BlueCross BlueShield of Louisiana

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Deep Brain Stimulation

Policy # 00024
Original Effective Date: 08/25/2005
Current Effective Date: 07/16/2014

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider unilateral deep brain stimulation (DBS) of the thalamus in patients with disabling, medically unresponsive tremor due to essential tremor (ET) or Parkinson's disease (PD) to be **eligible for coverage**.

Patient Selection Criteria
Coverage eligibility will be considered for deep brain stimulation (DBS) of the thalamus when the following criteria are met:

Disabling, medically unresponsive tremor defined as:

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

Based on review of available data, the Company may consider unilateral or bilateral deep brain stimulation (DBS) of the globus pallidus or subthalamic nucleus when patient selection criteria are met to be **eligible for coverage.**

Patient Selection Criteria
Coverage eligibility will be considered for unilateral or bilateral deep brain stimulation (DBS) of the globus pallidus or subthalamic nucleus when all of the following criteria are met:

- Parkinson's disease (PD) with all of the following:
  - Good response to levodopa; and
  - Minimal score of 30 points on the Unified Parkinson Disease Rating Scale when the patient has been without medication for approximately 12 hours; and
  - Motor complications not controlled by pharmacologic therapy.
- Patients aged greater than seven years with chronic, intractable (drug refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia and cervical dystonia (torticollis).

When Services Are Considered Not Medically Necessary
Based on review of available data, the Company may consider deep brain stimulation (DBS) to be **not medically necessary**** when the following contraindications are present:

- Patients who are not good surgical risks because of unstable medical problems or because of the presence of a cardiac pacemaker; or
- Patients who have medical conditions that require repeated magnetic resonance imaging (MRI); or
- Patients who have dementia that may interfere with the ability to cooperate; or

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- Patients who have had botulinum toxin injections within the last six months.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers deep brain stimulation (DBS) for the following indications to be **investigational:***

- Other movement disorders, including but not limited to:
  - Multiple sclerosis
  - Post-traumatic dyskinesia
  - Tardive dyskinesia
- Chronic cluster headaches
- Other psychiatric or neurologic disorders, including but not limited to:
  - Tourette syndrome
  - Depression
  - Obsessive compulsive disorder (OCD)
  - Anorexia nervosa
  - Alcohol addiction
  - Chronic pain
  - Epilepsy
- Any condition not meeting patient selection criteria.

Background/Overview

Deep brain stimulation involves the stereotactic placement of an electrode into the brain (i.e., hypothalamus, thalamus, globus pallidus, or subthalamic nucleus). DBS is used as an alternative to permanent neuroablative procedures for control of ET and PD. DBS is also being evaluated for the treatment of a variety of other neurologic and psychiatric disorders, including epilepsy, dystonia, cluster headache, Tourette syndrome, depression, and OCD.

DBS has been investigated as an alternative to permanent neuroablative procedures, such as thalamotomy and pallidotomy. The technique has been most thoroughly investigated as an alternative to thalamotomy for unilateral control of 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, or 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., the “on” state) and the nadir response during drug troughs (i.e., the “off” state). In addition, levodopa, the most commonly used anti-Parkinson's drug, may be associated with disabling drug-induced dyskinesias. Therefore, the optimal pharmacologic treatment of PD may involve a balance between optimal effects on Parkinson's disease symptoms versus the appearance of drug-induced dyskinesias. The effect of DBS on both Parkinson's disease symptoms and drug-induced dyskinesias has also been studied.

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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 that have been associated with high blood pressure, smoking, alcohol use, etc. However, the exact pathogenesis of cluster headaches is uncertain. Positron emission tomography (PET) scanning and magnetic resonance imaging (MRI) have shown the hypothalamic region may be important in the pathogenesis of cluster headaches. Alterations in hormonal/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 Tourette syndrome, epilepsy, OCD and major depressive disorders 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.

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 to surgery for permanent subcutaneous 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, the 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 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 side effects of neurostimulation, such as dysarthria, disequilibrium, or involuntary movements.

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FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
The U.S. FDA has approved the Activa Tremor Control System, manufactured by Medtronic Corp, MN, for deep brain stimulation. While the original 1997 FDA-labeled indications were limited to unilateral implantation of the device for the treatment of tremor, in January 2002, the FDA-labeled indications were expanded to include bilateral implantation as a treatment to decrease the symptoms of advanced Parkinson's disease that are not controlled by medication. In April 2003, the labeled indications were 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 received FDA approval through the Humanitarian Device Exemption (HDE) process. The Activa Tremor Control System consists of the following components: the implantable pulse generator, the 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 simulation, and a patient control magnet, which allows the patient to turn the pulse generator on and off, or change between high and low settings.

In February 2009, the FDA approved deep brain stimulation with the Reclaim device (Medtronic, Inc.) via the HDE process for the treatment of severe OCD.

Centers for Medicare and Medicaid Services (CMS)
Effective for services furnished on or after April 1, 2003, Medicare will cover unilateral or bilateral thalamic ventralis intermedius nucleus (VIM) DBS for the treatment of ET and/or parkinsonian tremor and unilateral or bilateral subthalamic nucleus (STN) or globus pallidus interna (GPi) DBS for the treatment of PD when the following conditions are met.

1. DBS devices must be U.S. 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 post-surgical 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 is not covered for ET or PD patients with any of the following:

1. Non-idiopathic Parkinson's disease or "Parkinson's Plus" syndromes.
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.
4. Structural lesions such as basal ganglionic stroke, tumor or vascular malformation as etiology of the movement disorder.
5. Previous movement disorder surgery within the affected basal ganglion.
6. Significant medical, surgical, neurologic or orthopedic co-morbidities contraindicating DBS surgery or stimulation.

Rationale/Source

The policy was originally based on 2 TEC Assessments; a 1997 TEC Assessment that focused on unilateral DBS of the thalamus as a treatment for tremor and a 2001 TEC Assessment that focused on the use of DBS of the globus pallidus and subthalamic nucleus for a broader range of PD symptoms. The observations and conclusions of the TEC Assessments are summarized here.

Unilateral Deep Brain Stimulation of the Thalamus for Tremor

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

Unilateral or Bilateral Stimulation of the Globus Pallidus or Subthalamic Nucleus for Parkinson's disease Symptoms

- A wide variety of studies consistently demonstrate that DBS of the globus pallidus or subthalamic nucleus 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 subthalamic nucleus, reduction in the required daily dosage of levodopa and/or its equivalents. The magnitude of these changes is both statistically significant and clinically meaningful.

- The beneficial treatment effect lasts at least for the 6–12 months observed in most trials. While there is not a great deal of long-term follow-up, the available data are generally positive.
- Adverse effects and morbidity are similar to those known to occur with thalamic stimulation.
- DBS possesses advantages to other treatment options. In comparison to pallidotomy, DBS can be performed bilaterally. The procedure is non-ablative and reversible.

Articles published since these two assessments continue to report positive outcomes for DBS for tremor and PD. In addition, periodic updates of the literature have identified reports on the use of DBS for a variety of neurologic and psychiatric conditions. Following is a summary of key studies.

Stimulation of the Thalamus for Essential Tremor and Tremor in Parkinson's Disease
In 2008, Schuurman and colleagues reported 5-year follow-up of 65 patients comparing thalamic stimulation and thalamotomy for treatment of tremor due to PD (45 patients), ET (13 patients), and multiple sclerosis (MS) (10 patients). After 5 years, 48 patients were available for follow-up: 32 with PD, 10 with ET, and 6 with MS. The primary outcome measure was functional status on the Frenchay Activities Index (FAI); secondary measures were tremor severity, frequency of complications, and patients' assessment of outcome. The mean difference in FAI scores was 4.4 (95% confidence interval [CI]: 1.1–7.7) after 6 months, 3.3 (95% CI: -0.03–6.6) after 2 years, and 4.0 (95% CI: 0.3–7.7) after 5 years in favor of stimulation. Tremor suppression was equally effective after both procedures, and stable in PD patients. A diminished effect was observed in half of the patients with ET and MS. Neurologic adverse effects were higher after thalamotomy. Subjective assessments favored stimulation. Hariz et al. evaluated outcomes of thalamic DBS in patients with tremor-predominant PD who participated in a multicenter European study and reported that, at 6 years post-surgery, tremor was still effectively controlled and appendicular rigidity and akinesia remained stable when compared with baseline.

Bilateral Stimulation of the Thalamus: In 2005, Putzke and colleagues reported on a series of 25 patients with ET treated with bilateral DBS for management of midline tremor (head, voice, tongue, trunk). 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 ($p<0.01$). Bilateral stimulation at months 3 and 12 was 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; 18 patients with ET had unilateral and 8 had bilateral implantation. 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 activity of daily living (ADL) scores. Unilateral stimulation patients 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, such as dysarthria and other speech difficulties, disequilibrium or balance difficulties, and abnormal gait, persisted despite optimization of the stimulation parameters.

Stimulation of the Globus Pallidus and Subthalamic Nucleus for Advanced Parkinson's Disease
A 2006 systematic review of 34 studies (921 patients) examined outcomes following subthalamic stimulation for patients with PD who had failed medical management (e.g., motor fluctuations, dyskinesia, and other medication side effects). Twenty studies, primarily class IV (uncontrolled cohorts or case series), were included in the meta-analysis. Subthalamic stimulation was found to improve ADL by 50% over baseline, as measured by the Unified Parkinson's Disease Rating Scale (UPDRS) part 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% improvement in the severity of motor symptoms while the patient was not taking medication. A strong relationship was found between the pre-operative dose response to L-dopa and improvements in both the UPDRS II and III. The analysis found a 56% reduction in medication use, a 69% reduction in dyskinesia, and a 35% improvement in quality of life with subthalamic stimulation.

In 2006, the German Parkinson Study Group reported a trial of 78 patient pairs with advanced PD and severe motor symptoms randomized to either subthalamic stimulation or medical management. Subthalamic stimulation improved severity of symptoms without medication in 55 of 78 pairs (from 48 to 28 on the UPDRS III). Improvements in quality of life were greater than medical management in 50 of 78 pairs (average change from 42 to 32 on the 100-point Parkinson's Disease Questionnaire), with 24% to 38% improvements in subscales for mobility, activities of daily living, emotional well-being, stigma, and bodily discomfort. Serious adverse events were more common with neurostimulation (13% vs. 4%) and included a fatal intracerebral hemorrhage. Witt et al. performed an ancillary protocol as part of this multicenter randomized, controlled trial (RCT) to assess neuropsychiatric consequences of DBS in patients with PD. One hundred-twenty-three patients with PD and motor fluctuations who were randomized to DBS or best medical treatment were included in the study. Neuropsychological and psychiatric examinations at baseline and 6 months post-implantation were compared. DBS of the subthalamic nucleus did not reduce overall cognition or affectivity. There was a selective decrease in frontal cognitive functions and an improvement in anxiety in patients after treatment that did not affect improvements in quality of life.

Weaver and colleagues reported 6-month outcomes of a multicenter RCT comparing DBS with best medical therapy for patients with advanced PD in 2009. Of 278 patients who were screened, 255 were randomized; 134 to best medical therapy and 121 to DBS (61 to stimulation of the globus pallidus and 60 to stimulation of the subthalamic nucleus). By intention-to-treat analysis, patients who received DBS gained a mean of 4.6 hours/day of "on" time without troubling dyskinesia compared to no hours gained for patients receiving best medical therapy ($p<0.001$). Seventy-one percent of DBS patients experienced clinically meaningful motor function improvements (i.e., $\geq$5 point change in UPDRS of motor function) versus 32% of best medical therapy group. Significantly greater improvements in quality-of-life measures were achieved by DBS patients. At least one serious adverse event occurred in 49 DBS patients versus 15 in the best medical

therapy patients, including 39 related to the surgical procedure and one death secondary to cerebral hemorrhage.

In 2010, Williams et al. reported results from an ongoing randomized, multicenter open-label trial (PD SURG) from 13 neurosurgical centers in the United Kingdom. Included in the study were 366 patients with PD that was not adequately controlled by medical therapy. Patients were randomized to surgery (all had DBS) and best medical therapy, or to best medical therapy alone. The study was designed to detect a 10-point difference (regarded as clinically important) in the Parkinson's disease questionnaire (PDQ) summary index. Five of 183 patients randomized to surgery did not have surgery, and 12 of 183 patients randomized to medical therapy had surgery within the first year of the study (patients were analyzed in the treatment group to which they were randomized). In 174 patients, the subthalamic nucleus was the surgical target, and 176 of 178 procedures were bilateral. At 1 year, the mean improvement in the primary outcome measure, the PDQ summary index, was 5.0 points in the DBS group and 0.3 points in the control group. The difference in mean change in PDQ between the 2 groups was -8.9 for the mobility domain, -12.4 for the daily living domain, and -7.5 for the bodily discomfort domain. Differences between groups in the other domains were not significant. Thirty-six (19%) patients had serious surgery-related adverse events; there was one procedure-related death. The most common surgery-related serious adverse events were infections (n=16).

Another European multicenter study assessed whether subthalamic stimulation might maintain quality of life and motor function if performed earlier in the course of the disease. Ten matched patient pairs younger than 55 years of age with mild to moderate motor signs were randomly assigned to DBS or medical management. There was no difference in the severity of parkinsonian motor disability while receiving medication. However, in the medically treated patients, both the daily dose of levodopa and the severity of levodopa-induced motor complications increased over the 18 months of the study (12% and 15%, respectively), while in the surgical patients the daily dose of levodopa was reduced by 57%, and the severity of levodopa-induced motor complications improved by 83%. Additional studies are needed to determine the long-term effect of subthalamic stimulation in this younger patient population.

Appleby et al. reported a meta-analysis of adverse events associated with DBS in order to assess the risks and benefits of the treatment as they relate to its potential use in the psychiatric setting in 2007. They concluded that DBS is an effective treatment for PD, dystonia, and ET, and rates of depression, cognitive impairment, mania, and behavior change are low. Prevalence of depression was 2–4%, mania 0.9–1.7%, emotional changes 0.1–0.2%, and suicidal ideation/suicide attempt was 0.3–0.7%. The completed suicide rate was 0.16–0.32%. In light of the rate of suicide in patients treated with DBS, particularly with thalamic and globus pallidus stimulation, the authors argue for prescreening patients for suicide risk.

Deep Brain Stimulation for the Treatment of Dystonia
DBS for the treatment of primary dystonia received FDA approval through the HDE process in 2003. The HDE approval process is available for conditions that affect fewer than 4,000 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. There were 3 studies that reported at least 10 cases of primary dystonia. In

these studies, clinical improvement ranged from 50% to 88%. A total of 21 pediatric patients were studied; 81% were older than 7 years. Among these patients, there was an approximate 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. The FDA Summary of Safety and Probable Benefit states, "Although there are a number of serious adverse events experienced by patients treated with deep brain stimulation, in the absence of therapy, chronic intractable dystonia can be very disabling and, in some cases, progress to a life-threatening stage or constitute a major fixed handicap. When the age of dystonia occurs prior to the individual reaching their full adult size, the disease not only can affect normal psychosocial development but also cause irreparable damage to the skeletal system. As the body of the individual is contorted by the disease, the skeleton may be placed under constant severe stresses that may cause permanent disfigurement. Risks associated with deep brain stimulation for dystonia appear to be similar to the risk associated with the performance of stereotactic surgery and the implantation of deep brain stimulation systems for currently approved indications, except when used in either child or adolescent patient groups."

Since the FDA approval, there have been additional published trials of deep brain stimulation for dystonia, which continue to report positive results. Vidailhet and colleagues reported the results of a prospective multi-institutional case series of 22 patients with primary generalized dystonia. Symptoms were evaluated prior to surgery and at several points up to 1 year of follow-up, in a double-blind fashion with the stimulator turned on and off. Dystonia scores were significantly better with the neurostimulator turned on. Vidailhet et al. compared outcomes at 3 years with those reported at 1 year for the 22 patients in their study of bilateral, pallidal DBS for generalized dystonia and found that the motor improvement observed at 1 year was maintained. At 3 years, measures of cognition and mood were unchanged from baseline and 1 year evaluations. Egidi et al. retrospectively reviewed records of 69 patients treated in multiple Italian centers with DBS implanted in the globus pallidus; 37 patients had primary and 32 had secondary dystonia. Improvement of at least 50% in Burke-Fahn-Marsden severity scale was reached by 45% of primary and 37% of secondary dystonia patients at 3–84 months' follow-up (longer than 24 months in half of the patients).

In 2006, the Deep-Brain Stimulation for Dystonia Study Group compared bilateral pallidal neurostimulation with sham stimulation in 40 patients with dystonia who had failed medical management (3-month randomized trial with a 6-month open-label extension). Blinded assessment with the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) found improvements in the movement score (16 points vs. 1.6 points in sham controls), which corresponded to a 39% reduction in symptoms. Disability scores improved by 4 points in the neurostimulation group compared with a 0.8-point improvement in the control subjects (38% improvement). The study found a 30% improvement in quality of life (change of 10 vs. 4 points in controls) following stimulation of the globus pallidus. There was high variability in baseline scores and in the magnitude of improvement; 6 patients (17%) were considered to have failed treatment (<25% improvement), 5 patients (25%) improved by more than 75%. No single factor was found to predict the response to treatment. Independent assessors found similar improvements in the control group after the 6-month open-label extension. Thirty-eight patients (95%) agreed to be followed up annually, and 80% of patients completed the 5-year follow-up. Intention-to-treat analysis showed significant improvements in dystonia severity at 6 months (-47.9%), 3 years (-61.1%), and 5 years (-57.8% compared with baseline).

The unmasked raters tended to score dystonia severity as higher than the 2 masked raters in the original study. Responder analysis (>25% on the BFMDRS) indicated a positive response in 83% of 36 patients at 6 months, 94% of 31 patients at 3 years, and 81% of 32 patients at 5 years. There were 21 serious adverse events that required hospitalization. Almost all serious adverse events were device-related including subcutaneous infection, lead dislodgement/lead breakage, and stimulator malfunction. The most common non-serious adverse event was dysarthria.

Stimulation of the Globus Pallidus for the Treatment of Tardive Dyskinesia and Tardive Dystonia
Stimulation of the globus pallidus has been examined as a treatment of tardive dyskinesia in a Phase II double-blinded (presence and absence of stimulation) multicenter study. The trial was stopped early due to successful treatment (greater than 40% improvement) in the first 10 patients.

Outcomes on motor function, quality of life, and mood in a series 9 patients treated with DBS of the globus pallidus internus 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 +/- 26.7% and 74.1 +/- 15.8%, BFMDRS disability scores by 62.5 +/- 21% and 88.9 +/- 10.3%, and Abnormal Involuntary Movement Scale (AIMS) scores by 52.3 +/- 24.1% and 69.5 +/- 27.6%, respectively. At last follow-up (mean 41 months, range 18- 90 months), BFMDRS motor scores were reduced compared to presurgical assessment by 83 +/-12.2%, BFMDRS disability score by 67.7 +/- 28%, and AIMS scores by 78.7 +/- 19.9%.

Epilepsy
In 2010, Fisher et al. reported a U.S. multicenter, double-blind, randomized trial of bilateral stimulation of the anterior nuclei of the thalamus for epilepsy (SANTE). Included were 110 patients 18-65 years-old, with partial seizures including secondarily generalized seizures, at least 6 per month, but no more than 10 per day. An additional 47 patients were enrolled in the study but did not undergo implantation. At least 3 antiepileptic drugs must have failed to produce adequate seizure control prior to baseline, with 1 to 4 antiepileptic drugs used at the time of study entry. Half of the patients were randomized to stimulation during a 3-month blinded phase; then all patients received unblinded stimulation. The 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 and stimulation off (-42.1% vs. -28.7%, respectively) was not significantly different. In the last month of the blinded phase, the stimulated group had a greater reduction in seizures compared with the control group (-40.4% vs. -14.5% in controls). The median change in seizure frequency was -41% at 13 months and -56% at 25 months. The stimulation group experienced fewer seizure-related injuries than patients in the control group (7.4% vs. 25.5%, respectively). Cognition and mood showed no group differences, but participants in the stimulated group were more likely to report depression (8 vs. 1) or memory problems (7 vs. 1 – both respectively) as adverse events. There was a progressive reduction in seizure frequency over long-term follow-up. By 2 years, 54% of patients had a seizure reduction of equal to or greater than 50%, and 14 patients (13%) were seizure-free for at least 6 months. The most common device-related adverse events were paresthesias in 18.2% of participants, implant site pain in 10.9%, and implant site infection in 9.1%. Eighteen participants (16.4%) withdrew from the study after the implantation because of adverse events. There were 5 deaths, none of which were considered to be device-related. Although some patients appear to have benefited from treatment during

the extended follow-up phase, the difference between groups in the blinded portion of the study was modest. Additional study is needed to establish the safety and efficacy of this treatment.

Huntington's Disease
No controlled trials of DBS for Huntington's disease were identified.

Multiple Sclerosis
In 2008, Schuurman and colleagues reported 5-year follow-up of 65 patients comparing thalamic stimulation and thalamotomy for treatment of tremor due to PD (45 patients), ET (13 patients), and MS (10 patients). After 5 years, 48 patients were available for follow-up: 32 with PD, 10 with ET, and 6 with MS. The primary outcome measure was functional status on the FAI; secondary measures were tremor severity, frequency of complications, and patients' assessment of outcome. The mean difference in FAI scores was 4.4 (95% CI: 1.1–7.7) after 6 months, 3.3 (95% CI: -0.03–6.6) after 2 years, and 4.0 (95% CI: 0.3–7.7) after 5 years in favor of stimulation. Tremor suppression was equally effective after both procedures, and stable in PD patients. A diminished effect was observed in half of the patients with ET and MS. Small numbers of patients with MS limit conclusions with respect to this condition.

Tourette Syndrome
A 2012 systematic review identified 25 published studies, representing data from 69 patients that reported on the efficacy of DBS in the treatment of Tourette syndrome. However, only 3 studies with methodologic quality ratings of fair to poor met the inclusion criteria for evidence-based analysis. These 3 studies are described below. The authors recommend that DBS continues to be considered an experimental treatment for severe, medically refractory tics.

Another systematic review from 2012 examined patient and target selection for DBS of Tourette syndrome. The majority of 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 subthalamic nucleus, caudate nucleus, globus pallidus internus, and the anterior limb of the internal capsule and nucleus accumbens. The review found no clear consensus in the literature for which patients should be treated and what the best target is. Additional study is needed to clarify these issues.

Three small cross-over studies of DBS for Tourette syndrome have been identified. One compared unilateral and bilateral thalamic stimulation (5 patients) and the other (3 patients) compared thalamic, pallidal, simultaneous thalamic and pallidal, and sham stimulation. The best improvements were found with the ventromedial pallidal stimulation.

In 2011, Ackermans et al. reported preliminary results of a double-blind crossover trial of thalamic stimulation in 6 patients with refractory Tourette syndrome. Tic severity during 3 months of stimulation was significantly lower than during the 3 months with the stimulator turned off, with a 37% improvement on the Yale Global Tic Severity Scale (mean 25.6 vs. 41.1) and a decrease in tic severity of 49% at 1 year after surgery compared to preoperative assessments (mean 21.5 vs. 42.2 – both respectively). Secondary outcomes (change in associated behavioral disorder and mood) were not altered by the stimulation. Serious

adverse events included one small hemorrhage ventral to the tip of the electrode, one infection of the pulse generator, subjective gaze disturbances, and reduction of energy levels in all patients. The interim analysis led to the termination of the trial. The authors commented that further RCTs on other targets are urgently needed since the search for the optimal one is still ongoing.

Hypothalamic Stimulation for the Treatment of Cluster Headaches and Facial Pain
Deep brain stimulation of the posterior hypothalamus for the treatment of chronic cluster headaches has been investigated, since functional studies have suggested cluster headaches have a central hypothalamic pathogenesis.

In 2010, Fontaine et al. published results from a prospective crossover, double-blind, multicenter study in 11 patients with DBS of the posterior hypothalamus for severe refractory chronic cluster headache. 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 by the weekly attacks frequency (primary outcome), pain intensity, sumatriptan injections, emotional impact, and quality of life (short-form 12 [SF-12]). During the randomized phase, no significant change in primary and secondary outcome measures was observed between active and sham stimulation. At the end of the open phase, 6 of 11 patients reported a greater than 50% reduction in the weekly frequency of attacks.

Another research group from Europe has published several case series (potentially overlapping) on DBS of the ipsilateral posterior hypothalamus in patients with chronic cluster headache. 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 3 of 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.

Treatment-Resistant Depression
A variety of target areas are being investigated in case series for DBS of treatment-resistant depression, including the subcallosal cingulate gyrus, the ventral capsule/ventral striatum, and the nucleus accumbens. No randomized controlled trials have been identified.

In 2012, Holtzheimer et al. reported a Phase I/II open-label trial of DBS with a single-blind sham lead-in phase for treatment-resistant unipolar and bipolar depression. Ten patients with treatment-resistant major depressive disorder and 7 patients with treatment-resistant bipolar II disorder were included in the study. Inclusion criteria included a current major depressive episode of at least 12 months' duration, a score of 20 or higher on the Hamilton Depression Rating Scale (HAM-D) not responding to at least 4 adequate antidepressant treatments, and a lifetime failure or inability to receive electroconvulsive therapy. The target of DBS was subcallosal cingulate white matter. The mean HAM-D score was 20.5 at the end of the sham lead-in phase, decreasing to 13.1 at 24 weeks (n=16), 13.6 at 1 year (n=14), and 7.3 at 2 years (n=11). Remission rates, defined as a HAM-D score of less than 8, were 18% at 24 weeks, 36% at 1 year, and 58% after 2 years. Response rates, defined as 50% or greater change in the HAM-D, were 41% after 24 weeks, 36% after 1 year and 92% after 2 years. The first 3 patients underwent a single-blind discontinuation phase after 24 weeks, and all 3 had full relapse with increased suicidal ideation. Because of patient safety

concerns, this phase was eliminated for subsequent patients. No patient achieving remission experienced a relapse during stimulation. Efficacy was similar for patients with major depression and those with bipolar depression.

Obsessive-Compulsive Disorder
A systematic review of DBS for OCD was published in 2011 by de Koning et al. The review included 9 case studies and 7 controlled studies with a blinded on-off phase. It was estimated from the published trials and case studies that more than 100 individuals have received experimental DBS for OCD in 5 different targets. These targets are the anterior limb of the internal capsule (ALIC), subthalamic nucleus, ventral capsule/ventral striatum, nucleus accumbens, and inferior thalamic peduncle. The most common measure of efficacy is a reduction in the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). The Y-BOCS is a 10-item scale in which higher scores reflect more intense symptoms, and a score of 24 or more (of a possible 40) is considered severe illness. Most studies designate a therapeutic response as a Y-BOCS reduction of 35% or more from the pretreatment baseline, with a reduction of 25% or more considered a partial response.

Subthalamic Nucleus: A crossover, double-blind, multicenter study of DBS of the subthalamic nucleus for treatment of refractory OCD was reported by Mallet et al. in 2008. Eighteen patients were enrolled, one withdrew and one required removal of the stimulator before randomization because of infection. Three months after surgery, 8 patients were randomly assigned to receive active stimulation for 3 months, followed by 1 month of washout, then 3 months of sham stimulation (on-off group). The other group followed the same treatment schedule in reverse (off-on group). New or worsening symptoms were classified as adverse events. Medication was held constant during the 10-month protocol, except for transient increase in benzodiazepine therapy in 3 patients and augmentation of neuroleptic treatment in one patient for exacerbated anxiety. The Y-BOCS score was significantly lower at the end of active stimulation than at the end of the sham stimulation (mean score, 19 +/- 8 vs. 28 +/- 7; p=0.01) independent of the group and the period. No significant carryover effect between treatment phases was detected. Patients who had active stimulation first (on-off group) tended to have a larger treatment effect than the off-on group (p=0.06).

Outcomes on secondary measures of global health and functioning were significantly better at the end of the stimulation period. Scores on Montgomery and Asberg Depression Scale (MADRS), Brief Scale for Anxiety, neuropsychological ratings, and self-reported disability (Sheehan Disability Scale) did not differ significantly at the end of treatment and sham sessions. Fifteen serious adverse events were reported in 11 patients, the most serious a parenchymal brain hemorrhage. Transient motor and psychiatric symptoms induced by active stimulation resolved spontaneously or with adjustment of stimulation settings. Seven behavioral adverse events were reported in 5 patients during stimulation. Hypomania was the main psychiatric serious adverse event; symptoms resolved with adjustment of stimulation settings. The authors note that the multicenter design might be a limitation of the study because of variation in targeting of stimulation. In addition, in order to preserve blinding, stimulation settings were kept below the threshold known to induce adverse effects and may have been too low to reduce symptoms. They conclude that their finding suggests that DBS may lessen severity of symptoms; however, serious adverse events did occur. Larger studies with longer follow-up are needed including evaluation of quality of life and ability to function in social and work situations.

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Nucleus Accumbens: Denys et al. reported a double-blind crossover study of bilateral DBS of the nucleus accumbens in 16 patients with refractory OCD in 2010. Patients with a score of equal to or greater than 28 on the Y-BOCS, and an equal to or greater than 5-year history of OCD that was refractory to medical treatment were included. Out of 101 patients screened for the study, 16 underwent implantation. The study consisted of an open 8-month treatment phase, followed by a double-blind crossover phase with randomly assigned 2-week periods of active or sham stimulation, ending with an open 12-month maintenance phase. Once a decrease in Y-BOCS was obtained, a standardized cognitive behavioral therapy (CBT) program was added. In the open phase, the mean Y-BOCS score decreased by 46% from 33.7 at baseline to 18.0 after 8 months. Nine of 16 patients were responders (Y-BOCS decrease $\geq$ 35%), with a mean decrease of 23.7 points. In the double-blind, sham-controlled phase (n=14), there was a mean 8.3 point difference in the Y-BOCS score between active and sham stimulation. Depression and anxiety decreased significantly, with a mean difference in Hamilton anxiety (HAM-A) scores of 12.1 and in HAM-D scores of 11.3. Except for mild forgetfulness and word-finding problems, no permanent adverse events were reported. The most prominent adverse event related to stimulation was elevated mood or hypomania.

A double-blind crossover study of unilateral DBS of the nucleus accumbens was reported by Huff et al. in 2010. Patients with a score of equal to or greater than 25 on the Y-BOCS, and an equal to or greater than 5-year history of OCD that was refractory to medical treatment were included. Ten patients received 3 months of DBS followed by 3 months of sham stimulation, or vice versa. After 6 months, stimulation was continued unblinded with the option to change stimulation parameters every 3 months (including activation of electrodes in the ALIC). The patients had an examination at baseline, within the first week, and at 3, 6, 9, and 12 months by a psychiatrist who was blinded to the treatment condition. The mean Y-BOCS at baseline was 32.2. There was no difference in Y-BOCS during the crossover period with a score of 27.9 during the on period and 31.1 during the off period. After 12 months the Y-BOCS had significantly decreased to 25.4. Logistic regression revealed no independent effect for changes in stimulation amplitude, changes in active contacts, or changes in medication. Five of 10 patients showed a decrease of equal to or greater than 25%, indicating a partial response. Only 1 patient showed a decrease in Y-BOCS of greater than 35%. Depression, global functioning, and quality of life improved within 1 year, while anxiety, global symptom severity, and cognitive function showed no significant changes.

Ventral Capsule/Ventral Striatum: Goodman et al. reported a double-blinded pilot crossover study of DBS of the ventral capsule/ventral striatum in 6 patients. Patients with a score of equal to or greater than 28 on the Y-BOCS and a 5-year or longer history of OCD that was refractory to medical treatment were included. All 6 patients had a lifetime diagnoses of major depression that was deemed secondary to OCD, 1 met criteria for a current diagnosis of major depression. The mean duration of illness was 24 years (range, 11-35 years). The first patient was implanted in 2003; the sixth patient completed 12 months of DBS in 2008. The baseline Y-BOCS was 33.7. For the crossover phase, there was a reduction of 5.33 points with the stimulator turned on (n=3) and -0.67 with the stimulator off (n=3, not significantly different). After 12 months of stimulation, 4 (66.7%) of patients were responders ($\geq$35% improvement and a score $\leq$16 on the Y-BOCS). Depressive symptoms improved significantly in the group as a whole; global functioning improved in the 4 responders. The authors concluded that future research should attend to subject selection, lead location, DBS programming, and mechanisms underlying the therapeutic benefits.

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Other
The evidence on deep brain stimulation for anorexia nervosa, alcohol addiction, and chronic pain consists of review articles or small case series. These are not adequate to make a determination of efficacy.

Summary
Deep brain stimulation has been shown to be effective for the treatment of tremor, advanced PD, and dystonia. Evidence for efficacy of DBS for Tourette syndrome, treatment-resistant depression, obsessive-compulsive disorder, tardive dystonia, and cluster headache is based on experience with small numbers of patients. In addition, the appropriate candidates and most effective target areas for DBS are under investigation. Additional controlled studies with a larger number of subjects are required to evaluate the role of DBS for these conditions.

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HCPCS	C1816, C1820, C1883, L8680, L8681, L8682, L8683, L8684, L8685, L8686, L8687, L8688, L8689
ICD-9 Diagnosis	300.3, 307.1, 303.90, 303.91, 332.0, 332.1, 333.1, 333.6, 333.79, 333.83, 333.85, 333.89, 338.21, 338.22, 338.28, 338.29, 338.3, 338.4, 340, 345.00, 345.01
ICD-9 Procedure	02.93, 86.94

Policy History

Original Effective Date: 08/25/2005
Current Effective Date: 07/16/2014
03/21/2002 Medical Policy Committee review
03/25/2002 Managed Care Advisory Council approval
06/24/2002 Format revision. No substance change to policy.
08/03/2004 Medical Director review

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Current Effective Date: 07/16/2014

08/17/2004	Medical Policy Committee review
08/30/2004	Managed Care Advisory Council approval
07/14/2005	Medical Director review
07/19/2005	Medical Policy Committee review. Clinical criteria revision. Coverage eligibility changes. Added investigational statement for DBS for cluster headaches.
08/24/2005	Managed Care Advisory Council approval
06/07/2006	Medical Director review
06/21/2006	Medical Policy Committee approval. Format revisions, FDA/Governmental, Rationale/Source. Coverage eligibility unchanged.
08/01/2007	Medical Director review
08/15/2007	Medical Policy Committee approval. No change to coverage eligibility.
08/06/2008	Medical Director review
08/20/2008	Medical Policy Committee approval. Tardive dyskinesia, Tourette syndrome, depression and epilepsy were added to the list of investigational indications.
08/06/2009	Medical Policy Committee approval
08/26/2009	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/01/2010	Medical Policy Committee approval
07/21/2010	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/07/2011	Medical Policy Committee approval
07/20/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/28/2012	Medical Policy Committee approval
07/27/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/04/2013	Coding Updated
06/27/2013	Medical Policy Committee approval
07/17/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/10/2014	Medical Policy Committee approval
07/16/2014	Medical Policy Implementation Committee approval. Added anorexia nervosa, alcohol addiction, and chronic pain as investigational indications.

Next Scheduled Review Date: 07/2015

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

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