So I'm going to talk to you about the surgery itself, we'll quickly go through the targets and some of the outcome data just to be clear on that. And I'll show you some videos of what it's like in the operating room, and then specifically we are going to talk about the difference between awake microelectrode guided brain based surgery, stereotactic brain based surgery, which is the traditional way to do DBS, and then interventional MRI guided DBS which was FDA approved in 2010 and which we've been doing here for the past 2 1/2 years.

So let's go right into the risks. So really regardless of the brain target with some caveats and of course it depends on the patient's age and do they have a risk for coagulopathy and other things like that which are specific to the patient I basically quote everyone the same risks, and that's with the bilateral simultaneous implantation. So that's doing both sides at the same time. There is about a !% chance for a symptomatic stroke, so that's 1% per side of any bleeding, 1/2% chance that that's going to give a permanent neurologic deficit, so you put the two sides together you have a 1% change overall to serious stroke with simultaneous bilateral implantation. So it is a low risk but it's a real risk and we have very frank conversations with the patents about that to make sure that they understand that this a brain surgery and that bleeding in the brain is a potential risk.

I tell them the real risk though is one of infection. So there is about a 5% rate of infection if you look across published studies. Our rate is actually slightly lower than that but we do have infections every once in a while. Most of the time we can treat these with antibiotics and what we'll do is admit the patient for IV antibiotics if there is a problem with the wound, and occasionally we have to explant the whole system. Now that's rare but we have had to do that. The thing that we want to prevent is infection in the brain. The hardware can always be reimplanted if indicated, if the patient desires if they were to get an infection.

And Jamie gave really just such a nice summary of the literature and overall gestalt of that literature which is - and this is what I get out of it, there is about a 5% chance for a mood or cognitive change and for patients that are really concerned about that it can be difficult to discuss and that's why because this is the hardest thing to predict. We do this surgery to improve motor outcomes in our mood and disorder patients to improve motor outcomes and we are very interested in the non-motor effects because this is under study and that's why we have a database setup and then we monitor this very carefully with that 6 month follow-up.

All right let's briefly go through the targets because I think one thing that you should get out of this course is just a kind of a basic knowledge of okay what are the targets, what was that place again where they put the electrodes for Parkinson's disease. So this is a schematic and I think Dr. Homayoun already showed one or similar to this but let me grab a pointer. You know we don't put the electrode in our Parkinson's patients at the site of pathology which is the substantia nigra down here in the mid-brain that's sending these dopaminergic fibers up into the striatum that degenerate, we put them downstream in this basal ganglia circuit. The basal ganglia is not responsible for the initiation of movement but it has a large role in controlling what we call move making gain or different factors related to how movement occurs.

So there are two primary outflow pathways from the basal ganglia, one is the globus pallidus and the other is subthalamic nucleus and the target in Parkinson's disease is either of those for the reasons that have been discussed before, possibly neuropsychological reasons or the thought that patients who really need to reduce the amount of dopaminergic medication they are may benefit better from subthalamic nucleus stimulation for whatever reason. Why that happens is still not clear.

I do what to mention even though Dr. Berman mentioned this, that after this and Dr. Homayoun as well, after this 2009 study came out in JAMA which was the VA, Veteran's Administration, cooperative study, a big multicenter trial that showed actually two papers. The first paper showed that in comparison to best medical therapy, so this is groups of physicians deciding on the best way to treat patients medically, but in randomized controlled fashion patients who underwent deep brain stimulation did better. So there is clear class I evidence for that and that's why DBS again for the correctly selected patient is the gold standard for medically refractory disease. And the reasons are there is a gain in on time of about 4 1/2 hours compared to 0 gain in medical group in that study, 70% of patients had significant motor improvements compared to half that in the best medical therapy and as Dr. Pardini mentioned quality of life improvements from this surgery are actually huge in that none of these measures improved in the medication group in this trial and 7 out of 8 did in the Parkinson population.

The other very relevant study is this one that Dr. Berman mentioned in younger patients and similar changes. So quality of life improvement of essentially 26% on average in the DBS population compared to a 1% worsening in the best medical therapy group. And you can see the data there for the motor component of the UPDRS with significant benefit in the DBS group compared to best medical therapy. And some of that has to do with the fact that medication can decrease in patients who undergo DBS but as you would imagine in the medical therapy group on average it's going to keep going up with the complications that come along with that.

So again these two studies have really changed the way the field thinks about Parkinson's disease because we now have objective data that patients essentially do better with DBS therapy assuming they meet the criteria and they are appropriately selected. So that's why we are having this symposium. And then a lot of the lessons that have been learned from movement disorder surgery are now in the process of being applied to other patients that we are going to hear about this afternoon, obsessive compulsive disorder, depression and epilepsy. And we are further away in terms of the objective data there for sure but there is a lot of work being done.

Okay, this is moving on to essential tremor, you've already been told that the target is thalamus. What's the data here? There will never be a large randomized controlled trial with DBS for essential tremor because it works too well. So anyone who is at this stage and saying yes I'm ready to go for essential tremor would never agree to be randomized to a nonsurgical arm because they know that surgery is going to work. There are multiple studies of single institution, etc. that have shown on average an 80% improvement in upper extremity tremor. It's a myth that the head and voice tremor with essential tremor don't improve, they actually usually do it's just harder to predict the extent to which they will and when they will. But they actually usually do improve as well, it's just that tremors distally improve much more quickly and easier than those are proximal, voice being the hardest. And as some of the other speakers alluded to there can be a lot of reasons why a patient might have a voice tremor so these are very careful discussions that we have. But in relation to essential tremor these actually usually do improve.

Now dystonia, Dr. Susky talked to us about the target being globus pallidus, what's the data there? There are now - so smaller numbers of patients have been studied, there are a lot less patients with dystonia than there are with Parkinson's disease. So this is actually a real concern of patient support groups and maybe some of you maybe are involved with them in the dystonia population because they really feel overshadowed by the Parkinson's group. But we've still learned a lot about how to treat these patients. If you look at the worldwide literature it's over 300 patients now, it sounds small in comparison to Parkinson's disease but it is hard to publish these, these trials. So for generalized and segmental dystonia, so segmental dystonia is dystonia that combines two adjacent body parts. If you look across and actually these are not U.S. studies but there are two studies, European literature that show Class I data for 40 to 70% improvement. It's a broad range but I tell patients that we are shooting for about a 50% improvement in your symptoms.

The best response by far is with patients with a DYT1 mutation, so these are usually picked up in the pediatric population and this is a home run for DBS. These are kids, pretzel kids, that literally just unwind over the course of stimulation and GP1. So occasionally these are caught in the adult population. If you are a practitioner that treats a pediatric population with dystonia it's important to do genetic testing because that can stratify their potential benefit of brain stimulation.

There are actually similar results in cervical dystonia but there are even less of these patients, there is not randomized control data but if you look across the studies again I tell patients about a 50% improvement on average. Now there is some patients who still are not going to respond really very well. You have those patients and there are some that it can take 2 years but the head is perfectly midline at 2 years and they are essentially for practical purposes not very symptomatic.

Even smaller numbers of patients with Meige syndrome, so that's a little bit of a misnomer because this should really be called craniocervical dystonia specifically or a mandibular dystonia with blepharospasm is Meige syndrome. So we do treat these patients with DBS as well.

And Dr. Hudak who is going to talk to us about targets in OCD has some very nice slides so I'm not going to talk about that now.

Okay, so this is what traditional deep brain stimulator surgery looks like. So here is the surgeon and assistant, here is Dr. Crayman, a neurophysiologist, here is Danielle Wagner our physician assistant who also participates in the operating room and helps with intraoperative stimulation and this is a patient from Pittsburgh who has given her permission to have this picture used. A very nice lady who had a rigid akinetic Parkinson's so probably have this on a slide but in case I don't this is also another myth that it's only the patients with tremor that are really going to get a benefit from DBS. That's not true, rigid akinetic patients essentially respond just as well in terms of their UPDRS improvements. It's just not as dramatic to see.

So this is a lady who ended up doing very well and she opted for awake surgery so this is part of the stereotactic frame, it's covered by a sterile towel here and it's what patients call the halo, it's not a halo like we've used for someone who has a cervical spine injury but it is a frame, stereotactic frame, that's what it is called, that is bolted to the skull. We do this with the patient essentially under conscious sedation, also known as twilight anesthesia. So our patients and the awake cases are asleep, some of them snoring at the beginning and into the case, but we wake them up in the middle of the case for the deep brain mapping portion because that's how in the absence of being able to see in real time where the electrode is going, now that's how we know for sure where we are.

Now the stereotactic frame on average has an accuracy on the order of 2 to 5 mm, I mean few academic centers with large volumes have errors above 2 or 3 mm. But still when you saw (inaudible) very small, it's a structure that's 7 or 8 mm long. So 2 mm is a big deal. So because we can't see it we can use brain mapping to verify where we are. Okay, so how does that work? Let's see if I can play this movie.

Okay, so you are going to hear the sounds of the brain and this is a schematic of a trajectory, so this is a sideways view or sagittal view of the structures in the brain. Here is the thalamus, here is the subthalamic nucleus. Below that is part of the substantia nigra and all of these sound differently as you pass an electrode through there. So we are recording electric activity and then we are amplifying that on a speaker. And this is what it sounds like. (SOUND) That's a single cell. (SOUND) This one is two units. (SOUND) And I'm not sure if you can appreciate the difference there but that was a higher density and a more constant firing of neurons which indicates that we passed through the bottom of the subthalamic nucleus and into the substantia nigra.

So sometimes we do this one time and it makes perfect sense, and then we move on and implant the stimulating electrode which is the permanent DBS electrode. This is done with an even smaller electrode that is just used for recording because it can record from single neurons. But sometimes it doesn't make sense, and so that's why we do this, we do a couple other tracks to verify where we are. So this is the critical part of the operation in awake cases and those sounds that you heard do not sound that good to patients asleep or under general anesthesia. Now it is possible to do this under general anesthesia and usually the localization is good enough, but the gold standard is to do this awake and even there is a difference between the patient's eyes open and closed in terms of the quality of the signals that we hear in the operating room.

Here is a video that's going to show you what this looks like in the OR. So this is a microelectrode guide that's attached to the stereotactic frames that's positioned above the patient's head and this is Dr. Kremens' computer in which we are watching action potentials in real time and then the audio is going to turn on in a minute so you can hear this. (SOUND)

Okay, I'm not sure if you could appreciate that at the end but at the final hand twist you could hear modulation of neural activity, you could hear a shhh, shhh, shhh and that's confirmation that we are in the motor sensory part of the given nucleus. Now we can find this in GPi, we can find this in STN. For our essential tremor cases because the target is so large we typically don't need to do microelectrode recording although that is still done in some centers, we don't do it here. So point being now think back to that slide at the beginning about different loops, circuitry loops in the brain and we want to make sure we are in the right loop. So in this case now we know we are in the motor territory so we've got a good spot and we can go on to implant the stimulating electrode.

Okay, let's talk about awake versus asleep DBS and let me just think about the time, so we've got plenty of time here I think. So awake surgery is traditional surgery with conscious sedation at the beginning and end, the patient awake in the middle, stereotactic frame based. it's microelectrode guided as I just showed you. There is the opportunity for intraoperative testing with the patient and it was FDA approved in 1997. So these are the points that we discuss with the patient when we are talking about different options, and patients can go online, we have videos online, we encourage them to you know read about former patients to read the information that we have online or the website and we want to make sure that they've seen pictures of what it's like to be in the operating room, and they have a good understanding of this.

And so patients tend to fall into two categories. The first category is oh wonderful, I'm going to be awake and you can, you know we can test this out and I'm anticipating surgery, this is going to be great, sign me up. And the other half says I would never have come to this office if I hadn't heard that you could do this asleep because I think that's insane. So what is asleep DBS? The way that we do it is in the MRI scanner, so we essentially turn the MRI scanner into an operating room. That allows the patient to be under general anesthesia because the way we are confirming that the electrode is in the right place is with serial MRI imaging. It's real time MRI guided, there is no intraoperative testing. Some people may see that as a downside because you lose the ability for physiologic confirmation if the electrode is in the right place. However it really should never be in the wrong place because we can see it. And we'll talk about how we know what the right place is based on the MRI in a minute, but I can safely tell you we have not had to reposition any of our electrodes. In our early data there doesn't appear to be any difference between using the MRI versus microelectrode recording. And this was FDA approved in 2010. So we have some patients that say oh this is the newer procedure, okay why don't you do it the way that it's been done for 25 years and we are quite happy to do that.

So this is what this looks like, literally we turn the MRI and we have a large bore MRI in which we can operate and I'm going to show you a video of what this looks like and this is one of our ones that's online so it's already narrated.

(VIDEO PLAYS)

This video illustrates the basic steps involved in performing implantation of deep brain stimulating electrodes in an MRI scanner. The surgery occurs with the patient asleep under general anesthesia even before entering the MRI scanner. Surgery occurs at the head of the magnet and the anesthesiologists monitor the patient's condition from the foot of the scanner. Real time MRI scans are sent to a software program where the exact target for electrode placement is planned and the site of the skull opening is determined. Next an aiming device is mounted to the skull at the indicated location, a hand controller is attached and the patient is returned to the center of the MRI for a series of scans. Through obtaining these real time images the software generates instructions for lining up the aiming device until the predicted error for hitting the target is less than 1/2 a mm. When the actual trajectory matches the plan trajectory the DBS electrode is implanted. An additional MRI scan is then obtained to verify that the electrodes are located directly in the planned target. Both types of surgery are expected to achieve the same outcome for patients.

Okay, so both are expected to achieve the same outcome and I'll tell you essentially this is a skull mounted aiming device that is temporarily attached, making an incision in the MRI scanner, put it on as you saw, have the patient scanned, manipulate the aiming device according to instructions from the software, and then everything is removed at the end and at the end of the day they are exactly the same as the patients that underwent wake surgery. If you'd like to see this device the company that makes it is MRI Interventions has some models in the back, you can actually play with this yourself and have a look at it and get a better understanding.

So you know why would anyone ever develop this because a DBS works well anyway with the frame, so there is a category of patients that have anxiety about surgery specifically that's so severe that even if they've known that they've been candidates for DBS for 6, 7 years just won't do it, either won't go talk to neurosurgery about it, won't talk to their neurologist about it in a serious conversation or will see a number of physicians and just can't proceed. So I've seen a lot of these patients that show up and they say I'm so happy to realize that you have this because there is just no way I could do this awake but I know that this is going to help me. So it's nice that we have that option. We have some patients that would be perfectly fine mentally to undergo awake surgery but the tremor is so severe or dyskinesia that it just makes it much easier to do this in the MRI. We also have patients that are older and maybe some of our patients are already confined to a wheelchair because they are debilitated, it would be extremely uncomfortable in the operating room and those patients often choose to undergo MRI surgery.

And again just to bring up the pediatric population, there are small numbers of pediatric indications for DBS. These are rare cases, however in my mind there is really no doubt that the MRI is best suited assuming that you are using an MR - a visible target which you would for dystonia and GPi and again the reason that we can do this is because we can see these targets very well on the MRI and I'm just realizing I omitted a scan of an MRI to show you. But because of people doing this surgery now for a long time publishing results on which parts of the subthalamic nucleus and globus pallidus are the motor territory. What are the effects of stimulation in the operating room or the long term outcomes looking back at the location of electrodes on postoperative MRI scans we essentially know where the territories are in these structures and that's why we feel that we can place the electrodes there and still expect the same benefit.

And we are actually pretty close to on time. I want to show this one video of a patient talking about his DBS experience because I think it encompasses a lot of the issues that we've talked about so far today. So I'll just play this and then you can think about your questions and then we'll do a Q&A before lunch and then we'll have the break for lunch.

(VIDEO PLAYS)

Well I was suffering primarily from tremors. My neurologist never hesitated to increase my prescription of Sinemet or add on Requip, just added on the medication. And then I found that my on and off times were growing every more compressed. I was becoming more off than on. My condition was deteriorating fairly quickly and I didn't think that medication could be the long term answer.

If I could tell you an amusing little story. Perhaps the most distressing thing of all was that I like to play a lot of golf and I could not tee up a golf ball. Finally one of my golfing partners or buddies would say oh here, let me tee it up for you, gee, you know. And it got that bad, I couldn't even put a ball on the tee.

Then Dr. Richardson came out to one of our support group meetings about 3 years ago or so, and I was very impressed with what he had to say and how his approach was different from what had been going on beforehand. I remember the day, October 7th of last year I had put in my month of waiting for any brain swelling to go down that naturally occurs with any kind of brain surgery. And Dr. Homayoun at the Kauffman Building in Oakland, a very expert neurologist programmer turned it on and immediately I became still, very still. My son Carl was over there in a chair and he says my God you are not shaking. Just like that. It's been that way ever - for just about a year now. I'm much more even tempered, I'm almost pleasant to be around again. I sleep much better at night. I can do activities again that I either couldn't do or didn't want to do when I had the Parkinson's prior to the DBS. And I engage much more in social activities again and I'm back to doing them again.

Okay, so you know I think that really speaks to the quality of life issue. Obviously this is a patient that did very well with essentially no complications at all so it's cherry picked, we didn't ask him to say the propaganda pieces. So I apologize for that. But you know I think he's a good example of it. This is a patient that we try to find. There was no question about his candidacy, he's someone who had known he was a candidate for some years and opted for the MRI procedure, that's what he's talking about in terms of the different approach.