Policy Statement

Unilateral deep brain stimulation of the thalamus may be considered medically necessary in patients with disabling, medically unresponsive tremor due to essential tremor or Parkinson disease.

Bilateral deep brain stimulation of the thalamus may be considered medically necessary in patients with disabling, medically unresponsive tremor in both upper limbs due to essential tremor or Parkinson disease.

Unilateral or bilateral deep brain stimulation of the globus pallidus or subthalamic nucleus may be considered medically necessary in patients with either of the following diagnoses and associated criteria:

- Parkinson disease and all of the following criteria are met:
  - a good response to levodopa
  - motor complications not controlled by pharmacologic therapy
  - one of the following:
    - a minimum score of thirty points on the motor portion of the Unified Parkinson Disease Rating Scale when the patient has been without medication for approximately twelve hours
    - Parkinson disease for at least four years
- Patients are seven years of age or older with chronic, intractable (drug-refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis)

Deep brain stimulation is considered investigational for the treatment of other movement, psychiatric, or neurologic disorders including, but not limited to:

- Alcohol addiction
- Alzheimer disease
- Anorexia nervosa
- Chronic cluster headaches
- Chronic pain
- Depression
- Epilepsy
- Multiple sclerosis
- Obsessive-compulsive disorder
- Post-traumatic dyskinesia
- Tardive dyskinesia
- Tourette syndrome

Policy Guidelines

Disabling, medically unresponsive tremor is defined as all of the following:

- Inadequate control by maximal dosage of medication for at least three months before implant
- Tremor causing significant limitation in daily activities

Contraindications to deep brain stimulation include:

- Patients who are not good surgical risks because of unstable medical problems or because of the presence of a cardiac pacemaker
- Patients who have dementia that may interfere with the ability to cooperate
- Patients who have had botulinum toxin injections within the last six months
Patients who have medical conditions that require repeated magnetic resonance imaging

Coding
Coding for deep brain stimulation consists of a series of CPT codes describing the various steps of the procedure; i.e., implantation of the electrodes, implantation of the pulse generator, intraoperative monitoring and programming of the electrodes, and postoperative neuroprogramming. The following CPT codes are applicable.

Implantation of Electrodes
- **61850**: Twist drill or burr hole(s) for implantation of neurostimulator electrodes, cortical
- **61863**: Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (e.g., 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 (e.g., 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 (e.g., 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 (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording; each additional array (List separately in addition to primary procedure)

* The four codes above recognize the option of the implantation of electrodes using microelectrode recording or not. In addition, if the patient is undergoing bilateral implantation of electrodes, one of the “each additional array” codes may be used. In some instances, patients undergo bilateral implantation in a staged procedure.

Implantation of Pulse Generator
- **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

Electronic Analysis
- **95970**: Electronic analysis of implanted neurostimulator pulse generator system (e.g., rate, pulse amplitude, pulse duration, configuration of waveform, battery status, electrode selectability, output modulation, cycling, impedance and patient compliance measurements); simple or complex brain, spinal cord, or peripheral (i.e., cranial nerve, peripheral nerve, sacral nerve, neuromuscular) neurostimulator pulse generator/transmitter, without reprogramming
- **95978**: Electronic analysis of implanted neurostimulator pulse generator system (e.g., rate, pulse amplitude and duration, battery status, electrode selectability and polarity, impedance and patient compliance measurements), complex deep brain neurostimulator pulse generator/transmitter, with initial or subsequent programming; first hour
- **95979**: Electronic analysis of implanted neurostimulator pulse generator system (e.g., rate, pulse amplitude and duration, battery status, electrode selectability and polarity, impedance and patient compliance measurements), complex deep brain neurostimulator pulse generator/transmitter, with initial or subsequent programming;
each additional 30 minutes after first hour (List separately in addition to code for primary procedure)

Neurostimulator analysis and programming is classified as either simple or complex. CPT codes 95978 and 95979 are time-based. Simple neurostimulators are defined as those affecting three or fewer neurostimulatory parameters (e.g., pulse amplitude, duration, and frequency, number of electrode contacts) while a complex device affects more than three parameters. In the setting of deep brain stimulation for tremor control, it is anticipated that the neuroprogramming and analysis would be classified as simple. However, deep brain stimulation of the globus pallidus and subthalamic nucleus stimulation requires intraoperative monitoring of more than one clinical feature (i.e., rigidity, dyskinesia, and tremor) and the neuroprogramming would probably be classified as complex.

Over time, patients may undergo several sessions of electronic analysis and programming to find the optimal programming parameters. CPT codes 95970, 95978, and 95979, described here, may be used.

The following HCPCS codes are for Deep Brain Stimulation:

- **L8680**: Implantable neurostimulator electrode, each
- **L8685**: Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
- **L8686**: Implantable neurostimulator pulse generator, single array, nonrechargeable, includes extension
- **L8687**: Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
- **L8688**: Implantable neurostimulator pulse generator, dual array, nonrechargeable, includes extension

### Description

Deep brain stimulation (DBS) involves the stereotactic placement of an electrode into a central nervous system nucleus (e.g., hypothalamus, thalamus, globus pallidus, and subthalamic nucleus). DBS is used as an alternative to permanent neuroablative procedures for control of essential tremor and Parkinson disease. DBS is also being evaluated for the treatment of a variety of other neurologic and psychiatric disorders.

### Related Policies

- Responsive Neurostimulation for the Treatment of Refractory Partial Epilepsy
- Spinal Cord Stimulation

### Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates [e.g., Federal Employee Program (FEP)] prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.
Regulatory Status

In 1997, the Activa® Tremor Control System (Medtronic) was cleared for marketing by the U.S. Food and Drug Administration (FDA) for deep brain stimulation. The Activa® Tremor Control System consists of an implantable neurostimulator, a deep brain stimulator lead, an extension that connects the lead to the power source, a console programmer, a software cartridge to set electrical parameters for stimulation, and a patient control magnet, which allows the patient to turn the neurostimulator on and off, or change between high and low settings.

The original FDA-labeled indications for Activa® were limited to unilateral implantation of the device for the treatment of tremor, but, in 2002, FDA-labeled indications were expanded to include bilateral implantation as a treatment to decrease the symptoms of advanced Parkinson disease not controlled by medication. In 2003, the labeled indications were further expanded to include “…unilateral or bilateral stimulation of the internal globus pallidus or subthalamic nucleus to aid in the management of chronic, intractable (drug refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis) in patients seven years of age or above.” This latter indication was cleared for marketing by the FDA through the humanitarian device exemption (HDE) process. In 2017, the indications for Parkinson disease were modified to include “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.”

In 2009, the Reclaim® device (Medtronic), a deep brain stimulator, was cleared for marketing by the FDA through the HDE process for the treatment of severe obsessive-compulsive disorder.

In 2014, the Brio Neurostimulation System (now called Infinity; St. Jude Medical Neuromodulation) was cleared for marketing by the FDA for the treatment of Parkinsonian tremor.

FDA product code: MHY.

Rationale

Background
Deep brain stimulation (DBS) involves the stereotactic placement of an electrode into the brain (i.e., hypothalamus, thalamus, globus pallidus, or subthalamic nucleus). The electrode is initially attached to a temporary transcutaneous cable for short-term stimulation to validate treatment effectiveness. Several days later, the patient returns for permanent subcutaneous surgical implantation of the cable and a radiofrequency-coupled or battery-powered programmable stimulator. The electrode is typically implanted unilaterally on the side corresponding to the most severe symptoms. However, use of bilateral stimulation using 2 electrode arrays has also been investigated in patients with bilateral, severe symptoms. After implantation, noninvasive programming of the neurostimulator can be adjusted to the patient’s symptoms. This feature may be important for patients with Parkinson disease (PD), whose disease may progress over time, requiring different neurostimulation parameters. Setting the optimal neurostimulation parameters may involve the balance between optimal symptom control and appearance of adverse effects of neurostimulation, such as dysarthria, disequilibrium, or involuntary movements.

DBS has been investigated as an alternative to permanent neuroablative procedures, such as thalamotomy and pallidotomy. DBS has been most thoroughly investigated as an alternative to thalamotomy for unilateral control of essential tremor (ET) and tremor associated with PD. More recently, there has been research interest in the use of DBS of the globus pallidus or subthalamic nucleus as a treatment of other parkinsonian symptoms, such as rigidity, bradykinesia, and akinesia. Another common morbidity associated with PD is the occurrence of motor fluctuations, referred to as “on and off” phenomena, related to the maximum effectiveness of drugs (i.e., “on” state) and the nadir response during drug troughs (i.e., “off” state). In addition, levodopa, the most commonly used anti-Parkinson drug, may be associated with disabling drug-induced
dyskinesias. Therefore, the optimal pharmacologic treatment of PD may involve a balance between optimal effects on PD symptoms and the appearance of drug-induced dyskinesias. The effect of DBS on both PD symptoms and drug-induced dyskinesias has also been studied.

DBS has also been investigated in patients with primary and secondary dystonia, defined as a neurologic movement disorder characterized by involuntary muscle contractions, which force certain parts of the body into abnormal, contorted, and painful movements or postures. Dystonia can be classified according to age of onset, bodily distribution of symptoms, and cause. Age of onset can occur during childhood or during adulthood. Dystonia can affect certain portions of the body (focal dystonia and multifocal dystonia) or the entire body (generalized dystonia). Torticollis is an example of a focal dystonia. Primary dystonia is defined when dystonia is the only symptom unassociated with other pathology. Treatment options for dystonia include oral or injectable medications (i.e., botulinum toxin) and destructive surgical or neurosurgical interventions (i.e., thalamotomies or pallidotomies) when conservative therapies fail. Secondary dystonia is a dystonia brought on by an inciting event, such as a stroke, trauma, or drugs. Tardive dystonia is a form of drug-induced secondary dystonia.

DBS has been investigated in patients with chronic cluster headaches. Cluster headaches occur as episodic attacks of severe pain lasting from 30 minutes to several hours. The pain is usually unilateral and localized to the eye, temple, forehead, and side of the face. Autonomic symptoms that occur with cluster headaches include ipsilateral facial sweating, flushing, tearing, and rhinorrhea. Cluster headaches occur primarily in men and have been classified as vascular headaches associated with high blood pressure, smoking, alcohol use, etc. However, the exact pathogenesis of cluster headaches is uncertain. Positron emission tomography scanning and magnetic resonance imaging have shown the hypothalamic region may be important in the pathogenesis of cluster headaches. Alterations in hormonal or serotonergic function may also play a role. Treatment of cluster headaches includes pharmacologic interventions for acute episodes and prophylaxis, sphenopalatine ganglion (SPG) blockade, and surgical procedures such as percutaneous SPG radiofrequency rhizotomy, and gamma knife radiosurgery of the trigeminal nerve.

The role of DBS in treatment of other treatment-resistant neurologic and psychiatric disorders, particularly epilepsy, Tourette syndrome, major depressive disorders, and obsessive-compulsive disorder, is also being investigated. Ablative procedures are irreversible and, though they have been refined, remain controversial treatments for intractable illness. Interest has shifted to neuromodulation through DBS of nodes or targets within neural circuits involved in these disorders. Currently, a variety of target areas are being studied.

Literature Review

Essential Tremor and Tremor in Parkinson Disease

Unilateral Stimulation of the Thalamus

This section was originally informed by a 1997 Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Assessment that focused on unilateral deep brain stimulation (DBS) of the thalamus as a treatment of tremor. The Assessment concluded:

- Tremor suppression was total or clinically significant in 82% to 91% of operated sides in 179 patients who underwent implantation of thalamic stimulation devices. Results were durable for up to 8 years, and adverse effects of stimulation were reported as mild and largely reversible.
- These results were at least as good as those associated with thalamotomy. An additional benefit of DBS is that recurrence of tremor may be managed by changes in stimulation parameters.

Studies identified in subsequent literature searches have supported the conclusions of the TEC Assessment. For example, in 2008, Schuurman et al reported 5-year follow-up of 68 patients comparing thalamic stimulation with thalamotomy for treatment of tremor due to Parkinson...
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disease (PD; 45 patients), essential tremor (ET; 13 patients), and multiple sclerosis (MS; 10 patients).2 Forty-eight (71%) patients were assessed at 5 years: 32 with PD, 10 with ET, and 6 with MS. The Frenchay Activities Index (FAI), the primary study outcome measure, was used to assess change in functional status; secondary measures included tremor severity, complication frequency, and patient-assessed outcomes. The mean difference (MD) between interventions, as measured on the FAI, favored thalamic stimulation at all time points: 4.4 (95% confidence interval [CI], 1.1 to 7.7) at 6 months, 3.3 (95% CI, -0.03 to 6.6) at 2 years, and 4.0 (95% CI, 0.3 to 7.7) at 5 years. The procedures had similar efficacy for suppressing tremors. The effect of thalamic stimulation diminished in half of the patients with ET and MS. Neurologic adverse effects were higher after thalamotomy. Subjective assessments favored stimulation.

Hariz et al (2008) evaluated outcomes of thalamic DBS in patients with tremor-predominant PD who participated in a multicenter European study and reported that, at 6 years postsurgery, tremor was still effectively controlled and appendicular rigidity and akinesia remained stable when compared with baseline.3

**Bilateral Stimulation of the Thalamus**

In 2005, Putzke et al reported on a series of 25 patients with ET treated with bilateral DBS for management of midline tremor (head, voice, tongue, trunk).4 Three patients died of unrelated causes, 1 patient was lost to follow-up due to transfer of care, and 1 patient did not have baseline evaluation; these patients were not included in the analysis. Patients were evaluated at baseline (before implantation of second stimulator), and at 1, 3, 6, 12, 24, and 36 months. At 12 months, evaluations were obtained from 76% of patients; at 36 months, 50% of patients were evaluated. The most consistent improvement on the Tremor Rating Scale during both unilateral and bilateral stimulation was found for head and voice tremor. The incremental improvement over unilateral stimulation through the first 12 months of bilateral stimulation was significant (p<0.01). For bilateral stimulation at months 3 and 12, outcome measures were significantly better than unilateral stimulation at month 3 (p<0.05). Small sample size limited analysis at months 24 and 36. Dysarthria was reported in 6 (27%) patients and disequilibrium in 5 patients after bilateral stimulation in staged implantations. No patient reported dysarthria and 2 reported disequilibrium before bilateral stimulation.

In 2006, Pahwa et al reported on long-term follow-up of 45 patients who underwent thalamic DBS, 26 of whom had ET; of these patients, 18 had unilateral and 8 had bilateral implantation.5 Sixteen patients with unilateral and 7 with bilateral stimulators completed at least part of the 5-year follow-up evaluations. Patients with bilateral stimulation had a 78% improvement in mean motor tremor scores in the stimulation on state compared with baseline at 5-year follow-up (p=0.02) and 36% improvement in activities of daily living (ADL) scores. Patients with unilateral stimulation improved 46% on motor tremor scores and 51% on ADLs (p<0.01). Stimulation-related adverse events were reported in more than 10% of patients with unilateral and bilateral thalamic stimulators. Most were mild and were reduced with changes in stimulation parameters. Adverse events in patients with bilateral stimulation (e.g., dysarthria and other speech difficulties, disequilibrium or balance difficulties, abnormal gait) persisted, despite optimization of the stimulation parameters.

**Section Summary: Essential Tremor and Tremor in Parkinson Disease**

A TEC Assessment concluded there was sufficient evidence that DBS of the thalamus results in clinically significant tremor suppression and that outcomes after DBS were at least as good as thalamotomy. Subsequent studies reporting long-term follow-up have supported the conclusions of the Assessment and found that tremors were effectively controlled 5 to 6 years after DBS.
Symptoms ASSOCIATED WITH PARKINSON DISEASE

Advanced Parkinson Disease

Stimulation of the Internal Segment of the Globus Pallidus Interna and Subthalamic Nucleus

This section was informed by a 2001 TEC Assessment that focused on the use of DBS of the internal segment of the globus pallidus interna (GPi) and subthalamic nucleus (STN) for a broader range of PD symptoms. The Assessment concluded:

- A wide variety of studies have consistently demonstrated that DBS of the GPi or STN results in significant improvements, as measured by standardized rating scales of neurologic function. The most frequently observed improvements consist of increased waking hours spent in a state of mobility without dyskinesia, improved motor function during "off" periods when levodopa is not effective, reduction in frequency and severity of levodopa-induced dyskinesia during periods when levodopa is working ("on" periods), improvement in cardinal symptoms of PD during periods when medication is not working, and, in the case of bilateral DBS of the STN, reduction in the required daily dosage of levodopa and/or its equivalents. The magnitude of these changes were both statistically significant and clinically meaningful.

- The beneficial treatment effect lasted at least for the 6 to 12 months observed in most trials. While there was not a great deal of long-term follow-up, the available data were generally positive.

- Adverse effects and morbidity were similar to those known to occur with thalamic stimulation.

- DBS possesses advantages to other treatment options. Compared to pallidotomy, DBS can be performed bilaterally. The procedure is nonablative and reversible.

A 2014 systematic review of randomized controlled trials (RCTs) by Perestelo-Perez et al compared the impact of DBS plus medication to medication alone (or plus sham DBS) on PD outcomes. Six RCTs (total N=1184 patients) were included in the review. Five trials exclusively involved bilateral stimulation to the STN and, in the sixth trial, half of the patients received stimulation to the STN and the other half had stimulation to the GPi. Motor function assessment was blinded in 2 trials and randomization method was described in 4 trials. Five studies reported motor function, measured by the Unified Parkinson’s Disease Rating Scale–III (UPDRS). In the off-medication phase, motor function was significantly higher with DBS than with control (weighted mean difference [WMD], 15.20; 95% CI, 12.23 to 18.18; standard mean difference [SMD], 1.35). In the on-medication phase, there was also significantly greater motor function with DBS than with control (WMD=4.36; 95% CI, 2.80 to 5.92; SMD=0.53). Meta-analyses of other outcomes (e.g., ADLs, quality of life [QOL], dementia, depression) also favored the DBS group.

An earlier (2006) systematic review included both RCTs and observational studies; reviewers examined the literature on subthalamic stimulation for patients with PD who had failed medical management. Twenty studies, primarily uncontrolled cohorts or case series, were included in the meta-analysis. Subthalamic stimulation was found to improve ADLs by 50% over baseline, as measured by the UPDRS-II (decrease of 13.35 points out of 52). There was a 28-point decrease in the UPDRS-III score (out of 108), indicating a 52% reduction in the severity of motor symptoms that occurred while the patient was not taking medication. A strong relation was found between the preoperative dose response to levodopa and improvements in both the UPDRS-II and -III scores. The analysis found a 56% reduction in medication use, a 69% reduction in dyskinesia, and a 35% improvement in QOL with subthalamic stimulation.

In 2007, a meta-analysis by Appleby et al found that the rate of suicidal ideation/suicide attempts associated with DBS for PD ranged from 0.3% to 0.7%. The completed suicide rate ranged from 0.16% to 0.32%. In light of the rate of suicide in patients treated with DBS, reviewers argued for prescreening for suicide risk.
Parkinson Disease with Early Motor Complications
In 2013, Schuepbach et al published an RCT evaluating DBS in patients with PD and early motor complications. Key eligibility criteria included age 18 to 60 years, disease duration of at least 4 years, improvement of motor signs of at least 50% with dopaminergic medication, and PD disease severity below stage 3 in the on-medication condition. At total of 251 patients enrolled, 124 of whom were assigned to DBS plus medical therapy and 127 to medical therapy alone. Analysis was intention to treat and blinded outcome assessment was done at baseline and 2 years.

The primary end point was mean change from baseline to 2 years in the summary index of the Parkinson Disease Questionnaire (PDQ-39), which has a maximum score is 39 points, with higher scores indicating higher QOL. Mean baseline scores on the PDQ-39 were 30.2 (SD=1.3) in the DBS plus medical therapy group and 30.2 (SD=1.2) in the medical therapy only group. At 2 years, the mean score increased by 7.8 points (SD=1.2) in the DBS plus medical therapy group and decreased by 0.2 points (SD=1.1) in the medical therapy only group. There was a significant difference between groups in the mean change, 8.0 (SD=1.6) (p=0.002). There were also significant between-group differences in major secondary outcomes, favoring the DBS plus medical therapy group (p<0.01 on each). These outcomes included severity of motor signs, ADLs, severity of treatment-related complications, and the number of hours with good mobility and no troublesome dyskinesia. The first 3 secondary outcomes were assessed using UPDRS subscales. Regarding medication use, the levodopa-equivalent daily dose was reduced by 39% in the DBS plus medical therapy group and increased by 21% in the medical therapy only group.

Sixty-eight patients in the DBS plus medical therapy group and 56 in the medical therapy only group experienced at least 1 serious adverse event (SAE). This included 26 SAEs in the DBS group that were surgery- or device-related; reoperation was necessary in 4 patients.

Globus Pallidus interna (GPI) vs Subthalamic Nucleus (STN) Stimulation
A number of meta-analyses have compared the efficacy of GPI and STN stimulation in PD patients. One 2016 meta-analysis included only RCTs comparing the 2 types of stimulation in patients with advanced PD and considered a range of outcomes. This review, by Tan et al (2016), included RCTs evaluating patients with PD who were responsive to levodopa, had at least 6 months of follow-up, and reported at least 1 of the following outcome measures: UPDRS-III, Beck Depression Inventory-II (BDI), levodopa-adjusted dose (LED), neurocognitive status, or QOL. Ten RCTs met eligibility criteria and were included in the quantitative synthesis. After 6 months, there were no significant differences in the UPDRS-III scores between the GPI and STN groups for patients in the off-medication/on-simulation state (5 studies; MD = -1.39; 95% CI, -3.70 to 0.92) or the on-medication/on-stimulation state (5 studies; MD = -0.37; 95% CI, -2.48 to 1.73). At the 12- and 24-month follow-up, only 1 to 3 studies reported data on the UPDRS-III score. A pooled analysis of LED, there was a significant difference between the GPI and STN groups, favoring STN (6 studies; MD=0.60; 95% CI, 0.46 to 0.74). However, the analysis of BDI-II scores favored the GPI group (4 studies; MD = -0.31; 95% CI, -0.51 to -0.12). Other meta-analyses had similar mixed findings and none concluded that 1 type of stimulation was clearly better than the other for patients with advanced PD.

Section Summary: Symptoms Associated With Parkinson Disease
A number of RCTs and systematic reviews of the literature have been published. A TEC Assessment concluded that studies on DBS of the GPI or STN have consistently demonstrated clinically significant improvements in outcomes (e.g., neurologic function). Other systematic reviews have also found significantly better outcomes after DBS than with a control intervention. One RCT compared the addition of DBS to medical therapy with medical therapy alone in patients with levodopa-responsive PD of at least 4 years in duration and uncontrolled motor symptoms. The trial found that that QOL at 2 years (e.g., motor disability, motor complications) was significantly higher when DBS was added to medical therapy. Meta-analyses of RCTs comparing GPI and STN have had mixed findings and did not show that 1 type of stimulation was clearly superior to the other.
Primary Dystonia

DBS for the treatment of primary dystonia received U.S. Food and Drug Administration (FDA) approval through the humanitarian device exemption (HDE) process in 2003. The HDE approval process is available for conditions that affect fewer than 4000 Americans per year. According to this approval process, the manufacturer is not required to provide definitive evidence of efficacy, but only probable benefit. The approval was based on the results of DBS in 201 patients represented in 34 manuscripts.\textsuperscript{17} Three studies reported at least 10 cases of primary dystonia. In these studies, clinical improvement with DBS ranged from 50\% to 88\%. A total of 21 pediatric patients were studied; 81\% were older than age 7 years. Among these patients, there was a 60\% improvement in clinical scores. As noted in the analysis of risk and probable benefit, the only other treatment options for chronic refractory primary dystonia are neurodestructive procedures. DBS provides a reversible alternative.

In 2017, Moro et al published a systematic review of literature published through November 2015 on primary dystonia (also known as isolated dystonia).\textsuperscript{18} Reviewers included studies with at least 10 cases. Fifty-eight articles corresponding to 54 unique studies were identified; most involved bilateral DBS of the Gpi. There were only 2 controlled studies, 1 RCT (Volkmann et al; described below) and 1 study that included a double-blind evaluation with and without stimulation. Twenty-four studies reported data using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) and were included in a meta-analysis. These studies enrolled a total of 523 patients (mean per study, 22 patients) and had a mean follow-up of 32.3 months (range, 6-72 months). In a pooled analysis of BFMDRS motor scores (scale range, 0-120; higher scores indicate more severe dystonia) from 24 studies, the mean increase in scores at 6 months compared with baseline was 23.8 points (95\% CI, 18.5 to 29.1 points). The mean increase in the motor score at last follow-up compared with baseline was 26.6 points (95\% CI, 22.4 to 30.9 points). The mean percentage improvement was 59\% at 6 months and 65\% at last follow-up. Fourteen studies reported BFMDRS disability scores (scale range, 0-30). Compared with baseline, the mean absolute change in the score was 4.8 points (95\% CI, 3.1 to 6.6 points) at 6 months and 6.4 points (95\% CI, 5.0 to 7.8 points) at last follow-up. The mean percentage improvement was 44\% at 6 months and 59\% at last follow-up.

The RCT, which was an industry-sponsored, patient- and observer-blinded evaluation of pallidal neurostimulation in subjects with refractory cervical dystonia, was published by Volkmann et al in 2014.\textsuperscript{19} The trial included 62 adults with cervical dystonia of at least 3 years in duration, a severity score of at least 15 on the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), and an unsatisfactory response to botulinum toxin injection and oral medication. Patients were randomized to DBS (n=32) or to sham stimulation (n=30). The primary outcome was change in the TWSTRS severity score at the end of the blinded study period (3 months); thereafter, all patients received open-label active stimulation. After 3 months, mean TWSTRS score improved by 5.1 points (95\% CI, 3.5 to 7.0 points) in the neurostimulation group and by 1.3 points (95\% CI, 0.4 to 2.2 points) in the sham group. The between-group difference was 3.8 points (95\% CI, 1.8 to 5.8 points; p=0.024). Findings were mixed on the prespecified secondary outcomes. There was significantly greater improvement in the neurostimulation than in the sham group on the TWSTRS disability score and the Bain Tremor Scale score, but not on the TWSTRS pain score or the Craniocervical Dystonia Questionnaire-24 score. During the 3-month blinded study period, 22 adverse events were reported in 20 (63\%) patients in the neurostimulation group and 13 adverse events were reported in 12 (40\%) patients in the sham group. Of these 35 adverse events, 11 (31\%) were serious. Additionally, 40 adverse events, 5 of which were serious, occurred during 9 months of the open-label extension period. During the study, 7 patients experienced dysarthria (i.e., slightly slurred speech), which was not reversible in 6 patients.

Section Summary: Primary Dystonia

A review prepared for the FDA and a 2017 systematic review have evaluated literature on DBS for primary dystonia. There are numerous small case series and 1 RCT. The RCT found that severity scores improved more after active than after sham stimulation. A pooled analysis of 24 studies,
mainly uncontrolled, found improvements in motor scores and disability scores after 6 months and at last follow-up (mean, 32 months).

**Tardive Dyskinesia and Tardive Dystonia**

Stimulation of the GPi was examined as a treatment for tardive dyskinesia in a 2007 multicenter case series, with a double-blind evaluation at 6 months (comparison of symptoms in the on and off positions). The trial was stopped early due to successful treatment (>40% improvement at 6 months) in the first 10 patients. In the double-blind evaluation of these patients, stimulation was associated with a mean decrease of 50% in the symptom score when the device was on versus off.

Outcomes on motor function, QOL, and mood in a series of 9 patients treated with DBS of the GPi for tardive dystonia were reported by Gruber et al in 2009. One week and 3 to 6 months after surgery, BFMDRS motor scores were improved by 56.4% and 74.1%, BFMDRS disability scores by 62.5% and 88.9%, and Abnormal Involuntary Movement Scale (AIMS) scores by 52.3% and 69.5%, respectively. At last follow-up (mean, 41 months; range, 18-90 months), BFMDRS motor scores were reduced compared with presurgical assessment by 83%, BFMDRS disability score by 67.7%, and AIMS scores by 78.7%.

**Section Summary: Tardive Dyskinesia and Tardive Dystonia**

One study of DBS in patients with tardive dyskinesia included a double-blind evaluation of DBS at 6 months. Symptoms decreased more with the device turned on but the study was small (10 patients were evaluated) and included only patients with DBS for 6 months. A subsequent case series included 9 patients. Additional studies evaluating more patients, especially RCTs or other controlled studies, are needed.

**Epilepsy**

In 2010, Fisher et al reported a U.S. multicenter, double-blind, randomized Stimulation of the Anterior Nuclei of the Thalamus for Epilepsy (SANTE) trial. Included were 110 patients, ages 18 to 65 years, who experienced at least 6 partial seizures (including secondarily generalized seizures) per month, but no more than 10 per day. (An additional 47 patients were enrolled in the trial but did not undergo implantation). At least 3 antiepileptic drugs must have failed to produce adequate seizure control before baseline, with 1 to 4 antiepileptic drugs used at the time of study entry. Patients were asked to keep a daily seizure diary during treatment. Half the patients were randomized to stimulation during a 3-month blinded phase; then all patients received unblinded stimulation.

Baseline monthly median seizure frequency was 19.5. During the first and second months of the blinded phase, the difference in seizure reduction between stimulation on (-42.1%) and stimulation off (-28.7%) did not differ significantly. In the last month of the blinded phase, the stimulated group had a greater reduction in seizures (-40.4%) compared with the control group (-14.5%).

Long-term outcomes of the SANTE trial were reported by Salanova et al in 2015. The uncontrolled open-label portion of the trial began after 3 months and, beginning at 13 months, stimulation parameters could be adjusted at the clinician’s discretion. Of the 110 implanted patients, 105 (95%) completed the 13-month follow-up, 98 (89%) completed the 3-year follow-up, and 83 (75%) completed 5 years. Among patients with at least 70 days of diary entries, the median change in seizure frequency from baseline was 41% at 1 year and 69% at 5 years (p<0.001 for both). During the trial, 39 (35%) of 110 patients had a device-related SAE, most of which occurred in the first several months after implantation. They included implant-site infection (10% of patients) and lead(s) not within target (8.2% of patients). Seven deaths occurred during the trial and none was considered to be device-related. Depression was reported in 41 (37%) patients following implant; in 3 cases, it was considered device-related. Memory impairment (nonserious) was reported in 30 (27%) patients during the trial, half of whom had a history of the condition. Although some patients appeared to benefit from treatment during the extended
follow-up phase, the difference between groups in the blinded portion of the trial, while significant, was modest overall.

**Section Summary: Epilepsy**

We identified 1 RCT with a 3-month blinded phase that evaluated DBS for treatment of epilepsy. Findings in the first 3 months were mixed: patients reported significantly fewer seizures in the third month, but not in the first or second month. In an uncontrolled follow-up period, patients reported fewer seizures compared to baseline as well as adverse events, including device-related SAEs in about one-third of patients. The risk-benefit ratio is uncertain.

**Multiple Sclerosis**

In 2008, Schuurman et al reported 5-year follow-up for 68 patients in a study comparing thalamic stimulation with thalamotomy for multiple indications, including 10 patients with MS. Trial details are discussed with essential tremor in the section on Unilateral Stimulation of the Thalamus. The small numbers of patients with MS in this trial limits conclusions that can be drawn.

**Section Summary: Multiple Sclerosis**

One RCT reporting on 10 MS patients is insufficient evidence for drawing conclusions on the impact of DBS on health outcomes for this population.

**Tourette Syndrome**

Several systematic reviews of the literature on DBS for Tourette syndrome have been published. Most recent systematic reviews (i.e., those published in 2015-2017) qualitatively described the literature. Only Baldermann et al (2016) conducted pooled analyses of study data. That review identified 57 studies on DBS for Tourette syndrome, 4 of which were randomized crossover studies. The studies included a total of 156 cases. Twenty-four studies included a single patient each and 4 had sample sizes of 10 or more (maximum, 18 patients). Half of the patients (n=78) received thalamus stimulation and the next most common areas of stimulation were the GPi anterior medial part (n=44) and post ventrolateral part (n=20). Two of the RCTs used thalamic stimulation, 1 used bilateral globus pallidus stimulation, and 1 used both. The primary outcome was the Yale Global Tic Severity Scale (YGTSS). In a pooled analysis of within-subject pre-post data, there was a median improvement of 53% in YGTSS score, a decline from a median score of 83 to 35 at last follow-up. Moreover, 81% of patients showed at least a 25% reduction in YGTSS score and 54% showed improvements of 50% or more. In addition, data were pooled from the 4 crossover RCTs: 27 patients received DBS and 27 received a control intervention. Targets included the thalamus and the globus pallidus. In the pooled analysis, there was a statistically significant between-group difference, favoring DBS (SMD=0.96; 95% CI, 0.36 to 1.56). Reviewers noted that the effect size of 0.96 is considered to be a large effect.

Another systematic review from 2012 examined patient and target selection for DBS for subjects with Tourette syndrome. Most clinical trials for DBS in Tourette syndrome have targeted the medial thalamus at the crosspoint of the centromedian nucleus, substantia periventricularis, and nucleus ventro-oralis internus. Other targets that have been investigated include the STN, caudate nucleus, GPi, and the anterior limb of the internal capsule and nucleus accumbens. Reviewers found no clear consensus in the literature for which patients should be treated and what the best target is.

The crossover RCT with the largest sample size was published by Kefalopoulou et al (2015). The double-blind trial included 15 patients with severe medically refractory Tourette syndrome; all received bilateral GPi surgery for DBS and were randomized to the off-stimulation phase first or the on-stimulation phase first for 3 months, followed by the opposite phase for the next 3 months. Of the 15 receiving surgery, 14 were randomized and 13 completed assessments after both on and off phases. For the 13 trial completers, mean YGTSS scores were 80.7 in the off-stimulation phase and 68.3 in the on-stimulation phase. The mean difference in YGTSS scores was an improvement of 12.4 points (95% CI, 0.1 to 24.7 points), which was statistically significant (p=0.048) after Bonferroni correction. There was no significant between-group difference in
YG TSS scores in patients randomized to the on-stimulation phase first or second. Three SAEs were reported, 2 related to surgery and 1 related to stimulation. Reviewers noted that the most effective target for DBS in patients with Tourette syndrome needs additional study.

**Section Summary: Tourette Syndrome**

A number of uncontrolled studies and 4 crossover RCTs have been published; in addition, there are several systematic reviews of the published literature. Most studies, including the RCTs, had small sample sizes (i.e., ≤15 patients) and they used a variety of DBS targets. A 2015 meta-analysis has suggested that DBS may improve outcomes in patients with Tourette syndrome. However, the optimal target for DBS is not known and additional controlled studies in larger numbers of patients are needed.

**Cluster Headache and Facial Pain**

DBS of the posterior hypothalamus for the treatment of chronic cluster headaches has been investigated, because functional studies have suggested cluster headaches have a central hypthalamic pathogenesis.

In 2010, Fontaine et al published results from a prospective crossover, double-blind, multicenter trial in 11 patients with DBS of the posterior hypothalamus for severe refractory chronic cluster headache.30 The randomized phase compared active and sham stimulation during 1-month periods and was followed by a 1-year open phase. Severity of cluster headache was assessed using the weekly attack frequency (primary outcome), pain intensity, sumatriptan injections, emotional impact, and QOL (12-Item Short-Form Health Survey). During the randomized phase, no significant changes in primary and secondary outcome measures were observed between active and sham stimulation. At the end of the open phase, 6 of 11 patients reported greater than 50\% reduction in the weekly frequency of attacks.

Another research group from Europe published 2 case series (potentially overlapping) on DBS of the ipsilateral posterior hypothalamus in patients with chronic cluster headache.31,32 Stimulation was reported to result in long-term pain relief (1-26 months of follow-up) without significant adverse effects in 16 patients with chronic cluster headaches and in 1 patient with neuralgiform headache; treatment failed in all 3 patients who had atypical facial pain. Controlled studies are needed to evaluate the long-term safety and effectiveness of DBS for chronic cluster headaches.

**Section Summary: Cluster Headache and Facial Pain**

Several case series and a crossover RCT have been published on DBS for cluster headache or facial pain. The RCT included 11 patients; there were no significant differences between groups receiving active and sham stimulation. Additional RCTs or controlled studies are needed.

**Treatment-Resistant Depression**

A variety of target areas are being investigated for DBS of treatment-resistant depression. A 2014 systematic review identified 22 published reports with 6 different approaches/targets, including the nucleus accumbens, ventral capsule/ventral striatum, subgenual cingulate cortex, lateral habenula, inferior thalamic nucleus, and medial forebrain bundle.33 Only 3 identified studies were controlled with sham stimulation periods, and at least 2 multicenter RCTs evaluating subgenual cingulate cortex and ventral striatum/ventral capsule DBS were terminated due to futility (interim analysis demonstrating very low probability of success if the trial was completed as planned). A 2015 systematic review identified a single published RCT on DBS for depression34; this trial is described next.

An industry-sponsored, double-blind RCT evaluating DBS of the ventral capsule/ventral striatum in patients with chronic treatment-resistant depression was published by Dougherty et al (2015).35 The trial included 30 patients with a major depressive episode lasting at least 2 years and inadequate response to at least 4 trials of antidepressant therapy. Participants were randomized to 16 weeks of active (n=16) or to sham (n=14) DBS, followed by an open-label continuation
phase. One patient, who was assigned to active treatment, dropped out during the blinded treatment phase. The primary outcome was clinical response at 16 weeks, defined as 50% or greater improvement from baseline on Montgomery-Asberg Depression Rating Scale (MADRS) score. A response was identified in 3 (20%) of 15 patients in the active treatment group and in 2 (14%) of 14 patients in the sham control group. The between-group difference in response was not statistically significant (p = 0.53). During the blinded treatment phase, psychiatric adverse events occurring more frequently in the active treatment group included worsening depression, insomnia, irritability, suicidal ideation, hypomania, disinhibition, and mania. Psychiatric adverse events occurring more frequently in the sham control group were early morning awakening and purging. Findings of this trial did not support a conclusion that DBS is effective for treating treatment-resistant depression.

In 2016, a crossover RCT evaluating active and sham phases of DBS stimulation in 25 patients with treatment-resistant depression was published by Bergfeld et al.36 Prior to the randomized phase, all patients received 52 weeks of open-label DBS treatment with optimization of settings. Optimization ended when patients achieved a stable response of at least 4 weeks or after the 52-week period ended. At the end of the open-label phase, 10 (40%) patients were classified as responders (≥50% decrease in the Hamilton Depression Rating Scale [HAM-D] score) and 15 (60%) patients were classified as nonresponders. After the 52 weeks of open-label treatment, patients underwent 6 weeks of double-blind active and sham stimulation. Sixteen (64%) of 25 enrolled patients participated in the randomized phase (9 responders, 7 nonresponders). Nine patients were prematurely crossed over to the other intervention. Among all 16 randomized patients, HAM-D scores were significantly higher at the end of the active stimulation phase (mean HAM-D score, 16.5) than the sham stimulation phase (mean HAM-D score, 23.1; p < 0.001). Mean HAM-D scores were similar after the active (19.0) and sham phases in initial nonresponders (23.0). Among initial responders, mean HAM-D score was 9.4 after active stimulation and 23 after sham stimulation. Trial limitations included the small number of patients in the randomized phase and potential bias from having an initial year of open-label treatment; patients who had already responded to DBS over a year of treatment were those likely to respond to active than sham stimulation in the double-blind randomized phase; findings may not be generalizable to patients with treatment-resistant depression who are DBS-naive.

**Section Summary: Treatment-Resistant Depression**

A number of case series and several RCTs evaluating DBS in patients with treatment-resistant depression have been published. Two RCTs were terminated for futility. Another RCT did not find a statistically significant difference between groups in the primary outcome (clinical response) and adverse psychiatric events occurred more frequently in the treatment than in the control group. More recently, a crossover controlled trial randomized patients to active or to sham stimulation after a year of open-label stimulation. There was a greater reduction in symptom scores after active stimulation, but only in patients who were responders in the open-label phase; these findings may not be generalizable.

**Obsessive-Compulsive Disorder**

Several systematic reviews evaluating DBS for obsessive-compulsive disorder (OCD) have been published.37-41 Two of these reviews included meta-analyses and pooled study findings. Kisely et al (2014) included only double-blind RCTs of active versus sham DBS.40 Five trials (total N=50 patients) met eligibility criteria and data on 44 patients were available for meta-analysis. Three were parallel-group RCTs with or without a crossover phase and 2 were only crossover trials. The site of stimulation was the anterior limb of the internal capsule (3 studies), the nucleus accumbens (1 study) and the STN (1 study). Duration of treatment ranged from 2 to 12 weeks. All studies reported scores on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), which is a 10-item clinician-rated scale, in which higher ratings reflect more intense symptoms, and a score of 24 or more (of a possible 40) indicates severe illness. Most studies designate a therapeutic response as a reduction in Y-BOCS score of 35% or more from the pretreatment baseline, with a reduction of 25% to 35% considered a partial response. Only 1 of the 5 studies compared the proportion of responders on the Y-BOCS as an outcome measure and that study did not find a
statistically significant difference between active and sham stimulation groups. All studies reported the outcome measure, mean reduction in Y-BOCS score. When data from the 5 studies were pooled, there was a statistically significantly greater reduction in the mean Y-BOCS in the active versus the sham group (MD = -8.49; 95% CI, -12.18 to -4.80). The outcome measure, however, does not permit conclusions on whether the between-group difference is clinically meaningful. Trial authors reported 16 SAEs including 1 cerebral hemorrhage and 2 infections requiring electrode removal. Additionally, nonserious transient adverse events were reported including 13 reports of hypomania, 6 of increase in depressive or anxious symptoms, and 6 of headaches.

A 2015 systematic review and meta-analysis by Alonso et al included studies of any type (including case reports) evaluating DBS for OCD and reporting changes in Y-BOCS score. Reviewers identified 31 studies (total N=116 patients). They did not report study type (i.e., controlled vs uncontrolled); however, the meta-analysis only included patients who received active treatment. Twenty-four (77%) studies included 10 or fewer patients. Most studies (24, including 83 patients) involved DBS of striatal areas. Of the remaining studies, 5 (27 patients) addressed STN stimulation and 2 (6 patients) addressed stimulation of the inferior thalamic peduncle. Twelve studies provided patient-level data and 4 provided pooled data on percentage of responders (i.e., >35% reduction in posttreatment Y-BOCS scores). Pooled analysis yielded a global percentage of responders of 60% (95% CI, 49% to 69%). The most frequent adverse events reported were worsening anxiety (25 patients) and hypomanic symptoms (23 patients). The review authors reported on the benefits and risks of DBS stimulation but could not draw conclusions about stimulation to any particular region or about the safety or efficacy of DBS for OCD compared with sham stimulation or other therapy.

**Section Summary: Obsessive-Compulsive Disorder**
The literature on DBS for OCD consists of several RCTs and a number of uncontrolled studies. Most studies had small sample sizes. Only 1 of the 5 RCTs identified in a 2015 meta-analysis reported the outcome measure of greatest interest—clinically significant change in Y-BOCS scores. Uncontrolled data have suggested improvements in OCD symptoms after DBS treatment, but have also identified a substantial number of adverse events. Additional blinded controlled studies are needed to draw conclusions about the impact of DBS on the net health benefit.

**Other Indications**
The evidence on use of DBS for anorexia nervosa, alcohol addiction, Alzheimer disease, Huntington disease, and chronic pain consists of small case series. They are inadequate evidence on which to make a determination of efficacy.

**Summary of Evidence**
For individuals who have essential tremor or tremor in Parkinson disease who receive deep brain stimulation (DBS) of the thalamus, the evidence includes a systematic review and case series. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. The systematic review (a TEC Assessment) concluded that there was sufficient evidence that DBS of the thalamus results in clinically significant tremor suppression and that outcomes after DBS were at least as good as thalamotomy. Subsequent studies reporting long-term follow-up have supported the conclusions of the Assessment and found that tremors were effectively controlled 5 to 6 years after DBS. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have symptoms (e.g., speech, motor fluctuations) associated with Parkinson disease (advanced or >4 years in duration with early motor symptoms) who receive DBS of the globus pallidus interna (GPI) or subthalamic nucleus (STN), the evidence includes randomized controlled trials (RCTs) and systematic reviews. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. One of the systematic reviews (a TEC Assessment) concluded that studies of DBS of the GPI or STN have consistently demonstrated clinically significant improvements in outcomes (e.g., neurologic function). Other systematic
reviews have also found significantly better outcomes after DBS than after a control intervention. An RCT in patients with levodopa-responsive Parkinson disease of at least 4 years in duration and uncontrolled motor symptoms found that quality of life at 2 years was significantly higher when DBS was provided in addition to medical therapy. Meta-analyses of RCTs comparing DBS of the GPi and STN have reported mixed findings and have not shown that 1 type of stimulation was clearly superior to the other. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have primary dystonia who receive DBS of the GPi or STN, the evidence includes systematic reviews, case series, and an RCT. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. A pooled analysis of 24 studies, mainly uncontrolled, found improvements in motor scores and disability scores after 6 months and at last follow-up (mean, 32 months). A double-blind RCT found that severity scores improved more after active than after sham stimulation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have tardive dyskinesia or tardive dystonia who receive DBS, the evidence includes case series, 1 of which included a double-blind comparison of outcomes when the DBS device was turned on versus off. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Few studies were identified and they had small sample sizes (≤10 patients). Additional studies, especially RCTs or other controlled studies, are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have epilepsy who receive DBS, the evidence includes 1 RCT. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Only 1 RCT was identified; in it, DBS had a positive impact during some parts of the blinded trial phase but not others, and a substantial number of adverse events were reported. Additional trials are required to determine the impact of DBS on the net health outcome. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have multiple sclerosis (MS) who receive DBS, the evidence includes 1 RCT. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. One RCT with 10 MS patients is insufficient evidence on which to draw conclusions about the impact of DBS on health outcomes in this population. Additional trials are required. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have Tourette syndrome who receive DBS, the evidence includes crossover RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Several small (≤15 patients) crossover trials and a 2015 meta-analysis have suggested that DBS may improve outcomes in patients with Tourette syndrome. However, the optimal target for DBS is unknown and additional controlled studies in larger numbers of patients are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have cluster headaches or facial pain who receive DBS, the evidence includes a randomized crossover study and case series. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. In the randomized study, the between-group difference in response rates did not differ significantly between active and sham stimulation phases. Additional RCTs or controlled studies are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have treatment-resistant depression who receive DBS, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. The only double-blind, parallel-group RCT in patients with depression did not find that DBS significantly increased the response rate compared with sham; and 2 other RCTs were stopped due to futility. A crossover controlled trial randomized patients to
active or to sham stimulation after a year of open-label stimulation. There was a greater reduction in symptom scores after active stimulation, but only in patients who were responders in the open-label phase; these findings may not be generalizable. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have obsessive-compulsive disorder who receive DBS, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. Among the RCTs on DBS for obsessive-compulsive disorder, only 1 has reported the outcome of greatest clinical interest (therapeutic response rate), and that trial did not find a statistically significant benefit for DBS compared to sham treatment. The evidence is insufficient to determine the effects of the technology on health.

For individuals who have anorexia nervosa, alcohol addiction, Alzheimer disease, Huntington disease, or chronic pain who receive DBS, the evidence includes case series. Relevant outcomes are symptoms, functional outcomes, quality of life, and treatment-related morbidity. RCTs are needed to evaluate the impact of DBS on health outcomes for these conditions. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Clinical Input from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests from Blue Cross Blue Shield Association, input was received from 2 academic medical centers and 2 physician specialty societies in 2014. Input supported the use of bilateral deep brain stimulation in patients with medically unresponsive tremor in both limbs.

Practice Guidelines and Position Statements

European Academy of Neurology

In 2016, the European Academy of Neurology (EAN) published guidelines on neuromodulation in management of chronic pain.42 EAN’s recommendation on deep brain stimulation (DBS) for treatment of neuropathic pain was inconclusive and based on a “very low” quality of evidence.

American Academy of Neurology

The American Academy of Neurology (AAN) updated its guidelines on the treatment of essential tremor (ET) in 2011.43 This update did not change the conclusions and recommendations of the 2005 practice parameters on DBS for ET.44 The guidelines stated that bilateral DBS of the thalamic nucleus may be used to treat medically refractory limb tremor in both upper limbs (level C, possibly effective), but that there were insufficient data on the risk/benefit ratio of bilateral versus unilateral DBS in the treatment of limb tremor. There was insufficient evidence to make recommendations on the use of thalamic DBS for head or voice tremor (level U, treatment is unproven).

The 2006 guidelines from AAN on the treatment of Parkinson disease (PD) with motor fluctuations and dyskinesia found that, although criteria are evolving, patients with PD considered candidates for DBS include those who are levodopa-responsive, nondemented, and neuropsychiatrically intact patients who have intractable motor fluctuations, dyskinesia, or tremor.45 AAN concluded that DBS of the subthalamic nucleus (STN) may be considered a treatment option in PD patients to improve motor function and to reduce motor fluctuations, dyskinesia, and medication usage (level C, possibly effective), but found evidence insufficient to make any recommendations about the effectiveness of DBS of the globus pallidus or the ventral intermediate nucleus of the thalamus in reducing motor complications or medication usage, or in improving motor function in PD patients.
The 2010 guidelines from AAN on the treatment of nonmotor symptoms of PD found insufficient evidence for the treatment of urinary incontinence with DBS of the STN. AAN found that DBS of the STN possibly improves sleep quality in patients with advanced PD. However, none of the studies performed DBS to treat insomnia as a primary symptom, and DBS of the STN is not currently used to treat sleep disorders.

The 2013 guidelines from AAN on the treatment of tardive syndromes have indicated that the available evidence, which consists of class IV studies comprising case reports or small case series, is insufficient to support or refute pallidal DBS for tardive syndromes.

American Society for Stereotactic and Functional Neurosurgery et al
The American Society for Stereotactic and Functional Neurosurgery and the Congress of Neurological Surgeons published a systematic review and guidelines on DBS for obsessive-compulsive disorder (OCD) in 2014. The document concluded that there was a single level I study supporting the use of bilateral STN DBS for medically refractory OCD and a single level II study supporting bilateral nucleus accumbens DBS for medically refractory OCD. It also concluded that the evidence on unilateral DBS was insufficient.

Canadian Network for Mood and Anxiety Treatments
The Canadian Network for Mood and Anxiety Treatments’ 2009 clinical guidelines for management of major depressive disorder in adults indicated that there was emerging evidence to support DBS as an experimental intervention for patients with treatment-refractory depression. There was no consensus on the most effective target brain region for implantation, although 3 regions have been explored (subcallosal cingulated gyrus, nucleus accumbens, ventral caudate/ventral striatum region).

European Society for the Study of Tourette Syndrome
The European Society for the Study of Tourette Syndrome published guidelines on DBS in 2011. Its guidelines stated that DBS for Tourette syndrome is still in its infancy and that there were no randomized controlled trials that have included a sufficiently large number of patients. There was general agreement among the workgroup members that DBS should only be used in adult, treatment-resistant, and severely affected patients, and it was highly recommended that DBS be performed in the context of controlled and double-blind trials including larger and carefully characterized groups of patients.

National Institute for Health and Care Excellence
The U.K.’s National Institute for Health and Care Excellence (NICE) has published guidance documents on DBS, as discussed in the following subsections.

Tremor and Dystonia
In 2006, NICE made the same statements for use of DBS for treatment of both tremor and dystonia. Unilateral and bilateral stimulation of structures responsible for modifying movements, such as the thalamus, globus pallidus, and the STN, which interact functionally with the substantia nigra, are included in both guidance statements. The guidance stated: “Current evidence on the safety and efficacy of deep brain stimulation for tremor and dystonia (excluding Parkinson’s disease) appears adequate to support the use of this procedure, provided that the normal arrangements are in place for consent, audit and clinical governance.”

Refractory Chronic Pain Syndromes (Excluding Headache)
The 2011 guidance from NICE indicated there is evidence that DBS for refractory chronic pain (excluding headache) is associated with serious risks. However, the procedure is “efficacious in some patients’ refractory to other treatments and, therefore, it may be used provided “normal arrangements are in place for consent, audit and clinical governance.” Patients should be informed that DBS may not control their chronic pain symptoms and that possible risks associated with this procedure include the small risk of death.
Intractable Trigeminal Autonomic Cephalalgias
The 2011 guidance from NICE indicated that the evidence on the efficacy of DBS for intractable trigeminal autonomic cephalalgias (e.g., cluster headaches) was “limited and inconsistent, and the evidence on safety shows that there were serious but well-known adverse effects. Therefore, “this procedure should only be used with special arrangements for clinical governance, consent, and audit or research.”\(^{52}\)

Refractory Epilepsy
The 2012 guidance from NICE indicated that the evidence on the efficacy of DBS for refractory epilepsy was limited in both quantity and quality\(^{53}\): “The evidence on safety showed that there are serious but well-known adverse effects. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research.”

Parkinson Disease
In 2003, NICE stated that the evidence on the safety and efficacy of DBS for treatment of Parkinson disease (PD) “appears adequate to support the use of the procedure, provided that normal arrangements are in place for consent, audit, and clinical governance.”\(^{54}\)

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
Effective for services furnished on or after April 1, 2003, Medicare covers unilateral or bilateral thalamic ventralis intermedius nucleus (VIM) DBS for the treatment of ET and/or parkinsonian tremor and unilateral or bilateral STN or globus pallidus interna (GPI) DBS for the treatment of PD when the following conditions are met:\(^{55}\)

1. DBS devices must be FDA-approved devices for “DBS or devices used in accordance with FDA-approved protocols governing Category B Investigational Device Exemption (IDE) DBS clinical trials.”
2. For thalamic VIM DBS, patients must meet all of the following criteria:
   a. “Diagnosis of ET based on postural or kinetic tremors of hand(s) without other neurologic signs, or diagnosis of idiopathic PD (presence of at least 2 cardinal PD features (tremor, rigidity or bradykinesia)) which is of a tremor-dominant form.
   b. Marked disabling tremor of at least level 3 or 4 on the Fahn-Tolosa-Marin Clinical Tremor Rating Scale (or equivalent scale) in the extremity intended for treatment, causing significant limitation in daily activities despite optimal medical therapy.
   c. Willingness and ability to cooperate during conscious operative procedure, as well as during postsurgical evaluations, adjustments of medications and stimulator settings.”
3. For STN or GPI DBS, patients must meet all of the following criteria:
   a. “Diagnosis of PD based on the presence of at least 2 cardinal PD features (tremor, rigidity or bradykinesia).
   b. Advanced idiopathic PD as determined by the use of Hoehn and Yahr stage or Unified Parkinson's Disease Rating Scale (UPDRS) part III motor subscale.
   c. L-dopa responsive with clearly defined ‘on’ periods.
   d. Persistent disabling Parkinson’s symptoms or drug side effects (e.g., dyskinesias, motor fluctuations, or disabling ‘off’ periods) despite optimal medical therapy.
   e. Willingness and ability to cooperate during conscious operative procedure, as well as during post-surgical evaluations, adjustments of medications and stimulator settings.”

DBS is not covered for ET or PD patients with any of the following:
2. Cognitive impairment, dementia or depression, which would be worsened by or would interfere with the patient's ability to benefit from DBS.
3. Current psychosis, alcohol abuse or other drug abuse.
Structural lesions such as basal ganglionic stroke, tumor or vascular malformation as etiology of the movement disorder.

Previous movement disorder surgery within the affected basal ganglion.

Significant medical, surgical, neurologic or orthopedic co-morbidities contraindicating DBS surgery or stimulation.”

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 1.

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NCT: national clinical trial.

*a* Denotes industry-sponsored or cosponsored trial.

**References**


### Documentation for Clinical Review

Please provide the following documentation (if when requested):
- History and physical including: previous treatment plan and response
- Pharmacological treatment: including type of drug(s), dosage, duration of use, and responses (if applicable)

### Post Service
- Operative report(s)

### Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

**MN/IE**

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.
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<tr>
<td>61863</td>
<td>Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; first array</td>
<td></td>
</tr>
<tr>
<td>61864</td>
<td>Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; each additional array (List separately in addition to primary procedure)</td>
<td></td>
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<tr>
<td>61867</td>
<td>Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording; first array</td>
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<tr>
<td>61868</td>
<td>Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording; each additional array (List separately in addition to primary procedure)</td>
<td></td>
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<tr>
<td>61885</td>
<td>Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array</td>
<td></td>
</tr>
<tr>
<td>61886</td>
<td>Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to 2 or more electrode arrays</td>
<td></td>
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<tr>
<td>95970</td>
<td>Electronic analysis of implanted neurostimulator pulse generator system (e.g., rate, pulse amplitude, pulse duration, configuration of wave form, battery status, electrode selectability, output modulation, cycling, impedance and patient compliance measurements); simple or complex brain, spinal cord, or peripheral (i.e., cranial nerve, peripheral nerve, sacral nerve, neuromuscular) neurostimulator pulse generator/transmitter, without reprogramming</td>
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</tr>
<tr>
<td>95978</td>
<td>Electronic analysis of implanted neurostimulator pulse generator system (e.g., rate, pulse amplitude and duration, battery status, electrode selectability and polarity, impedance and patient compliance measurements), complex deep brain neurostimulator pulse generator/transmitter, with initial or subsequent programming; first hour</td>
<td></td>
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<tr>
<td>95979</td>
<td>Electronic analysis of implanted neurostimulator pulse generator system (e.g., rate, pulse amplitude and duration, battery status, electrode selectability and polarity, impedance and patient compliance measurements), complex deep brain neurostimulator pulse generator/transmitter, with initial or subsequent programming; each additional 30 minutes after first hour (List separately in addition to code for primary procedure)</td>
<td></td>
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<tr>
<td>HCPCS</td>
<td>L8680</td>
<td>Implantable neurostimulator electrode, each</td>
</tr>
<tr>
<td>L8685</td>
<td>Implantable neurostimulator pulse generator, single array, rechargeable, includes extension</td>
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</table>
### Deep Brain Stimulation

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
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<tr>
<td></td>
<td>L8686</td>
<td>Implantable neurostimulator pulse generator, single array, nonrechargeable, includes extension</td>
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<tr>
<td></td>
<td>L8687</td>
<td>Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension</td>
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<tr>
<td></td>
<td>L8688</td>
<td>Implantable neurostimulator pulse generator, dual array, nonrechargeable, includes extension</td>
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<table>
<thead>
<tr>
<th>ICD-10 Procedure</th>
<th>Code</th>
<th>Description</th>
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<tr>
<td></td>
<td>00H00MZ</td>
<td>Insertion of Neurostimulator Lead into Brain, Open Approach</td>
</tr>
<tr>
<td></td>
<td>00H03MZ</td>
<td>Insertion of Neurostimulator Lead into Brain, Percutaneous Approach</td>
</tr>
<tr>
<td></td>
<td>00H04MZ</td>
<td>Insertion of Neurostimulator Lead into Brain, Percutaneous Endoscopic Approach</td>
</tr>
<tr>
<td></td>
<td>00H60MZ</td>
<td>Insertion of Neurostimulator Lead into Cerebral Ventricle, Open Approach</td>
</tr>
<tr>
<td></td>
<td>00H63MZ</td>
<td>Insertion of Neurostimulator Lead into Cerebral Ventricle, Percutaneous Approach</td>
</tr>
<tr>
<td></td>
<td>00H64MZ</td>
<td>Insertion of Neurostimulator Lead into Cerebral Ventricle, Percutaneous Endoscopic Approach</td>
</tr>
<tr>
<td></td>
<td>00HE0MZ</td>
<td>Insertion of Neurostimulator Lead into Cranial Nerve, Open Approach</td>
</tr>
<tr>
<td></td>
<td>00HE3MZ</td>
<td>Insertion of Neurostimulator Lead into Cranial Nerve, Percutaneous Approach</td>
</tr>
<tr>
<td></td>
<td>00HE4MZ</td>
<td>Insertion of Neurostimulator Lead into Cranial Nerve, Percutaneous Endoscopic Approach</td>
</tr>
<tr>
<td></td>
<td>00P00MZ</td>
<td>Removal of Neurostimulator Lead from Brain, Open Approach</td>
</tr>
<tr>
<td></td>
<td>00P03MZ</td>
<td>Removal of Neurostimulator Lead from Brain, Percutaneous Approach</td>
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<td>Removal of Neurostimulator Lead from Cerebral Ventricle, Percutaneous Approach</td>
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<td>Removal of Neurostimulator Lead from Cerebral Ventricle, Percutaneous Endoscopic Approach</td>
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<tr>
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<tr>
<td></td>
<td>00PE4MZ</td>
<td>Removal of Neurostimulator Lead from Cranial Nerve, Percutaneous Endoscopic Approach</td>
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</table>

**ICD-10 Diagnosis**

All Diagnoses

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### Policy History

This section provides a chronological history of the activities, updates, and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
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<tbody>
<tr>
<td>12/18/2009</td>
<td>New policy, Portions of this policy have been derived from the previously existing BSC Medical Policy Bilateral Deep Brain Stimulation for Parkinsons</td>
<td>Medical Policy Committee</td>
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**Definitions of Decision Determinations**

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

**Prior Authorization Requirements (as applicable to your plan)**

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member’s health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member’s eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.