Medical Coverage Policy

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Deep Brain, Motor Cortex and Responsive Cortical Stimulation

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Overview

This Coverage Policy addresses the proposed indications for deep brain stimulation, motor cortex and responsive cortical stimulation.

Coverage Policy

Deep Brain Stimulation

Deep brain stimulation (DBS) is considered medically necessary for the treatment of ANY of the following:

- chronic, medically intractable primary dystonia (including generalized and/or segmental dystonia, hemidystonia, or cervical dystonia/torticollis) for an individual seven years of age or older when used in accordance with the Humanitarian Device Exemption (HDE) specifications of the U.S. Food and Drug Administration (FDA)

- chronic, medically intractable Parkinson disease (PD) when an FDA-approved device is used in accordance with the FDA-approved indications and an individual meets ALL of the following criteria:
    - has intractable motor fluctuations or dyskinesia
    - is levodopa-responsive
    - does not have a significant mental impairment (e.g., dementia, severe depression) or a medical (e.g., stroke, cardiovascular disease) or surgical (e.g., previous ablative surgery such as thalamotomy, pallidotomy) contraindication to DBS
- chronic, medically intractable essential tremor (ET) when an FDA-approved device is used in accordance with the FDA-approved indications
- chronic, medically intractable epilepsy when an FDA-approved device is used in accordance with the FDA-approved indications and an individual meets ALL of the following criteria:
    - aged 18 years or older
    - has partial onset seizures with or without secondary generalization
    - has not responded to three or more antiepileptic medications

The replacement/revision of a deep brain stimulator generator/battery and/or lead/electrode and/or patient programmer is considered medically necessary for an individual who meets ALL of the above criteria and the existing generator/lead/programmer is no longer under warranty and cannot be repaired.

DBS for any other indication including, but not limited to, obsessive-compulsive disorder is considered experimental, investigational or unproven.

Responsive Cortical Stimulation

Responsive cortical stimulation (e.g., NeuroPace® RNS® System) is considered medically necessary when ALL of the following criteria are met:

- age 18 years or older
- partial onset seizures
- seizures are refractory to two or more antiepileptic medications
- experiencing an average of three or more disabling seizures (e.g., motor partial seizures, complex partial and/or secondarily generalized seizures) per month over the three most recent months
- diagnostic testing confirms localized seizure onset to one or two foci
- not a candidate for focal resection epilepsy surgery
- not a candidate for vagus nerve stimulation

The replacement/revision of a responsive cortical stimulation neurostimulator/battery and/or leads and/or monitor is considered medically necessary for an individual who meets ALL of the above criteria and the existing neurostimulator/lead/monitor is no longer under warranty and cannot be repaired.

Motor Cortex Stimulation

Motor cortex stimulation for any indication is considered experimental, investigational or unproven.

General Background

Deep Brain Stimulation

Deep brain stimulation (DBS) involves the delivery of continuous, high-frequency electrical impulses to an area in the brain responsible for movement. The procedure is reversible and causes no permanent damage. Prior to implantation, a stereotactic rigid frame, or frame based system, is secured to the patient's skull, and the initial targeted area is selected using an imaging technique (e.g., magnetic resonance imaging [MRI], computed tomography [CT] or ventriculography). An alternative to the frame-based system is the frameless stereotactic system which may use external fiducial markers and/or internal anatomic landmarks. An electrode is introduced into the brain and test simulations are performed to evaluate and adjust tremor amplitude, diffusion of stimulation and determination of the threshold for paresthesias and speech disturbances. The electrode is connected to a computerized pulse generator which is typically implanted underneath the skin near the collarbone. The DBS

system may be implanted either unilaterally or bilaterally, depending on the distribution of the patient's symptoms. When the intended targets include both sides of the brain, two separate systems are implanted. The system also includes a handheld therapy controller and a control magnet. Batteries in the generators typically last from three to five years and are replaced in an outpatient procedure. Some newer devices may have a rechargeable battery (Weintraub, et al., 2007; Holloway, et al., 2005).

DBS is used for a carefully selected subset of individuals with chronic primary dystonia including generalized and/or segmental dystonia, cervical dystonias (i.e., torticollis), and hemidystonia. In addition, DBS is considered an established intervention for the treatment of medically refractory essential tremor (ET), Parkinson disease (PD), and epilepsy. DBS is not a first line therapy and is generally considered when the individual cannot tolerate or has failed pharmacotherapy or when pharmacotherapy is no longer effective.

There are two different types of leads that are used for DBS. Conventional leads are four-contact cylindrical leads that provide a relatively uniform current spread in all directions (omnidirectional) including areas that may result in unwanted side effects. Directional leads have the potential to allow for the minimum current necessary for stimulation which is unknown with conventional DBS systems. Directional leads provide a reduction in electrode size and reduce the electrode surface area. The ability to steer electrical current may result in a reduction of activated tissue volume, improving clinical efficacy of deep brain stimulation by reaching the expected beneficial effects at a lower current. In addition, directional leads could potentially increase the current threshold at which side effects appear. Challenges with a directional lead include anatomical targeting and the ability and time to search for the best parameter settings.

U.S. Food and Drug Administration (FDA)
The Activa® Dystonia Therapy System (Medtronic Neurological, Minneapolis, MN) was FDA-approved under the Humanitarian Device Exemption (HDE) process. The device was approved for "unilateral or bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) to aid in the management of chronic, intractable (i.e., drug-refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (i.e., torticollis) in patients seven years of age or above" (FDA, 2003). The product is currently being marketed as Medtronic DBS Therapy for Dystonia (Medtronic, 2021).

The Activa® Tremor Control System (Medtronic) was approved by the FDA under the premarket approval process (PMA) for "unilateral thalamic stimulation for the suppression of tremor in the upper extremity in patients who are diagnosed with essential tremor or Parkinsonian tremor not adequately controlled by medications and where the tremor constitutes a significant functional disability" (FDA, 1997). The product is currently being marketed as Medtronic DBS Therapy for Essential Tremor (Medtronic, 2021).

The Activa® Parkinson's Control Therapy System (Medtronic) was FDA approved in 2002 as a PMA device for "bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) for adjunctive therapy in reducing some of the symptoms of advanced, levodopa-responsive Parkinson's disease that are not adequately controlled with medication". In November 2015 the FDA modified the approval of Medtronic's DBS devices for the treatment of Parkinson disease to read "bilateral stimulation of the internal globus pallidus (gpi) or the subthalamic nucleus (stn) using Medtronic DBS therapy for Parkinson's disease is indicated for adjunctive therapy in reducing some of the symptoms in individuals with levodopa-responsive Parkinson's disease of at least 4 years' duration that are not adequately controlled with medication". The product is currently being marketed as Medtronic DBS Therapy for Parkinson's Disease (Medtronic, 2021).

There are three different types of Activa neurostimulators. The Activa SC neurostimulator is a single channel device that delivers stimulation to one side of the brain through a lead wire. Two SC neurostimulators may be used to stimulate areas on both sides of the brain. The Activa PC is a dual channel device that can deliver stimulation to one or both sides of the brain using two lead wires and has a nonrechargeable battery. The Activa RC neurostimulator is a rechargeable deep brain stimulation device, works with the SenSight™ Directional Lead System and has up to 15 years of longevity. It is 1.5 T Bull Body MRI accessable under certain conditions (Medtronic, 2021). The SenSight directional lead system received FDA approval on May 25, 2021 (FDA, 2021).

The Percept™ PC neurostimulator is the next generation of the Activa PC. The Percept PC features BrainSense™ technology to record brain signals using the implanted directional sensing DBS lead. The signals can be

recorded while it delivers therapeutic stimulation. The information recorded is used to guide treatment. The Percept PC is full body 3T and 1.5T MRI eligible. Battery life is >5 years (Medtronic, 2021).

The Brio Neurostimulation System (Abbott Medical, formerly St. Jude Medical, Plano, TX) was FDA approved in 2015 as a PMA device for the following indications: 1) bilateral stimulation of the subthalamic nucleus (STN) as an adjunctive therapy to reduce some of the symptoms of advanced levodopa-responsive Parkinson's disease that are not adequately controlled by medications; 2) unilateral or bilateral stimulation of the ventral intermediate nucleus (VIM) of the thalamus for the suppression of disabling upper extremity tremor in adult essential tremor patients whose tremor is not adequately controlled by medications and where the tremor constitutes a significant functional disability. The approval was based on a randomized controlled trial of patients, age 18–80 years with PD for at least five years duration. The Brio is a rechargeable system (FDA, 2015). This is now marketed as the St. Jude Medical Infinity™ DBS system.

On September 19, 2016, the St. Jude Medical Infinity™ DBS system (Abbott, Austin, TX) was FDA approved as a supplement to an earlier Premarket Approval (PMA) for the St. Jude Medical Brio Neurostimulation system. This approval was for a change in design, components, specifications, and material. It was the first FDA approved system to feature a directional lead, designed to deliver electrical current to a specific target in the brain and therefore, proposed to minimize unwanted side effects from brain stimulation to non-targeted areas. According to the manufacturer, the Infinity DBS System is indicated for "bilateral stimulation of the subthalamic nucleus (STN) as an adjunctive therapy to reduce some of the symptoms of advanced levodopa-responsive Parkinson's disease that are not adequately controlled by medications, and unilateral or bilateral stimulation of the ventral intermediate nucleus (VIM) of the thalamus for the suppression of disabling upper extremity tremor in adult essential tremor patients whose tremor is not adequately controlled by medications and where the tremor constitutes a significant functional disability." The Infinity directional lead has eight independent electrode contacts distributed throughout the lead. Each electrode can be turned on or off to facilitate the desired stimulation direction, shape and length for targeting and adjustment as needed. According to the manufacturer, the system is the first DBS system to use a wireless iOS™ platform (an Apple mobile operating system). An iPad mini™ (Apple, Inc.) clinician programmer is used by the physician for programming of the device, and patients use an iPad Touch® (Apple, Inc.) controller for symptom control. The system is used for the treatment of Parkinson's disease or essential tremor and can be upgraded without surgical intervention. Abbott and St. Jude Medical merged in 2017 (Abbott, 2020; FDA; 2016).

The Vercise™ DBS system (Boston Scientific, Valencia, CA) was FDA approval on December 15, 2017. The device was approved for use in bilateral stimulation of the subthalamic nucleus (STN) in the treatment of patients with moderate to advanced levodopa-responsive Parkinsons disease (PD), which is not adequately controlled with medication (FDA, 2017). Additional approval for the Vercise PC Deep Brain Stimulation (DBS) System and the Vercise Gevia DBS System was received on January 10, 2019. On Dec 29, 2020, The Vercise PC and Vercise Gevia DBS systems received expanded indications to include bilateral stimulation of the internal globus pallidus (GPi) as an adjunctive therapy to reduce some of the symptoms of advanced levodopa-responsive Parkinsons disease that is not adequately controlled by medications (FDA, 2020). The Vercise Genus DBS System received FDA approval on January 21, 2021 (FDA, 2021). The Cartesia deep brain directional lead received FDA approval on January 18, 2019.

The Vercise™ DBS system is a 16-output, multiple-channel, constant-current, implantable pulse generator (IPG) with a rechargeable battery. The system is proposed to allow steerable axial shaping of the electrical stimulation field, with adjustment of current on every contact. The Standard Lead consists of eight cylindrical contacts with each contact having its own power source (Boston Scientific, 2021). The Vercise Cartesia Directional Lead has eight contacts segmented circumferentially to allow both axial and rotational stimulation selectivity. Each segmented contact covers 90 degrees of the Lead circumference. The Vercise PC IPG is a 16 contact non-rechargeable IPG. The Vercise Gevia DBS system is a 16 contact rechargeable IPG with full-body MRI access. The Vercise Genus DBS system can be used with either a standard or directional lead, has three options for implantable pulse generators (IPG) (low-profile, contoured single- and dual-channel rechargeable and non-rechargeable) that are MRI Conditional and have wireless Bluetooth connectivity. The rechargeable IPGs have a 15 year battery life. The Vercise Genus non-rechargeable and rechargeable IPGs have either 16 contact or 32 contact ports with eight contacts per port.

In February 2009, the Medtronic Reclaim™ DBS™ Therapy for OCD system was FDA approved as a HDE device and is "indicated for bilateral stimulation of the anterior limb of the internal capsule (AIC) as an adjunct to medications and as an alternative to anterior capsulotomy for treatment of chronic, severe, treatment-resistant obsessive-compulsive disorder (OCD) in adult patients who have failed at least three selective serotonin reuptake inhibitors (SSRIs)". The power source for bilateral Reclaim™ DBS Therapy for OCD is a one or two dual-program Activa PC neurostimulator or a two single-program Activa SC neurostimulators.

The HDE labeling for the Reclaim system stated that "The safety and probable benefit of DBS for the treatment of OCD has not been established for the following:

- patients with Tourette's syndrome
- patients with primary subclassification of hoarding
- patients whose OCD is documented to be less than five years duration
- patients whose Yale-Brown Obsessive-Compulsive Scale (YBOCS) score is less than 30
- patients who have not completed a minimum of three adequate trials of first and/or second line medications with augmentation
- patients who have not attempted to complete an adequate trial of cognitive behavior therapy (CBT)
- patients with a previous surgical ablation procedure (e.g., capsulotomy)
- patients who are pregnant
- patients who are under the age of 18 years
- patients with dementia
- patients with coagulopathies or who are on anticoagulant therapy
- patients without comorbid depression and anxiety
- patients with neurological disorders
- patients with other serious medical illness including cardiovascular disease, renal or hepatic failure, and diabetes mellitus"

The labeling also stated that **"**Physicians should carefully consider the potential risks of implanting the brain stimulation system in patients with comorbid psychiatric disorders, including:

- bipolar disorder
- body dysmorphic disorder
- expanded personality impulse-control disorders or paraphilias
- psychotic disorder
- severe personality disorders
- substance abuse
- the inability to control suicidal impulses or a history of suicide attempts

The brain stimulation system may aggravate the symptoms of comorbid psychiatric disorders" (FDA, 2009).

Dystonia
Dystonia refers to a diverse group of movement disorders characterized by involuntary muscle contractions that may cause twisting and repetitive movements or abnormal postures. Primary dystonia often begins focally in the legs and progresses to a generalized (i.e., involving all of the body) syndrome. Secondary dystonias are induced by a disease or ingested substance. Dystonias may also be categorized as focal (i.e., one area of the body is involved, such as hemidystonia, cervical dystonia or torticollis), or segmental involving two or more areas.

Treatment options for dystonia include oral medications and chemodenervation (e.g., botulinum toxin [BTX], type A or type B injection therapy). Invasive interventions and surgery for dystonia are generally reserved for those patients who have significant disabilities and are refractory to aggressive medication therapy and BTX. Deep brain stimulation (DBS) is a reversible, surgical option used for the treatment of primary dystonia including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia or torticollis. DBS is indicated for individuals age seven years and older who do not respond to pharmacotherapy (i.e., medically intractable).

Literature Review: Systematic reviews, randomized controlled trials and case series have reported improvement in tremor, speech, walking, performance of activities of daily living, reduction in medication usage, mood and quality of life following DBS in patients with dystonia (Rodrigues, et al., 2019; Sarubbo, et al., 2012; Cif, et al., 2010; Mueller, et. al., 2008; Vidailhet, et al., 2007; Hung, et al., 2007; Kiss, et al., 2007; Grips, et al., 2007; Tisch, et al., 2006; Kupsch, et al., 2006; Diamond, et al., 2006; Vidaihet, et al., 2005; Zorzi, et al., 2005; Halbig, et al., 2005; Starr, et al., 2004; Kupsch, et al., 2003).

Essential Tremor (ET) and Parkinson Disease (PD)
Essential tremor (ET) is a common movement disorder characterized by postural tremor of the outstretched upper limbs that is absent at rest, not worsened by movement, and not associated with extrapyramidal or cerebellar signs. For most individuals with ET, symptoms can be managed with propranolol and primidone. Alcohol ingestion temporarily reduces ET symptoms, an effect that may last from 30 minutes to several hours. If medications and alcohol ingestion fail to provide adequate relief, patients with severe, chronic and medically intractable ET become candidates for surgical interventions (e.g., thalamotomy and pallidotomy).

Parkinson disease (PD) is a slowly progressive, chronic neurodegenerative disorder resulting from the death of the cells of the substantial nigra which contain dopamine. Eventually, lack of dopamine leads to hyperactivity in the internal globus pallidus (GPi) resulting in direct over stimulation of the GPi and over stimulation of the subthalamic nucleus (STN) which contributes to the existing over stimulation of the GPi.

Levodopa therapy effectively relieves symptoms in approximately 95% of PD patients. However, over the course of 5–10 years, most levodopa-responsive patients manifest increasingly severe and frequent motor fluctuations and dyskinesia. Motor fluctuations are alterations between periods of being "on," during which the patient experiences a positive response to medication, and being "off," during which the patient experiences a reemergence of the Parkinson symptoms that were suppressed during the "on" state. Motor fluctuations sometimes can be reduced or delayed by changing the schedule and amount of levodopa. Other medicines may be added to levodopa to help with motor fluctuations, such as dopamine agonists, COMT inhibitors, or MAO-B inhibitors. Dyskinesia consists of levodopa-related abnormal, involuntary movements. When levodopa therapy fails, propranolol may be administered as an adjuvant treatment and anticholinergic medications can counteract symptoms in some patients (Liang and Tarsy, 2021).

Patients with PD who are considered candidates for DBS include those who have been successfully treated with levodopa, but have become unresponsive to the medication (i.e., levodopa-resistant). In general, patients who have a significant mental impairment (e.g., dementia, severe depression, affective disorders, psychosis, and cognitive deficit) are not considered candidates for DBS. The presence of a significant mental impairment may preclude the ability of the patient to respond to stimulation testing during insertion of the device to assist in proper lead placement and to properly operate the stimulator following insertion. In some cases, it has been reported that DBS may worsen pre-existing mental conditions (e.g., dementia, cognitive deficits/impairment). Co-morbidities and medical contraindications (e.g., cardiovascular disease, stroke) to implantation are taken into consideration. Surgical contraindications include patients with previous ablative surgery (e.g., thalamotomy, pallidotomy) or conditions that may increase the risk of intracranial hemorrhage (Benabid, 2009; Olanow, et al., 2009).

Literature Review: Systematic reviews, meta-analysis, randomized controlled trials and case series support the safety and efficacy of DBS for the treatment of ET and PD (Vitek, et al., 2020; Schuepbach, et al., 2013; Weaver, et al., 2012; Flora, et al., 2010; Zhang, et al., 2010; Folett, et al., 2010; Williams, et al., 2010; Weaver, et al., 2009; Tir, et al., 2007; Deuschl, et al., 2006; Kleiner-Fisman, et al., 2006; Temel, et al., 2006; Visser-Vandewalle, et al., 2005; Rodriguez-Oroz, et al., 2005; Kraus, et al., 2004; Puzke, et al., 2004; Renhcrona, et al., 2003; Deep-Brain Stimulation for Parkinson's Disease Study Group, 2001; Koller, et al., 2001; Obwegeser, et al., 2001; Ondo, et al., 2001b; Vesper, et al., 2002; Schuurman, et al., 2000).

Professional Societies/Organizations: Based on a systematic review of the literature, the Congress of Neurological Surgeons (Rughani, et al., 2018) made the following level 1 recommendations (generally accepted principles for patient management that reflect a high degree of clinical certainty) on deep brain stimulation for the treatment of Parkinson's disease:

- "Given that bilateral STN DBS [subthalamic nucleus deep brain stimulation] is at least as effective as bilateral GPi DBS [globus pallidus internus deep brain stimulation] in treating motor symptoms of Parkinson's disease (as measured by improvements in UPDRS-III scores [Unified Parkinson's Disease Rating Scale, Part III]) consideration can be given to the selection of either target in patients undergoing surgery to treat motor symptoms.
- When the main goal of surgery is reduction of dopaminergic medications in a patient with Parkinson's disease, then bilateral STN DBS should be performed instead of GPi DBS.
- There is insufficient evidence to make a generalizable recommendation regarding the target selection for reduction of dyskinesias. However, when the reduction of medication is not anticipated and there is a goal to reduce the severity of "on" medication dyskinesias, the GPi should be targeted.
- When considering improvements in quality of life in a patient undergoing DBS for Parkinson's disease, there is no basis to recommend bilateral DBS in one target over the other.
- If there is significant concern about cognitive decline, particularly in regards to processing speed and working memory in a patient undergoing DBS, then the clinician should consider using GPi DBS rather than STN DBS, while taking into consideration other goals of surgery.
- If there is significant concern about the risk of depression in a patient undergoing DBS, then the clinician should consider using pallidal rather than STN stimulation, while taking into consideration other goals of surgery.
- There is insufficient evidence to recommend bilateral DBS in one target over the other in order to minimize the risk of surgical adverse events."

The Quality Standards Subcommittee of the American Academy of Neurology (Zesiewicz, et al., 2011; reaffirmed 2017) practice parameter on therapies for ET stated that DBS of the Vim thalamic nucleus is effective in reducing contralateral limb tremor in medically refractory ET. Bilateral DBS is necessary to suppress tremor in both upper extremities, but there are insufficient data regarding the risk-benefit ratio of bilateral versus unilateral DBS in the treatment of ET. Both DBS and thalamotomy are effective in suppressing tremor in ET; however, DBS is associated with fewer adverse events. The decision to use either procedure should be based on each individual's circumstances and risk for intraoperative complications.

Epilepsy
Epilepsy is a common condition with repeated seizures caused by abnormal bursts of electrical activity in certain areas in the brain. Seizures may cause problems with muscle control, movement, speech, vision and/or awareness. Deep brain stimulation (DBS) of the thalamus, STN, cerebellum, hippocampus, caudate nucleus, mammillary nuclei and anterior nucleus of the thalamus (ANT) has been proposed for the treatment of drug-refractory epilepsy. The ANT, the centromedian nucleus of the thalamus, and the hippocampus are most frequently employed. It has also been proposed that individuals who do not respond to vagal nerve stimulation or surgical resection may be DBS candidates (Bouwens, et al., 2018; Middlebrooks, et al., 2018; Cukiert and Lehtimake; 2017; Cukiert, et al., 2017; Halpern, et al., 2008; Villanueva, et al., 2007).

U.S Food and Drug Administration (FDA): FDA approved the Medtronic DBS system for the treatment of epilepsy on Apr 27, 2018. The System is indicated for bilateral stimulation of the anterior nucleus of the thalamus (ANT) as an adjunctive therapy for reducing the frequency of seizures in individuals 18 years of age or older diagnosed with epilepsy characterized by partial-onset seizures, with or without secondary generalization, that are refractory to three or more antiepileptic medications. "The Medtronic DBS System for Epilepsy has demonstrated safety and effectiveness for patients who average six or more seizures per month over the three most recent months prior to implant of the DBS system (with no more than 30 days between seizures). The Medtronic DBS System for Epilepsy has not been evaluated in patients with less frequent seizures." The main components of the device include the implantable Active PC neurostimulator (INS), leads, extension, external neurostimulator (ENS), clinician programmer, and patient programmer (FDA, 2018).

Literature Review: Salanova et al. (2021) reported the 10 year results of the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE) randomized controlled trial. The results included the effectiveness and safety of deep brain anterior thalamus stimulation after seven and 10 years for the improvement in seizure reduction, and to report on the incidence of sudden unexpected death in epilepsy (SUDEP). A total of 73 subjects of the initial 110 (66%) were evaluated at the seven year visit and 62/110 (56%) at the 10 year with an

average age of 37.1 ± 11.8 years and 47.9% female. The average number of years with epilepsy was 22.5 ± 13.9 and the median baseline seizure per month was 17. Sixteen patients (21.9%) had previous resective surgery and 32 (43.8%) had a prior vagus nerve stimulation (VNS) implant. Primary outcomes measured included seizure severity (Liverpool Seizure Severity Scale) and quality of life in epilepsy (Quality of Life in Epilepsy Inventory-31 [QOLIE-31] scale). Secondary outcomes included adverse event monitoring and the incidence of SUDEP. The sample of subjects used to determine the incidence of SUDEP included data from two sources: the SANTE study and the pilot studies at five centers. The median seizure frequency percent reduction from baseline at seven years was 75% ($p<0.001$) with 74% having ≥ 50% reduction in total seizures. Significant reductions were self-reported by subjects in the following areas: “most severe” seizures (71%), focal impaired awareness seizures (FIASs; 78%), focal to bilateral tonic–clonic seizures (FBTCSs; 71%), and focal aware seizures (FASs; 92%) ($p<0.010$ for all). Eighteen percent (n=20) were seizure free for six consecutive months, nine subjects (8%) for more than two years, one subject for five years and one for six years. At seven years, the median percent seizure reduction from baseline was 75% ($p<0.05$) for subjects who had previously tried VNS, 78% for those without prior VNS ($p<0.001$) and 69% ($p=0.084$) for those who had previous resective surgery. The subgroup analysis showed a median seizure reduction of 78% for temporal lobe seizures ($p<0.001$), 86% for frontal lobe seizures ($p=0.129$) and 39% ($p=0.320$) for other seizures at seven years of follow-up. The improvements from baseline on the Liverpool Seizure Severity Scale and QOLIE-31 reported in the five-year follow-up study were maintained at year seven (both measures, $p<0.001$ compared to baseline). Forty-three percent of subjects experienced a clinically meaningful change on the QOLIE-31, which is defined as a 5-point change from baseline. Eighty-four percent (54/64) of subjects reported that they were satisfied or greatly satisfied with the results of their therapy. There were no unanticipated serious adverse events. Events related to DBS or epilepsy from implant to 10 years, included implant site infection in 12.7% of subjects (1-year rate of 7.3%) and leads not within target in 8.2%. Most device related events occured during the operative phase. Other adverse events included depression in 37.3% of subjects (two thirds had history of depression), memory impairment in 30.0% of subjects (half had history of memory impairment), and suicidality in 10.0%. There were eight deaths in the study, one occurring prior to implant and not included in the calculations. No death was directly attributed by the investigator to the implant, device, or therapy. The SUDEP rate for the SANTÉ study was 2.1 deaths/1000 person-years, inclusive of definite or probable SUDEP. There was no SUDEP in the pilot follow-up subjects, bringing the overall rate to 2.0 deaths/1000 person-years, based on 1,014 person-years of device experience. The overall mortality rate in the study, based on seven subject deaths post implant, was 6.9 per 1000 person-years. Author noted limitations included the effect of discontinuation of subjects who did poorly and the use of adjunctive therapies, such as anti-seizure medications and their potential impact on the long-term results. The authors also noted that the study was not powered to address SUDEP rate variations. Long term results showed that with ongoing DBS therapy subjects continued a trend for improvement in seizure reduction.

Herrman et al. (2019) conducted a prospective, randomized, double-blinded study to evaluate seizure frequency and safety of anterior thalamic nucleus (ATN) deep brain stimulation (DBS) for the treatment of epilepsy. Eighteen patients were blinded to receive active stimulation or no stimulation for six months. All patients received active stimulation after the first six months. Eligible patients were adults aged 18–70 years, minimum IQ of 70, diagnosed with focal epilepsy, with or without secondary generalization. Exclusion criteria were psychogenic non-epileptic seizures, generalized epilepsy, pregnancy, other neurological diseases and serious medical conditions including psychiatric illnesses. All patients were not candidates for resective epilepsy surgery. Patients were followed up at 3, 6, 9 and 12 months for changes in seizure frequency, changes in types of seizures and possible adverse effects. There was no significant difference in seizure frequency between the two groups at the end of the blinded period at six months. Three patients experienced an increase in seizure frequency (>20%) which curtailed adding an additional 20 patients to the study, as was planned. Adverse events included: an increase in seizure activity (n=3), headache, dizziness, vertigo, memory deficit, transient depression, “strange thoughts”, changed perception of reality, problems finding words and altered circadian seizure pattern. Reported positive effects included: more energy, better sleep, shorter and less intense seizures, shorter postictal phase, less frequent seizures with corresponding falls and traumas, and better cognitive functioning. Author noted study limitations included a possible micro-lesion effect. Additional limitations included the small patient population and short-term follow-up. The main finding was that there was no significant difference in seizure frequency after the blinded period between patients with or without stimulation.

Chang and Xu (2018) conducted a systematic review and meta-analysis of studies investigating DBS in patients with refractory temporal lobe epilepsy (TLE). The primary outcome was remarkable seizure reduction (RSR) in

the last reported follow-up. RSR was defined as a seizure frequency reduction of at least 70%. Study inclusion criteria were: (1) postoperative seizure outcomes following DBS collected from at least four patients with refractory TLE, (2) a mean or median follow-up of ≥ 1 year, and (3) outcomes measured with a seizure frequency reduction scale or comparable tool. Eight case-control studies (n=61) met inclusion criteria. The postoperative RSR rate pooled from the eight included studies was 59%. Hippocampal and anterior thalamic nuclei (ATN) sites of stimulation had similar odds of producing RSR. Only one of the eight studies examined seizure outcomes after DBS was delivered to the thalamic nuclei.

Li and Cook (2018) conducted a systematic review of the literature to evaluate DBS for the treatment of drug-resistant epilepsy. One randomized controlled trial and sixteen noncontrolled studies investigated DBS of the anterior nucleus of the thalamus (DBS-ANT). With the exception of two studies (n=87 and 110), patient populations ranged from 2–16. Four randomized controlled trials and nine noncontrolled studies evaluated DBS of hippocampus (HC) with patient populations ranging from 2–95. Two randomized controlled trials and six noncontrolled trials evaluated stimulation of the centromedian nucleus of the thalamus (CMT) (n=2–11) and two randomized controlled trials and six noncontrolled studies evaluated cerebellum DBS. One study reported on stimulation of the nucleus accumbens (NA). Mean follow-up from the studies primarily ranged from ten days to four years and the type of epilepsy varied. Outcome measures were varied and results were conflicting with some studies reporting no improvement in outcomes and others reporting significant improvement (e.g. reduction in seizure frequency). Pooled data indicated that stimulation of the anterior nucleus of the thalamus (ANT) and hippocampus (HC) resulted in a decrease in the frequency of refractory seizures. Half of all patients from clinical studies experienced a 46%-90% seizure reduction with ANT-DBS and a 48%-95% seizure reduction with HC-DBS. The efficacy of stimulation of CMT, CB, STN, and other targets were inconclusive due to the lack of evidence. Adverse events were either surgical (e.g., hemorrhage, wound infection, implant site pain), stimulation-related (e.g., worsening/new seizures, paresthesia, dizziness, memory/cognitive changes) and equipment related events including lead migration, lead displacement, lead fracture, erosions and equipment infections. The authors noted that response to DBS for the treatment of epilepsy varied based on the presence of structural abnormalities found on imaging for ANT and HC stimulation, electrode placement and the types of seizure/syndromes being treated. Limitations of the studies included: small patient populations; short-term follow-ups; risk of bias; patient-recorded seizure events; and heterogeneity of the types of seizures, target areas stimulated, patient characteristics, data collection methods and outcome reporting and criteria.

Zhou et al. (2018) conducted a systematic review of the literature to investigate the safety and efficacy of DBS for the treatment of epilepsy. Forty-one articles met the inclusion criteria of reporting clinical outcomes involving at least one patient. The most frequently studied stimulation targets were the ANT (n=20 studies; 220 patients), CMT (n=7 studies; 35 patients), HCP (n=10 studies; 73 patients), and other alternative targets (n=7 studies). Some studies evaluated multiple targets and were included more than once. Overall, the number of patients per study ranged from 1–16 and follow-ups ranged from 48 hours to five years. ANT, CMT and HCP with responder rates of 44%–100%, 50%–100%, and 60%–100%, respectively were reported. Other alternative targets have demonstrated varying degrees of success.

Sprengers et al. (2017) conducted a Cochrane systematic review of randomized controlled trials to assess the safety, efficacy and tolerability of deep brain (DBS) and cortical (neocortex and cerebellar cortex) (DBS) stimulation for the treatment of refractory epilepsy. Twelve randomized controlled trials met inclusion criteria. Comparators included sham therapy, respective surgery or antiepileptic drug therapy. Outcomes included seizure freedom, responder rate, percentage seizure frequency reduction, adverse events, neuropsychological outcomes and quality of life. Follow-ups ranged from one to three months. The studies included: anterior thalamic DBS (one study; n=109), centromedian thalamic DBS (two trials; n=20), cerebellar stimulation (three trials; n=22), hippocampal DBS (four trials; n=21), nucleus accumbens (one trial; n=4) and responsive ictal onset zone stimulation (one trial; n=191). According to the authors, moderate-quality of evidence did not statistically or clinically demonstrate significant changes in the number of subjects who were seizure-free or had a ≥ 50% reduction in seizure frequency one to three months following anterior thalamic DBS in (multi) focal epilepsy, responsive ictal onset zone stimulation in (multi) focal epilepsy patients and hippocampal DBS in (medial) temporal lobe epilepsy. A statistically significant reduction in seizure frequency was found for anterior thalamic DBS compared to sham stimulation, responsive ictal onset zone stimulation, and hippocampal DBS. Both anterior thalamic DBS and responsive ictal onset zone stimulation did not demonstrate a clinically meaningful impact on quality of life following three months of DBS. No statistically significant effects were reported following

centromedian thalamic DBS, nucleus accumbens DBS and cerebellar stimulation. The limited number of patients preclude firm statements on safety and tolerability of hippocampal DBS. Adverse events included postoperative asymptomatic intracranial hemorrhage and postoperative soft tissue infections.

Troster et al. (2017) reported on the incidence of memory and depression adverse events (AE) in the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE) randomized control trial blinded phase (first three months). Additionally, they reported on the relationship of memory and depression to objective neurobehavioral measures, baseline characteristics, quality of life and long-term neurobehavioral outcome (through year seven). The SANTE trial investigated deep brain stimulation (DBS) of the anterior nucleus of the thalamus (ANT) for treatment of localization related epilepsy. Patients (n=110) were included if they were adults with at least six partial or secondarily generalized seizures per month who had failed at least three antiepileptic drugs. Excluded were patients with IQ <70, inability to complete neuropsychological testing, nonepileptic seizures, and any of the following in the five years preceding baseline evaluation: history of substance abuse, psychiatric illness hospitalization, suicide attempt, or symptoms of psychosis (hallucinations, delusions) not related to medication or an ictal or post-ictal state. Neuropsychological measures were tested using the following: verbal memory: California Verbal Learning Test, Second Edition (CVLT-II) Trials 1–5 total and long delay free recall; visual memory: Brief Visuospatial Memory Test–Revised (BVMT-R) total recall and delayed recall; and depression: Profile of Mood States (POMS) Depression scale. Neuropsychological assessments were conducted at three months and one month prior to implantation and at week four, month four, month seven, and annually through year seven following implantation. At three months, the control patients crossed over to DBS. During the blinded phase adverse events were reported as follows: depression (active n=8, 14.8%; control n=1, 1.8%) (p=0.016) and memory AE (active n=7, 13%; control n=1, 1.8%) (p=0.032). In half of the active group (n=4/8) depression and all memory events resolved. Other adverse events reported included: “confusional state” (7.4% active, 0% control) and “anxiety” (9.3% active, 1.8% control). Seven year evaluation reported no significant cognitive declines, neurobehavioral problems (e.g., apathy, disinhibition), subjective cognitive declines, or affective distress (depressive and anxious symptoms). Author noted limitations included the lack of statistical power and lack of a long-term control group.

Salanova et al. (2015) reported on the efficacy and safety results of the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE) randomized control trial. The SANTE trial investigated deep brain stimulation of the anterior nucleus of the thalamus (ANT) for the treatment of localization related epilepsy (Fisher et al., 2010). The objective of the research was whether seizure frequency continued to improve over time with open-label anterior thalamic stimulation. Starting 13 months after device implantation, stimulation parameters were adjusted at the investigators’ discretion and the subjects (n=110) were followed for an additional four years. Subjects were included if they were adults with at least six partial or secondarily generalized seizures per month who had failed at least three antiepileptic drugs. Excluded were patients with IQ <70, inability to complete neuropsychological testing, or progressive neurologic deficits. Primary outcomes measured included efficacy (seizure diary), Liverpool Seizure Severity Scale (LSSS), and 31-item Quality of Life in Epilepsy (QOLIE-31). Safety was addressed by adverse event collection and neuropsychological measures. Thirty patients were lost in follow up including four deaths unrelated to DBS. One sudden unexpected death was due to epilepsy. The seizure frequency median change decrease from baseline was statistically significant at one year (41%) and at five years (69%) (p<0.001 for both). In both the LSSS and QOLIE-31, a higher value reflects improvement. The outcomes at one and five years were statistically significant. The mean improvement from baseline in the LSSS was 13.4 (n=103) at one year and 18.3 (n=81) at five years (p<0.001 for both). The mean improvement from baseline in QOLIE-31 scores at one year was 5.0 (n=102) and at five years was 6.1 (n=80) (p<0.001 for both). Neuropsychological test composite scores showed statistically significant gains from baseline to five years including attention (p<0.001), executive function (p<0.001), depression (p=0.039), tension/anxiety (p=0.027), total mood disturbance (p= 0.0016), and subjective cognitive function (p<0.001). Adverse events included: implant site pain in 23.6% (at any time) (20.9% in five years); paresthesias including tingling, vibration, or shocking sensations at the stimulator implant site in 22.7%(22.7% in five years); implant site infection in 12.7% (12.7% in five years); therapeutic product ineffective in 10.0% (8.2% in five years); discomfort in 9.1% (9.1% in five years); lead(s) not within target in 8.2% (8.2% in five years); sensory disturbance in 8.2% (8.2% in five years); memory impairment in 7.3% (6.4% in five years), implant site inflammation in 7.3% (7.3% in five years), dizziness in 6.4% (6.4% in five years); postprocedural pain in 6.4% (6.4% in five years); extension fracture in 5.5% (4.5% in five years); and neurostimulator migration in 5.5% (5.5% in five years). Other adverse events included depression reported in 37.3% (32.7% in five years), suicidal ideation 11.8% (n=13 patients) (8.2% in

five years), and memory impairment 27.3% (25.5% in five years). Overall, seizure frequency was reduced from baseline. Author noted limitations include lack of a long-term control group and no detailed analysis of medication changes during the follow-up phase.

Fisher et al. (2010) conducted a multicenter, double-blind, randomized controlled trial (n=110) to evaluate DBS for the treatment of epilepsy. Patients underwent bilateral stimulation of the anterior nuclei of the thalamus for epilepsy (SANTE). Diagnosis included medically refractory partial seizures including secondarily generalized seizures. Postoperatively, patients kept a daily diary of seizure activity for primary analysis. One month following implantation, patients were randomized to stimulation (n=54) or no stimulation (n=55) (one outlier patient was excluded due to lack of diary information). The intent-to-treat (ITT) analysis, with exclusion of the one patient, across the three-month blinded phase favored the stimulation group (p=0.039) and showed a significant decrease in seizure activity (p=0.039). Complex partial seizures significantly improved more in the stimulation group compared to the no stimulation group (p=0.041, outlier removed). The severity of seizures decreased more in the stimulated group (p=0.047) and injuries from seizures was greater in the control group (p=0.01). Effectiveness of therapy was dependent on the region of the seizure origin. Patients with seizure origin in frontal, parietal or occipital regions did not demonstrate significant differences in seizure reduction between the two groups. Following completion of the blinded period, 108 patients received stimulation for an additional 1–10 months. ITT analysis of patients who elected to continue stimulation following the blinded period revealed a 50% responder rate in 81 patients (54%) at 25 months, and 42 patients (67%) at 37 months. Three patients had > 50% worsening of seizures. At the two-year follow-up, 13 of 81 patients (16%) had a $\geq$ 90% median seizure frequency reduction compared to baseline. Fourteen patients (13%) were seizure-free for at least six months, eight patients (7.3%) for at least one year, four patients (3.6%) for at least two years, and one patient (0.9%) was seizure-free for more than four years. Adverse events included paresthesia, infection, implant site pain, depression, asymptomatic hemorrhages and new seizure events. Eighteen patients withdrew due to adverse events. Limitations of the study include the small, heterogeneous patient population and the short-term follow-ups.

Other Conditions
DBS has been proposed for the treatment of multiple other disorders including: addictions (e.g., smoking, alcohol); aggressive behavior; Alzheimer disease; anorexia nervosa; camptocormia; cancer; cerebral palsy; cluster headache; chronic pain; central pain from spinal cord injury; depression; Huntington's disease; Lesch-Nyhan syndrome; Lewy body dementia; movement disorders secondary to structural lesions (e.g., basal ganglionic stroke, tumor or vascular malformation); multiple sclerosis tremor; non-idiopathic Parkinson disease ("Parkinson Plus"); obesity; restless leg syndrome; short-lasting, unilateral, neuralgiform headache (SUNCT); tardive dyskinesia; tremors of the head and voice; trigeminal neuralgia; trigeminal neuropathy; Tourette syndrome (i.e., Tics); secondary tremors from birth injury, trauma, toxins and stroke; and disorders of consciousness (e.g., minimally conscious, vegetative state) (Contreras López, et al., 2021; Gouveia, et al., 2021; Maltête, et al., 2021; Potes, et al., 2021; Jinnah, 2020; Nyhan, et al., 2014; Taghva, et al., 2012; Lyons, 2011; Prévinaire, et al., 2009; Larson, 2008; Damier, et al., 2007; Kern and Kumar 2007; Mink, et al., 2006; Skidmore, et al., 2006; Anderson and Arciniegas, 2004).

There is insufficient evidence in the published peer-reviewed scientific literature to support DBS for the treatment of any of these conditions. Studies are primarily in the form of case reports and case series with small patient populations (n=2–10) and short-term follow-ups. In some studies, various areas of the brain are used for stimulation and there is a lack of consensus as to which area/areas should be targeted for each condition. Definitive patient selection criteria have not been established. Comparison of DBS to established pharmacotherapy and surgical interventions is lacking. DBS devices are not FDA approved for treatment of these conditions.

Cerebral Palsy: Cerebral palsy (CP) is one of the most common causes of secondary dystonia. Approximately 10%–15% of patients develop a dyskinetic movement disorder which starts in early infancy and progresses throughout adulthood. Patients may become severely disabled in their motor function. DBS is a proposed treatment option for those individuals in whom pharmacotherapy is ineffective and/or the side effects limit dosing. There is insufficient evidence to support DBS for CP dyskinesia.

Bohn et al. (2021) conducted a systematic review and meta-analysis to evaluate pharmacological and neurosurgical interventions in patients with cerebral palsy and dystonia. Forty-six studies including nineteen non-randomized studies (n=5-37) evaluating deep brain stimulation met inclusion criteria. Evidence certainty was assessed as very low for all outcomes. A meta-analysis of 16 studies (n=173) suggested an improvement in dystonia. The analysis of 15 studies (n=168) revealed that the mean difference improvement in the Burke–Fahn–Marsden Dystonia Rating Scale movement (BFMDRS-Movement) was -12.1 (16.8% improvement). The minimal clinically important difference (MCID) for individuals with primary dystonia is 16.6%. Eleven studies (n=109) reported standardized mean difference (SMD) in improvement of motor function of -0.30. Five studies (n=78) reported using validated measures of pain/comfort had a SMD improvement of 1.0. Two studies (n=18) reported clinically significant changes in the Canadian Occupational Performance Measure in both performance scores (in 54-100% of participants) and satisfaction scores (in 54-80% of participants) at 12 months. One study (n=5) reported participants achieved 67% of their goals at 12 months using the Goal Attainment Scale. Four studies (n=50) reported on the 36-item Short-Form Health Survey using physical functioning, vitality, and mental health domains to estimate the effect on quality of life (QoL). Improvement in the mean difference of physical functioning (11.4), vitality (13.4), and mental health (12.9) were higher than the MCIDs established for individuals with primary dystonia. Most common adverse events included infections requiring hardware removal (7-40%) and stimulation-induced dysarthria (17-30%). Author noted limitations include heterogeneity in study design, small patient populations and short term follow up.

Koy et al. (2013) conducted a systematic review and meta-analysis to evaluate DBS for the treatment of dyskinetic cerebral palsy. Twenty articles consisting of 11 case reports and 19 case series (n=3-14) met inclusion criteria. The analysis included 68 patients who had undergone DBS and outcomes were assessed by the Burke-Fahn-Marsden Dystonia Rating Scale movement (BFMDRS-M) and disability scores (BFMDRS-D). At the 12-month median follow-up, a significant improvement was seen in the postoperative BFMDRS-M ($p<0.001$) and the BFMDRS-D ($p<0.001$). The authors noted that the published results were “very variable” and overall, response for secondary dystonia was “far less dramatic” than reported results for primary dystonia. Limitations of the meta-analysis include the low level of evidence, small number of patients, heterogeneity of the procedures and selection of primary DBS target, variable short-term follow-up times with some studies only reporting one post-operative BFMDRS score, and quality-of-life data was only reported in four studies.

Chronic Pain: DBS has been proposed for the treatment of various types of chronic, intractable pain. However, because of surgical and nonsurgical treatment interventions, its use has substantially decreased (Kern and Kumar, 2007). Two studies were initiated in the 1980s seeking FDA approval but were prematurely concluded; thus, DBS for the treatment of chronic pain has not received FDA approval (Owen, et al., 2007). Studies are primarily in the form of case series with small patient populations (n=34–56) and short term follow-ups (Owen et al., 2007; Rasche, et al., 2006).

Deer et al. (2020) conducted a current systematic review of the literature of deep brain stimulation (DBS) for the treatment of pain. Five studies (two randomized control trials (n=10-11), one observational, two case series) with study dates of 1990, 2006, 2010, 2013, and 2017 were included. Studies included small patient populations, short term-follow-ups, heterogeneity of diagnosis and surgical approach. there is insufficient evidence to support the use of DBS for the treatment of pain.

In a meta-analysis, Bittar et al. (2005) found six studies, case series and retrospective reviews, which met inclusion criteria. Follow-up ranged from one month to 15 years. A variety of stimulation sites and methods were utilized. Patients selected for DBS included individuals with pain of known organic origin who failed or poorly tolerated conventional therapies and did not have neuroses/psychoses or severe depression. Twenty-four different pain etiologies (n=1–103) were included (e.g., phantom limb and stump pain, spinal cord pain and/or injury, peripheral neuropathy/radiculopathy, cancer pain and anesthesia dolorosa). The authors reported that DBS was more effective for nociceptive pain than for deafferentation pain ($p<0.01$). Success rates of up to 80% were reported in patients with low back pain (n=103) and failed back surgery syndrome (n=59).

Cluster Headache: A cluster headache is a severe, chronic headache that typically occurs in cyclical patterns (i.e., clusters) on one side of the face at the same time of the day for several weeks. Due to the severity of pain, cluster headaches are often referred to as “suicide headaches.” Treatment options include pharmacotherapy and oxygen administration. DBS has been proposed for the treatment of severe cluster headaches that are refractory

to medical management, but there is insufficient evidence in the published peer-reviewed literature to supports its effectiveness in this patient population.

Fontaine et al. (2010) conducted a randomized, crossover, double-blind, multicenter study including 11 patients with refractory chronic cluster headaches. Patients were randomized to two, one-month periods of active stimulation vs. sham stimulation separated by a one-week wash-out period. Thereafter, a 10-month open phase was conducted. At the end of the crossover period, there was no significant difference in the frequency of weekly attacks in either group. Following the 10-month open phase, the frequency of the attacks significantly decreased (p=0.08) and patients reported reduced emotional impact. Three "serious" adverse events included an infection requiring removal of the device, loss of conscious with hemiparesia, and severe micturition syncope episodes with hypotension. The study is limited by the small patient population and the short-term follow-up. As the authors noted, due to the conflicting results in the blinded phase and the open phase additional randomized controlled trials are needed to determine the clinical utility of DBS for cluster headaches.

Depression: Depression is an illness characterized by persistent sadness, anxiety, hopelessness, helplessness, pessimism, and a loss of energy and interest in activities. It typically interferes with the activities of daily living and normal functioning (Hauptman, et al., 2008). DBS has been proposed for the treatment of chronic depression nonresponsive to conventional therapies (e.g., behavioral therapies, pharmacotherapy). There is insufficient evidence in the peer-reviewed literature to support DBS for depression. Studies are primarily in the form of small case series (n=15–20) with short-term follow-ups (Narang, et al., 2016; Lozano et al., 2012; Kennedy, et al., 2011; Malone, et al., 2009; Lozano et al., 2008).

Wu et al. (2021) conducted a systematic review and meta-analysis to assess the efficacy and safety of deep brain stimulation (DBS) for treatment-resistant depression (TRD). Seventeen studies (n=233) met inclusion criteria with two randomized control trials and 16 case series, comparative studies and pilot studies. Patients (n=4-20) were aged 42 to 50.7 years old and follow-ups from three months to five years. Inclusion criteria were studies with patients diagnosed with TRD based on the diagnostic and statistical manual of mental disorders, 4th edition (DSM-IV); intervention of DBS targeting various nerve nuclei; outcomes of response decline, remission, and recurrence rates; and adverse events (AE). Response rate was 56% (ranging from 43–69%), remission rate 35% (ranging from 27–44%), and recurrence rate 14% (ranging from 4–25%). AE rate was 67% (ranging from 54–80%). The median rate of suicidal attempt was 16.7% (ranged from 4–80%) and of suicide was 4.8% (ranged from 3.3–12.5%). The author noted limitations included: small patient populations, heterogeneity of study design, patient characteristics and outcomes measurement. The authors concluded that DBS therapy is still in the stage of exploration and cannot be used as a recommended intervention for TRD.

Kisely et al. (2018) conducted a systematic review and meta-analysis to investigate the clinical efficacy and safety of deep brain stimulation (DBS) for the treatment of depression. A total of seven double-blinded randomized control trials and two single-blinded cross over trials met inclusion criteria. Patient population ranged from 4–90 (n=200 patients). Included studies were single- or double placebo controlled, crossover, and parallel-group trials in which DBS was compared with sham treatment using validated scales: Beck Depression Inventory (BDI), Hamilton Depression Rating Scale (HAM-D), and Montgomery–Asberg Depression Rating Scale (MADRS). Studies were excluded if they did not have a sham comparator. The intervention was deep brain stimulation to the sub-callosal cingulate (SCC) gyrus (n=5 studies), the medial forebrain bundle (n=2 studies), the related structures of the anterior limb of the internal capsule (n=1 study) and ventral capsule/striatum (n=1 study). The comparator was sham treatment. The primary outcome measured was a reduction in depressive symptoms using a validated scale. Secondary outcomes included comorbid psychiatric symptoms, global functioning, cognition, and adverse effects. Length of follow-up ranged from one day to 26 weeks. Outcome results were conflicting. Four studies reported no significant difference between active and sham control groups. For those studies that reported an improvement in depression rating scales on active treatment, a positive response time varied from 1–8 weeks. There was no significant difference in the secondary outcomes measures of quality of life, global functioning, or neuropsychiatric outcomes. The most frequent adverse events were increased depression (n=33), device related discomfort (n=38), pain/erosion around the incision (n=23), agitation (n=15), headache (n=24) and infection (n=14). Other serious adverse events included hemorrhage, delirium, nausea/vomiting, hearing/visual disturbances, seizures, suicide attempts, suicidal ideation, seizures, fatigue and hospital admission. Limitations of this review included the small patient populations, short term follow ups, limited

number of studies, and low quality of the studies. Patient selection criteria, length of optimization period and target location for deep brain stimulation have not been established. Additional well-designed multi-center randomized controlled trials are needed to establish the safety and efficacy of this treatment for depression.

Zhou et al. (2018) conducted a systematic review and meta-analysis to investigate the safety and efficacy of deep brain stimulation (DBS) for the treatment of depressive symptoms in treatment-resistant depression (TRD). A total of 14 studies met the inclusion criteria. The number of patients per study ranged from 3–25. Included studies investigated DBS for improvement of depressive symptoms that were evaluated using either the Hamilton depression rating scale (HDRS) or Montgomery–Asberg depression rating scale (MARDS) in TRD patients. Studies that added or changed anti-depressants during the DBS trial were excluded. Abstracts, case studies, reviews, and duplicate cohorts were also excluded. Deep brain stimulation was used targeting one of these four regions of the brain: subcallosal cingulate gyrus (SCG), ventral capsule/ventral striatum (VC/VS), medial forebrain bundle (MFB), and nucleus accumbens (NAcc). The primary outcome was a decrease in depressive symptoms as evaluated by HDRS and MARDS scores from baseline to post treatment. Length of follow up was up to 12 months, but varied between studies. The overall response rate showed a significant reduction in HDRS after DBS stimulation in the four regions: SCG ($p<0.00001$), VC/VS ($p=0.005$), MFB ($p=0.0001$), and NAaa ($p=0.003$). The pooled results of the MADRS also showed a reduction in the following areas: SCG ($p=0.001$), VC/VS ($p=0.0002$), and MFB ($p<0.0007$). Adverse events included pain (incisional site [n=7] and headache [n=9]), infection (n=8), swollen eye (n=12), nausea, dizziness, worsening depression (n=12), suicide attempts (n=10), agitation (n=12) and sleep disturbances (n=10). Limitations of this review include heterogeneity of clinical trial designs, varying treatment durations and stimulation parameters, lack of comparators and small sample sizes. The optimal target brain regions and treatment stimulation for DBS for the treatment of depression have not been determined. Well designed, multi-institutional studies with large patient populations are needed to determine the safety and efficacy of this DBS for this subpopulation.

Bergfeld et al. (2016) conducted a randomized, cross-over study (n=25) to investigate DBS for treatment-resistant depression (TRD). Patients first entered a 52-week open-label trial during which they received bilateral implants of four contact electrodes followed by optimization of DBS. The optimization phase ended when a stable response of at least four weeks was reached or after a maximum of 52 weeks. Medication adjustments were made as clinically indicated. Immediately following the open-label phase of the study, patients entered the randomized, double-blind crossover phase consisting of two blocks of six weeks during which the DBS stimulator was on (active) or off (sham). The 17-item Hamilton Depression Rating Scale (HAM-D-17) was the main outcome measure used in the optimization phase. The primary outcome of the crossover phase was the difference in the HAM-D-17 scores (range 0–52; higher score more severe symptoms) between active and sham DBS. Responders were defined as experiencing a ≥◦50% decrease of the HAM-D-17 score compared with baseline and partial responders were defined as achieving ≥◦25 but <◦50% decrease of the HAM-D-17 score. Remission was defined as a HAM-D-17 score of ≤◦7 at optimization of settings. In the optimization phase significant improvements were accomplished in the mean HAM-D-17 scores which decreased from 22.2 at baseline to 15.9 ($p=0.001$), Montgomery-Åsberg Depression Rating Scale scores decreased from 34.0 to 23.8 ($p<0.001$), and Inventory of Depressive Symptomatology–self-report scores changed from 49.3 to 38.8 ($p=0.005$). Following the optimization phase, ten patients (40%) were classified as responders and 15 (60%) as nonresponders. Nine responders and seven nonresponders entered the randomized crossover phase. During active DBS, patients scored significantly lower on the HAM-D-17 scale (13.6 than during sham DBS (23.1) ($p<0.001$). Serious adverse events included severe nausea during surgery (n=1), suicide attempt (n=4) and suicidal ideation (n=2). Limitations of the study include the small patient population, short-term follow-up and loss of nine patients to randomization. Also, the optimization phase exceeded the maximum of 52 weeks in six patients, which could have led to a higher response rate. Larger randomized controlled trials and further specification of targets and the most accurate setting optimization are needed to support DBS for the treatment of TRD.

Berlim et al. (2014) conducted a systematic review and meta-analysis to evaluate DBS of the subgenual cingulate cortex (SCC) for treatment-resistant depression. Four observational studies (n=66) met inclusion criteria. Remission rates were 16.7% at three months (n=66), 24.1% at six months (n=66) and 26.3% at 12 months (n=63). Response rates were 36.6% at three months, (n=66), 53.9% at six months (n=66) and 39.9% at 12 months. There was a significant reduction in depression rates between months three and six ($p=0.001$), but not thereafter. Loss to follow-up at 12 months was 10.8%. In addition, the studies were open label with short-

term follow-up and small patient populations. There is insufficient evidence to support DBS of SCC for treatment-resistant depression.

Morishita et al. (2014) conducted a systematic review to evaluate the safety and efficacy of DBS for treatment-resistant major depressive disorder (MDD). A total of 22 clinical trials met inclusion criteria. Five unique DBS approaches using different targets were identified. The targets included nucleus accumbens, ventral striatum/ventral capsule, subgenual cingulate cortex, lateral habenula, inferior thalamic nucleus, and medial forebrain bundle. Only one published controlled trial was found. All studies treated patients with severe, medication refractory MDD, or rarely bipolar disorder and three studies were controlled with sham stimulation. Overall the response rates (percentage of patients with>50% improvement on the Hamilton Depression Rating Scale) ranged from 40%–60%. Most complications were minor surgery-related issues (e.g., superficial infection). Completed suicide and suicide attempts were the most significant adverse events following DBS surgery and happened following DBS with and without stimulation. Several studies excluded patients with suicidal ideation. Limitations of the studies included: small patient populations; heterogeneity of inclusion criteria and outcome measures; duplication of patients across studies. The authors noted that no class I evidence exists in the literature supporting DBS for MDD. The optimal DBS targets are unclear. Therefore, DBS for MDD is considered experimental.

The Canadian Network for Mood and Anxiety Treatments (CANMAT) (Milev, et al., 2016) conducted a systematic review to update the 2009 guidelines for the treatment of adults with unipolar major depressive disorders and concluded that DBS was still considered investigational. According to the authors, evidence investigating DBS for the treatment-resistant depression (TRD) is based on nonrandomized, open-label studies with small patient populations (n<20). Response rates were reported between 30%–60% and remission rates 20%–40% at 3–6 month follow-ups. Two multicenter randomized controlled trials comparing DBS to sham were discontinued due to lack of efficacy. The optimal stimulation parameters for various brain targets and outcomes reporting long-term effects and treatment for relapse are unknown.

Multiple Conditions: Appleby et al. (2007) conducted a meta-analysis of 546 relevant articles (i.e., 303 clinical trials, 72 case series, 130 case reports) to “characterize the risks and benefits of DBS and to assess its possible use within the psychiatric setting.” Three percent of the studies included patients with headaches, chronic pain, epilepsy, OCD and depression. Improvements in mentation, mood and behavior were reported in ten studies, six studies reported worsening and two reported no change. An improvement in chronic pain was reported in 26 studies, with no improvement in three studies and worsening of pain in two studies. Improvements in OCD scores were reported in eight studies with one study reporting no differences. Six studies indicated an improvement in anxiety, seven studies included improved cognition, three reported worsening of cognition, and in 13 studies cognition was unchanged. Three studies used depression as the primary indicator of treatment outcomes and 34 used depression as a secondary measure. Of the studies evaluating depressive symptoms, an improvement was reported in 83.3% of the studies, 2.7 % reported worsening and 14% reported no change. The authors stated that because of the number of studies that did not report on post-DBS mood, the findings of improvement in depressive symptoms should be treated with caution. Following implantation, suicide/attempted suicide and episodes of depression, hypomania and anxiety were reported. Limitations of the studies included: the heterogeneity of the studies, categorical variables (i.e., improvement, no improvement) in outcome measures, lack of outcomes separated by lead placement site, inclusion of case reports and the lack of studies that reported side effects.

Multiple Psychiatric Disorders:
Naesström et al. (2016) conducted a systematic review to identify studies on DBS for psychiatric indications. Fifty-two studies including case reports (n=10) and case series met inclusion criteria. Eighteen studies (n=112) investigated DBS for chronic, therapy-resistant OCD in six different anatomical targets and nine studies (n=100) used DBS in five different targeted areas for the treatment of chronic, therapy-resistant MDD. Additional studies included DBS for the treatment of Tourette’s syndrome (n=57), primary anxiety disorder, alcohol addiction, anorexia nervosa, heroin addiction and autism with aggression and self-mutilation. The most common reported complications were infection and hardware malfunction. Limitations of the studies included: small patient populations (n=3–26), heterogeneity of treatment targets, short-term follow-ups (e.g., < 24 months), lack of a comparator, heterogeneity in evaluation tools and definitions of response and remission. The safety and efficacy of the different stimulation targets and which targets are effective for which conditions have not been established.

Nangunoori et al. (2013) conducted a systematic review and meta-analysis in order to better characterize the evidence supporting DBS for major depressive disorder (MDD), obsessive-compulsive disorder (OCD) and Tourette's syndrome (TS). Studies were included that used a primary, single, standardized outcome scale. A total of 24 studies met inclusion criteria. Four studies were related to MDD (n=48), ten to OCD (n=64) and ten to TS (n=46). Meta-analysis showed that all studies had a clinically detectable and statistically significant reduction in disease-specific outcome scale scores when DBS was used. The average improvement was 2.47 standard deviations for MDD, 2.77 for OCD and 2.97 for TS. Limitations of the studies included the lack of randomized controlled trials, the limited number of studies with small patient populations, short-term follow-ups, and heterogeneity of secondary outcome measures, stimulation parameters and OCD studies.

Lakhan and Callaway conducted a systematic review of clinical trials (n=17), including case series (some with randomization of on/off sessions) and case reports to evaluate outcomes of DBS for the treatment of obsessive-compulsive disorder (OCD) and treatment resistant depression (TRD). Nine OCD studies (n=42 total patients; range, 1–18 per study), seven TRD studies (n=67 total patients; range 1–21 per study), and one study with one patient with both disorders met inclusion criteria. Follow-up ranged from 3–39 months. Due to the sparse data, meta-analysis could not be conducted. The authors noted that the reports of suicide and psychoses following DBS were "disturbing," and criteria for patient selection and electrode placement need to be established.

Multiple Sclerosis (MS): Multiple sclerosis (MS) is a disease of the central nervous system (CNS) that is characterized by areas of demyelination in the white matter of the brain and by recurrent exacerbations of neurologic dysfunction. It is estimated that approximately 10% of MS patients have disabling tremors. Although DBS has been proposed as a treatment option for MS, there is insufficient evidence to support the safety and efficacy of DBS for this condition.

Obsessive-Compulsive Disorder (OCD): OCD is a type of anxiety disorder in which individuals have unwanted thoughts (obsessions) and repeated behaviors (compulsions) over and over again. Severe cases of OCD can be disabling and interfere with activities of daily living and relationships. Treatment for OCD may include pharmacotherapy (e.g., selective serotonin reuptake inhibitors [SSRIs] and/or antipsychotic medications) and/or psychotherapy. DBS has been proposed as a treatment option for chronic, severe OCD in individuals who are unresponsive to adequate medical and behavioral therapy including, but not limited to failure of at least three SSRIs (Kuhn, et al., 2010; FDA, 2009; Mallet, et al., 2008).

There is insufficient evidence in the published peer-reviewed literature to support DBS for the treatment of OCD. Studies are primarily in the form of small case series (n=2–16) (De Vloo et al., 2018; Ooms, et al., 2013; Denys, et al., 2010; Okun, et al., 2007; Greenberg, et al., 2006; Rauch, et al., 2006) and case reports. Available randomized control trials include small patient populations (n=1–24) (Bouwens vander Vlis et al., 2021; Mosley et al., 2021).

Bouwens van der Vlis et al. (2021) conducted a systematic review to evaluate the cognitive outcome following deep brain stimulation (DBS) for refractory obsessive-compulsive disorder (OCD). Fifteen studies (n=178) consisting of five randomized controlled crossover studies, five observational studies, one pilot study, two case series, and two case reports (n=1-24) were included. Primary outcomes were cognitive outcomes measured by any neuropsychological assessment. A total of 37 neuropsychological tests were used within the 15 studies reporting on cognitive outcome following DBS for OCD. Variable outcomes of DBS were observed in the domains of attention, memory, executive functioning, and in particular cognitive flexibility. Author noted limitations included heterogeneity in study design, stimulation targets, variable data presentation and diversity of neuropsychological tests.

In a health technology assessment, Hayes (2020) reported that the effectiveness of DBS for treatment of highly refractory OCD remains uncertain. A total of 10 studies were identified including eight randomized controlled cross over studies, one double blind crossover study and one prospective pretest/posttest study. The overall quality of the evidence was deemed very low due to poor quality studies with small patient populations and short term follow ups. Other limitations of the studies included heterogeneity of the treatment characteristics, population overlap in some studies and lack of comparator. Well designed studies with larger patient

populations, long term follow up and a comparator are needed to determine the safety and efficacy of DBS for OCD.

Alonso et al. (2015) conducted a systematic review and meta-analysis to evaluate DBS for the treatment of obsessive-compulsive disorder. Thirty-one studies (n=116) with small patient populations (n=1–16) met inclusion criteria. Subjects were implanted in striatal areas—anterior limb of the internal capsule, ventral capsule and ventral striatum, nucleus accumbens and ventral caudate (n=83), the subthalamic nucleus (n=27) and in the inferior thalamic peduncle (n=6). Ages ranged from 18–75 years and subjects had a diagnosis of OCD according to the Diagnostic and Statistical Manual of Mental Disorders IV or International Classification of Diseases criteria. Included studies assessed the efficacy of DBS on OCD according to changes on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores (13 studies; n=66) or percentage of responders defined by standardized criteria. Global percentage of Y-BOCS reduction was estimated at 45.1% and global percentage of responders at 60.0%. Data on quality of life was available on 29 patients and various outcome measures were used. No significant differences were detected in efficacy between implant targets. Five patients were lost to follow up. A total of 161 adverse effects were reported and most were considered mild, transient and reversible. Limitations of the studies included: the small patient populations; lack of a comparator; heterogeneity of outcome measures for QOL; heterogeneity of anatomical targeting, electrode design and stimulation parameters; and short duration of sham periods (minutes to three months). The authors also noted that information on OCD symptom dimension, which emerged as one of the clinical predictors of response, was not assessed using specifically designed tools in any study even though it was available for 95 patients. Due to the small number of patients meta-analysis could not be conducted. Clinical predictors of response, response rates and patient selection criteria need to be established.

Kisely et al. (2014) conducted a systematic review and meta-analysis of double-blind randomized controlled trials of DBS vs. sham for the treatment of psychiatric conditions (e.g., OCD, major depression, anorexia nervosa). Five studies met inclusion criteria and all investigated DBS for the treatment of OCD. Data analysis was done on 44 patients. The main outcome was a reduction in obsessive symptoms as measured by the Yale-Brown Obsessive Compulsive Scale (YBOCS). Duration of treatment ranged from 2–12 weeks. Patients treated with DBS had a significantly lower mean score ($p<0.001$), representing partial remission, but one-third of the patients (n=16) experienced significant adverse effects (e.g., intracerebral hemorrhage, infection) There were no differences between the two groups in terms of other outcomes. Two studies reported outcomes for depression and anxiety in OCD patients and no statistically significant differences were seen between DBS and sham ($p=0.09$). Limitations of the studies included the small patient populations (n=4–16), use of difference DBS target areas in the brain, and short duration of treatment (2–12 weeks). Because all of the subjects had severe treatment-resistant OCD, the result cannot be generalized to patient with less severe symptoms. Meta-analysis could not be conducted. DBS remains an experimental treatment in adults for severe, medically refractory psychiatric conditions.

Kohl et al. (2014) conducted a systematic review to identify and evaluate the effectiveness of different targeted structures in the brain for deep brain stimulation for the treatment of obsessive-compulsive disorder. A total of 25 studies (n=109) that reported five brain stimulation targets met inclusion criteria. Targeted structures included: anterior limb of the internal capsule (n=14), nucleus accumbens (n=37), ventral capsule/ventral striatum (n=29), subthalamic nucleus (n=23) and inferior thalamic peduncle (N=6). Studies were primarily in the form of case reports or small case series (n=3–16). With the exception of one study with a follow-up of 51 months, follow-ups were less than 36 months. Eleven studies had a follow-up of one year or less. Some studies had overlapping patients (n=27). Results were similar regardless of the targeted structure, no superior structure was identified. Some studies reported improvement in symptoms but must be viewed with caution due to the poor methodology of the studies, small patient populations, short-term follow-ups and lack of a comparator.

A multicenter randomized controlled trial by Mallet et al. (2008) compared stimulation of the subthalamic nucleus to sham stimulation in 16 patients, age range 18–60 years, with a primary diagnosis of OCD. Patients were unresponsive to pharmacotherapy (e.g., at least three serotonin-reuptake inhibitors) and cognitive behavioral therapy. The on-off group underwent DBS stimulation followed by sham stimulation and the off-on group underwent sham stimulation followed by DBS stimulation. The stimulation periods involved two 3-month phases (i.e., month 3 to month 6 and month 7 to month 10) separated by a 1-month washout phase. Patients received medications during the trial. Following DBS, a significant decrease was seen in the Yale-Brown Obsessive-

Compulsive Scale (Y-BOCS) score (p=0.01). The on-off group had a significantly larger treatment effect than the off-on group (p=0.06). The Global Assessment of Functioning (GAF) score and the Clinical Global Impression (CGI) score were significantly improved after DBS compared to sham (p=0.005, p=0.008, respectively). At the end of the first three months, six (75%) patients were responders based on the Y-BOCS score and eight (100%) were responders based on the GAF scores compared to three (38%) responders following sham. No significant differences following DBS or sham were seen in the scores on the Montgomery and Asberg Depression Scale (MADRS), the Brief Scale for Anxiety, and the Sheehan Disability Scale. Due to the adverse events (i.e., intracerebral hemorrhage, infections requiring removal of the electrode) the authors stated that the benefits should be weighed carefully against the risks. Author-noted limitations included the variable deep brain stimulation settings used, small patient population and short duration of the study.

The American Society for Stereotactic and Functional Neurosurgery and the Congress of Neurological Surgeons (CNS), Endorsed by the CNS and American Association of Neurological Surgeons updated the 2014 guidelines (Hamani, et al. 2014) in 2020 (Staudt, et al., 2021). A systematic review of the literature included an additional 10 studies. The additional studies included one double blind randomized crossover trial (n=24), one prospective study (n=30) focusing on adverse events and eight case series (n=6-22) with follow ups ranging from 6-31 months. Based on these low level studies, the task force made the following recommendations:

- “clinicians should consider bilateral subthalamic nucleus DBS for the treatment of patients with medically refractory OCD as effective (Level 1 - evidence from one or more-well designed, randomized controlled clinical trial). This recommendation is based on one randomized controlled trial (n=8) and two case series.
- clinicians may use bilateral nucleus accumbens or bed nucleus of stria treminalis DBS for the treatment of patients with medically refractory OCD (Level 2 - evidence from one or more well-designed comparative study including non-randomized cohort studies, case-control studies, and less well-designed randomized controlled trials).” This second recommendation is based on six case series.

In their practice guideline for the treatment of OCD, the American Psychiatric Association (2013) described DBS as a “less-well-supported” monotherapy that may be considered after first and second-line therapies have been exhausted but clarify that there is little supporting evidence (e.g., few small trials or case reports or uncontrolled case series). DBS has been reported to show efficacy in individuals with severe, highly treatment-resistant OCD, but the procedure is not without its risk.

Tardive Dyskinesia: Tardive dyskinesia is a neurological syndrome characterized by repetitive, involuntary, purposeless movements and caused by the long-term use of neuroleptic drugs. Additional features may include grimacing; tongue protrusion; lip smacking, puckering and pursing; rapid eye blinking; and rapid movements of the arms, legs, and trunk.

In a prospective phase two multicenter study, Damier et al. (2007) investigated DBS in patients with severe TD refractory to medical management (n=10). Patients had been treated with antipsychotic medication for depression, schizophrenia or childhood disintegrative disorder. At the six-month follow-up, a double-blind evaluation resulted in successful outcomes by a decrease in the Extrapyramidal Symptoms Rating Scale, including choreic movements and dystonia score, by more than 40% (p=0.05). A significant decrease in the Abnormal Involuntary Movement Scale score (p=0.006) was also reported.

Tourette Syndrome (Tics): Tourette syndrome (TS), also known as chronic motor tic, chronic multiple tics, Gilles de la Tourette's disease or syndrome (GTS), habit spasms, maladie de tics, and paulitis tics, is a chronic neuropsychiatric disordered characterized by motor (e.g., repetitive involuntary movements of the face, head, upper body) and phonic, or vocal (e.g., sniffing, grunting, barking) tics. TS is often associated with behavioral abnormalities such as attention-deficit hyperactivity disorder and OCD. The waxing and waning characteristics of tics makes it difficult to investigate the safety and efficacy of DBS. It has been proposed for patients who have not received adequate benefit from behavioral therapy and pharmacotherapy. Current studies include small patient populations, and the optimal DBS target for these individuals has not been defined. Studies have primarily been in the form of case reports and case series with small patient populations and short-term follow-ups. The overall body of evidence agrees that there is insufficient evidence to support DBS for the treatment of Tourette’s syndrome (Welter, et al., 2017; Naesström et al., 2016; Servello, et al., 2016; Zhang, et al., 2016; Cannon, et al., 2012; Kuhn, et al., 2010; Ackermans, et al., 2008; Mink, et al., 2006).

The American Academy of Neurology (AAN) (Pringsheim et al., 2019) conducted a systematic literature review and developed practice guideline recommendations on the assessment and management of tics in people with Tourette syndrome and chronic tic disorders. AAN acknowledged there is limited information from randomized clinical trials for analysis and interpretation and there is no consensus on the optimal brain target for the treatment of tics. The recommendations regarding deep brain stimulation (DBS) stated a multidisciplinary evaluation should be completed including a mental health professional, confirmation of diagnosis and medication failure over multiple classes of medications and then DBS may be considered for severe, treatment-refractory, and self-injurious tics.

Baldermann et al. (2016) conducted a systematic review and meta-analysis of DBS for Tourette syndrome (TS). Fifty-seven studies (n=156) and data from 48 of those studies (case reports and case series) were pooled for analysis. The Yale Global Tic Severity Scale (YGTSS) was the primary outcome measure. Secondary outcome measures included subscores of the YGTSS (Impairment, Tic Severity comprising motor tics and vocal tics), modified Rush Videobased Tic Rating Scale (mRVRS). If available, values of the Beck Depression Inventory (BDI) and the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) were assessed. Overall, DBS resulted in a significant median improvement of 52.68% (n=156; p<0.001) for the Global YGTSS at last available follow-up, median improvement rates of 48% for tic severity (n=73; p<0.001) and significant improvement in the mRVRS (n=27; p<0.001). Motor tics decreased by a median of 38.56% (n=71; p<0.001) and vocal tics by 40% (n=70; p<0.001). Comparing reduction rates of motor and vocal tics revealed a significantly higher mean tic reduction was seen for vocal tic vs. motor tic (p=0.012). The authors noted that the outcome varied across the sample, with some patients experiencing complete remission and others showing no improvement at all and the evidence was of low quality. Other limitations include the small patient populations, nine studies did not use the YGTSS, and the lack of randomized controlled studies. Well-designed randomized controlled trials and identification of effective target points are needed to support DBS for the treatment of TS.

Piedad et al. (2012) conducted a systematic review to determine which patients with Tourette syndrome (TS) should be treated with DBS and the best target areas for electrode placement. Thirty-six studies met inclusion criteria including case reports, three case series and three randomized controlled trial. Based on the available data, the authors noted that it was “suggested” that the best candidates are patients with significant functional impairment due to tic symptoms and are nonresponsive to conventional pharmacotherapy and behavioral interventions. The globus pallidus internus and thalamus appeared to be the safest and most effective targets, especially for patients with “pure” TS and patients with comorbid obsessive-compulsive symptoms, anxiety and depression. There is a lack of consensus on treatment-refractoriness and large randomized controlled trials are needed to establish patient selection criteria and the appropriate target areas for placement.

The European Society for the Study of Tourette Syndrome (ESSTS) (Muller-Vahl, et al, 2011) conducted a systematic review of the literature to evaluate DBS for the treatment of Tourette syndrome (TS). Twenty four studies (n=63) including three randomized controlled trials, 18 case reports and three case series were reviewed. ESSTS concluded that DBS should only be used in “treatment resistant and severely affected adults” and “highly” recommended that it be in the context of controlled clinical trials.

The Tourette Syndrome Association (Mink, et al., 2007) convened a group of TS and DBS experts to develop guidelines for the early use and potential clinical trials of DBS for the treatment of TS believing that investigation of DBS for TS was justified due to the success of DBS with other disorders. The subgroup stated that although DBS has the potential to be an effective therapy for a carefully selected subgroup of TS patient’s “there are many unknowns about the potential applications” of DBS and investigation is warranted.

Responsive Cortical Stimulation

Closed-loop, responsive cortical stimulation involves the implantation of electrodes which are connected to a generator that provides electrical stimulation to specific areas of the brain in response to abnormal brain activity. This technology is different from an open-loop or nonresponsive technique (e.g. deep brain stimulation) which delivers a continuous or intermittent electrical stimulation at programmed intervals. Closed-loop, responsive cortical stimulation is supported by the published peer-reviewed literature as an adjunctive treatment option for a carefully identified subpopulation of patients with medically refractory partial epilepsy who are not candidates for

surgery or for vagal nerve stimulation (Heck, et al., 2014; Fridley et al., 2012; Morrell, et al., 2011; Skarpaas and Morrell, 2009).

Epileptic seizures are classified as partial or generalized depending on whether they begin focally at one or two points in the brain (i.e., a partial-onset seizure) or bilaterally with multiple foci (i.e., a generalized seizure). Standard therapy includes antiepileptic medication, vagal nerve stimulator and/or surgical removal of seizure focus. Partial seizures can generalize secondarily and result in tonic-clonic activity in which the person loses consciousness accompanied by muscle stiffness and jerking movements. In a subset of patients with medically refractory partial epilepsy, electrical cortical stimulation has been proposed as an adjunctive therapy to pharmacotherapy.

The RNS® System (NeuroPace, Inc. Mountain View, CA) is a responsive cortical stimulation closed-loop system. It is proposed as a treatment option for patients who have medically refractory partial epilepsy with partial onset seizures, are refractory to two or more antiepileptic medications and have one of the following seizure types: 1) simple partial motor: seizures characterized by alteration in motor function without change in awareness; 2) complex partial: seizure includes impairment in awareness and/or 3) generalized tonic, clonic or tonic-clonic seizures. RNS is not indicated for the treatment of generalized epilepsies in which seizures arise from all areas of the brain at the same time.

The system includes an implantable RNS® neurostimulator, a Depth Lead (implanted within the brain) and a NeuroPace® Cortical Strip Lead (implanted on the brain surface). Each lead contains four electrodes. The leads to be implanted are selected based on the location of the seizure focus: subdural cortical, depth, or a combination of the two. The Cortical Strip Leads are recommended for seizure onsets on the surface of the cortex, where the lead can be placed over the focus. The Cortical Strip Leads come in three lengths and are implanted through a craniotomy. The Depth Leads are recommended for seizure onsets beneath the cortical surface (e.g., within the mesial temporal lobe, within subcortical lesions) where the lead can be placed within the seizure focus. Depth Leads come in four different configurations. These leads may be implanted using stereotactic techniques through a burr hole in the skull. The leads are placed at the seizure focus as determined by radiologic imaging, presurgical electroencephalogram (EEG) recordings, or phase II subdural electrocorticogram (ECoG) monitoring. The neurostimulator is a programmable, battery powered, microprocessor-controlled device that delivers a short train of electrical pulses to the brain through the implanted leads. The neurostimulator is implanted in the cranium flush with the skull, is extradural and does not come in contact the brain. Up to four leads may be implanted with only two leads connected to the neurostimulator at any given time. Once in place, the neurostimulator is covered by the scalp.

External components of the system include the programmer, laptop computer with software and a Wand that allows remote monitoring of brain activity. The Wand is used to retrieve stored data from the neurostimulator. Using the programmer, the physician programs the initial setting and makes follow-up adjustments as needed based on brain activity and response to stimulation. The typical patient receives brief bursts (100–200 msec) of high-frequency stimulation with a total cumulative stimulation time of less than six minutes a day. The programmer also allows visualization of the patient's brain electrical activity (electrocorticogram [ECoG]) in real-time and the ability to upload the patient's ECoGs stored in the RNS neurostimulator. The patient is provided a magnet that is swiped over the neurostimulator to record brain activity during a seizure. This activity enables the physician to identify the event during data review. The magnet can also be used to temporarily stop stimulation. The neurostimulator has to be replaced every 2.0–3.7 years when the battery reaches its end of service. If the existing leads are functioning properly and there are no problems, the same leads will be connected to the new stimulator. It is recommended that the leads not be removed if the stimulation is not successful due to potential damage to brain tissue.

U.S. Food and Drug Administration (FDA): The RNS System (NeuroPace, Inc. Mountain View, CA) is FDA approved by the premarket approval (PMA) application process. The device is indicated “as an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures who have undergone diagnostic testing that localized no more than two epileptogenic foci, are refractory to two or more antiepileptic medications, and currently have frequent and disabling seizures (motor partial seizures, complex partial seizures and/ or secondarily generalized seizures). The RNS System has demonstrated safety and effectiveness in patients who average three or more disabling seizures per month over the three most recent

months (with no month with fewer than two seizures), and has not been evaluated in patients with less frequent seizures". Exclusion criteria in the FDA clinical trial included subjects who did not have an implanted vagus nerve stimulator or an implanted device that delivers electrical energy to the head, had not had surgery for the treatment of epilepsy within the preceding six month, and had not been diagnosed with active psychosis, severe depression or suicidal ideation in the preceding year. If subject had a VNS, it must have been explanted (excluding leads) prior to or at the time of RNS implantation. VNS must have been discontinued for at least three months prior to enrollment (FDA, 2013).

Continued approval of the PMA was contingent upon the submission of yearly reports including model number, number of devices sold and distributed. Also, NeuroPace must conduct and report on a long-term treatment study to establish safety (adverse event rates) and effectiveness (average disabling seizure frequency) through seven years. Successful responder rate is defined as sustained ≥ 50% reduction in total disabling seizures from baseline. Quality of life will also be measured.

Literature Review
Studies in the form of randomized controlled trials and prospective case series have evaluated responsive cortical stimulation for the treatment of medically refractory partial epilepsy with partial onset seizures. Reduction in seizures ranged from 47%–60% and a responder rate of up to 59% was reported. One study reported a 50% or greater reduction in seizures with 16% of participant seizure free following implantation. Some subjects remained on antiseizure medication while up to 9% of responders had a reduction in pharmacotherapy or discontinuation of anticonvulsants. No significant cognitive declines were reported on neuropsychological outcome measures. Significant improvement in verbal learning was reported depending on the area of brain involved. Up to 44% of subjects reported a statistically significant improvement in quality of life (QOL) ($p<0.001$) and 16% reported a decline in QOL. The most common device related adverse events were implant site infection (< 9.0%) involving soft tissue and neurostimulator explantation (<5%) (Bergey, et al., 2015; Heck, et al., 2014; Loring, et al., 2015; Meador, et al., 2015; Morrell, et al., 2011).

Motor Cortex Stimulation

Motor cortex stimulation (MCS), also referred to as cerebral cortex stimulation or extradural motor cortex stimulation (EMCS), is primarily proposed for relief of refractory neuropathic pain and involves implantation of epidural electrodes in the cerebral cortex. Although the exact mechanism of MCS is unknown, it has been hypothesized that it may induce the release of endogenous opioids in various brain structures, resulting in pain relief (Cheng and Eskandar, 2010; Maarrawi, et al., 2007).

Typically, temporary placement of a MCS device is performed to determine if the device will relieve the pain. If the patient consistently (e.g., 3–14 days) experiences at least a 50% reduction in pain, a second surgery is performed to permanently connect the electrodes and implant the programmable device under the skin near the collarbone. Image-guided localization (e.g., magnetic resonance imaging [MRI], functional MRI [fMRI], computerized tomography) and intraoperative mapping using somatosensory evoked potential (SSEP), intraoperative stimulation of the cortex, and/or neuronavigation are used to locate the precise placement of the electrodes, which is critical for successful pain relief. Electrodes are introduced through a burr hole or frontoparietal craniotomy into the protective layer covering the motor cortex area (epidural) of the brain, placed over the targeted area and connected to a programmable pulse generator. The lead wire from the programmable device goes up the back of the neck under the scalp to the electrodes (Cheng and Eskandar, 2010; Levy, et al., 2010; Arle and Shils, 2008).

Because MCS is a less invasive procedure than other invasive surgical procedures such as DBS, it is proposed to be a safer procedure with less serious complications. MCS has been proposed for treatment when invasive procedures have failed or when patients are not appropriate candidates for an invasive procedure. Some proponents of MCS report that MCS is less harmful than long-term opioid use. However, serious complications including intracranial bleeding; infection; permanent neurological deficits; and seizure activity, especially during programming and reprogramming of the MCS device have been reported (Cheng and Eskandar, 2010; Levy, et al., 2010; Maarrawi, et al., 2007).

MCS was initially used for the treatment of medically refractory central pain syndrome following ischemic or hemorrhagic stroke and facial neuralgias (e.g., trigeminal neuralgia, postsurgical trigeminal deafferentation such as anesthesia dolorosa, postherpetic neuralgia). However, its use has been proposed for the treatment of other conditions including: neuropathic pain following spinal cord injuries (e.g., supraspinal pain after hemorrhage and infarction), post-stroke pain, chronic pain, amyotrophic lateral sclerosis (ALS), thalamic pain syndrome, plexus avulsion, dysphagia, Parkinson disease, dystonia, spasticity, multiple sclerosis, chronic regional pain syndrome (CRPS), phantom limb pain, epilepsy, chronic neuropathic orofacial pain syndrome, and peripheral nervous system lesions. MCS has also been used for intraoperative monitoring (Henssen, et al., 2020; Tanei, et al., 2011; Cheng and Eskandar, 2010; Levy, et al., 2010; Fontaine, et al., 2009; Prévinaire, et al., 2009; Arle and Shils, 2008).

U.S. Food and Drug Administration (FDA): There are no devices approved by the FDA for motor cortex stimulation.

Literature Review: There is insufficient evidence in the published peer-reviewed literature to support the safety and efficacy of MCS for any indication. Studies are primarily in the form of case reports and case series with small heterogeneous patient populations (n=3–10) and short-term follow-ups. Outcomes regarding the benefits of MCS are conflicting. Some studies reported that the initial pain relief following MCS was not sustained over time and in some cases, worsening of pain followed MCS. Surgical techniques, electrode placement, device programming, outcome measures and patient selection criteria have not been established.

Fontaine et al. (2009) conducted a systematic review to evaluate the safety and efficacy of MCS for the treatment of chronic neuropathic pain. Fourteen studies (n=210), case series and retrospective reviews, met inclusion criteria. Reported mean follow-up was 30.5 months (range, several weeks to ten years). Overall, 56.7% of patients reported a 40%–50% (good) improvement in pain. Sixty-nine patients with ≥ 1 year follow-up reported a good response, and in two studies with 49-month follow-up, 47% and 22.6% of patients reported good results. The reported Visual Analog Scale scores for 76 patients reflected an average 56.6% improvement in postoperative scores. The most common adverse events were intraoperative or trial stimulation period seizures, infections and hardware-related problems. The authors stated that these results should be viewed with caution due to the limited number of studies that were primarily retrospective study designs with heterogeneous small patient populations (n=3–31). Short-term follow-up, loss of efficacy and the variable surgical techniques, stimulation settings and electrode placement were other noted limitations.

A limited number of randomized controlled trials have evaluated the use of MCS for the treatment of neuropathic pain comparing outcomes of on/off stimulation. In a crossover trial, Lefaucheur et al. (2009) reported that patients with trigeminal neuralgia (n=4), brachial plexus lesion (n=4), neurofibromatosis type-1 (n=3), upper limb amputation (n=2), herpes zoster ophthalmicus (n=1), atypical orofacial pain secondary to dental extraction (n=1), and traumatic nerve trunk transection in a lower limb (n=1) did not experience sustained pain relief during the crossover phase of the trial. Of the 12 patients who participated in the open study phase, 60% reported a mean pain relief of 48% on Visual Analog Scale scores at 12 months follow-up. In a study involving 11 patients (Velasco, et al., 2008) with chronic deafferentation pain syndromes (n=11), three patients reported no improvement following a temporary trial of MCS. The remaining patients who underwent permanent implantation reported a significant reduction in pain ($p<0.01$) during the one-year follow-up. The authors stated that “given the heterogeneous information that one gathers from the literature on MCS, it is impossible at present to draw a conclusion concerning candidates for this treatment.”

Use Outside of the US

Deep brain stimulation (DBS): DBS systems are approved for use in Europe.

The European Federation of Neurological Society and the Movement Disorder Society-European Section (EFNS/MDS-ES) (Albanese, et al., 2011) task force conducted a systematic literature review and published evidence-based recommendations for the diagnosis and treatment of dystonia. The recommendations stated that pallidal DBS is a good option for primary generalized or segmental dystonia and cervical dystonia following failure of medication or botulinum toxin. In general, pallidal DBS is less effective in secondary dystonia with the exception of tardive dystonia.

In their guidelines on neurostimulation for neuropathic pain, the European Federation of Neurological Societies (EFNS) (Cruccu, et al., 2007) stated that the literature primarily consisted of case series including patients with central post-stroke pain (CPSP) (n=20 case series with much overlap; 143 non-overlapping patients) and facial neuropathic pain (n=8 case series; 60 patients). Success rates ranged from 0%–100% for CPSP and 43%–100% for facial pain. Most studies did not have comparators, and outcome and treatment assessments were dissociated. Only case reports were found on patients with phantom pain, brachial plexus, nerve trunk lesion, spinal cord lesions and complex regional pain syndrome (CRPS). Based on these studies, EFNS stated that "MCS is useful in 50–60% of patients with CPSP and central or peripheral facial neuropathic pain, with small risk of medical complications," but the evidence was insufficient to support MCS for any other condition.

In an interventional procedures guidance, the National Institute for Health and Clinical Excellence (NICE) (United Kingdom) (2020) stated that the evidence of the safety and efficacy of DBS for refractory epilepsy in adults differs according to the site of stimulation. The evidence is limited in quantity and quality for anterior thalamic targets and should only be used with special arrangements for clinical governance, consent, and audit or research. The evidence is inadequate in quantity and quality for targets other than the anterior thalamus.

The National Institute for Health and Clinical Excellence (NICE) (United Kingdom) 2017 guidance on the management of Parkinson's disease in adults stated that DBS should not be offered to people with PD whose symptoms are adequately controlled with medical therapy. DBS can be considered for people with advanced Parkinson's disease whose symptoms are not adequately controlled by best medical therapy.

In a guidance document for DBS for tremor and dystonia, the National Institute for Health and Clinical Excellence (NICE) (United Kingdom) (2006) stated that the current evidence supports the safety and efficacy of DBS as a treatment modality for tremor and dystonia. Dystonia may be treated conservatively or surgically. Conservative treatment only treats the symptoms, and surgical intervention (i.e., thalamotomy and pallidotomy) may not render long-term benefits.

Medicare Coverage Determinations

	Contractor	Policy Name/Number	Revision Effective Date
NCD	National	Deep Brain Stimulation for Essential Tremor and Parkinson's Disease (160.24)	4/01/2003
LCD		No Local Coverage Determination found	

Note: Please review the current Medicare Policy for the most up-to-date information.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Deep Brain Stimulation

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
61863	Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; first array
61864	Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalamic

	nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; each additional array (List separately in addition to primary procedure)
61867	Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording; first array
61868	Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording; each additional array (List separately in addition to primary procedure)
61880	Revision or removal of intracranial neurostimulator electrodes
61885	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array
61886	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to 2 or more electrode arrays
61888	Revision or removal of cranial neurostimulator pulse generator or receiver

HCPCS Codes	**Description**
C1767	Generator, neurostimulator (implantable), nonrechargeable
C1778	Lead, neurostimulator (implantable)
C1787	Patient programmer, neurostimulator
C1816	Receiver and/or transmitter, neurostimulator (implantable)
C1822	Generator, neurostimulator (implantable), high frequency, with rechargeable battery and charging system
C1883	Adaptor/extension, pacing lead or neurostimulator lead (implantable)
C1897	Lead, neurostimulator test kit (implantable)
L8679	Implantable neurostimulator, pulse generator, any type
L8680	Implantable neurostimulator electrode, each
L8681	Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only
L8682	Implantable neurostimulator radiofrequency receiver
L8683	Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver
L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
L8686	Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension
L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
L8688	Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension

Responsive Cortical Stimulation

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	**Description**
61850	Twist drill or burr hole(s) for implantation of neurostimulator electrodes, cortical
61860	Craniectomy or craniotomy for implantation of neurostimulator electrodes, cerebral, cortical
61863	Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; first array
61864	Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalamic

	nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; each additional array (List separately in addition to primary procedure)
61880	Revision or removal of intracranial neurostimulator electrodes
61885	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array
61886	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to 2 or more electrode arrays
61888	Revision or removal of cranial neurostimulator pulse generator or receiver

HCPCS Codes	Description
C1767	Generator, neurostimulator (implantable), nonrechargeable
C1778	Lead, neurostimulator (implantable)
C1787	Patient programmer, neurostimulator
C1816	Receiver and/or transmitter, neurostimulator (implantable)
C1883	Adaptor/extension, pacing lead or neurostimulator lead (implantable)
C1897	Lead, neurostimulator test kit (implantable)
L8679	Implantable neurostimulator, pulse generator, any type
L8680	Implantable neurostimulator electrode, each
L8681	Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only
L8686	Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension
L8688	Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension

Motor Cortex Stimulation

Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description
61850	Twist drill or burr hole(s) for implantation of neurostimulator electrodes, cortical
61860	Craniectomy or craniotomy for implantation of neurostimulator electrodes, cerebral, cortical
61880	Revision or removal of intracranial neurostimulator electrodes
61885	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array
61886	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to 2 or more electrode arrays
61888	Revision or removal of cranial neurostimulator pulse generator or receiver

HCPCS Codes	Description
C1767	Generator, neurostimulator (implantable), nonrechargeable
C1778	Lead, neurostimulator (implantable)
C1787	Patient programmer, neurostimulator
C1816	Receiver and/or transmitter, neurostimulator (implantable)
C1820	Generator, neurostimulator (implantable), with rechargeable battery and charging system
C1822	Generator, neurostimulator (implantable), high frequency, with rechargeable battery and charging system
C1883	Adaptor/extension, pacing lead or neurostimulator lead (implantable)
C1897	Lead, neurostimulator test kit (implantable)
L8679	Implantable neurostimulator, pulse generator, any type
L8680	Implantable neurostimulator electrode, each
L8681	Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only

L8682	Implantable neurostimulator radiofrequency receiver
L8683	Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver
L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
L8686	Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension
L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
L8688	Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension

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