08:37):

DBS is particularly beneficial for the core motor function. So tremor, stiffness and slowness. And I counsel people to expect that however they feel when their medications are working at their best, when they're in their best "on state," DBS can enable you feel that way more of the time. On average the research shows by four or five hours more per day. There's an additional benefit which is that some people have carefully controlled medication and DBS can have benefit for tremor above and beyond what is sometimes accomplished by medications.

### Dr. Soania Mathur (00:09:16):

What about dyskinesia? I mean, that's a known side effect of Parkinson's medications. A dopaminergic replace (sound dropped) impact, a negative impact on quality of life for patients to patients? No. Any improvement in these aspects of this disease? Can it sort of help with that aspect of management?

#### Dr. Haug (00:09:36):

Certainly so, in a couple of ways. The stimulation itself can have a beneficial effect on dyskinesias and with some of the targets that can be used in the brain for DBS (sound dropped) medication reduction with the STN target in the brain is if I about 30%. And so sometimes that medication reduction allows an improvement in dyskinesias as well.

#### Dr. Soania Mathur (00:10:07):

Great. We'll talk about those sort of targets that the DBS can access in a, in a few minutes. Dr. Brown D Stewart, we also know that, as Dr. Haug had mentioned that DBS targets mainly the motor symptoms of this disease, specifically tremor, but we also know that non motor symptoms including mood disorders, sleep disorders, pain and that sort of thing could really adversely affect quality of life for patients. So which symptoms sort of are in challenging and don't seem to respond in your, in your opinion?

#### Dr. Helen Brontë-Stewart (00:10:40)

Yeah, thanks for asking the next question. I think this is very interesting because there is new evidence out that's quite surprising. In fact that deep brain stimulation, and this has been studied in the STN actually kind of improve some of the non-motor signs. So, some of the autonomic signs, for instance, orthostatic hypotension. So that's when your blood pressure drops, when you stand up, when you (sound dropped) get better. But there's also some evidence that other aspects

such as orthostatic hypertension, aspects of GI motility and urinary dysfunction actually do improve on DBS. Interestingly pain, musculoskeletal or dystonic pain can also improve on some aspects of sleep disorders. I think it's also very interesting that the freezing of gait that improves with medication can also improve with DBS. However, over the long-term it seems that there's a more of a medication and DBS refractory freezing of gait that can kind of appear. Things I think is very important when we talk about timing is that the things that don't improve tend to be those symptoms that people may experience in the more advanced stages of disease such as cognitive impairment, a difficulty with swallowing, difficulty with speech. And unfortunately, there isn't much evidence that deep brain stimulation can improve those. So, it really begs the question with all the evidence that we have now of some of the other symptoms that improve as to the timing. And I think that really also feeds into the dyskinesia and motor fluctuations scenario.

Dr. Soania Mathur (00:12:30)

What about falls, Dr. Brontë-Stewart?

#### Dr. Helen Brontë-Stewart (00:12:32)

Falls are a really interesting aspect, and I think one of the reasons that there's so much variety of data about falls is that you can fall for many reasons. So just kind of simplifying it. The overall evidence has suggested that maybe people can fall more after having STN DBS, but I think the variation of factors going on, the aspects of falling that are going to be difficult to improve with deep brain stimulation of those that have a great contribution of cognitive impairment to them, which we know is a, a primary risk of falling. There's something that we call retropulsion. So there's a an aspect of balance problems in Parkinson's where you tend to have your center of mass going backwards and, as you know, you don't have much of your feet backwards to hind you to support you so you, you're likely to fall backwards. So we call this the limit of stability. And if you're made more mobile by the DBS, unfortunately you can pop off that limit of stability more easily and faster. And you may not have the reaction time to pull yourself back. So, the full aspect I think is quite complicated. You can't just, it's like balance. You can't sort of say one word and understand how everybody falls. It's very different.

#### Dr. Soania Mathur (00:13:56)

Very different. Dr Foote, what criteria, when you're sent a patient do you use to determine who's eligible for DBS? Like what type of patients do you find are the best candidates? Who tends to have the best outcome?

## Dr. Kelly Foote (<u>00:14:11</u>):

Well I'm assuming we're limiting this to Parkinson's disease and not other indications for deep brain stimulation. So, within a diagnosis of Parkinson's disease I think is an important place to begin. There are things that look like Parkinson's disease that don't respond well to deep brain stimulation or typically to dopaminergic medications that Parkinson's patients typically benefit from. So, one predictor of (sound dropped) is and also unfair is those patients who get the most dramatic benefit from the medications are the same patients who tend to get the most dramatic benefit from deep brain stimulation therapy. The patient who has Parkinson's disease, that responds well to the medication is a good place to start. And then there's a complex risk benefit

analysis that ensues. That for us is a multidisciplinary thing that I'm sure we're going to talk about it a little bit more in a while. But basic things are diagnosis of Parkinson's disease, responsive to medication and you know, no excessive risk of surgery. And so, if you are 90 years old and you had a heart attack six months ago and you're on blood thinners and you weigh 500 pounds and you have diabetes and you smoke, then you're not a good candidate. So just listed off some of the things that we look at.

#### Dr. Soania Mathur (<u>00:16:10</u>):

That's, important for sure. Dr Ponce are there certain criteria that exclude patients from, other than the comorbidities that Dr. Foote talked about and not responding to medications and not having diagnosis in the first place? Are there other things that you look at that would make you a little nervous or consider? Not offering the, the treatment to, to a patient.

### Dr. Fransisco Ponce (00:16:34):

One of the things I really look at with a patient is insight. How much insight they have in their condition and their journey with Parkinson's, with a neurologist. Depending upon the expertise and the comfort of the neurologist, what it means to have a medication responsive symptoms versus medication refractory symptoms, what their on state is when they kind of look at that profile of, this is what on is, this is off, these are the fluctuations. And they're like, yeah, that's right. I want to capture that state. And that's where I want to be and that's where I'm going to have brain surgery. And I think that insight really depends upon kind of where they're coming from with their neurologist and how they enter neurologists has communicated and informed them what Parkinson's is and what medication responsiveness is and this notion of motor fluctuations and those are the patients who do really well. I think that a lot when a patient comes in and says, my neurologist referred me to you because medications don't work. And I'm like, well, that's not a real starter. And, medications are going to affect Parkinson's. And so, this kind of intuition on the patient's part, that medications don't work, that's why I'm here. You know, got to take a step back. And I think that that's where that kind of journey toward DVS is so critical in the education. Because I think if they go to the first meeting with a neurosurgeon and they start talking about motor fluctuations, but they don't come into that appointment already with a sense of what this is, what this means to have Parkinson's disease and to be at the stage of Parkinson's, I think those patients don't have a right expectations per se. And that's what we try to navigate them toward in their journey toward DBS.

#### Dr. Soania Mathur (00:18:21):

Right. So Dr. Haug, before you send a patient to Dr. Ponce or Dr. Foote and there's a significant workup that needs to happen before then, before your patients undergo DBS surgery to make sure that the procedure makes sense for them and they have no factors that would be problematic. Or if you had to be cautious about. What workup do your patients undergo to determine whether they're eligible or not eligible. And I'm sort of thinking also about factors like cognition or mood disorders and that sort of thing. If you could take us through that, that'd be great.

## Dr. Aaron Haug (00:18:55):

There are multiple diagnostic tests and evaluations that are part of the evaluation process. It's important for a patient to have what's called an "on-off evaluation" where they at one point are in the clinic and that are best on state with medication and they go through a full Parkinson disease symptom rating, scale and examination. And we get one number there. And then on a separate occasion, the patient comes into the office with no Parkinson medication in their system, whether that's 12 or 24 hours off of medication. And we look at the difference so that not just the provider team but also the patient and the family can see, well this is really what difference we're getting from medication. And we want there to be a significant medication response. So, in addition to the "on-off" medication evaluation, we typically have a baseline MRI scan of the brain to evaluate the structure of the brain and detailed neuropsychological testing, which is several hours. Kind of like when high school students take the SATs. This is a detailed cognitive testing to establish a baseline to look for any red flag areas that may suggest a baseline, significant cognitive impairment that might give us some pause before proceeding further with the surgery. In addition to those, which are kind of the three most critical pieces, often there are meetings in advance of a final determination or decision about surgery with occupational therapy, speech therapy, physical therapy, multiple disciplines to have as clear of a picture of where we're starting from and as clear of an understanding of where we hope to get with DBS.

## Dr. Soania Mathur (<u>00:20:42</u>):

All right. Marty, how did you find that workup? I know I went through it not that long ago. I haven't had DBS and I found the off time was pretty difficult to tolerate. Although I know it's absolutely necessary.

### Marty Acevedo (00:20:58):

Well, the psych testing was pretty. And so that was four to five hours of testing and very difficult reasoning and cognitive skills. But it was important to do that. PT, OT and speech were equally as important. Being off for me wasn't that much of a problem because I was very, very responsive and receptive to cover up of Levodopa, which is why I have the dyskinesia, so that wasn't as big of a problem for me. The workup was necessary. I think the main thing that that needs to happen with a person considering DVS that have to have reasonable expectations.

## Dr. Soania Mathur (<u>00:21:40</u>):

Right. Yeah. That reasonable expectations I think is, is really vital for sure. Dr sir, we talk again about quality of life being the primary goal and often DBS for people in the general community, they kind of consider it a sort of a later option later in the course of your disease. But then there's also been some talk about DBS having better outcomes if done earlier in the disease. Could you sort of explain the current thought on the timing of DBS for patients?

#### Dr. Helen Brontë-Stewart (00:22:08):

Yes, absolutely. It gets back to the things we've been talking about. So, Dr. Haug said, you know, when the patients develop these motor fluctuations and dyskinesia is, that's really a turning point in that disease because at that point the medication becomes not only your friend but your enemy. And so, it becomes more difficult to find that balance of what we call good on time without dyskinesias. Now, what's, we've really been lucky in that we now have evidence to

tell us that in fact people do better when they have deep brain stimulation. And this, again, this was a European study and it's called the early STEM study and it was done only in the STN, but it showed us that in fact if people were referred within three years of developing dyskinesia and the meantime was 1.8 years, they then randomize them to STN DBS plus best medical therapy or best medical therapy alone. And then looked at the outcomes with the primary outcome being quality of life after two years. And they found that the combined therapy was better than medication in quality of life in motor score and non-motor scores and in the medication complications. Now you have to remember that that study wasn't a sham surgery, so perhaps people were expecting to get better with DBS. But it still provides us with really good evidence that in fact, we shouldn't be waiting till people develop those symptoms such as cognitive impairment, difficulty swallowing, which don't respond to DBS. But we've spent all those years when we now have evidence that they could have done perhaps better with combined therapy, and they're more likely to have fewer risk factors and overall morbidity from the procedure. So I think, I think we've always, as movement disorder specialists and neurosurgeons have said, we've always encouraged people to be referred a little earlier, but now I think we have very good evidence to tell us that in fact, that would be a really good idea if people were referred a little bit earlier. That was a mean of seven and a half years of duration of Parkinson's disease overall as opposed to the oldest studies, which was 11 to 14 years. So a good four to five years prior.

### Dr. Soania Mathur (<u>00:24:37</u>):

This kind of ties into one question that a listener had, and they are asking you to DBS impact Parkinson's disease progression, per se

## Dr. Helen Brontë-Stewart (00:24:46):

Do you want me to answer that? Sure. So, let me preface this by saying, because a Dr. Foote is going to talk about this. There is evidence in research that we are doing to suggest that in fact for the cardinal motor signs, DBS can alter the progression of these. There is also preliminary evidence that was published in our neurology journal by the group at Vanderbilt who did a very long washout period of medication and deep brain stimulation. They were actually looking at operating for people even before they got to the stage of dyskinesia. And although there was no difference between medication and DBS plus medication on the outcome when they washed people off medication and DBS for a week. So they're in the hospital. They found that the people who had had deep brain stimulation, that trauma had not progressed to the other side of the body nor got worse, but the people who were on best medical therapy, their tremor had progressed. So I think you have to take this as very early preliminary studies, but it, it is out there that there's some evidence that things might be slowing down.

#### Dr. Soania Mathur (00:26:04):

It'd be much easier if we had a biomarker to confirm that.

#### Dr. Helen Brontë-Stewart (00:26:07):

Well, we do. Yeah, we do. But you have to record it. But yes, we do.

#### Dr. Soania Mathur (00:26:13):

Yeah. Dr Foote, did you want to add anything to that?

## Dr. Kelly Foote (<u>00:26:16</u>):

Well, I would just say the evidence is inconclusive currently about that. So I don't ever promise that deep brain stimulation is going to alter the course of Parkinson's disease. There is some interesting evidence, I actually was involved in a research project 25 years ago with some monkeys that we operated on in France that that was suggestive of a beneficial effect in terms of altering the course of the disease. However, this study that Dr. Brontë-Stewart just cited, there's a pretty reasonable expectation that when you implant a DBS electrode in the brain there is an impact from doing that. That will cause a lesion effect. Before we did deep brain stimulation, we used to make lesions in the brain in these same regions. And there is a small, we call it a microlesion effect that would be therapeutically beneficial just from implanting the DBS lead. So, finding a difference between the washed-out DBS patient and the patient who has never had DBS does, doesn't surprise me.

### Dr. Soania Mathur (00:27:36):

Okay. So, say now we have a patient that has qualified and meets all the standards that we think are a good candidate for DBS. There are a few companies that sort of make DBS systems. Lisa and Steven, if you don't mind, chiming in at this point. Maybe Lisa, you can go first. Can you explain a little bit about the type of device that your company makes and what sort of battery technology you may be using, that sort of thing?

### Lisa Johanek (00:28:06):

Sure. I'd be happy to. So as Dr. Brontë-Stewart mentioned earlier, DBS is essentially a pacemaker type device. So one of the main components is a neurostimulator or a pacemaker type device that gets implanted underneath the skin, usually in the chest area. And any other main component are leads or small wires that are implanted into the brain. So the pacemaker sends small electrical signals to areas of the brain. There are different types of those pacemakers and the two main types are either rechargeable systems, which means that you would have to continuously recharge them, maybe top them off once a week and the duration of recharge will depend on the different parameters that are being used. And then the other main type is non-chargeable device, which means that you don't have to recharge it, but you may have to, the battery will wear out at some point and you would need to replace the device. So those are the two main implanted components. And then you would have external components to like a programmer that looks somewhat like a cell phone or maybe even based on cell phone technology that lets you turn the system on and off or in some cases change the settings of the device.

Dr. Soania Mathur (<u>00:29:22</u>): All right, Steven?

#### Steven Carcieri (00:29:27):

Yeah, so our system has the same components that Lisa described. So, all DBS systems, will have those common components of the battery and the remote control for controlling stimulation. A few other pieces that are interesting. would be the actual electrodes that are in the brain. So, some of those electrodes can be designed differently and that's one thing that makes our system a little bit different is that we have some smaller electrodes and then there's software that can be

used for programming the device and that can allow the doctor to see how much stimulation they are delivering to the brain so they can they can control how much electrical current is being delivered and then visualize it relative to the patient's anatomy. So those are just a few features that I think are in addition to what Lisa mentioned already.

## Dr. Soania Mathur (00:30:36):

Great. Thank you. I know Abbott also makes a DBS system. Does anyone here on the panel have experience with that one in particular and they can say a few words? about the Abbott system, Dr. Foote or Dr Ponce or Dr. Brontë-Stewart.

## Dr. Fransisco Ponce (<u>00:30:56</u>):

We've implanted a few of those. I think, the directional lead is something that's been very exciting. That's something that we have with Boston and with Abbott. The rechargeable technology continues to improve. I think we've seen that with some of the newer devices, very kind of patient friendly recharge system. 15 years, that's what both Medtronic and Boston scientific have, has been a real appeal. So, we've seen a, a draw toward recharge technology in my practice at least, but for some people, it's very cumbersome. I think that's something that Abbott has as a solid non rechargeable generator at this time. But I think that the combination of the user interface, the iPhone or whatever, the directionality I think those are two things that we're seeing in the, in the newer implants.

#### Dr. Soania Mathur (00:31:49):

So, it seems to me that, it's going to be a matter of what patients want, as well as probably surgical comfort in using certain products. So, a lot seems to be available as options for patients, which is great. Dr. Ponce, could you maybe tell us what the surgical prep involves? Like how once they come to you and you've decided you're going to do DBS, do they go on for more testing? Do they go on a wait list? How does it work at your center?

### Dr. Fransisco Ponce (00:32:16):

So yeah, I emphasize to patients, the three steps, the three keys to good outcomes. One is patient selection. Number two is safe and accurate surgery. And number three (sound dropped) falls into step two. So that's why having the right neurological care, the right neurologist is so key to the success of this therapy. And so with number two, with the safe and accurate surgery, once we've kind of checked the boxes off of neuropsychology, on-off testing for Parkinson's disease and that's usually where they are, once they get to me, we're pretty much almost ready to go. And in fact, with education, my experiences after about 15 minutes with a patient and like I said, do you have any other questions? And they'd say, when can you get this done? I mean, this is an amazing therapy and it's underutilized. So, the journey that patients take to DBS is impressive, and I think that there's a lot of opportunity, with how to kind of adjust that journey because they get very enthusiastic and they can't wait. So, what we do is at that point in my practice, we basically set them up for an MRI. A three-dimensional MRI, so we can visualize targets directly. And we're able to initiate the scheduling process at that point. And typical lab to preop testing before they go to surgery. But we've done enough with the kind of the pre neurosurgical consultation workflow so that by the time they see me, we could get them on the next week. So the wait list, I think we're usually about four to six weeks. And if you'd get insurance

authorization and things like that, that's usually the kind of a reasonable interval between, the neurosurgical consultation and the actual surgery.

## Dr. Soania Mathur (00:34:01):

Is that sort of a national kind of average wait time four to six weeks in the US

## Dr. Fransisco Ponce (<u>00:34:08</u>):

I think so. I think it depends upon the bandwidth, and I think that in academics, some people may do fewer days of surgery a week or things like that. I think that, in the US, patients do kind of have that expectation to, once they're ready to go, they want to go. They may wait, years for it. But when it's time, they want it yesterday.

## Dr. Soania Mathur (<u>00:34:33</u>):

We wait a little longer here in Canada, but we get to it eventually. Dr Foote, can you give us an idea of what DBS surgery actually involves for the patient, the logistics of it, how long it takes, when you're in there, how long patients usually stay in hospital afterwards, that sort of thing.

## Dr. Kelly Foote (00:34:52):

Well interestingly, it's somewhat variable from center to center. What the actual operative experience is going to be. There are a few different ways that deep brain stimulation they performed and some different schools of thought about what the best way is to do this to surgery. My assumption is that every neurosurgeon who does deep brain stimulation surgery is doing it the way she or he is doing it because they believe that they're doing their best and that the way they do it is going to produce the best outcomes for their patients. So, I wouldn't be overly concerned about, variation in technique. Although I will say as with most things and you'll hear this advice if you ever ask anything about any kind of surgery. You should ask the surgeon if he's done it before and, the more a surgeon and frankly, the more a center does deep brain stimulation I think the better, on average the patient outcomes are going to be. So, I guess the point of that is you want to make sure you're going to an experienced DBS center which is more than just a surgeon. I would say my involvement in the process is only responsible for maybe 25% of the outcome. And I take all the credit, but I'm not the one producing the outcome. The preoperative work in choosing the right patient, choosing the right target in the brain, choosing among various ways of doing the operation to minimize the risk and maximize the benefit for each specific patient. This sophisticated workup actually primes us to get a good outcome much in a higher percentage of the time. And frankly the difference between a center that gets 70% good outcomes and a center that gets 90% good outcomes is not observable or is not easily seen by the casual observer. So going to an experience center is really important. So as Dr. Ponce said, I will echo his comment that the interoperative part is only a piece of it. The preoperative part, as I mentioned, very important interoperative, making sure that the DBS lead gets into the right place in the brain with the fewest complications possible, and then managing the patient and the device postoperatively is critically important as well. So, it's a little bit unusual as surgeries go because it does require an entire team, a center approach.

## Dr. Soania Mathur (00:37:59):

No, I agree. I'm married to a surgeon, so I know that the experience of the surgeon is obviously important, but it's, it really is a team approach. If one member of the team is weak, it makes it hard for everybody. Marty, what was your experience like on your day of your surgery?

## Marty Acevedo (<u>00:38:13</u>):

Well, I went into the hospital. I was supposed to be in the first case that morning, but someone came in with a battery that had to be replaced, so I was bummed. I was in and the actual operating room for about six hours. I had an awake type surgery, but I was really pretty sedated. Conscious sedation woke up with in a recovery room and went to the neuro ICU where they did neuro checks all night. The next morning I was evaluated by PT and my surgeon and was discharged. So I was home by noon, the day after surgery. So that was pretty smooth. I felt great after surgery, no pain. It was pretty easy for me. You know, other people, my husband waiting was a little more difficult, but it was an easy day for me.

## Dr. Soania Mathur (00:39:00):

That's amazing. That's good to hear. And Dr. Ponce, Marty mentioned, awake, I know that DBS can be done when the patient's asleep or awake. Who makes that decision and why is one chosen over the other?

### Dr. Fransisco Ponce (<u>00:39:14</u>):

I think it's like Dr. Foote said you know, we develop a way, we know what our outcomes are. And we get comfortable with saying with, in my case, the structural anatomy and knowing that if I hit something anatomically, where we're going to get the results that the patient and the neurologist are expecting. I think the bark is worse than the bite for awake. I've heard Dr. Brontë-Stewart speak many times and I suspect her patients kind of just charge into the OR, and they're ready for awake. And I think that patients tolerate very awake very well. But I think kind of as I've looked, in Arizona at Journey kind of, it's like walking through the line for a roller coaster where like the corkscrew and the double, and there's a self-selection that takes place before they actually get onto the roller coaster. And so, I think that some patients, I think once they're there, awake is not a bad experience and it can be very efficient. And it's very safe and when interpreting the recordings and the testing can really guide you to the sweet spot. But I think that I do think that there's a self-selection that takes place in terms of patients who don't only elect for holes drilled and permanent implants, but also the experience. And so, I think I started doing asleep in my first year in practice after having been trained in Toronto doing awake surgery. And I think if I had been practicing another five, seven years, doing awake, I might've been less kind of, adventurous to try something different. Knowing that my neurologist, my patients are doing fine. So, I think a lot of it is kind of how you were trained and kind of at what point in your career. I know surgeons, in their sixties, very efficient and they're awake, they're not going to change it and, and their patients are happy, the neurologist is happy. So, I think like Dr. Foote has said, I think that we're kind of getting to a point where the key is a competent surgeon who's got experience and not so much, which one works better than the other. So, I kind of made a transition to all asleep about three years ago just because in my conversation with patients, I think the awake versus asleep conversation, was more misleading, I felt. And I'm very Frank with them in terms of kind of why we do it that way.

#### Dr. Soania Mathur (00:41:43):

Okay. So, yeah, that makes sense, actually, whatever you're comfortable with makes sense. All surgical procedures, Dr. Foote have risks associated with them. So, what are some of the risks that you talk about with your patients when they're going for DBS?

## Dr. Kelly Foote (<u>00:42:03</u>):

Yeah. Interesting question. I would say the biggest risk of deep brain stimulation surgery may surprise you, but it relates to something that came up earlier and that is failure to meet expectations. And that's why, the patient who goes through our center and as part of the evaluation for deep brain stimulation is going to meet with 10 different specialists. And every one of them reinforces, this is what we expect, and each of these patients, each of these specialists that they see is an expert in some domain of Parkinson's disease, like a physical therapist or an occupational therapist or a neuropsychologist who measures cognitive function. But the reason I say, they're are also DBS experts, so each of these people has evaluated hundreds of patients both before and after DBS surgery. And so they know what, what to expect and they can educate the patient, with regard to your walking problem, I've seen lots of patients like you and here is what I would predict you're going to see after surgery. And that's so incredibly helpful. And postoperatively in the early days when we used to, when we started doing deep brain stimulation, we would have outcome measures that we would declare a success if the UPDRS four went from something to something. And there were times when we did such a poor job of setting the patient's expectations that we would do the operation, we would get exactly the outcome we expected and we would look at the numbers and we would high five each other saying, "Oh, this is a great operation." And meanwhile the patient was expecting that this one thing that they cared about the most was going to get better and it didn't. And if they had asked us specifically, we could have said, "Oh, that doesn't get better. You need to factor that into your decision making and you need to understand that that won't get better. We can predict that it won't." So, so number one, risk is failure to meet expectations. So, we spend a lot of time and energy on setting expectations. Then the other risks, I think the things that people worry about are the catastrophic complications. Fortunately at good centers, those sorts of complications where a brain injury occurs because it's brain surgery, there is always the risk that you could have an injury to the brain, a stroke or a hemorrhage that could result in you ending up worse off after the operation than you were before. Fortunately, though, at good centers, that's less than 1% of the people who have this operation. And rightfully so because this is elective brain surgery. And if those sorts of catastrophic events happened with much more frequency than that, then this would not be an acceptable risk to take. So, I would say serious brain injury is a risk, but it's a very low risk. Risk of worsening of balance, Risk of worsening of swallowing, risks of worsening of cognitive issues in patients who are having cognitive issues. These are all things that we try to quantify up front and predict postoperatively. And these are all risks that we can mitigate by changing the way we do the operation. For example, sometimes in our preoperative meeting when we're discussing a certain patient's case the neuropsychologist might say, "this patient is already having problems with word finding. Verbal fluency is problematic. And I can predict based on our past experience that if you use this target in the brain, that's likely to worsen a little bit. And in this particular patient, if it gets worse, it really could affect their ability to communicate and their quality of life. So, my recommendation to you, Dr. Foote, is you should do a different operation. You should put, put the DBS lead in this other target to protect this patient from that risk." And so that's very helpful to me.

#### Dr. Soania Mathur (00:46:36):

Right. Dr. Brontë-Stewart, we've talked about that before when we were talking about the placement of the leads, you know, whether it's the subthalamic nucleus or the globus pallidus interna. And how do you decide which area to target or to recommend targeting for your patients?

#### Dr. Helen Brontë-Stewart (00:46:54):

Well, I completely agree with Dr Foote. I think this is a discussion that occurs and the DBS, what we call surgical review board where everybody is discussed at length, every person who wants DBS and among all the members of the team. And there are centers who believe that, the one target, the GPI might be a bit better for people who have mild cognitive impairment or perhaps with speech, and there are other centers who mainly implant in the subthalamic nucleus. So one of the differences that I don't think we've mentioned up to now is when you implant in the subthalamic nucleus, as I think Dr Haug said, you can reduce your medication and that is often how the dyskinesia is improve. Whereas if you implant in the globus pallidus the dyskinesias, can improve directly from the effect of the surgery itself, from the lead placement, but they don't necessarily reduce medication. So if you have something that is a side effect exacerbated by, or induced by, medication and that is a goal for the patient to come down on their medication, then you may be thinking that you may want to target the subthalamic nucleus. And I couldn't agree more with Dr. Foote about this idea of aligning expectations. It's so important to have those discussions with the patient because sometimes things come up though that we want even realizing.

## Dr. Kelly Foote (<u>00:48:32</u>):

Can I just expand on that a little? I started the practice probably, 20 years ago because I had this early experience of failing to meet expectations. Every single patient that I do deep brain stimulation operation on, I have a conversation with them in which I ask them to list the symptoms that bother them the most in order of importance to them. And we make a list together of the three to five things that they are really hoping will get better. And they say, "this is the thing that bothers me the most. If this got better, it would most improve my quality of life." And then when we rank those things, and then in our discussions, in our planning meeting, we can say, for example, if problematic dyskinesias when I take my medications, is the number one, number two a problem on that patient's list, I am much more likely to select the GPI target because in my experience, when I stimulate in the GPI, even in very severe dyskinesias I can almost always suppress those problematic movements. So, having that sort of approach I think is very helpful.

#### Dr. Soania Mathur (<u>00:49:54</u>):

So, can you solve those dyskinesias more with GPI than the reduction of medication. So, there's a greater degree of improvement with targeting the GPI compared to reducing medications?

### Dr. Kelly Foote (00:50:09):

In my experience, yes, it's more reliable.

#### Dr. Soania Mathur (00:50:14):

Okay. Very interesting. Dr Ponce, we hear sometimes about bilateral DBS. And do you usually do it? I mean, how often do you do it on both sides and what would be the reason too or is that just something that's not done?

#### Dr. Fransisco Ponce (00:50:35):

So over 95% of what I do is bilateral, and I know Dr. Foote has a lot of data and experience doing unilateral as well. So, I think so much of this journey is really informed by, their kind of lifetime relationship with their neurologist, right? I've one neurologist who kind of may go with unilateral and the patients have such trust in her that they don't second guess, they roll with it, they're good with it. Parkinson's is a bilateral disease and I think that my goal for my patients is to kind of get them in, get them out, get them back in the game, so not to have them tethered to more surgeries with me and we can get that second lead in. Usually we're doing the dominant side first anyway, so we can do, you know, left side of the brain for the right side of the body and for speech. So we can place that second lead accurately and efficiently and then they're kind of done with the brain surgery part. And we're not looking at the, six months later saying, Hey, do you guys want to come? You want to come back for another operation? And I've had a number of patients who came in saying, Hey, it's all in one side, just want one side. And then six months later they're like, I'm here for the other side now. And so again, sort of approach of how to most efficiently, effectively bring this therapy that's been around for decades to those patients who stand to benefit from it. My tendency, because it doesn't take that much longer to put that second lead in and the desire of patients and neurologists. My practice has really been one where we do more than 95% bilateral.

## Dr. Soania Mathur (<u>00:52:17</u>):

So, you can place both leads in, and if the one is not needed, you can program that later. You can program the leads differently. That's correct?

## Dr. Fransisco Ponce (<u>00:52:27</u>):

Right. Yeah, exactly. And that's what we'll do if they really are unilateral in their symptoms. Again, sometimes I'll have a neurologist who does mostly bilateral and sometimes, she's says let's do just a unilateral. Well that's a big deal if she's saying let's go with that. But if they have any kind of, you know, on the, "on-off" testing when they come off medication, they do have the choice to kind of leave that side off and it's in reserve so that again, 10 years later they're not coming back for another surgery when that side becomes bothersome enough.

## Dr. Soania Mathur (00:52:59):

Yeah, that makes sense, actually. Marty, I mentioned about the programming, what has been your regards to that experience between when you had the surgery, you went home the next day, and then how long before you went in for another visit to look at things and programming. How did that work for you?

## Marty Acevedo (00:53:26):

Well, I had an immediate response before I thought it was ever programmed just from the lesion effect that Dr. Foote mentioned. I was able to reduce my medication by half before I ever had the generator placed and programming. But that programming was done two weeks later. I'm predominantly symptomatic on my left side, so the right side was programmed, the left side is not. It's on very minimal settings still, after four years. I've had very good response to programming have been doing very well. Just some problems of late with changes in my movement disorder specialists and their different preferences and such, and that's caused a few issues that we're working through and I'm doing very, very well now.

## Dr. Soania (00:54:05):

That's great. What's improved? Like what symptoms have improved for you specifically and what symptoms remain challenging for you?

## Marty Acevedo (<u>00:54:19</u>):

Well, I don't have dyskinesia anymore. That was the big thing for me. My freezing of gait has improved. I think that was partially through work with physical therapy as well. Interestingly, my balance has improved. I haven't fallen since before surgery and I was falling before. And this wasn't mentioned, but I've had some improvement in my cognition since the surgery itself. So overall it's changed my life and gave me my life back and allowed me to live my life to the quality I was excused to and to exercise, which helps to other symptoms with Parkinson's and perhaps to delay the progression of this disease.

#### Dr. Soania Mathur (00:54:56):

That's amazing. That's wonderful to hear. Dr Foote, Marty mentioned the programming sort of process. How does that work? Who does it, you know, why does it seem that some people have an easier time like Marty, but there are stories from our community where people have had a much more difficult time finding the right setting. And if you just explain a little bit about what that process is like for patients.

#### Dr. Kelly Foote (00:55:20):

Well, I'll start by saying, if I'm honest about this, the patients who have an experience like Marty's where they go in for programming, everything goes relatively smoothly. It's not a complicated process. After two or three visits, they feel like they're getting great benefit. Those are patients in whom the DBS leads are well positioned in the brain. And frankly, the difference between the patient who has that frustrating experience of, I've been going back for programming sessions every month for the past year, and I still don't feel like I've got the benefit that we all expected going into this. Those are patients frequently for whom the DBS lead is imperfectly positioned in the brain. And no amount of expert programming can overcome an anatomically poorly positioned DBS lead because we just can't affect a circuit that we're trying to effect, stimulating in the wrong place. Now the directional leads offer some promise of improving that situation. But I think it's important to understand that the difference between success and failure in this operation can be as little as a millimeter and a half to two millimeters in the brain. So, you got to get it right in the right place. Now to the second part of your question,

sorry. At our institution we implant the DBS lead, we implant the pulse generator in a separate outpatient procedure on the day that the pulse generator is implanted, we activate the DBS system at what we call quick and dirty programming settings. Based on our observations intraoperatively we can predict which of the DBS contacts is likely to be beneficial. We don't spend a lot of time with extensive programming on the day that the post generator is implanted because the patients are coming out of general anesthesia and they're, not quite normal. I don't know if you've ever tried to collaborate with a drunk person, but it's a collaborative process, programming is. So, we program them just so they'll get some preliminary benefit and then within a week or two, they have their first appointment at the Fixel Institute at the programming center with people who do it all day every day, and they have a more formalized a programming session. Dr. Okun who's the main neurologist that I work with tells the Parkinson patients to expect up to six months of monthly visits for iterative programming. They give you some settings and you go home and try them out and then you come back and make adjustments.

#### Dr. Soania Mathur (00:58:34):

Right. Dr. Brontë-Stewart, is that what you find as well in terms of frequency of visits every six months or so once things are stabilized at your center as well?

### Dr. Helen Brontë-Stewart (00:58:43):

Yeah, so we do things slightly differently. We don't program right away. We wait for three weeks also until, so fluid shifting has settled down in the brain, partly because sometimes if we start to early, the patient may have some symptoms that already more to do with the brain still settling down. They also have often a microlesion effect. So, we wait for things to settle down, treat them with a normal medication. And then we do a very extensive programming where we do what we call the therapeutic window on each contact or electrode of both leads. So, we do this with quantitative testing, so we find the minimum intensity current or voltage at which they get some benefit for each electrode. And we switched from side to side so that we don't get sort of a cumulative stimulation on one side. And then we go back, and we go up on each electrode and we find the current or the voltage at which they get side effects. And so, what we have what we call our roadmap that is very useful for the rest of time actually. And so, we know exactly the therapeutic window, the intensity that they got benefit and the intensity they got side effects. And we can then choose our leads that we'll start with. But I think one of the most important things that many of us learned, as we got more experienced with DBS is how to manage the DBS and the medication. And so, I'm going to talk specifically about subthalamic nucleus, deep brain stimulation. But for instance, for the person who's had a lot of dyskinesias before surgery. Just the STN DBS itself early on can promote dyskinesias. So you have to be very careful. You might have an electrode that has a good therapeutic window and you found that say two milliamps or two volts that the patient actually really, that tremor was gone, and they felt fantastic. You can't necessarily go there right away. So you have to back off, and then what I say to patients is I'm doing this kind of see-saw where over the next three to six months I will be gradually changing over to being mostly DBS as opposed to mostly medication. But you can't just do that right away. And we know there are several problems. For instance, if people withdrawal their medication too fast, they can then develop what a nasty case of depression that is basically only treatable with dopaminergic medication. And this is mainly seen with dopamine agonist therapy. So we've learned that we have to do this very gradually. And then there's another aspect, which is

tremor. So, tremor will go away when we do stimulation in the operating room. It'll be fantastic. It's exciting for the awake patient and the whole team to see the tremor just go away and then it'll go with initial programming. But I always warn people that for the first three to six months it can come back, but that's not to get worried about. It's that it just seems to take some time to really entrain those circuits. And then after about three to six months, different for every person, then the tremor really settles down, and it's amazing how there's just this period at the beginning where you have to be very, very cautious. If you go too high, too quickly, the next day or the day after, it doesn't happen right away. The patient will call and say, I'm so dyskinetic, I can't even stand up or sit down. And so, it's very important to take this very gradually and manage the medications and the DBS together.

## Dr. Soania Mathur (01:02:20):

Right. That makes sense. Dr. Haug there's couple of questions about after the DBS procedure and one is that, does speech become a problem after DBS?

#### Dr. Aaron Haug (01:02:39):

Yeah, speech can sometimes be a problem before DBS and as has been commented on earlier, knowing what the speech function is at baseline is an important factor. But speech issues after DBS can relate to a couple of different things. It can relate to the lead itself and some of the structures that are passed through as the lead is getting to the target, which is kind of in the center of the brain. And then separate from that or in addition to that, sometimes it relates to the stimulation that's being transmitted through those wires. And so, if a person is experiencing speech difficulty after DBS, then there are sometimes, a process of trying to figure out, well, is it something structural from the leads being where they are or is it stimulation induced? And sometimes that involves a period of days of having the stimulation turned off to see if the speech difficulties are effected by having it off.

#### Dr. Soania Mathur (01:03:37):

And what about cognition, Dr. Haug?

### Dr. Aaron Haug (01:03:40):

Cognition is something that, it's interesting, Marty to hear you say that you feel like your cognition is better after surgery. I wonder whether that might be an effect of medication adjustments. Cognition after surgery, some of the research from 10 or more years ago shows that potentially one of the targets, the STN may be a little bit harsher on cognition than the GPI target potentially is. And it's particularly one of the aspects of thinking and memory that's related to speech, lexical fluency kind of thinking and speaking off the top of your head that can sometimes be negatively affected. And that seems to be in most cases a structural issue from the presence of the lead rather than the impact of the stimulation being given through that lead.

### Dr. Soania Mathur (01:04:37):

Are there any markers that you look for, any things on history that you would look for to say that this person would be at higher risk for these complications?

#### Dr. Aaron Haug (01:04:46):

That's really where the baseline neuropsychological testing comes into play. We'll particularly look at some measures of speech related to what we call semantic fluency. Being able to answer how many animals can you think of off the top of your head in 60 seconds? That sort of test. If someone doesn't do great on that before DBS, then that's one of the potential reasons that we would consider one target versus another. Or also just know in advance that there may be some cognitive issues that could potentially be worsened by surgery.

### Dr. Soania Mathur (<u>01:05:23</u>):

Yeah, it's funny, those tests are often harder when you're in the moment, compared to when you think about it ahead of time, I must say. Dr. Brontë-Stewart, what treatments do patients have that have had DBS and it no longer seems to be having the same effect that they had hoped it would have. I mean a years down the road. Are there other treatment options that you would say are available to those patients currently?

#### Dr. Helen Brontë-Stewart (01:05:49):

Oh, that's a great question. So currently many of the problems that patients experience as the disease progresses are problems or symptoms that are coming from what we call other networks. So I always tell people this brain pacemaker is local therapy. It's only going to be affecting the circuits that it's sitting in. It's not a cure. It's not going to, it's not going to cure Parkinson's disease. And so as the disease progresses, some of the signs that people develop such as cognitive impairment as we've talked about are not those that are necessarily involved in the motor sockets. And so people may experience difficulty with cognition. And one of the interesting aspects is those circuits also may be involved in postural control and some aspects of gait. And this is specifically, I'm talking about the [inaudible] network and there's a lot of research now going on looking at that network as possibly another target or deep brain stimulation. t's not evidence based yet. It's not available. But I think people, as we have more understanding with some of the really advanced imaging that's being done such as this [inaudible] modeling, I think gets back to something that Dr. Ponce was saying, is that we now know quite well exactly where in these small structures, the best site is for placement of these leads. So, when you have very accurate targeting and you can go there. However, we also know that there are some signs that may develop early on that are not amenable to DBS in those motor circuits because they are coming from problems in other circuits. So, I think it's very, very important, and this gets back to Dr. Foote's statement about align expectations. To understand that Parkinson's disease is a system wide disease in the brain, unfortunately. And it can, as it progresses, it can affect other circuitry. And I think that's probably one of the biggest reasons that people find that they're not doing so well after a while.

### Dr. Soania Mathur (01:08:02):

Right. And that ties into actually, one viewer's question and I'll pose this to you, Dr. Ponce, they're asking whether the leads can be moved once they're placed. Is there any way, if, if you find that maybe they're not getting the most benefit from where the leads are placed, is that just an intraoperative or is there an approach that you use postop?

#### Dr. Fransisco Ponce (01:08:24):

Yeah so, we were talking about complications and risks and there's kind of four things that I kind of keep my eye on as I swing for the fences with DBS. Where I think like a lot of the surgical issues can be addressed and that's making sure the integrity of the circuits is maintained that we don't break the circuit up on implant, bleeding in the brain, we talked about that, infection, and then accuracy. So, circuits, hemorrhage, infection and accuracy. Those are kind of like, you keep your eye on that and you're going to do really well. And with accuracy, we can reposition. I think that in my ideal world, if somebody were to have a problem after an operation the neurologist could actually tell me what direction we need to move the lead based upon surveying the anatomy surrounding the area. So, say they're not getting optimal Parkinson's control, but they're getting a paresthesia, tingling at a very low threshold or their mouth is drying and then neurologist says, that this needs to go make medial. I'm like, great, I got it. Yeah, I think you can learn a lot from the side effects, and you can do that intraoperatively with an awake patient and that can guide repositioning just like a CT in it and repositioning. So, we can reposition intraoperatively, and we use different modalities, whether it be intraoperative imaging or test emulation or microelectrode recording. After surgery if that ends up being an issue with a patient. I think a good programming, a good neurologist could interpret the findings in the clinic to say, that this is too lateral, or this is to posterior. And one of the advantages I think with directional leads today is that if you have a well-placed lead, you can draw the current in certain directions to kind of fine tune avoidance of side effects and maximizing benefits. One thing that I've seen in a lot of literature that coming out of the past seven years is that a lot of the most efficacious locations for symptomatic control kind of march in the direction of side effects. For example, the internal capsule fibers, the fibers for motor function, you kind of want to almost nudge up to those fibers without falling off the cliff. We're at a very low threshold. You start getting side effects in which case you have basically an unprogrammable contact. But we're seeing kind of this therapeutic window appears to be very good to as we kind of nudge up to these. And that's where directionality being able to steer the current away can give us what we need to kind of fully optimize that so-called well positioned to lead. So I think that it's always a big deal to go back to surgery and reposition and I think increasingly it's more of the air ball, the one that's like kind of in left field that we would do that for. And hopefully as we continue to have more experience with directionality, that can be something that kind of fine tunes. Something where we're just a little bit too close to the capsule or a little bit too close to the sensory thalamus, for example.

#### Dr. Soania Mathur (01:11:40):

That kind of leads into the future of DBS, which I wanted to bring Lisa and Steven back into the discussion. Are there any upcoming developments in your company's efforts when it comes to DBS stimulator technology that you'd like to share with us? Lisa, we'll start with you.

### Lisa Johanek (<u>01:11:57</u>):

Sure. Maybe if you, let me touch on to two different topics. One development that's already available is this idea of MRI conditional safety. So this is a need that we've appreciated from our physicians and patients over the years that after a system is implanted, patients may need to go under diagnostic testing with MRI. And so testing needs to be done with the DBS systems to ensure MRI conditional safety. And so today, many devices on the market will have some sort of MRI conditional safety, which is really great to see all that testing then being translated into the

products. So, it's important for patients to understand this, I think, and then ask about the different conditions under which an MRI could be conducted with the DBS implant. The second thing I would like to touch on in terms of new innovations coming up is the need for partnership with physicians, and Medtronic has been partnering with physicians over the last few years to help enable specifically research into a sensing capabilities of devices. So this is looking at signals that can be sensed from the brain and we've partnered with physicians to enable their research, which has started to give more information on how these signals relate to the disease state of Parkinson's disease and also how medications might change and change these brain signals. So we're still really excited just that we've been a partner in this research and development phase and we're excited to see how these developments translate in the future.

Dr. Soania Mathur (<u>01:13:41</u>):

Great. And Steven, your thoughts?

## Stephen Carcieri (01:13:44):

Yeah, so at Boston scientific, a lot of our innovations have been focused on precise delivery of stimulation, right? So several people have mentioned directional leads and we're very focused on research on newer directional electrode designs. They're designed to precisely target areas of the brain where DBS is therapeutic and steer away and a avoid reaches of the brain that might lead to stimulation related side effects. And so when you introduce that additional sort of stimulation capability, then there's also a concern about complexity. And so we want to make sure that the system remains very user friendly and very simple. And so, we are also innovating a lot in the area of software that allow both software for programming the device but then also for surgical planning and helping place the leads accurately. So those are some of the areas that we're really focused on.

#### Dr. Soania Mathur (01:14:51):

Thank you, and as Parkinson's disease specialists for our physicians on our panel today, are there technologies or interventions that you in particular are excited about that are coming down the pipeline? Anyone care to speak on something other than the what's been discussed already?

#### Dr. Helen Brontë-Stewart (01:15:08):

I can certainly talk about closed loop. So I think as we discussed at the very beginning of this really interesting webinar is that we can talk about DBS as a brain pacemaker. And if you think about cardiac pacemakers as the people in Medtronic know very well in the very early days, they were these devices that didn't know what the heart was doing and they were these big wires that were put in the chest. And they helped people who had slaved, very, very slow heart rates but they often cause problems because they were sort of stimulating in a blind fashion. And up to now deep brain stimulation has what we call being called an open loop brain pacemaker. So, it doesn't know what the brain rhythms are doing that it's modulating. And as I think Lisa said, we also didn't realize that medication also modulate those rhythms and gets back to this question of a biomarker. And I often provide this analogy that if you, if you're or your parents, physician was treating you or them for high blood pressure with two drugs, both of which lowered the blood pressure, but they never measured the blood pressure, you would be a little concerned. And for many, many years, that's all we've been able to do. And I think what's going to be really

interesting is now that as it gets closer to having brain pacemakers that can actually sense the brain rhythms from the device, like cardiac pacemakers, they may be able to adapt to medication. They may be able to just move in a smarter way. And I think that to me is one of the really exciting things that is on its way.

Dr. Soania Mathur (<u>01:16:56</u>):

Great. Dr. Foote?

Dr. Kelly Foote (<u>01:16:59</u>):

Helen just took the words out of my mouth. I have to say that that of all the various technological advancements, that's the one that I think is the biggest paradigm shift. And I don't know when it will happen, but I believe that it will happen. That eventually DBS is going to be an adaptive stimulation therapy that will continuously monitor the signals from the brain and deliver therapeutic stimulation in response to those signals to optimize the treatment in a more intelligent way. It just sort of makes intuitive sense that that would be a better way to do it. And so a lot of us are working on trying to make that successful.

Dr. Soania Mathur (01:17:44):

Dr. Haug, anything else to add to that, about future developments?

Dr. Aaron Haug (<u>01:17:50</u>):

I would maybe reiterate that I think that it's great that there's innovation going on in the field, but I think that the biggest decision is probably yes, DBS or no DBS. And the second decision, which is also quite important is which system and which target. But I think that part of what we all have the goal of emphasizing here is that we all think DBS is a fantastic therapy for appropriately selected patients. And it can really be a life changing therapy,

Dr. Soania Mathur (01:18:22):

Right. Dr Ponce. Any interventions that are coming down the pipeline that you're excited about that we haven't talked about?

Dr. Fransisco Ponce (01:18:29):

Yeah, I think that there's kind of two categories. One is how to treat the existing cohort that's getting DBS with more fancy tools and more technology. And another one is how to expand the cohort receiving DBS because it's an underutilized therapy. And I think there's a lot of barriers for entry in terms of streamlining of programming. Once you have the patient implanted, working patients up. And I think having smarter programming, through anatomy, through incorporation, knowing where the leads are and having that positioning within the programmer make the trial and error process of getting that patient from, immediately postop to optimize DBS programming I think is going to be key. And I think those advances are going to make this more accessible to more neurologists and to more patients.

#### Dr. Soania Mathur (01:19:24):

Right. With just a few minutes remaining, I'd like to ask our physicians one final question and then Marty, you'll have the final word. For someone who may be at a point where they're really considering DBS what is the one important thing that they should keep in mind while making that decision? If there's one thing just in a sentence or two, what you think is most important for patients to keep in mind? Dr. Brontë-Stewart?

## Dr. Helen Brontë-Stewart (01:19:55):

I think we've covered it. I think the thing I really, really want to see is that the person themselves can have what I call see past DBS. Can see how DBS is going to be integrated with their life. Obviously, we've talked about aligning expectations, but I'm really encouraged when it's the person themselves wanting DBS, not their family, not the doctor, but where they really want DBS. I know it sounds strange, but to me that is actually a predictor of success.

```
Dr. Soania Mathur (01:20:28): Right. Dr Foote.
```

## Dr. Kelly Foote (<u>01:20:32</u>):

I'll echo that, and it give you a slightly different perspective. Typically, when a patient with Parkinson's disease is exposed to the idea for the first time of deep brain stimulation, the response, not surprisingly is no way, no one is drilling a hole in my head. And then as, as their symptoms worsen gradually and as their quality of life gradually deteriorates, they reach a point. The threshold is different for everyone, but they reach a point where they say, tell me one more time about this surgical treatment and how it might help me. And then when they get to the point that their neurologist refers them to a DBS center, typically our patients, they go through this two or three day process, and then by the end of it, after they've spoken with all these various experts about what DBS would be expected to change in their lives, now DBS is an emergency, I need it today. And I think that's encouraging to me because it goes to what Dr. Brontë-Stewart said, it's the sophisticated patient who understands what DBS can do for them that has the best outcome. So we tried to turn all the patients into those sophisticated patients with that preoperative process. If we can.

```
Dr. Soania Mathur (<u>01:22:07</u>): Dr. Haug?
```

#### Dr. Aaron Haug (01:22:10):

I agree with all of that. I think of having a virtual toolbox for the treatment of Parkinson's and DBS is probably the single biggest tool in that toolbox. And for all the reasons that we've discussed it. So it's not a tool for everyone as we've discussed, but I think that the five or six hundred people that took the time to join the call, that's hopefully something that you can talk more with your provider about and see whether it might be an option for you.

```
Dr. Soania Mathur (<u>01:22:51</u>): Dr. Ponce?
```

#### Dr. Fransisco Ponce (01:22:55):

Let's see. They said a lot. Can you, can you repeat the question because I hear each other a lot.

## Dr. Soania Mathur (01:23:00):

Basically, for someone who may be at the point where they're thinking about, really seriously considering DBS, what is the one important thing that they should keep in mind?

#### Dr. Fransisco Ponce (01:23:08):

So DBS not a treatment of last resort. It's not experimental. There's a very clear kind of line in the sand where one becomes a candidate and it's proven to improve to improve quality of life. So, I think just like Dr. Foote was saying about, no brain surgery, no holes, you know, it's sort of in the spectrum of conditions. There is some sort of a, is Parkinson's a surgical condition? Right. I'll leave it as a question rather than a statement. But, but the, the role for surgery in the treatment of Parkinson's is well established and it will improve one's quality of life.

#### Dr. Soania Mathur (01:23:50):

Excellent. And Marty, as I promised, the last words of advice on this topic are yours. What advice do you have for someone who's debating whether or not to undergo DBS? Like based on your own experience.

## Marty Acevedo (01:24:01):

Learn as much as you can about DBS. Ask a lot of questions. Have an open line of communication and trust with your providers. And realize that while DBS is not a cure, it can vastly improve your quality of life. And in my situation, although DBS isn't for everyone, it's the best thing I could have done for myself. It gave me my life back and allows me to live my life well.

#### Dr. Soania Mathur (01:24:26):

That's very powerful. I like to thank the entire panel for sharing your time and your expertise and also to all those in the virtual world who are joining us as well. I hope you found the discussion helpful and educational. And remember, we don't have a choice when it comes to the having this disease or not the diagnosis really isn't in our control, but how we face the challenges that this disease brings into our life is really within our control to determine. So choose to optimize your quality of life, educate yourself, empower yourself, and celebrate your daily victories. And thank you everyone once again and until next time.