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Intro: You're listening to audio from one of our Third Thursdays Webinars on Parkinson's research. In these webinars, expert panelists and people with Parkinson's discuss aspects of the disease and the Foundation's work to speed medical breakthroughs. Learn more about the Third Thursdays Webinars at [michaeljfox.org/webinars](http://michaeljfox.org/webinars). Thanks for listening.

Soania Mathur: Good afternoon. Thank you for joining us for today's Third Thursdays Webinar. I'm doctor Soania Mathur, family physician of Parkinson's patients for the last 21 years, and co-chair of The Michael J. Fox Foundation Patient Council. I also have the pleasure of being your moderator today. As you know, unfortunately there's currently no cure for our disease. But there are a variety of treatment options that our medical team can offer us. Directed at managing our symptoms, minimizing side effects and optimizing our quality of life. Because really, until there is a cure, it's really all about quality of life. The treatments that will give each of us the best life experience differ from individual to individual, much like many aspects of this disease. In conjunction with our medication, surgical options including deep brain stimulation (DBS) and focused ultrasound (FUS), can help manage Parkinson's symptoms for some but these procedures are not for everyone.

Today, our panelists will discuss what these procedures are all about, who should consider these treatments and when, and what someone may expect after surgery. Let's meet our panelists. The first is my good friend Richie Rothenberg, who's also a member of the Patient Council, actually one of the founding members. He was diagnosed with Parkinson's disease at age 36, about 15 years ago. He had DBS surgery in 2010 and 2011. And he'll explain why there's two date here. We'll share his experience. Welcome, Richie.

Richie Rothenberg: Thank you, good morning. Or good afternoon.

Soania: Good morning, where you are I think. Next is Dr. Paul Fishman, who is a professor of Neurology at the University of Maryland and chief of neurology services at Maryland VA Healthcare Systems. He's led some of the first trials of focused ultrasound therapy in Parkinson's so we feel very lucky to have him here today. Hello, Dr. Fishman.

Dr. Paul Fishman: Hello, and thank you for inviting me.

Soania: Oh, absolutely. Finally, Dr. Joohi Jimenez-Shahed, is director of the Deep Brain Stimulator Program at Baylor College. She's also leading a new DBS registry to better understand how people can have better outcomes with this treatment. Hi Dr. Shahed, welcome.

Dr. Joohi Jimenez-Shahed: Good afternoon. Thank you for having me.

Soania: Absolutely. Richie, I'd like to start with you and your story because you've actually lived what we're talking about today. And, I'm really interested to hear what you have to say. So can you share with us, when you were diagnosed, and what your journey has been like up until this time?

Richie: Yes, I was diagnosed in 2004. And, my journey was very exciting. It was very, it progressed very rapidly. My disease, and my tolerance has increased so I need more and more. And I was very disconnected as a result of all the levodopa. And, I was eligible for the surgery, so I decided to go ahead and have it after about seven years of disease progression.

Richie: And I had it in 2010, in the fall. And I had it again in 2011, in the winter.

Soania: And why was that?

Richie: And the story behind that was because I was one of the lucky few that got a Staph infection from the surgery, despite the luck of the odds. The unluck of the odds, with any surgery that you do. So they had to remove it, completely. The good news was I was able to tolerate the length of the surgery. They were able to put everything and program me when they redid it in February 2011.

Soania: And how have things been since then?

Richie: Well things have been, pretty amazing physically. I still have Parkinson's, I still have symptoms of Parkinson's, non-motor symptoms, as well as motor symptoms. I still freeze at times, but less so. I still take my medication, but a little less than I took when I was at my height before the surgery. The surgery has really modified, pretty much eliminated dyskinesia. And it has, in combination with levodopa treatment and programming assistance, it's been much smoother. The "on" and "off" periods have been much less severe. And it means a lot, I mean it's like a new lease on life for me. In terms of the profound impact it's had on my life, my ability to work, the ability to live my life and be with my family, get remarried and have two more kids. It was really remarkable, but I want to be a little cautiously optimistic. I can be realistically excited about the DBS procedure because the reality is Parkinson's is still here, still effects my daily life. But I have a great tool on hand with DBS.

Soania: Yeah, I mean I vouch for that. I saw you before and after surgery and there really was remarkable difference in terms of your functioning for sure.

Richie: You can't get away with using Parkinson's as an excuse for getting what you want when you don't look like you have Parkinson's because people see me and think, "I wouldn't have any idea he had Parkinson's." So, that was the nice thing, but also, people still sympathize with you I think, but it's definitely, you get to drop into the world less obtrusively.

Soania: Right. Yeah, things do change for sure.

So we're going to discuss DBS and focused ultrasound, what they are, and how they're working and so forth, and give us more detail. But, Dr. Fishman, can you tell me, at what point in your practice, do you tend to recommend when patients consider moving forward in their treatment regimen to include a surgical treatment?

Dr. Fishman: Well, I think for both DBS and FUS, surgical treatment is pretty much the general treatment for any condition, which is you've tried a good-faith effort to manage the patient medically. And, there are symptoms that you can't manage medically, you're either limited by side effects or the effect of just the medication. And, in particular, for both DBS and FUS, the commonest group of patients are the patients who have a fluctuating response to medication. For good candidates for DBS actually, sadly, are sometimes patients who respond well to levodopa, but have a fluctuating response. That is it doesn't last very long, patients have fluctuated between the "on" period where the medications are working well, and an "off" period, where their Parkinson's symptoms of stiffness, slowness, difficulty walking are occurring. And, just like Richie mentioned, with years of levodopa treatment, during an "on" period, many Parkinson's patients will develop involuntary movements. And those involuntary movements sometimes are just, you know, mildly bothersome. But they can actually interfere with normal movement. So again, a fluctuating response to levodopa is probably the most common reason why we'll offer surgical therapy to people with Parkinson's.

And the second group is that even though levodopa is a wonderful medication, the Parkinson's medications work well, there's a certain group of Parkinson's patients, where the tremor just can't be controlled. And that's the second group of patients who opt for surgical therapy. Where, in spite of best medical management, there's a tremor that interferes with day to day life.

Soania: So it's not a time thing, in terms of, it's not like within a certain number of years, you should have considered a surgical treatment, it's more on a case by case basis. Is that right?

Dr. Fishman: It does, but a lot of times these are time-dependent. In early phases of Parkinson's, the medications work well. And Patients can expect that comment about a tremor, where sometimes, relatively early in the disease, it's clear that the tremor is blowing through all the medications that are tried. So for most patients with Parkinson's, fluctuating response occurs in that so called, "middle phase," you know, after several years.

And the other part, sadly, is usually after a decade or more with Parkinson's, many Parkinson's patients like Richie mentioned, develop more non-motor problems. And the most really serious, disabling non-motor problems occurring late in the disease are problems with thinking and memory. You know, dementia, and problems with balance. Frequent falling. And since neither of

those are particularly improved by DBS, problems with thinking really are at risk of worsening, that's why we talk about those patients in the "middle phase," being the best surgical candidates.

Soania: Right. So, Dr. Shahed, Dr. Fishman just mentioned the cognitive issues that might determine whether someone should go for a surgical intervention. Are there some general criteria to consider, when you have someone come in for DBS?

Dr. Shahed: Yes. I think Dr. Fishman mentioned a lot of them. I mean we like to, you know we never just sort of see a patient in clinic and decide it's time for surgery. We usually try to go through a more detailed assessment of what the problems are, the way the medications are working, and really trying to get a grasp of what types of symptoms are present. And have a conversation about whether or not those are things that can actually get better. One of that last things that we want to do, is to sign people up for a difficult procedure that then doesn't really have a chance of helping them with the symptoms that are most bothersome to them. So typically, we will have patients come into our clinic, off their medications for Parkinson's, and we'll assess the severity of their symptoms. We'll give them their usual dose of Parkinson's medication and then reassess to see what kinds of things get better. And that really helps us guide our conversation with the patient about what we really think will improve or not. And so, we're really kind of looking for those dynamics.

Dr. Shahed: And a lot of that conversation will also include the discussion of the timings of the medications, the dosing of the medications, whether or not they're having those fluctuations or the dyskinesias. And then we put all that information together, combined with what we call a neuro-psychological assessment to determine whether or not surgery is an appropriate option for our patients. So it's kind of hard to say that there are very specific criteria. Those are not really well-defined. But this is sort of the general sense of how we approach those patients and try to make the best decision about whether DBS can help them.

Soania: So it seems like, you do have a little bit of a checklist that you're looking for in terms of testing, but it's a lot about patient expectations as well. So even if someone is a good candidate, if they have unreasonable expectations of what's going to happen after surgery, would that preclude them from having the surgery?

Dr. Shahed: Yeah, I mean that's part of the conversation that we will have. I think surgery, especially deep brain stimulation surgery, it's important to remember, and I think Richie kind of alluded to this as well, that it doesn't cure the Parkinson's. People still will experience some difficulties related to their Parkinson's and so, we certainly don't want to have an unreasonable expectation that a certain symptom will get better. And then have a patient be disappointed afterwards. And so, I wouldn't necessarily say that having, well, I guess maybe the way I would put it, is that we just have very careful conversations about what it is that they should or shouldn't expect from the surgery in order for them to be very

well prepared for what the ultimate outcome would be. And so, in situations like that where somebody maybe is expecting too much, you know, we would just have that conversation and kind of refocus and try to make it, clearly understood what would or wouldn't get better before proceeding.

Soania: That's part of the overall assessment I think. And, the expectations, managing expectations is key to every sort of treatment, everything that we do. But, does it, is it considered a component of a neuro-psychological assessment, or is it just part of the overall conversation you have with patients?

Dr. Shahed: Yeah, the neuro-psychological assessment is primarily to assess the cognitive functioning. So the thinking skills, the memory skills, the thought processing, those kinds of things. As well as, kind of an overall assessment of behavior and mood. So it's more to get a snapshot of what's going on there, in order to, both determine risk for surgery. So, as Dr. Fishman mentioned, if people have significant cognitive decline, already at the time they are thinking of DBS, there is risk of further decline, and we don't want to expose the patients to further harm. But there's also the aspect of this which gets into mood, anxiety levels, things like that, that may influence how a patient copes with their post-operative course. And so, to a certain extent, yes I would agree with you, that, that neuro-psychological assessment does get at some of those issues, but we bring that information back to the patient, in combination with a very clear discussion about that levodopa response to guide kind of what we think is likely to be better. The surgery really works best for the symptoms that get better with levodopa, with the exception of the tremors Dr. Fishman pointed out.

Soania: And what if someone has a history of mood disorders, depression and anxiety seem so common in Parkinson's disease. How does that factor in? I've heard obviously that you said, it can get worse, or make it more difficult to cope with the procedure, but does it apply into your decision?

Dr. Fishman: Well again, I think the issue is to make sure that, that's adequately treated. Again, there's not a rush to surgery. We looked at this several years ago, and if patients have well-controlled anxiety and depression by the time they get to surgery that usually doesn't inhibit their outcome. But again, once those things are identified, they need to be treated and controlled before the surgical procedure.

Soania: That makes sense actually. Dr. Shahed, I'd like to start with you on this one. Most people heard about DBS and Richie explained his experience with it. And people probably know it involves some sort of brain surgery, but may not be familiar with the details. Could you please give our listeners a better idea of what DBS is exactly? And how we think it works?

Dr. Shahed: Sure. This kind of a common question, it's also sometimes a difficult question. Because, the honest answer is that we don't have a very precise idea of the exact changes that are happening on a cellular level. But one of the things that you can think about, in terms of brain function, is that the movement

coordination kind of functions as a circuit. And we know that in Parkinson's disease, this sort of circuit is not really functioning in a healthy way. And that's why we get symptoms like tremor, or rigidity, or bradykinesia, or difficulties with walking and balance.

And so within that circuit, the idea of deep brain stimulation is that you can insert an electrode into an area of that circuit, and you can deliver a very focused amount of energy, or electricity into that circuit. And try to help it work a little bit better to kind of reset it. And if you can reset the circuit to function perhaps in a more, normal way, then we can reduce the symptoms of Parkinson's disease.

And so you, hopefully people on the call can see the picture up there, but you see the pulse generators which are placed in the chest. This is kind of the control center of the DBS, where we can program it to deliver the energy in the way that we want it to be delivered. And the tips of those wires that you see, the electrodes there, are in the deep structures of the brain, within those brain circuits that control movement. So the deep brain stimulator functions in some ways like a pacemaker that people may be familiar with that are used for cardiac and heart conditions. The difference being that the tip of the wire is in the brain. And, we control it through that battery that's in the chest.

So that's kind of a broad, sort of, overview of how the stimulator itself works.

Soania: Right. Thank you. Dr. Fishman, I've heard that there's different areas of the brain that are stimulated depending on the patient. Could you tell us a little bit about that?

Dr. Fishman: Sure, and again surgery, just to put this in a little historical perspective, surgery for Parkinson's related conditions, predated DBS by probably about 30 years. And, that's how we learned about those centers. There's one center in the thalamus, the ventral intermediate nucleus of the thalamus usually goes by, a lot of these things usually go, by their initials, V-I-N. And that is the preferred center when the target is a severe tremor. And that's true for not only Parkinson's related tremors, but non-Parkinson's related tremors, such as central tremor.

The most common center, which is really the common center for deep brain stimulation is one that goes by the initials S-T-N or, subthalamic nucleus. And that is, again for all three of the major symptoms of Parkinson's. People have those fluctuations, they may have rigidity, slowness, tremor or all combinations of the above. They respond to levodopa. But yet, they have this erratic fluctuating response to levodopa. And that's the commonest of all of the targets.

The third target, which Richie was talking about, and probably the one when patients, usually somewhat younger patients, who develop relatively early in

their course. These involuntary movements that are from years of levodopa, called levodopa-induced dyskinesias, involuntary movements, and in particular, the center that's called the GPI, or globus pallidus interna, that center works for all of the Parkinson's symptoms, but it's particularly good for these abnormal movements. Sometimes patients will have these periods of painful abnormal stiffness called dystonia and abnormal posture, and that's the preferred for that constellation of symptoms. GPI is the preferred location. And that's actually true for all forms of surgery, whether they're DBS or not.

Soania: Okay, got it. Richie, you said you had GPI is what started with your DBS. Is that right?

Richie: Yes I did. I think that dyskinesia was the most overt symptom that was being addressed in my case.

Soania: And, can you give us an idea, now that we know, kind of what the surgery is about, what was the experience like, logically, for you in terms of how did it all come about and what the experience like being in there?

Richie: Well, logically it was as, I like to say, it's as fun a surgery as you can imagine, because you wake up in the middle of it and they program you while you're awake, which means they test the levels of the DBS connecting, connections, while you're awake so you can do, like vocal patterns and they can test how much they can give, which is enough voltage to provide the treatment, but not too much so we aren't too tongue-tied. So, it's very interesting. There are some interesting videos on the web of people who played guitar while they were doing their programming mid surgery. I mean, I'm not very sensitive to someone having their instruments in my brain, and so it didn't bother me to be awake. For some people that might be a deterrent, but part of the whole calculation of having the surgery is the experience of the surgery as well, I think.

Soania: Right. And, Dr. Shahed, if someone is sort of queasy about being awake for the procedure, can it be done while someone is asleep under anesthetic?

Dr. Shahed: Actually, yes, it can. There's actually several ways that the procedure itself can be done. The part that Richie was referring to is, sort of, the most traditional method, which allows, you know, the patient being awake allows for us to listen to the electrical signals of the brain as we are passing through various structures to make sure that we're actually targeting the spot that we intended to target, and then the testing itself allows for us to measure to make sure that both, symptoms can get better, and the patient doesn't experience side effects that would make it hard for them to use that stimulator once all is said and done. So, the other ways that the procedure can be done, some centers are actually doing this using image guidance alone, and so rather than listening to those electrical recordings they can use imaging software to very precisely target the structure and when it's done under that procedure or under that technique, patients can actually be fully asleep, so there are different ways that this can be done to make the procedure more comfortable for patients.

Soania: And, Dr. Fishman, maybe you could tell us a little bit about what happens after the DBS is implanted. What's the, sort of, course of recovery?

Dr. Fishman: Well, recovery is fairly quick as far as brain surgery goes. We're talking about the insertion of a wire into brain, and usually patients stay overnight and they're stable by the next day, and usually they go home. They very well may not have much benefit because at this point all the experience of turning it on has been with an external device. They usually come back after they've recovered, usually within the first, within a week or so, and that's an outpatient procedure, that's really putting in the post generator, which is very similar to a pacemaker. And from a surgical point of view, it's just like coming in for, as with millions of Americans have had, of having a pacemaker implanted. That's done under general anesthesia. That's a same-day procedure. And, the entire system is connected and usually about a few days to a week after that, usually within a couple weeks of the initial brain procedure, they come back for programming. We tend to allow the brain to heal before programming just because the results of the stimulation are more consistent after, basically, the brain is kind of tacked down and stuck to that electrode.

So, again, three, the first, the surgical procedure, the brain procedure where you stay overnight, you come back to same-day surgery to have the whole thing hooked up, and then you come back as an outpatient to have it really turned on in that programming session where, usually at least an hour, that it takes to find the exact pattern of stimulation that going to be best for that patient.

Soania: Is there an average amount of time? I have a couple of questions from people listening, about timing. What course of time should they expect to have to, you know, have it fine-tuned in order for it to work? Is there an average time that is appropriate?

Dr. Shahed: So I usually, this is Joohi, I usually tell patients that it takes about six months to do that process of fine tuning the stimulation and the reason for that is that it takes a little bit of stimulation adjustment and then a little bit of medication adjustment. So, we have to, kind of, try to find the balance between both of those aspects now. And for some people that may take up to six months. For some individuals it may occur in a shorter period. It all depends on, well it depends on a number of different factors really, but I, you know, kind of the average time that I tell them is to give me six months to, kind of, sort that out.

Richie: In my case, anecdotally, it was about six months for me to get the levels working in a functional manner. But, then to dovetailed a little bit from that, it becomes a part of the overall treatment protocol now. So, I don't have to go in, previously, I kept my levels on the same level for a couple years now, but it's always part of the discussion that I have with my doctor when I see him, with my doctors when I see them. So, and it's one of the positive aspects of the surgery, post-surgery, or pre-surgery is the nature of the interaction with the doctors. The doctors who generally have to tell, sort of, bad stories about progression and about how it gets worse and it's hard to deal with, to the same

doctors the next week are looking at you like you're a positive story. But, you can improve dramatically with Parkinson's, even if you're not stopping the overall disease underneath it.

Soania: Right. So, drastically sometimes, yeah. This is, sort of, after your second treatment or second surgery, and I have a couple of questions and maybe Dr. Fishman you could take this one, or Dr. Shahed, what are the risks associated with having DBS surgery? I mean, all surgical procedures, or treatment of any sort, have risks, and what are some of the risks with DBS other than infection?

Dr. Fishman: Well, the basic risks are the same for all surgical procedures. The risks of all surgery are bleeding and infection. And the, all teams do their best to control that because, frankly, the most serious place you can have either bleeding or infection, is within brain. So, again, the use of antibiotics, sterile procedures are really at the core to ensure that there is no infection. And, because not only is DBS, again, the risk of infection within brain, but it's usually referred to a foreign body. Anything that's implanted into the body, and particularly into brain, it's very difficult for the immune system to clear that infection and so, when a serious infection occurs, it may not be able to be controlled with antibiotics. In that situation, whether it's an implanted hip or DBS system, it has to be taken out and replaced.

The other most serious, most feared, is bleeding. Now, bleeding does occur, you know, in two or three percent of patients, but most of those bleedings are small and they don't have any clinical symptom. But, bleeding that is substantial can cause stroke-like symptoms, it can cause weakness, interfere with language, seizures can occur. So, again, you're probing physically into brain and, again, all teams make sure that patients are well informed and do everything they can to control bleeding. Imaging to try to identify any significant blood vessels so that the path of the DBS doesn't hit a blood vessel. Patients have to be off aspirin, off anticoagulants, for a time to reduce the risk of bleeding. Blood pressure has to be well controlled before the DBS process.

So, again, every surgical procedure, every surgical concern form says bleeding and infection, and every DBS team does their best to minimize those within brain.

Soania: Right. How quickly did that happen for you Richie? How quickly after your first surgery did you notice that?

Richie: It was in November I had the surgery, end of November, and then by New Year's Eve, I spent New Year's Eve 2011 getting it all removed. I saw the doctor and the doctor said, the doctor came over to my house actually because I sent him a picture of the infection, and he then said, we're going to the hospital right now. So, it was an urgent situation, but I was perfectly, I had no other symptoms except for the, actually just the physical symptoms of the infection.

Soania: Right. So, those are more serious risks. Dr. Shahed, there is the likelihood of side effects alluded to potential worsening cognitive issues, if they exist pre-surgery, but are there other side effects that people have to be concerned about?

Dr. Shahed: Yeah, the ones that you guys were just talking about are the surgical side effects and, I guess, there is a different combination of symptoms that can occur as a result of the programming. And so, programming the DBS device, as Dr. Fishman was talking about, there's different places in the brain that you can stimulate, and because those are different anatomic regions and because the areas that are kind of close to those are different, there are sometimes different side effects that can occur with the different locations of stimulation that people get.

Dr. Shahed: Some of the most common ones though, are things like tightening sensations of a body part. So, when we are doing the deep brain stimulator, usually, for the most, most commonly we would do stimulation on both sides of the brain, but it's the right brain electrode that controls the left body and then vice versa. So, if somebody's electrode was being programmed then on one half of the body, if they were experiencing side effects of tightening sensations, or tingling sensations, sometimes there's face pulling. These are things that indicate to us that we need to change the way the stimulation is being delivered in order to continue to allow the patient to get the clinical benefit without some of the side effects.

Other things that people may experience are changes in speech. Sometimes the adjustments may have a negative consequence on the walking or the balance. And, so, these are all things that need to be assessed both at the time that the programming is being done, but then also when the patient comes back for their next follow up visit. Now the good thing about deep brain stimulation is that if one of these side effects is experienced, then we usually can find a way to reprogram it to minimize or even eliminate that particular problem. And that's really one of the great advantages of having a stimulator device as opposed to some of the other earlier surgeries that Dr. Fishman was talking about where those side effects might not be reversible.

Soania: And, how long does this work for? How long does DBS therapy remain effective?

Dr. Shahed: When we do the surgery, again, we are commonly, as was mentioned, trying to address things like the fluctuations and the dyskinesias, or perhaps the tremor, and so, the studies indicate that those symptoms of Parkinson's disease can be continued to be controlled for a number of years. And some of the studies have now shown up to 10, sometimes even longer, benefits, in those initial symptoms that were being addressed; so the tremor, the rigidity, the slowness of the movements, all of those, kind of, cardinal Parkinson's features, along with the fluctuations and dyskinesias. So those things can, you know, remain effective over, sort of, a number of years. The things that maybe are less likely to be controlled with the stimulator are things like speech issues, or cognitive issues, or swallowing problems and some balance issues. And those are the parts of this that maybe are not as easily addressed with stimulation and are likely to

continue to progress despite the fact that we make continued adjustments to the stimulator.

Soania: And Richie, have you found that to be the case in your situation, that there are some things ...

Richie: Yes, the, I mean ... I'm sorry, go ahead and finish.

Soania: No go ahead.

Richie: The moral of the story, I think is that is sort of the beginning of the conversation. I still have Parkinson's, I need to address issues that arise from Parkinson's even if I'm feeling really good physically. So, it's an issue with treatment for my voice, for some balance issues, and for lifestyle, just being able to remember that you don't get a pass to prevent you from eating right, sleeping right, stressing less and exercising daily.

Soania: Right, right.

Richie: You can, sort of, think that you can get away with it, but you can't. And, the amazing thing is it is immediate. It's not like you work for 6 months and then the doctor is able to just make an adjustment and you walk out doing much better. So it's ...

Soania: Yeah, that's amazing.

Richie: Pretty interesting.

Soania: It must be very interesting experience I would imagine. Maybe we go on and talk about focused ultrasound and Dr. Fishman, you had mentioned about how surgical procedures or what we call ablative surgery or disruption or lesioning of the brain tissue has been around for a while, and focused ultrasound is a little different I guess in that it doesn't require a scalpel. I mean, scalpels are replaced with sound waves, which I guess disrupt brain circuits that are responsible for things like tremors. Is that a fair description, and I know you've done such extensive research on the procedure, could you elaborate further about what this is and how it works?

Dr. Fishman: Focused ultrasound sometimes has been described, in Parkinson surgery, as both a step forward and a step backward at the same time. So, it's a way of doing old fashion lesion surgery, again, where you destroy a specific brain area as opposed to implant an electrode and essentially, in most cases, inhibit the abnormal signal. But the advance is there's no physical probe. It's done by, and similar to the way radiation has been used to destroy tumors, it's done by an array of sound waves, in this case over a thousand, that target, under the MRI, a brain area, and we are really talking about, which is what's needed for any form of this type of brain surgery, millimeter type accuracy, and destroying it.

Because the big difference between it and DBS is this is not a modifiable procedure. What happens on the table, in this case in the MRI, is what happens for better or for worse.

You don't have the opportunity, like with DBS, of modifying it, but changing the stimulation parameters, you know, as Dr. Shahed mentioned, if you have problems such as speech difficulty with it, you can change the way the stimulation is applied and change it. If you want this programming process of getting the best clinical outcome. So, there is no implantable device here. It's for better or worse. There's no programming. There is no physical probe and, so, it's the same, again same goal as DBS, to approach a target and in this case, and again, like DBS the patient is treated awake, off their medications, so that their symptoms are as florid as possible. Just like DBS, and Richie's experience, you're going to see improvement on the table and the patient is monitored very carefully because as we gradually destroy that brain target, first with lower levels of energy, we want to make sure no side effects spread from, in this case, heat. When all that sound energy converges on the target, we're really destroying it by coagulating it. And not only does the MRI look at brain location, but the MRI can actually measure, as we're doing it, brain temperature. So if we're in centigrade of normal is 37, and we heat a spot of brain up until 47, just like if you had, God forbid, that kind of a fever, your brain wouldn't be functioning very well. What we'll do is we'll interfere with function of that brain location, we'll know that the spread of the heat is at the target, the patient will, again, periodically go in and out of the MRI, and my role as a neurologist is the exact same as my role when we do DBS.

Are good things happening? Meaning, are the patient's symptoms going away as we gradually do this? And if there's the beginnings of anything bad happening, if it's, depending on location, is there numbness of the hand? Is there interference with vision? Is there interference with speech? Is there weakness to say, "Oh, I think we're spreading a little off target. We need to adjust the target"? And one of the things that, again similarities and differences that goes on in DBS as well, is it's fairly easy to move that probe up and down. You have the manipulator that's on a drive, and you just turn the knob, and it moves up and down a few millimeters, but if you're not happy with that path, you literally have to make another path. So you have to pull the probe out, move it over a little, and there's usually a great deal of discussion about whether or not you want to go left, right, forward, or back for that second pass, to make sure you hit the target on the second pass.

With focused ultrasound, our adjustments in location are invisible to the patient. They're done by the operator, Dr. Eisenberg, who is our chair of neurosurgery, and again, it's our DBS team. Dr. Eisenberg has done all of our DBS, he's the pilot on all of our focused ultrasounds. But again, it's done in a control room, and we can move forward, backwards, left, or right with the turn of a knob, meaning by changing the target of the array. Because again, once we're done, we're done, for better or worse.

Soania: And who is eligible for this treatment? Is it the same things you look at when you look at a patient being eligible for a DBS? Which types of patients would benefit most from this treatment and criteria?

Dr. Fishman: Again, it's even a little more limited. It's significantly more limited because right now, and one of the reasons that DBS was invented is that serious complications occurred in the old days when we attempted to treat two sides of the brain. And particularly, what Dr. Shahed mentioned before, left brain is controlling right arm and right leg, and right brain is controlling left arm and left leg, but the two brain sides share those muscles in the middle. And the muscles in the middle are involved in speech, swallowing, balance. And in the old days, when we did both sides, some patients got serious complications.

So right now, we're just beginning ... All of the patients who have been currently treated, virtually all of them have only had brain lesions on one side, so when it comes to Parkinson's, we've really targeted patients where their disease is very one-sided. Again, just about, from a safety point of view, to try to approach the second side, but it hasn't been done yet.

Soania: That's very interesting actually because oftentimes, it does progress to the other side, so I guess you do the more dominant or effected side.

Dr. Fishman: Yeah. And like I said, one of the real breakthroughs of DBS was that ability to do both sides, and if those middle of the brain, middle of the body side effects like speech interference occurred, you can usually get around them with programming.

Soania: And because there's no probe being inserted, is infection and bleeding less likely or reduced with focused ultrasound?

Dr. Fishman: They're dramatically less likely. There has been one small bleed in over a thousand FUS cases that had no consequences. Actually, one of my patients. And the only infections that have occurred have actually been some minor skin infections where the frame is placed. There have been no brain infections.

Soania: And Dr. Shahed, could you tell us a little bit more about the DBS registry you're involved with?

Dr. Shahed: Sure. The project that we're currently working on, we've called it RAD-PD, this is the Registry for the Advancement of Deep Brain Stimulation in Parkinson's Disease. A group of us have been interested in this question of why patients who are otherwise seemingly eligible and good candidates as we've talked about today may have differences in their outcomes. And despite our best efforts of looking at things like their levodopa response and looking at their neuropsychology and choosing patients appropriately, there are still differences in the ways that, or the outcomes that people will have.

So one of the main goals of this registry is to really, in a very systematic way, follow a group of patients who have undergone deep brain stimulation surgery and measure the same things in the same patients each time for up to a period of five years. And by looking at that data very systematically, we can then start looking at treatment patterns, we can look at response patterns, we can start to identify maybe some of the best practices of deep brain stimulation. I think one of the things that we haven't had a chance to talk about yet is, even though we all sort of, in a general sense, approach patients the same way, there's still differences and preferences that certain centers might have compared to others, and really we don't have a great way of understanding which are the actual best ways to kind of do it.

So whether that's from a surgical standpoint, or whether that's from a programming standpoint, or whether that's from a medication management standpoint, those best practices are actually not clearly defined. We have a general sense of how we need to do it, but how can we really understand those procedures and outcomes better so that we can make sure that all of our patients have the best chance for the best outcomes? And that's really kind of the purpose behind this registry is to collect all of this data systematically so we can start answering those questions.

Soania: Very interesting.

Richie: I have one question for Dr. Shahed. Who is eligible for the registry? Are the people who are getting surgery eligible?

Dr. Shahed: Yeah, no, that's a great question. So we have a group of 20 sites that we've identified that we will be working with on this registry for the time being. Our goal is to expand that in the future, but for right now, we're starting with 20, and we're looking at any patients who are coming to those sites for evaluations for deep brain stimulation. So understandably, some of those patients may be evaluated and don't get surgery, and some of those patients may be evaluated and do go on to get surgery, so we're really trying to look at the time that they are even considering the procedure. So before the surgery, when those evaluations are occurring, that on/off evaluation that we talked about, that would be the time that we would be approaching these patients to participate. But any patient at that time who was doing it would be eligible.

Soania: Okay. Another thing that's listed on this slide is DBS stimulator technology. What are the new developments when it comes to DBS stimulator technology, Dr. Shahed?

Dr. Shahed: There are ... Actually, this is a very exciting time in the world of deep brain stimulation. What we have now are different companies that are manufacturing different devices that have different capabilities. One of the most exciting advances that has recently become available in the last couple of years is a different electrode design, so the part of the DBS that's actually in the brain. The way that it is structured is that there's ... traditionally has been that there's four

locations on that contact, and all of the ... the whole point of the procedure is to be able to get the best ... get a contact, one of those four contacts within the structure that we're trying to stimulate, and then the next step is trying to stimulate it in a way that works for the patient without causing side effects.

So now, one of the new advances has been the development of a new electrode that allows us to steer the current in different directions, and we have more than just those four options in terms of finding the best settings for that individual patient. So that has been a really exciting advance, and we're looking actively to see how exactly to use that and how that will impact the ultimate outcome for patients with Parkinson's. Another advancement that's kind of in the works and is hopefully on the horizon is a device that can actually sense the brain activity and use those signals to deliver the stimulation more intelligently.

Dr. Shahed: One of the reasons that we think that people are more likely to have some of these stimulation-related complications is because the stimulator is on all the time, it's on 24/7, and if there's a way that we can allow the brain to receive the stimulation only when either certain symptoms are present or when there are certain characteristics of that brain activity, then we might be able to, A) be more efficient about the stimulation and use less battery, and B) maybe reduce the side effects that people are having.

Soania: That's very interesting. I mean, Dr. Fishman, of course this can't be done in the field of focused ultrasound, where it's more of an inflation surgery, but are there other ... is there anything new in the field of focused ultrasound as it is itself, and are there other applications for this technology that you're looking at?

Dr. Fishman: Well, the applications, it's really ... focused ultrasound is kind of following the path of DBS. So DBS identifies targets, and focused ultrasound is starting to attack a lot of those targets. There has been worldwide focused ultrasound for patients with obsessive-compulsive disorder and severe depression. Our own center is looking at patients with refractory pain. For Parkinson's disease, as I said, only last November was focused ultrasound approved for any form of Parkinson's, and those are patients who have severe tremors, again, in the thalamic target. We're looking at the dyskinetic target, and a group in Spain, Dr. Biza and some very bold neurologists, neurosurgeons, and patients are looking at the subthalamic nucleus because that is a very powerful nucleus in the sense that if you over-treat it, you may release very wild abnormal movements. So far, that hasn't occurred, but that's been the one that ... that's why the commonest DBS location is just being approached at this point.

So those are the things following the DBS path and trying to see if we can reproduce some of that? One of the things we're looking at very intensively is, I think was mentioned, that some patients after DBS deteriorate cognitively. And especially if they have some cognitive issues to begin with. And it's not really known why. And the question is, are they deteriorating cognitively because of the effects of DBS at the target, or are they deteriorating because of the path

that that physical probe takes going through brain? We now have a path list technology where all of the damage we're doing is that target, and that's why we're following all of our patients very closely with neuropsychological testing, to see if we can resolve that issue to minimize that.

And the other, which is ... when we talk about focused ultrasound now, we're talking about very high intensities of ultrasound to the point where about 10 percent of patients, we just can't get enough energy through the skull to make that brain lesion, but with lower amounts of energy, one can do other things, and the most significant other thing that focused ultrasound can do, which has huge potential for Parkinson's disease, is it can open up the so-called blood/brain barrier. In general, a lot of therapeutics, particularly gene therapy or growth factors, they won't get into brain from blood. And what focused ultrasound can do, and there have been several very reputable groups that have done this in animals, they can use focused ultrasound to vibrate open in a region the blood/brain barrier, then they inject their gene therapy or their growth factor, and they get results that are normally gotten by physically injecting that into brain.

The first groups of patients have already undergone this procedure in Alzheimer's disease, where the thought is that this will accelerate that, and there are plans in the not distant future to look at certain forms of therapy to see if one can look at patients with Parkinson's disease and give what the goal of things, what are usually referred to as disease modifying therapies, some form of therapy that can make the nerve cells function better, keep them from eventually dying. And like I said, that's on the horizon with focused ultrasound.

Soania: Yeah. That has huge potential, for sure. So we're coming toward the end of our time, but I tried to weave questions into the conversations that our audience had, but one of the questions we haven't touched on, and I don't know if you want to take it, Dr. Fishman or Dr. Shahed, is we're getting a few questions on use of both. Can someone have DBS then focused ultrasound or vice versa?

Dr. Fishman: Well, I guess I'll take that because I know a little bit. First, I'll say there's very little experience with that. And as I mentioned, focused ultrasound is a one-shot deal. There have been patients, like with all these procedures, who have failed. So again, a failure with focused ultrasound does not prevent the patient from now having successful DBS, and I know there have been a couple patients where that's actually been published. And that's to be expected, because in the days when DBS first came in, there were a lot of patients who had lesional surgery and their symptoms came back or they got worse, and many of those patients either had the same or different locations with DBS and got benefit. So benefit with DBS after lesion, there's a lot of evidence that say that could work.

But on the other hand, there's only some animal safety data. The question is, can one do focused ultrasound with a DBS in place? And the answer is that is a much dicier procedure. I don't know. I think there have been a couple patients who, even if it's taken out, it's changed the whole way sound waves interact

with the brain. But again, there's some animal work that says at least on the second side, you might be able to do it, but right now, that's somewhat speculative and potentially dangerous. The question is, would the focused ultrasound heat up the probe or dislodge it or move it? That's one thing you don't want to happen.

Soania: Yeah, no, absolutely. But thank you so much for that information. I know people are wondering about that aspect. Before we go, I'd like to give Richie a moment to answer this final question. How has DBS impacted your life?

Richie: On the whole, it's impacted very positively. I was in a condition where I was not working anymore, not able to live my life the way I wanted to, I was not married, I had my teenage kids, but they were ... it was hard for me to interact with them in a very positive way for conversations and emotionally. But the DBS, the fact of it, when it was turned on for me, I could resume my life and live a life that was just exceeding all of my pre-Parkinson's dreams. I have a great relationship with my big kids, I have two six-year-old twin girls, and life has really been great. Not without its challenges, but it's been a great life as opposed to being on total disability and unable to function, really, before the surgery.

Soania: On that note, I'd like to thank everyone kindly for joining us today. I hope you feel that your time was well spent and you found the discussion and saw it as invaluable. And thank you, Richie, and Drs. Shahed and Fishman for sharing your expertise. You both were very much appreciated. And remember, those of us with Parkinson's have no choice in our diagnoses, but how we face the challenges is really ours to determine. So empower yourself by educating yourself as much as you can about this disease, and until next time, be well and live your best life. Thank you.

Michael J. Fox: This is Michael J. Fox. Thanks for listening to this podcast. Learn more about The Michael J. Fox Foundation's work and how you can help speed a cure at [MichaelJFox.org](http://MichaelJFox.org).