# Deep Brain and Cortical Stimulation (for Louisiana Only)

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Instructions for Use

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## Application

This Medical Policy only applies to the state of Louisiana.

## Coverage Rationale

### Deep Brain Stimulation

Deep brain stimulation (excluding directional deep brain stimulation) is proven and medically necessary for treating the following when used according to U.S. Food and Drug Administration (FDA) labeled indications, contraindications, warnings and precautions:

- Idiopathic Parkinson's disease
- Essential tremor
- Primary Dystonia including generalized and/or segmental dystonia, hemidystonia and cervical dystonia (torticollis)

The following are unproven and not medically necessary due to insufficient evidence of efficacy:

- Deep brain stimulation for treating conditions other than those listed above as proven. These include but are not limited to:
  - Secondary Parkinsonism
  - Secondary Dystonia
  - Depression
  - Obsessive-compulsive disorder (OCD)
  - Epilepsy
  - Tourette syndrome
  - Cluster headache
  - Impulsive or violent behavior
  - Chronic pain
  - Trigeminal neuralgia
  - Movement disorders caused by multiple sclerosis (MS)
  - Phantom limb pain
  - Stroke pain

- Directional deep brain stimulation that enables specific steering of current towards targeted lesions for treating any condition including but not limited to:
  - Parkinson's disease
  - Dystonia
  - Tremor

See the Description of Services section for more information regarding directional deep brain stimulation devices.

### Responsive Cortical Stimulation

Responsive cortical stimulation (e.g., NeuroPace® RNS® System) is proven and medically necessary for treating Partial Onset Seizures when used according to U.S. Food and Drug Administration (FDA) labeled indications, contraindications, warnings and precautions.

Responsive cortical stimulation is unproven and not medically necessary for treating conditions in individuals who do not meet the above criteria due to insufficient evidence of efficacy.

## Definitions

Generalized Seizures: Seizures engaging networks across both cerebral hemispheres (Epilepsy Foundation, 2017).

Partial Seizures, Partial Onset Seizures, or Focal Onset Seizures: Seizures originating within networks limited to one cerebral hemisphere (Epilepsy Foundation, 2017).

Primary Dystonia: A movement disorder in which dystonia is the only symptom and there is no known acquired cause of the dystonia. Primary Dystonia may occur for unknown reasons or may be inherited (Phukan et al., 2011; American Association of Neurological Surgeons, 2018).

Secondary Dystonia: Secondary Dystonia occurs with illness, after trauma or following exposure to certain medications or toxins (Phukan et al., 2011).

Secondary Parkinsonism: Secondary Parkinsonism occurs as a result of head trauma, metabolic conditions, toxicity, drugs, or other medical disorders.

## Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

| CPT Code | Description |
|---|---|
| 61850 | Twist drill or burr hole(s) for implantation of neurostimulator electrodes, cortical |
| 61860 | Craniectomy or craniotomy for implantation of neurostimulator electrodes, cerebral, cortical |
| 61863 | Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (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) |

| CPT Code | Description |
|---|---|
| 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) |
| 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 two or more electrode arrays |
| 64999 | Unlisted procedure, nervous system |



| HCPCS Code | Description |
|---|---|
| L8679 | Implantable neurostimulator, pulse generator, any type |
| L8680 | Implantable neurostimulator electrode, each |
| L8682 | Implantable neurostimulator radiofrequency receiver |
| 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 of Services

## Deep Brain Stimulation

Deep brain stimulation (DBS) delivers electrical pulses to select areas of the brain (e.g., the internal globus pallidus interna (GPi), subthalamic nucleus (STN) or ventral intermediate nucleus (VIM) of the thalamus) via surgically implanted electrodes. The mechanism of action is not completely understood, but the goal of DBS is to interrupt the pathways responsible for the abnormal movements associated with movement disorders such as Parkinson's disease and essential tremor. The exact location of electrodes depends on the type of disorder being treated, and unlike standard surgical ablation, which causes permanent destruction of the targeted area, DBS is reversible and adjustable. The DBS device consists of an implantable pulse generator (IPG) or neurostimulator, an implantable lead with electrodes and a connecting wire. The neurostimulator is approximately the size of a stop watch and is similar to a cardiac pacemaker. Subcutaneous extension wires connect the lead(s) to the neurostimulator which is implanted near the clavicle or, in the case of younger individuals with primary dystonia, in the abdomen. Conventional deep brain stimulation systems deliver stimulation using cylindrical electrodes or Ring Mode (omnidirectional) stimulation, which stimulate neurons around the entire circumference of the lead. Directional deep brain stimulation uses a directional lead designed to steer electrical current to relevant areas of the brain while avoiding areas that may cause side effects. Several independent electrode contacts can be programmed, creating a more customized therapy. The St. Jude Medical Infinity™ DBS System is used for directional deep brain stimulation.

When used according to U.S. Food and Drug Administration (FDA) indications, deep brain stimulation is used to treat selected individuals with Parkinson's disease, essential tremor, and primary dystonia. Most forms of Parkinson's disease are idiopathic (having no specific known cause). In secondary Parkinsonism, the symptoms are a result of head trauma, metabolic conditions, toxicity, drugs, or other medical disorders. Primary dystonia occurs on its own, apart from any illness. Secondary dystonia can occur with illness, after trauma or following exposure to certain medications or toxins. Types of dystonia include:

- Generalized – Affects multiple areas of the body
- Focal – Affects one specific area of the body, such as the neck (cervical dystonia or torticollis), eyelid (blepharospasm) or hand (writer's cramp)
- Segmental – Affects two or more adjacent parts of the body

- Multifocal – Affects two nonadjacent parts of the body
- Hemidystonia – Affects one side of the body
- Cervical dystonia or torticollis

### Responsive Cortical Stimulation (Closed-Loop Implantable Neurostimulator)

The RNS® System (NeuroPace, Inc.) is intended to detect abnormal electrical brain signals that precede seizures and deliver electrical stimulation in response to try to normalize electrical brain activity and prevent seizures. The device includes a neurostimulator that is placed in the skull and leads that are placed in the seizure-originating areas of the brain. The system's intended benefits include seizure prevention, fewer adverse events than other neurostimulation methods, and data transmission from the individual's home to clinicians.

## Clinical Evidence

### Deep Brain Stimulation

#### *Parkinson's Disease and Essential Tremor*

Evidence from available published studies indicates that deep brain stimulation (DBS) provides clinically and statistically significant improvements in patients with Parkinson's disease (PD) and essential tremor (ET).

In a meta-analysis, Peng et al. (2018) assessed the long-term efficacy of deep brain stimulation (DBS) of the subthalamic nucleus (STN) and globus pallidus interna (GPi) for Parkinson disease (PD). A total of 5 studies with 890 subjects (437 patients in the STN-DBS group and 453 patients in the GPi-DBS group) were included in the analysis. The study results showed no significant differences between STN-DBS and GPi-DBS in the long-term efficacy of unified Parkinson disease rating scale section (UPDRS) III scores including motor subtypes. The authors concluded that STN-DBS and GPi-DBS improve motor function and activities of daily living for PD.

Roper et al. (2016) conducted a systematic review and meta-analysis on gait speed in patients with PD to summarize the effectiveness of DBS. A random effects model meta-analysis on 27 studies revealed a significant overall standardized mean difference medium effect size equal to 0.60. Based on the synthesis of the 27 studies, the authors determined the following: (1) a significant and medium effect size indicating DBS improves gait speed; (2) DBS improved gait speed regardless of whether the patients were tested in the on or off medication state; and (3) both bilateral and unilateral DBS led to gait speed improvement. According to the authors, the current analysis provides objective evidence that both unilateral and bilateral DBS provide a therapeutic benefit on gait speed in persons with PD.

Tan et al. (2016) conducted a systematic review and meta-analysis to compare DBS stimulation of globus pallidus internus (GPi) and subthalamic nucleus (STN) which are the most targeted locations for the procedure. Clinical outcomes of motor function, non-motor function, and quality of life (QOL) were collected for the meta-analysis. Ten eligible trials with 1,034 patients were included in the analysis. Unified Parkinson's disease rating scale III (UPDRS-III) scores were collected at 6, 12, and 24 months postsurgery separately to assess the motor function of the patients. A statistically significant effect in favor of the GPi DBS was obtained in the off-medication/on-stimulation phase of UPDRS-III at 12 months. However, GPi DBS showed an opposite result at 24 months. In the on-medication/on-stimulation phase, GPi DBS obtained a worse outcome compared with STN DBS. Compared with STN DBS, increased dosage of levodopa equivalent doses was needed in GPi DBS. Meanwhile, Beck Depression Inventory II scores demonstrated that STN has a better performance. As for neurocognitive phase postsurgery, GPi DBS showed better performance in three of the nine tests, especially in verbal fluency. Use of GPi DBS was associated with a greater effect in eight of the nine subscales of QOL. The authors concluded that GPi and STN DBS significantly improve advanced Parkinson's patients' symptoms, functionality, and QOL. According to the authors, the question regarding which target is superior remains open for discussion. An understanding of the target selection depends on individual symptoms, neurocognitive/mood status, therapeutic goals of DBS (e.g., levodopa reduction), and surgical expertise.

In a meta-analysis of randomized controlled trials (RCTs), Perestelo-Perez et al. (2014) described the efficacy of DBS in improving motor signs, functionality and quality of life of PD patients. Six RCTs (n=1,184) that compared DBS plus medication versus medication alone were included in the analysis. The results showed that DBS significantly improves patients' symptoms, functionality and quality of life. Effects sizes are intense for the reduction of motor signs and improvement of functionality in the off-medication phase, in addition to the reduction of the required medication dose and its associated complications. Moderate

effects were observed in the case of motor signs and time in good functionality in the on-medication phase, in addition to the quality of life. Although the number of RCTs obtained is small, the total sample size is relatively large, confirming the efficacy of DBS in the control of motor signs and improvement of patients' functionality and quality of life.

To assess the current state of knowledge on essential tremor (ET) therapy and make recommendations based on the analysis of evidence, Zappia et al. (2013) reviewed the literature regarding pharmacologic and surgical therapies, providing a quality assessment of the studies and the strength of recommendations for each treatment. A systematic literature review was performed to identify all the studies conducted on patients with ET. Based on the results of the review, thalamic deep-brain stimulation was recommended for refractory ET.

In a National Institute for Health and Care Excellence (NICE) Guidance for Parkinson's disease in adults, NICE states that deep brain stimulation should be considered for individuals with advanced Parkinson's disease whose symptoms are not adequately controlled by best medical therapy (NICE 2017).

## Professional Societies

### *American Academy of Neurology (AAN)*

The AAN issued an update of the 2005 American Academy of Neurology practice parameter on the treatment of essential tremor (ET) in 2011(Zesiewicz et al.). The following conclusions and recommendations for deep brain stimulation were unchanged from the 2005 practice parameter:

- DBS of the VIM thalamic nucleus may be used to treat medically refractory limb tremor in essential tremor (Level C - possibly effective, ineffective, or harmful for the given condition in the specified population).
- There is insufficient evidence to make recommendations regarding the use of thalamic DBS for head or voice tremor (Level U - data inadequate or conflicting given current knowledge, treatment is unproven).
- DBS has fewer adverse events than thalamotomy (Level B - probably effective, ineffective, or harmful for the given condition in the specified population). However, the decision to use either procedure depends on each patients circumstances and risk for intraoperative complications compared to feasibility of stimulator monitoring and adjustments.

The updated 2011 practice parameter indicated that there were no additional trials (published between 2004 and April 2010) rated better than Class IV that examined the efficacy and safety of deep brain stimulation (DBS) of the thalamus for the treatment of ET.

### *Dystonia*

Moro et al. (2017) conducted a systematic review and meta-analysis to evaluate the clinical evidence of the efficacy of deep brain stimulation (DBS) of the globus pallidus internus (GPi) in isolated inherited or idiopathic dystonia. In total, 24 studies were included in the meta-analysis, comprising 523 patients. The mean absolute and percentage improvements in Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) motor score at the last follow-up (mean 32.5 months; 24 studies) were 26.6 points and 65.2%, respectively. The corresponding changes in disability score at the last follow-up (mean 32.9 months; 14 studies) were 6.4 points and 58.6%. Multivariate meta-regression of absolute scores indicated that higher BFMDRS motor and disability scores before surgery, together with younger age at time of surgery, were the main factors associated with significantly better DBS outcomes at the latest follow-up. Reporting of safety data was frequently inconsistent and could not be included in the meta-analysist. The authors concluded that patients with isolated inherited or idiopathic dystonia significantly improved after GPi-DBS. Better outcomes were associated with greater dystonia severity at baseline. According to the authors, these findings should be taken into consideration for improving patient selection for DBS.

Andrews et al. (2010) analyzed combined published results of individual patient outcomes following DBS for all types of dystonia. Data was available in 157 studies for 466 patients with all forms of dystonia. The subclassification of these patients included 344 with primary forms of dystonia, 10 with myoclonus dystonia, 19 with heredodegenerative dystonias and 93 who had DBS for secondary dystonia. Patients with primary forms of dystonia, myoclonus dystonia, subtypes of heredodegenerative dystonia and tardive dystonia have a greater than 50% mean improvement in dystonia severity following DBS. Among patients with primary generalized dystonia, multiple regression analysis showed that a shorter duration of symptoms, a lower baseline severity score and DYT1 positive status were all independently associated with a significantly higher percentage improvement from surgery. Patients with other forms of heredodegenerative and secondary dystonia have variable responses, making prediction of response in future patients difficult.

Koy et al. (2013) performed a meta-analysis and analyzed the published literature regarding deep brain stimulation and secondary dystonia to evaluate the effect on cerebral palsy, a common cause of secondary dystonia. Twenty articles that included 68 patients with cerebral palsy undergoing deep brain stimulation assessed by the Burke-Fahn-Marsden Dystonia Rating Scale were identified. Most articles were case reports reflecting great variability in the score and duration of follow-up. The mean Burke-Fahn-Marsden Dystonia Rating Scale movement score was 64.94 ± 25.40 preoperatively and dropped to 50.5 ± 26.77 postoperatively, with a mean improvement of 23.6% at a median follow-up of 12 months. There was a significant negative correlation between severity of dystonia and clinical outcome. The authors concluded that deep brain stimulation can be an effective treatment option for dyskinetic cerebral palsy. The authors stated that in view of the heterogeneous data, a prospective study with a large cohort of patients in a standardized setting with a multidisciplinary approach would be helpful in further evaluating the role of deep brain stimulation in cerebral palsy.

In a systematic review, Macerollo and Deuschl (2018) analyzed the currently available literature reporting cases with either tardive dystonia (a form of secondary dystonia) or tardive dyskinesia treated with DBS. Thirty-four level VI studies and one level II study with 117 patients were included. Level I studies were not identified. Only four of the patients had tardive dyskinesia. All the others had tardive dystonia. The majority had globus pallidus internum (Gpi-DBS) (n = 109). Patients had a mean age of 47.4 (± SD 14.7) years. The duration of follow-up was 25.6 months ± 26.2. The Abnormal Involuntary Movement Scale was reported in 51 patients with an improvement of 62 ± 15% and the Burke-Fahn-Marsden scale was reported in 67 cases with an improvement of 76 ± 21%. Reported adverse events were surgery-related in 7 patients, stimulation-induced in 12, and psychiatric in 3 patients. These reports suggest favorable effects of DBS and it seems to be relatively safe. The authors indicated that DBS is still a last resort for tardive syndrome (TS) and stimulation parameters and implanted targets are empirical, based on the benefit observed in other more widely explored diseases such as essential tremor and dyskinesia in PD. According to the authors, the limited available data and the lack of a prospective controlled trial prevent them from making final conclusions and recommendations.

The National Institute for Health and Care Excellence (NICE) issued a guidance stating that the current evidence supports the safety and efficacy of DBS as a treatment modality for dystonia. Dystonia may be treated conservatively or surgically. Conservative treatment only treats the symptoms, and surgical intervention (i.e., thalamotomy and pallidotomy) may not render long-term benefits. Patient selection and management should be managed by a multidisciplinary team specializing in the long-term care of patients with movement disorders (NICE, 2006).

### *Tourette Syndrome*

Servello et al. (2016) performed a systematic review of the published studies on deep brain stimulation (DBS) for Tourette's syndrome (TS). The majority of studies were case reports or small series. The thalamus and the globus pallidus internus appear to be the most promising targets. However, in light of the great methodological diversity, a balanced comparison of clinical outcome and understanding of the role of DBS in TS remains problematic. The authors concluded that despite 16 years of experience with DBS in TS a consensus on many issues, foremost on target selection and the age of inclusion continue to be missing. According to the authors, class I evidence with larger patient populations, are urgently needed in order to evaluate the role of DBS in TS.

Baldermann et al. (2016) conducted a systematic literature review to evaluate the efficacy of beep brain stimulation (DBS) for severe cases of Tourette syndrome that failed to respond to standard therapies. In total, 57 studies were eligible, including 156 cases. Overall, DBS resulted in a significant improvement of 52.68% in the Yale Global Tic Severity Scale (YGTSS). Analysis of controlled studies significantly favored stimulation versus off stimulation with a standardized mean difference of 0.96. Disentangling different target points revealed significant YGTSS reductions after stimulation of the thalamus, the posteroventrolateral part and the anteromedial part of the globus pallidus internus, the anterior limb of the internal capsule and nucleus accumbens with no significant difference between these targets.

A significant negative correlation of preoperative tic scores with the outcome of thalamic stimulation was found. Despite small patient numbers, the authors conclude that DBS for GTS is a valid option for medically intractable patients. Different brain targets resulted in comparable improvement rates, indicating a modulation of a common network. According to the authors, the results of this pooled meta-analysis are encouraging but it should be noted that these results are mainly based on studies that must be classified as evidence level IV, according to the classification of the American Academy of Neurology. The authors stated that the efficacy and the individual side effect profile of DBS must be further tested by double blinded, randomized controlled trials with larger sample sizes.

In a randomized, double-blind, controlled trial, Welter et al. (2017) assessed the efficacy of anterior internal globus pallidus (aGPi) DBS for severe Tourette's syndrome. The study included patients aged 18-60 years with severe and medically refractory Tourette's syndrome from eight hospitals specialized in movement disorders. Enrolled patients received surgery to implant bilateral electrodes for aGPi DBS; 3 months later they were randomly assigned (1:1 ratio with a block size of eight; computer-generated pairwise randomization according to order of enrolment) to receive either active or sham stimulation for the subsequent 3 months in a double-blind fashion. All patients then received open-label active stimulation for the subsequent 6 months. Patients and clinicians assessing outcomes were masked to treatment allocation; an unmasked clinician was responsible for stimulation parameter programming, with intensity set below the side-effect threshold. Nineteen patients were enrolled in the trial. The investigators randomly assigned 17 (89%) patients, with 16 completing blinded assessments (seven [44%] in the active stimulation group and nine [56%] in the sham stimulation group). There was no significant difference in YGTSS score change between the beginning and the end of the 3 month double-blind period between groups. During the following 6 month open-label period, stimulation decreased motor and vocal tic severity, with evidence of an improvement in occupational activities and life satisfaction. Fifteen serious adverse events were reported in 13 patients, of which eight events were related to the surgical procedure or hardware. According to the authors, future research is needed to investigate the efficacy of aGPi DBS for patients over longer periods with optimal stimulation parameters and to identify potential predictors of the therapeutic response.

In a randomized, double-blind, crossover trial, Kefalopoulou et al. (2015) recruited eligible patients (severe medically refractory Tourette's syndrome, age ≥20 years) from two clinics for tertiary movement disorders. Enrolled patients received surgery for globus pallidus internus (GPi) DBS and then were randomly assigned in a 1:1 ratio (computer-generated pairwise randomization according to order of enrollment) to receive either stimulation on-first or stimulation off-first for 3 months, followed by a switch to the opposite condition for a further 3 month period. Patients and rating clinicians were masked to treatment allocation; an unmasked clinician was responsible for programming the stimulation. Fifteen patients were enrolled in the study. Fourteen patients were randomly assigned and 13 completed assessments in both blinded periods (seven in the on-first group, six in the off-first group). Mean Yale Global Tic Severity Scale (YGTSS) total score in these 13 patients was 87·9 at baseline, 80·7 for the off-stimulation period, and 68·3 for the on-stimulation period. All 15 patients received stimulation in the open-label phase. Overall, three serious adverse events occurred (two infections in DBS hardware at 2 and 7 weeks postoperatively, and one episode of deep-brain-stimulation-induced hypomania during the blinded on-stimulation period); all three resolved with treatment. The authors concluded that GPi stimulation led to a significant improvement in tic severity, with an overall acceptable safety profile. According to the authors, future research should concentrate on identifying the most effective target for DBS to control both tics and associated comorbidities, and further clarify factors that predict individual patient response.

Martinez-Ramirez et al. (2018) assessed the efficacy and safety of deep brain stimulation (DBS) in a multinational cohort of patients with Tourette syndrome using the International Deep Brain Stimulation Database and Registry. The registry included 185 patients with medically refractory Tourette syndrome who underwent DBS implantation from January 1, 2012, to December 31, 2016, at 31 institutions in 10 countries worldwide. These patients received DBS implantation in different regions of the brain depending on their symptoms. The mean (SD) total Yale Global Tic Severity Scale score improved from 75.01 (18.36) at baseline to 41.19 (20.00) at 1 year after DBS implantation. The mean (SD) motor tic subscore improved from 21.00 (3.72) at baseline to 12.91 (5.78) after 1 year, and the mean (SD) phonic tic subscore improved from 16.82 (6.56) at baseline to 9.63 (6.99) at 1 year. The overall adverse event rate was 35.4% (56 of 158 patients. The most common stimulation-induced adverse effects were dysarthria (10 [6.3%]) and paresthesia (13 [8.2%]). The authors concluded that deep brain stimulation was associated with symptomatic improvement in patients with Tourette syndrome but also with important adverse events. Long-term assessments will be necessary to monitor adverse effects and determine if DBS has lasting effects on symptoms.

A European guideline on DBS was developed by a working group of the European Society for the Study of Tourette Syndrome (ESSTS). A systematic literature search was conducted and expert opinions of the guidelines group contributed also to the recommendations. Of 63 patients reported so far in the literature, 59 had a beneficial outcome following DBS with moderate to marked tic improvement. However, randomized controlled studies including a larger number of patients are still lacking. Although persistent serious adverse effects (AEs) have hardly been reported, surgery-related (e.g., bleeding, infection) as well as stimulation-related AEs (e.g., sedation, anxiety, altered mood, changes in sexual function) may occur. According to the ESSTS working group, at the present time, DBS in TS is still in its infancy. Due to both different legality and practical facilities in different European countries these guidelines, therefore, need to be understood as recommendations of experts. However, among the ESSTS working group on DBS in TS there is general agreement that, at present time, DBS should only be used in adult, treatment resistant, and severely affected patients. It is highly recommended to perform DBS in the context of controlled trials (Müller-Vahl et al. 2011).

The First World Congress on Tourette Syndrome and Tic Disorders was held in June of 2016 in London by the Tourette Association of America, Tourette's Action (UK), and the European Society for the Study of Tourette Syndrome. Topics included the use of depth and cortical surface electrodes to investigate the neurophysiology of tics on the background of the evolving field of deep brain stimulation (DBS). The authors indicated that in addition to the conventional treatments of pharmacotherapy and behavioral therapy, alternative approaches are also evolving, ranging from neurosurgical stereotactic DBS, which has a limited evidence base (Mathews and Stern, 2016).

### *Depression*

Kisely et al. (2018) performed a systematic review and meta-analysis on the effectiveness of deep brain stimulation (DBS) in depression. Cochrane Central Register of Controlled Trials, PubMed/Medline, Embase and PsycINFO, Chinese Biomedical Literature Service System, and China Knowledge Resource Integrated Database were searched for single- or double placebo-controlled, crossover, and parallel-group trials in which DBS was compared with sham treatment using validated scales. Ten papers from nine studies met inclusion criteria, all but two of which were double-blinded RCTs. The main outcome was a reduction in depressive symptoms. It was possible to combine data for 190 participants. Patients on active, as opposed to sham, treatment had a significantly higher response and reductions in mean depression score. However, the effect was attenuated on some of the subgroup and sensitivity analyses, and there were no differences for most other outcomes. In addition, 84 participants experienced a total of 131 serious adverse effects, although not all could be directly associated with the device or surgery. Finally, publication bias was possible. The authors concluded that DBS may show promise for treatment-resistant depression but remains an experimental treatment until further data are available.

McGirr and Berlim (2018) conducted a meta-review of meta-analyses published in the past decade on therapeutic neuromodulation (i.e., repetitive transcranial magnetic stimulation, transcranial direct current stimulation, vagus nerve stimulation and deep brain stimulation) for major depression. According to the authors, vagus nerve stimulation and deep brain stimulation (although more challenging to investigate) have demonstrated preliminary effectiveness, particularly during longer-term follow-up.

In a systematic review, Naesström et al. (2016) reviewed the current studies on psychiatric indications for deep brain stimulation (DBS), with focus on obsessive-compulsive disorder (OCD) and major depressive disorder (MDD). A total of 52 studies met the inclusion criteria with a total of 286 unique patients treated with DBS for psychiatric indications; 18 studies described 112 patients treated with DBS for OCD in six different anatomical targets, while nine studies included 100 patients with DBS for MDD in five different targets. The authors concluded that DBS may show promise for treatment-resistant OCD and MDD but the results are limited by small sample size and insufficient randomized controlled data. According to the authors, other psychiatric indications are currently of a purely experimental nature.

Berlim et al. (2014) conducted a systematic review and exploratory meta-analysis to investigate deep brain stimulation (DBS) applied to the subgenual cingulate cortex (SCC) as a potential treatment for severe and chronic treatment-resistant depression (TRD). Data from 4 observational studies were included in the analysis, totaling 66 subjects with severe and chronic TRD. Twelve-month response and remission rates following DBS treatment were 39.9% and 26.3%, respectively. Also, depression scores at 12 months post-DBS were significantly reduced. There was a significant decrease in depression scores between 3 and 6 months, but no significant changes from months 6 to 12. Finally, dropout rates at 12 months were 10.8%. The authors concluded that DBS applied to the SCC seems to be associated with relatively large response and remission rates in the short- and medium- to long-term in patients with severe TRD. Also, its maximal antidepressant effects are mostly observed within the first 6 months after device implantation. According to the authors, these findings are clearly preliminary and future controlled trials should include larger and more representative samples, and focus on the identification of optimal neuroanatomical sites and stimulation parameters.

Morishita et al. (2014) performed a systematic review of the literature pertaining to DBS for treatment-resistant depression to evaluate the safety and efficacy of this procedure. The reviewers identified 22 clinical research papers with 5 unique DBS approaches using different targets, including nucleus accumbens, ventral striatum/ventral capsule, subgenual cingulate cortex, lateral habenula, inferior thalamic nucleus, and medial forebrain bundle. Among the 22 published studies, only 3 were controlled trials, and 2, as yet unpublished, multicenter, randomized, controlled trials evaluating the efficacy of subgenual cingulate cortex and ventral striatum/ventral capsule DBS were recently discontinued owing to inefficacy based on futility analyses. Overall, the published response rate to DBS therapy, defined as the percentage of patients with > 50% improvement

on the Hamilton Depression Rating Scale, is reported to be 40-70%, and outcomes were comparable across studies. The authors concluded that DBS for MDD shows promise, but remains experimental and further accumulation of data is warranted.

A Comparative Effectiveness Review was prepared for the Agency for Healthcare Research and Quality (AHRQ) on Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults. The report indicated that clinical trial data on some of the developing nonpharmacologic interventions, such as deep brain stimulation were insufficient (from the published literature) to include them in the report. The authors stated that as the evidence bases grow to support the efficacy of such nonpharmacologic interventions, the newer strategies should be included in comparative effectiveness study designs (Gaynes et al. 2011).

## Professional Societies

### *American Psychiatric Association (APA)*

In a clinical practice guideline for the treatment of patients with major depressive disorder, the APA states that electroconvulsive therapy remains the treatment of best established efficacy against which other stimulation treatments (e.g., VNS, deep brain stimulation, transcranial magnetic stimulation, other electromagnetic stimulation therapies) should be compared. The APA did not assign a rating for the use deep brain stimulation in treating depression (Gelenberg et al. 2010).

### *Epilepsy*

In a meta-analysis and systematic review, Chang and Xu identified possible predictors of remarkable seizure reduction (RSR) for deep brain stimulation (DBS) in patients with refractory temporal lobe epilepsy (TLE). The authors conducted a comprehensive search of English-language literature published since 1990 that addressed seizure outcomes in patients who underwent DBS for refractory TLE. A pooled RSR rate was determined for eight included studies. RSR rates were analyzed relative to potential prognostic variables. Random- or fixed-effects models were used depending on the presence or absence of heterogeneity. The pooled RSR rate among 61 DBS-treated patients with TLE from 8 studies was 59%. Higher likelihood of RSR was found to be associated with lateralization of stimulation, lateralized ictal EEG findings, and a longer follow-up period. Seizure semiology, MRI abnormalities, and patient sex were not predictive of RSR rate. Hippocampal and anterior thalamic nuclei (ATN) sites of stimulation had similar odds of producing RSR. The authors concluded that DBS is an effective therapeutic modality for intractable TLE, particularly in patients with lateralized EEG abnormalities and in patients treated on the ictal side. Studies with higher levels of evidence and larger populations are needed to determine if DBS is effective for treating epilepsy.

Zhou et al. (2018) evaluated the studies published on the topic of open-loop DBS for epilepsy over the past decade (2008 to present). Among the 41 articles included in the analysis, 19 reported on stimulation of the anterior nucleus of the thalamus, 6 evaluated stimulation of the centromedian nucleus of the thalamus, and 9 evaluated stimulation of the hippocampus. The remaining 7 articles reported on the evaluation of alternative DBS targets. The authors evaluated each study for overall epilepsy response rates as well as adverse events and other significant, non-epilepsy outcomes. According to the authors, one level I trial, the SANTE trial, supported the safety and efficacy of stimulating the anterior nucleus of the thalamus and the hippocampus for the treatment of medically refractory epilepsy. Level III and IV evidence supports stimulation of other targets for epilepsy. Ongoing research into the efficacy, adverse effects, and mechanisms of open-loop DBS is required.

Sprengers et al. (2017) assessed the efficacy, safety and tolerability of DBS and cortical stimulation for refractory epilepsy based on randomized controlled trials (RCTs). The RCTs selected for the review compared deep brain or cortical stimulation versus sham stimulation, resective surgery, further treatment with antiepileptic drugs or other neurostimulation treatments (including vagus nerve stimulation). Twelve RCTs were identified, eleven of these compared one to three months of intracranial neurostimulation with sham stimulation. The authors concluded that except for one very small RCT, only short-term RCTs on intracranial neurostimulation for epilepsy are available. Compared to sham stimulation, one to three months of anterior thalamic DBS ((multi)focal epilepsy), responsive ictal onset zone stimulation ((multi)focal epilepsy) and hippocampal DBS (temporal lobe epilepsy) moderately reduce seizure frequency in refractory epilepsy patients. Anterior thalamic DBS is associated with higher rates of self-reported depression and subjective memory impairment. According to the authors, there is insufficient evidence to make firm conclusive statements on the efficacy and safety of hippocampal DBS, centromedian thalamic DBS, nucleus accumbens DBS and cerebellar stimulation. There is a need for more, large and well-designed RCTs to validate and optimize the efficacy and safety of invasive intracranial neurostimulation treatments.

In a National Institute for Health and Care Excellence (NICE) Guidance for deep brain stimulation for refractory epilepsy, NICE stated that the evidence on the efficacy of deep brain stimulation for refractory epilepsy is limited in both quantity and quality. NICE recommends that this procedure should only be used with special arrangements for clinical governance, consent and audit or research (NICE 2012).

### *Obsessive Compulsive Disorder (OCD)*

In a systematic review, Vázquez-Bourgon et al. (2017) evaluated the current scientific evidence on the effectiveness and applicability of deep brain stimulation for refractory obsessive-compulsive disorder (OCD). The critical analysis of the evidence shows that the use of DBS in treatment-resistant OCD is providing satisfactory results regarding efficacy, with assumable side-effects. However, there is insufficient evidence to support the use of any single brain target over another. The authors concluded that the use of DBS for OCD is still considered to be in the field of research, although it is increasingly used in refractory-OCD, producing in the majority of studies significant improvements in symptomatology, and in functionality and quality of life. According to the authors, it is important to implement random and controlled studies regarding its long-term efficacy, cost-risk analyses and cost/benefit.

In a systematic review, Naesström et al. (2016) reviewed the current studies on psychiatric indications for deep brain stimulation (DBS), with focus on obsessive-compulsive disorder (OCD) and major depressive disorder (MDD). A total of 52 studies met the inclusion criteria with a total of 286 unique patients treated with DBS for psychiatric indications; 18 studies described 112 patients treated with DBS for OCD in six different anatomical targets, while nine studies included 100 patients with DBS for MDD in five different targets. The authors concluded that DBS may show promise for treatment-resistant OCD and MDD but the results are limited by small sample size and insufficient randomized controlled data. According to the authors, other psychiatric indications are currently of a purely experimental nature.

Hamani et al. (2014) conducted a systematic review of the literature and developed evidence-based guidelines on DBS for OCD that was sponsored by the American Society for Stereotactic and Functional Neurosurgery and the Congress of Neurological Surgeons (CNS) and endorsed by the CNS and American Association of Neurological Surgeons. Of 353 articles identified, 7 were retrieved for full-text review and analysis. The quality of the articles was assigned to each study and the strength of recommendation graded according to the guidelines development methodology of the American Association of Neurological Surgeons/Congress of Neurological Surgeons Joint Guidelines Committee. Of the 7 studies, 1 class I and 2 class II double-blind, randomized, controlled trials reported that bilateral DBS is more effective in improving OCD symptoms than sham treatment. The authors concluded that based on the data published in the literature, the following recommendations can be made: (1) There is Level I evidence, based on a single class I study, for the use of bilateral subthalamic nucleus DBS for the treatment of medically refractory OCD. (2) There is Level II evidence, based on a single class II study, for the use of bilateral nucleus accumbens DBS for the treatment of medically refractory OCD. (3) There is insufficient evidence to make a recommendation for the use of unilateral DBS for the treatment of medically refractory OCD. The authors noted that additional research is needed to determine which patients respond to deep brain stimulation and if specific targets may be more suitable to treat a specific set of symptoms.

## Professional Societies

### *American Psychiatric Association (APA)*

In a Guideline Watch Practice Guideline for the Treatment of Patients with Obsessive-Compulsive Disorder, the APA states that new studies are available on deep brain stimulation (DBS) and other somatic treatments, but the overall strength of evidence for these treatments remains low (APA, 2013).

### *Other Disorders*

Deep brain stimulation (DBS) has also been investigated for other disorders including Alzheimer's disease (Bittlinger and Muller, 2018; Smith et al., 2012; Hardenacke et al., 2013), impulsive or violent behavior (Franzini et al., 2005), chronic and poststroke pain (Lempka et al., 2017, Cruccu et al., 2016; Jung et al., 2015, NICE, 2011), cluster headache (Fontaine et al., 2010),), movement disorders of multiple sclerosis (Oliveria et al., 2017; Hosseini et al., 2012; Mandat et al., 2010). Studies investigating DBS for treatment of other conditions are mainly trials with small sample sizes and short-term follow-up. Further well-designed studies are needed to demonstrate the benefits of deep brain stimulation for these disorders.

## Professional Societies

### *American Headache Society (AHS)*

The AHS guideline on the treatment of cluster headache gave a recommendation of probably ineffective for use of deep brain stimulation for treating cluster headaches (Robbins et al., 2016).

## Directional Deep Brain Stimulation

In a prospective, double-blind trial, Dembek et al. (2017) investigated whether directional deep brain stimulation (DBS) of the subthalamic nucleus in Parkinson's disease (PD) offers increased therapeutic windows, side-effect thresholds, and clinical benefit. In 10 patients, 20 monopolar reviews were conducted to identify the best stimulation directions and compare them to conventional circular DBS. In addition, circular and best-directional DBS were directly compared in a short-term crossover. Motor outcome was also assessed after an open-label follow-up of 3 to 6 months. Stimulation in the individual best direction resulted in significantly larger therapeutic windows, higher side-effect thresholds, and more improvement in hand rotation than circular DBS. Rigidity and finger tapping did not respond differentially to the stimulation conditions. There was no difference in motor efficacy or stimulation amplitudes between directional and circular DBS in the short-term crossover. Follow-up evaluations 3 to 6 months after implantation showed improvements in motor outcome and medication reduction comparable to other DBS studies with a majority of patients remaining with a directional setting. The authors concluded that directional DBS can increase side-effect thresholds while achieving clinical benefit comparable to conventional DBS. However, the question of whether directional DBS improves long-term clinical outcome needs to be investigated in the future.

Steigerwald et al. (2016) evaluated directional deep brain stimulation (DBS) effects on parkinsonian motor features and adverse effects of subthalamic neurostimulation. Seven Parkinson's disease (PD) patients were implanted with the novel directional DBS system for bilateral subthalamic DBS underwent an extended monopolar review session during the first postoperative week, in which current thresholds were determined for rigidity control and stimulation-induced adverse effects using either directional or ring-mode settings. Effect or adverse effect thresholds were modified by directional settings for each of the 14 subthalamic nucleus (STN) leads. Magnitude of change varied markedly between leads, as did orientation of optimal horizontal current steering. The authors concluded that directional current steering through chronically implanted segmented electrodes is feasible, alters adverse effect and efficacy thresholds in a highly individual manner, and expands the therapeutic window in a monopolar review as compared to ring-mode DBS. According to the authors, study limitations include the unblinded and subjective clinical rating of rigidity and adverse effect thresholds, no comparison to standard ring DBS, lack of long-term clinical follow-up, and small number of subjects.

Timmermann et al. (2015) conducted a prospective, multicentre, non-randomized, open-label intervention study of an implantable DBS device (Vercise PC System that uses a steerable axial shaping of the electrical stimulation field) at six specialist DBS centers at universities in six European countries. Patients were included if they were aged 21-75 years and had been diagnosed with bilateral idiopathic Parkinson's disease with motor symptoms for more than 5 years. Participants underwent bilateral implantation in the subthalamic nucleus of a multiple-source, constant-current, eight-contact, rechargeable DBS system, and were assessed 12, 26, and 52 weeks after implantation. The primary endpoint was the mean change in unified Parkinson's disease rating scale (UPDRS) III scores (assessed by site investigators who were aware of the treatment assignment) from baseline (medication-off state) to 26 weeks after first lead implantation (stimulation-on, medication-off state). Of 53 patients enrolled in the study, 40 received a bilateral implant in the subthalamic nucleus and their data contributed to the primary endpoint analysis. Improvement was noted in the UPDRS III motor score 6 months after first lead implantation compared with baseline, with a mean difference of 23·8. One patient died of pneumonia 24 weeks after implantation, which was judged to be unrelated to the procedure. 125 adverse events were reported, the most frequent of which were dystonia, speech disorder, and apathy. 18 serious adverse events were recorded, three of which were attributed to the device or procedure (one case each of infection, migration, and respiratory depression). All serious adverse events resolved without residual effects and stimulation remained on during the study. The authors concluded that the multiple-source, constant-current, eight-contact DBS system suppressed motor symptoms effectively in patients with Parkinson's disease, with an acceptable safety profile. According to the authors, future trials are needed to investigate systematically the potential benefits of this system on postoperative outcome and its side-effects. This study was funded by Boston Scientific.

There is limited evidence comparing directional deep brain stimulation with traditional deep brain stimulation methods of stimulation. Long-term follow-up of large cohorts are needed to determine the effectiveness and long-term results of directional deep brain stimulation.

## Responsive Cortical Stimulation

Morrell et al. (2011) conducted a multicenter, double-blind, randomized controlled trial that assessed the safety and effectiveness of responsive cortical stimulation as an adjunctive therapy for partial onset seizures in adults with medically refractory epilepsy. A total of 191 adults with medically intractable partial epilepsy were implanted with a responsive neurostimulator connected to depth or subdural leads placed at 1 or 2 predetermined seizure foci. The neurostimulator was programmed to detect abnormal electrocorticographic activity. One month after implantation, subjects were randomized 1:1 to receive stimulation in response to detections (treatment) or to receive no stimulation (sham). Efficacy and safety were assessed over a 12-week blinded period and a subsequent 84-week open-label period during which all subjects received responsive stimulation. Seizures were significantly reduced in the treatment compared to the sham group during the blinded period and there was no difference between the treatment and sham groups in adverse events. During the open-label period, the seizure reduction was sustained in the treatment group and seizures were significantly reduced in the sham group when stimulation began. There were significant improvements in overall quality of life and no deterioration in mood or neuropsychological function. According to the authors, responsive cortical stimulation reduces the frequency of disabling partial seizures, is associated with improvements in quality of life, and is well-tolerated with no mood or cognitive effects. This study provides Class I evidence that responsive cortical stimulation is effective in significantly reducing seizure frequency for 12 weeks in adults who have failed 2 or more antiepileptic medication trials, 3 or more seizures per month, and 1 or 2 seizure foci. The RNS system manufacturer NeuroPace sponsored this study and participated in acquisition of data, statistical analysis, study supervision, and approval of the data. Therefore, a conflict of interest may exist.

Heck et al. (2014) published the final two-year results of the responsive neurostimulation (RNS) pivotal randomized multicenter double-blinded controlled trial described above (Morrell, et al., 2011) to assess the safety and effectiveness of responsive stimulation at the seizure focus as an adjunctive therapy to reduce the frequency of seizures in adults with medically intractable partial onset seizures arising from one or two seizure foci. Subjects with medically intractable partial onset seizures from one or two foci were implanted, and 1 month postimplant were randomized 1:1 to active or sham stimulation. After the fifth postimplant month, all subjects received responsive stimulation in an open label period (OLP) to complete 2 years of postimplant follow-up. All 191 subjects were randomized. The percent change in seizures at the end of the blinded period was -37.9% in the active and -17.3% in the sham stimulation group. The median percent reduction in seizures in the OLP was 44% at 1 year and 53% at 2 years, which represents a progressive and significant improvement with time. The serious adverse event rate was not different between subjects receiving active and sham stimulation. Adverse events were consistent with the known risks of an implanted medical device, seizures, and of other epilepsy treatments. There were no adverse effects on neuropsychological function or mood. According to the authors, responsive stimulation to the seizure focus reduced the frequency of partial-onset seizures acutely, showed improving seizure reduction over time, was well tolerated, and was acceptably safe.

Jobst et al. (2017) reported on the patients from the Morrell, et al. (2011) and Heck et al. (2014) randomized controlled trial to evaluate the seizure-reduction response and safety of brain-responsive stimulation in adults with medically intractable partial-onset seizures of neocortical origin. Patients with partial seizures of neocortical origin were identified from prospective clinical trials of a brain-responsive neurostimulator (RNS System, NeuroPace). The seizure reduction over years 2-6 postimplantation was calculated by assessing the seizure frequency compared to a preimplantation baseline. Safety was assessed based on reported adverse events. Additional analyses considered safety and seizure reduction according to lobe and functional area (e.g., eloquent cortex) of seizure onset. There were 126 patients with seizures of neocortical onset. The average follow-up was 6.1 implant years. The median percent seizure reduction was 70% in patients with frontal and parietal seizure onsets, 58% in those with temporal neocortical onsets, and 51% in those with multilobar onsets. Twenty-six percent of patients experienced at least one seizure-free period of 6 months or longer and 14% experienced at least one seizure-free period of 1 year or longer. Stimulation parameters used for treatment did not cause acute or chronic neurologic deficits, even in eloquent cortical areas. The rates of infection (0.017 per patient implant year) and perioperative hemorrhage (0.8%) were not greater than with other neurostimulation devices. The authors concluded that brain-responsive stimulation represents a safe and effective treatment option for patients with medically intractable epilepsy, including adults with partial-onset seizures of neocortical onset, and those with onsets from eloquent cortex.

Meador et al. (2015) reported on the patients from the Morrell, et al. (2011) and Heck et al. (2014) randomized controlled trial to evaluate quality of life, which was a supportive analysis, and for mood, which was assessed as a secondary safety endpoint. The study was a multicenter randomized controlled double-blinded trial of responsive neurostimulation in 191 patients with medically resistant focal epilepsy. During a 4-month postimplant blinded period, patients were randomized to receive responsive stimulation or sham stimulation, after which all patients received responsive neurostimulation in open label to complete 2years. Quality of life (QOL) and mood surveys were administered during the baseline period, at the end of the

blinded period, and at year 1 and year 2 of the open label period. The treatment and sham groups did not differ at baseline. Compared with baseline, QOL improved in both groups at the end of the blinded period and also at 1year and 2years, when all patients were treated. At 2years, 44% of patients reported meaningful improvements in QOL, and 16% reported declines. There were no overall adverse changes in mood or in suicidality across the study. Findings were not related to changes in seizures and antiepileptic drugs, and patients with mesial temporal seizure onsets and those with neocortical seizure onsets both experienced improvements in QOL. The authors concluded that treatment with targeted responsive neurostimulation does not adversely affect QOL or mood and may be associated with improvements in QOL in patients, including those with seizures of either mesial temporal origin or neocortical origin.

Bergey et al. (2015) reported on patients who were involved in the Morrell et al. (2011) and Heck et al. (2014) studies and transitioned to this open-label study that assessed the long-term efficacy and safety of responsive direct neurostimulation in adults with medically refractory partial onset seizures. All participants were treated with a cranially implanted responsive neurostimulator that delivers stimulation to 1 or 2 seizure foci via chronically implanted electrodes when specific electrocorticographic patterns are detected (RNS System). Participants had completed a 2-year primarily open-label safety study (n=65) or a 2-year randomized blinded controlled safety and efficacy study (n=191); 230 participants transitioned into an ongoing 7-year study to assess safety and efficacy. The average participant was 34 (±11.4) years old with epilepsy for 19.6 (±11.4) years. The median preimplant frequency of disabling partial or generalized tonic-clonic seizures was 10.2 seizures a month. The median percent seizure reduction in the randomized blinded controlled trial was 44% at 1 year and 53% at 2 years and ranged from 48% to 66% over postimplant years 3 through 6 in the long-term study. Improvements in quality of life were maintained. The most common serious device-related adverse events over the mean 5.4 years of follow-up were implant site infection (9.0%) involving soft tissue and neurostimulator explantation (4.7%). The authors concluded that acute and sustained efficacy and safety were demonstrated in adults with medically refractory partial onset seizures arising from 1 or 2 foci over a mean follow-up of 5.4 years. This experience supports the RNS System as a treatment option for refractory partial seizures. This study provides Class IV evidence that for adults with medically refractory partial onset seizures, responsive direct cortical stimulation reduces seizures and improves quality of life over a mean follow-up of 5.4 years.

Loring et al. (2015) collected neuropsychological data from subjects participating in the open-label arm of a randomized controlled trial of responsive neurostimulation with the RNS System from (Morrell et al. (2011) and Heck et al. (2014). Primary cognitive outcomes were the Boston Naming Test (BNT) and Rey Auditory Verbal Learning (AVLT) test. Neuropsychological performance was evaluated at baseline and again following 1 and 2 years of RNS System treatment. Follow-up analyses were conducted in patients with seizure onset restricted to either the mesial temporal lobe or neocortex. No significant cognitive declines were observed for any neuropsychological measure through 2 years. When examined as a function of seizure onset region, a double dissociation was found, with significant improvement in naming across all patients, and for patients with neocortical seizure onsets but not in patients with mesial temporal lobe (MTL) seizure onsets. In contrast, a significant improvement in verbal learning was observed across all patients, and for patients with MTL seizure onsets but not for patients with neocortical onsets. According to the investigators, treatment with the RNS System is not associated with cognitive decline when tested through 2 years.

A guideline published by the U.S. Department of Veterans Affairs in 2014, titled Department of Veterans Affairs Epilepsy Manual, mentioned using the responsive neurostimulation (RNS) System to treat epilepsy. In the Investigational Treatments section, this guideline states that although RNS has positive results (in a randomized trial), the overall effectiveness of this device was only slightly superior to vagus nerve stimulation (VNS) during the blinded phase of this study. The guideline concludes that RNS is currently considered a potential treatment option for patients with two seizure foci, or with a single focus not amenable to resection (Husainet al., 2014).

# U.S. Food and Drug Administration (FDA)

## Deep Brain Stimulation

Deep brain stimulation is a procedure and, therefore, not subject to FDA regulation. However, any medical devices, drugs, and/or tests used as part of this procedure may require FDA regulation.

### *Parkinson's Disease and Essential Tremor*

The FDA approved the Activa® Tremor Control System (Medtronic) on July 31, 1997. The device is indicated for unilateral thalamic stimulation for the suppression of tremor in the upper extremity in patients who are diagnosed with essential tremor or

Parkinsonian tremor not adequately controlled by medications and where the tremor constitutes a significant functional disability. In 2015, the FDA labeled indications for Activa Tremor Control System for Parkinson's disease was 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." See the following websites for more information:

- http://www.accessdata.fda.gov/cdrh_docs/pdf/p960009.pdf
- http://www.accessdata.fda.gov/cdrh_docs/pdf2/H020007b.pdf
- https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P960009S229

(Accessed October 16, 2018)

A January 14, 2002 Premarket Approval (PMA) supplement expanded use to include bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) as an adjunctive therapy in reducing some of the symptoms of advanced, levodopa-responsive Parkinson's disease that are not adequately controlled with medication. Available at: http://www.accessdata.fda.gov/cdrh_docs/pdf/P960009S007b.pdf. (Accessed October 16, 2018)

On June 12, 2015, the FDA approved the Brio Neurostimulation System (St. Jude Medical), an implantable deep brain stimulation device intended to help reduce the symptoms of Parkinson's disease and essential tremor. See the following website for more information: http://www.accessdata.fda.gov/cdrh_docs/pdf14/P140009a.pdf. (Accessed October 16, 2018)

On September 19, 2016, the FDA approved a Premarket Approval (PMA) application bundles supplement (P140009/S001) approving the use of the St. Jude Medical Infinity™ DBS System. One of the Infinity DBS System's features is a directional lead, which will send the electrical impulses only toward its intended target instead of in all directions as current systems do. The FDA approval for the Infinity DBS System is a supplement to an earlier PMA (P140009) for the St. Jude Medical Brio Neurostimulation system. According to the manufacturer, the Infinity DBS System and the Brio Neurostimulation System have the same indications for use. See the following website for more information: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P140009. (Accessed October 16, 2018)

On December 8, 2017, the FDA approved a Premarket Approval (PMA) application (P150031) for the Vercise™ Deep Brain Stimulation (DBS) System (Boston Scientific Corp.). The Vercise DBS System is indicated for use in bilateral stimulation of the subthalamic nucleus (STN) as an adjunctive therapy in reducing some of the symptoms of moderate to advanced levodopa-responsive Parkinson's disease (PD) that are not adequately controlled with medication. The Vercise DBS System includes a Stimulator with DBS Leads for stimulation of selected targets (i.e., the subthalamic nucleus) in the brain. DBS Extensions are used to connect the DBS Leads to the Stimulator implanted near the clavicle. The Vercise DBS System utilizes current steering across eight contacts per DBS Lead, which is intended to provide precise positioning of stimulation. The Stimulator is controlled by a handheld Remote Control, and can be programmed by a Clinician Programmer using the Bionic Navigator™ Software. See the following website for more information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_template.cfm?id=p150031. (Accessed October 16, 2018)

### *Dystonia*

On April 15, 2003, the Activa® Dystonia Therapy System (Medtronic) received a Humanitarian Device Exemption (HDE) from the FDA for unilateral and bilateral stimulation of the internal globus pallidus or the subthalamic nucleus and is indicated as an aid in the treatment of chronic, intractable (drug refractory), primary dystonia, including generalized and segmental dystonia, hemidystonia and cervical dystonia. Activa Dystonia Therapy is limited to use in implanting centers that receive Institutional Review Board (IRB) approval for the procedure. The safety and effectiveness of Activa Dystonia Therapy have not been established through a full PMA study. The therapy is approved for patients who are seven years of age and older. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfhde/hde.cfm?id=H020007. (Accessed October 16, 2018)

### *Other Indications*

On March 28, 2005, the Activa® Deep Brain Stimulation Therapy System was designated as a Humanitarian Use Device (HUD) for the treatment of chronic, treatment-resistant obsessive compulsive disorder (OCD) in a subset of patients. However, the FDA does not list a Humanitarian Device Exemption (HDE) approval for authorization to market the device.

On February 19, 2009, the Reclaim™ Deep Brain Stimulation Therapy device was designated as an HUD for the treatment of obsessive compulsive disorder (OCD). This device is indicated for bilateral stimulation of the anterior limb of the internal capsule (AIC) as an adjunct to medications and as an alternative to anterior capsulotomy for treatment of chronic, severe,

treatment-resistant OCD in adult patients who have failed at least three selective serotonin reuptake inhibitors (SSRIs). See the following website for more information: https://www.accessdata.fda.gov/cdrh_docs/pdf5/H050003a.pdf. (Accessed October 16, 2018)

On April 27, 2018, the FDA approved the Medtronic DBS System for Epilepsy for bilateral stimulation of the anterior nucleus of the thalamus (ANT) as an adjunctive therapy for reducing the frequency of seizures in individuals 18 years of age or older diagnosed with epilepsy characterized by partial-onset seizures, with or without secondary generalization, that are refractory to three or more antiepileptic medications. The FDA indicated that the Medtronic DBS System for Epilepsy has demonstrated safety and effectiveness for patients who average six or more seizures per month over the three most recent months prior to implant of the DBS system (with no more than 30 days between seizures). The Medtronic DBS System for Epilepsy has not been evaluated in patients with less frequent seizures. See the following website for more information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P960009S219. (Accessed October 16, 2018)

## Responsive Cortical Stimulation

The FDA approved the NeuroPace RNS Neurostimulator System on November 14, 2013. The device is indicated as an adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures who have undergone diagnostic testing that localized no more than two epileptogenic foci, are refractory to two or more antiepileptic medications, and currently have frequent and disabling seizures (motor, partial seizures, complex partial seizures and/or secondarily generalized seizures). The RNS System has demonstrated safety and effectiveness in patients who average three or more disabling seizures per month over the three most recent months (with no month with fewer than two seizures), and has not been evaluated in patients with less frequent seizures.

The RNS System is contraindicated for:

- Patients with risk factors for surgical complications such as active systemic infection, coagulation disorders (such as the use of antithrombotic therapies), or platelet count below 50,000.
- Patients who have implanted medical devices that deliver electrical energy to the brain.
- Patients who are unable or do not have the necessary assistance to properly operate the NeuroPace remote monitor or magnet.

The following medical procedures are contraindicated for patients with an implanted RNS System. The procedures may send energy through the implanted brain stimulation system causing permanent brain damage, which may result in severe injury, coma, or death. Brain damage can occur from any of the listed procedures even if the RNS neurostimulator is turned off, the leads are not connected to the neurostimulator, or the neurostimulator has been removed and any leads (or any part of a lead) remain:

- MRI
- Diathermy procedures (high-frequency electromagnetic radiation, electric currents, or ultrasonic waves used to produce heat in body tissues) (Patients should not be treated with any type of shortwave, microwave, or therapeutic ultrasound diathermy device, on any part of the body, regardless of whether the device is used to produce heat.)
- Electroconvulsive therapy
- Transcranial magnetic stimulation

See the following website for more information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P100026. (Accessed October 16, 2018)

## Additional Products

- Activa® Tremor Control Therapy (Medtronic, Inc.)
- Activa® Parkinson's Control Therapy (Medtronic, Inc.)
- Activa® Dystonia Therapy (Medtronic, Inc.)
- Kinetra® neurostimulator (Medtronic, Inc.)
- Soletra® neurostimulator (Medtronic, Inc.)

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# Policy History/Revision Information

| Date | Summary of Changes |
|---|---|
| 04/01/2021 | Template Update<br>• Removed *Related Policies* and *CMS* sections<br>• Updated *Instructions for Use*; replaced reference to "MCG™ Care Guidelines" with "InterQual® criteria" |
| 02/01/2021 | Template Update<br>• Reformatted policy; transferred content to new template |
| 01/01/2020 | • Created state-specific policy version for Louisiana (no change to guidelines) |
| 01/01/2019 | • Reorganized policy template:<br>  ○ Simplified and relocated *Instructions for Use*<br>  ○ Removed *Benefit Considerations* section<br>• Updated and reformatted coverage rationale:<br>  ○ Simplified content<br>  ○ Modified language to clarify the listed services are:<br>  ▪ Proven *and* medically necessary (as described)<br>  ▪ Unproven *and* not medically necessary (as described)<br>• Added definition of:<br>  ○ Primary Dystonia<br>  ○ Secondary Dystonia<br>  ○ Secondary Parkinsonism<br>• Updated list of applicable CPT codes to reflect annual code edits; removed 95978 and 95979<br>• Updated supporting information to reflect the most current description of services, clinical evidence, FDA information, and references<br>• Archived previous policy version CS030.G |

# Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Policies are intended to be used in connection with the independent

professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.