KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Procedural Treatments for Epilepsy

- Adjunctive Treatment for Partial Onset Epileptic Seizures
- gammaCore Sapphire non-invasive vagus nerve stimulator
- Medical Diagnoses
- Responsive Neurostimulation (RNS)—NeuroPace®
- Treatment Resistant Depression
- Vagus Nerve Stimulation

Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	Vagus Nerve Stimulation (VNS) (160.18) Electrical Nerve Stimulators (160.7) Treatment of Motor Function Disorders with Electric Nerve Stimulation (160.2)
Local Coverage Determinations (LCD)	None
Local Coverage Article	None
Kaiser Permanente Medical Policy	Due to the absence of an active NCD, LCD, or other coverage guidance, Kaiser Permanente has chosen to use their own Clinical Review Criteria, **"Responsive Neurostimulation"** for medical necessity determinations. Use the Non-Medicare criteria below.

For Non-Medicare Members

Service	Criteria
Implantable Vagus Nerve Stimulator	A. Adjunctive Treatment for Epilepsy • No medical necessity review is required for this service B. Mental Health Diagnoses • MCG* B-821-T, Vagus Nerve Stimulation, Implantable: Behavioral Health Care. This service is not covered per MCG Guidelines. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access. C. All other non-Mental Health Diagnoses • MCG* A-0424, Vagus Nerve Stimulation - Implantable. This service is not covered for any diagnoses besides epilepsy per MCG guidelines. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.
Non-Invasive Vagus Nerve Stimulator	MCG* A-0998, Vagus Nerve Stimulation- Transcutaneous. This service

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gammaCore Sapphire	is not covered per MCG guidelines. For access to the MCG Clinical Guidelines criteria, please see the MCG Guideline Index through the provider portal under Quick Access.
Responsive Neurostimulation (e.g., NeuroPace® RNS System)	I. Responsive neurostimulation is considered medically necessary as an adjunctive therapy for patients with focal epilepsy who meet **ALL** of the following criteria: • Individual is 18 years or older; and • Device is FDA approved (PMA or 510k only); and • Diagnosis of partial onset seizures (e.g., motor focal seizures, complex focal seizures, or secondary generalized seizures); and • Average of 3 or more disabling, partial onset seizures (excluding spells, cardiogenic syncope and other non-epileptiform seizures, if present) per month for 3 consecutive months; and • Has undergone diagnostic testing that identified no more than 2 epileptogenic foci; and • Failed greater than or equal to 2 antiepileptic medications; and • Failure of, contraindication to, or not a candidate for other surgical treatments for epilepsy including: ○ Focal resective epilepsy surgery (e.g., patients with an epileptic focus near the eloquent cerebral cortex or who have bilateral temporal epilepsy may not be candidates for this surgery); ○ Vagus Nerve Stimulator • Do not have any of the following contraindications for responsive neurostimulation device placement: ○ 3 or more specific seizure foci ○ Presence of primary generalized epilepsy ○ Presence of a rapidly progressive neurologic disorder II. The replacement/revision of a responsive cortical stimulation neurostimulator/battery and/or leads and/or monitor is considered medically necessary for an individual who meets ALL of the above criteria and the existing neurostimulator/lead/monitor is no longer under warranty and cannot be repaired. III. Responsive neurostimulation is considered **investigational** for all other indications, including but not limited to patients with focal epilepsy who do not meet the above Criteria.

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background

The Cyberonics Vagus Nerve Stimulator (VNS) Therapy System is a device similar in design and function to a cardiac pacemaker. It consists of a constant current pulse generator implanted in the anterior chest wall and a bipolar stimulating electrode that is wrapped around the left vagal nerve in the neck. A magnet controlled by the patient can turn off the device.

In 1985, there were initial animal studies to test VNS, and devices were implanted in humans beginning in 1988. The first clinical application was to treat epilepsy. Research on epilepsy treatment suggested that VNS might reduce

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dysphoria in some patients. Moreover, VNS has been found to increase levels of a metabolite of serotonin in epilepsy patients, an effect similar to that seen after successful treatment of depression. These findings led to an interest in using VNS for patients with treatment-resistant depression (Goodnick et al., 2001).

In July 1997, the FDA granted pre-market approval for the Cyberonics VNS device to be used as an adjunctive treatment for medically refractory partial onset seizures in patients over 12 years of age. In July 2005, the FDA approved the device for patients 18 and older with treatment-resistant depression who failed to respond to at least 4 courses of adequate medication or electroconvulsive therapy (ECT).

Evidence and Source Documents

Adjunctive Treatment for Partial Onset Epileptic Seizures Vagus Nerve Stimulation for Treatment-Resistant Depression
Responsive Neurostimulation (RNS)—NeuroPace®

Medical Technology Assessment Committee(MTAC)

Vagal Nerve Stimulation (VNS) as an Adjunctive Treatment for Partial Onset Epileptic Seizures

BACKGROUND

Repetitive stimulation of the vagal nerve has been shown to reduce the frequency of seizures in various animal models of epilepsy. Epilepsy is typically treated with anti-epileptic medications and in some cases surgical resection of the epileptic focus. Despite the efficacy of these treatments, 25-50% of patients with epilepsy continue to experience seizures and/or suffer harms from continued use of anti-epileptic medications. The NeuroCybernetics Prosthesis (NCP) Vagal Nerve Stimulator (VNS) is a device (similar in design and function to a cardiac pacemaker) which consists of a constant current pulse generator implanted subcutaneously in the anterior chest wall and a bipolar stimulating electrode which is wrapped around the left vagal nerve in the neck. A magnet controlled by the patient can initiate stimulation (when the patient senses the onset of a seizure) or can turn off the device depending on how it is placed against the device. The mechanism by which the VNS reduces epileptic seizures is still unknown, however it has been shown that stimulation of the vagal nerve has the ability to affect brain wave activity.

02/10/1999: MTAC REVIEW

Vagal Nerve Stimulation (VNS) as an Adjunctive Treatment for Partial Onset Epileptic Seizures

Evidence Conclusion: Recently published evidence from a large, well designed, multicenter trial of 254 patients randomized to high or low Vagal nerve stimulation demonstrates that the use of VNS in the treatment of medically refractory patients reduces seizure frequency by approximately 28% compared to baseline and 13% compared to an active control group receiving low stimulation. This translates into an average reduction of 3 seizures per week. Adverse events such as voice alteration, cough and pharyngitis during stimulation are reported to occur in 25-60 percent of subjects but are generally well tolerated. Patients receiving high VNS also reported significant improvement in their perception of well-being. A randomized controlled trial of 114 patients reports a similar beneficial effect of VNS. Data from an open extension trial of the first 67 patients exiting the RCT demonstrates that all patients chose to either continue high stimulation or switch from low to high stimulation for up to 15 months. Four out of five patients in this group demonstrated continuing clinically significant reductions in seizure frequency over 15 months with 5 drop-outs (8%) due to lack of efficacy and no drop-outs due to side effects from stimulation. **Articles**: Handforth, A et al. Vagus Nerve Stimulation Therapy for Partial Onset Seizures: A Randomized Active- Control Trial. N*eurology*1998; 5:48-55 See Evidence Table**.** The Vagus Nerve Stimulation Group, A Randomized Controlled Trial of Chronic Vagus Nerve Stimulation for Treatment of Medically Intractable Seizures. *Neurology, 1995; 45:224-230.* See Evidence Table**.** Vagus Nerve Stimulation for Treatment of Partial Seizures: 3. Long-Term Follow-Up on First 67 patients exiting a Controlled Study. *Epilepsia, 1994;35:637-643.* See Evidence Table.

The use of the NeuroCybernetics Prosthesis (NCP) Vagal Nerve Stimulator (VNS) for treating patients with medically refractory partial onset seizures has been approved by the FDA and therefore meets *Kaiser Permanente Medical Technology Assessment Criteria*.

Vagus Nerve Stimulation for Treatment-Resistant Depression

BACKGROUND

The Cyberonics Vagus Nerve Stimulator (VNS) Therapy System is a device similar in design and function to a cardiac pacemaker. It consists of a constant current pulse generator implanted in the anterior chest wall and a bipolar stimulating electrode that is wrapped around the left vagal nerve in the neck. A magnet controlled by the patient can turn off the device.

In 1985, there were initial animal studies to test VNS, and devices were implanted in humans beginning in 1988. The

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first clinical application was to treat epilepsy. Research on epilepsy treatment suggested that VNS might reduce dysphoria in some patients. Moreover, VNS has been found to increase levels of a metabolite of serotonin in epilepsy patients, an effect similar to that seen after successful treatment of depression. These findings led to an interest in using VNS for patients with treatment-resistant depression (Goodnick et al., 2001).

In July 1997, the FDA granted pre-market approval for the Cyberonics VNS device to be used as an adjunctive treatment for medically refractory partial onset seizures in patients over 12 years of age. In July 2005, the FDA approved the device for patients 18 and older with treatment-resistant depression who failed to respond to at least 4 courses of adequate medication or electroconvulsive therapy (ECT). VNS passed MTAC evaluation criteria in 1999 for epilepsy. In 2005, it was reviewed for treatment-resistant depression and failed MTAC evaluation criteria. At that time, all of the major studies were conducted by the same group of researchers (A. John Rush and colleagues) with links to the device manufacturer. There was one published RCT (Rush et al., 2005), with negative findings. A post-hoc sub-group analysis of the Rush RCT with a historical control group (George et al., 2005), a design subject to bias, found a benefit of the treatment for a selected group of patients. FDA approval of the VNS device for depression remains controversial. Citing a lack of efficacy data and concerns about safety, an FDA review team decided not to approve the new indication for the Cyberonics device. Instead, the team recommended additional data from RCTs. The Director of the FDA's Center for Devices and Radiological Health (CDRH) overruled the team and granted pre-market approval. The Director agreed with Cyberonics researchers that it would be unethical to conduct a blinded treatment study with patients with major depression.

The FDA approval in 2005 included a request to Cyberonics for additional post-marketing controlled studies (Shuchman, 2007).

12/05/2005: MTAC REVIEW

Vagus Nerve Stimulation for Treatment-Resistant Depression

Evidence Conclusion: There is insufficient evidence that VNS is effective therapy for treatment-resistant depression. All of the major studies were conducted by the same group of researchers. This research team has close financial links with the device manufacturer which could bias study methodology, analysis and/or results reporting. The single published RCT (Rush et al., 2005) had negative findings. There was not a statistically significant between-group difference in the primary outcome, 3-month HAM-D response, between groups receiving active and placebo VNS therapy. A subsequent non-randomized study (George et al., 2005) followed-up a portion of the RCT study patients, and compared findings to a group of depressed patients who were participating in a different study. The George study found a significant difference in the primary outcome, change in the Inventory of Depressive Symptomatology (IDS) score, favoring the VNS therapy group. The study is subject to selection bias due to the use of different patient populations, and the exclusion of patients who responded to sham treatment in the RCT. It is also subject to observation biases because patients did not receive a consistent intervention e.g. those in the VNS group had different lengths of treatment, and possible bias in the selection of the primary outcome (IDS score was the only significant efficacy outcome in the RCT). A limitation of all of the published studies was that the eligibility for participation did not match the FDA definition of treatment-resistant depression. The studies required patients to have failed a minimum of 2 courses of medication whereas the FDA approved VNS therapy for depressed patients who have failed at least 4 treatments.

Articles: The published empirical studies on VNS therapy for depression were conducted by a single research group with close links to the manufacturer, A. John Rush and colleagues. As described in the recent BlueCross BlueShield review (2005), these studies were: D01: Case series with n=50 patients, D02: 3-month randomized controlled trial with n=233, D02 extension arm. 12 month follow-up of selected patients who participated in study D02, D04: Case series of patients not receiving VNS. This study was used to form a comparison group to the 12- month extension of study D02. *Articles critically appraised were:* Publication reporting the results of the RCT, D02: Rush AJ, Marangell LB, Sackeim HA et al. Vagus nerve stimulation for treatment-resistant depression: A Publication comparing 12-month outcomes in the D02 extension and the D04 comparison group: George MS, Rush AJ, Marangell LB et al. A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. Biol Psychiatry 2005; 58: 364-373. See Evidence Table

The use of Vagus nerve Stimulation in the treatment of treatment-resistant depression does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

06/01/2009: MTAC REVIEW

Vagus Nerve Stimulation for Treatment-Resistant Depression

Evidence Conclusion: Conclusions of the 2005 MTAC review were as follows: There is insufficient evidence that VNS is an effective therapy for treatment-resistant depression. All of the major studies were conducted by the same group of researchers that had close financial links with the device manufacturer. The single published RCT (Rush et al., 2005) had negative findings. There was not a statistically significant between-group difference in the primary outcome, 3-

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month HAM-D response, between groups receiving active and placebo VNS therapy. A subsequent non-randomized study (George et al., 2005) followed-up a portion of the RCT study patients and compared findings to a group of depressed patients who were participating in a different study. The George study, which was subject to selection and observation biases, found a significant difference in the primary outcome, change in the Inventory of Depressive Symptomatology (IDS) score, favoring the VNS therapy group. As of May 2009, there is still insufficient evidence to determine whether VNS is effective for depressed patients who have failed antidepressant treatment. There were no additional RCTs or non-randomized comparative studies. A new case series (Schlaepfer) with 74 patients recruited from 9 sites in Europe found a 34% response rate at 3 months (end of active treatment period), which increased to 47% at the 12 month follow-up. The Schlaepfer case series represents a low grade of evidence. There was no comparison group, so response with a different treatment or no treatment is not known. Also, patients were not blinded, and they had regular clinic visits, both of which could affect responses to a subjective outcome measure like the HAMD.

Articles: The Pubmed search yielded 13 articles. Only 9 of these were actually on depression (the rest addressed epilepsy, Alzheimer's disease or rapid-cycling bipolar disorder). Of the 9 articles on depression, 3 were reviews or opinion pieces, 3 were basic research on brain changes during VNS and 3 were empirical studies. Two of the 3 empirical studies were subanalyses of the Rush et al. (2005) RCT. On closer inspection, neither of these analyses was eligible for MTAC review. The Nierenberg et al. (2008) study did not compare outcomes associated with active vs. sham VNS; instead the investigators compared the effects of VNS on bipolar vs. unipolar depressed participants within the Rush RCT. The other sub-analysis, Burke et al. (2006) evaluated the effect of concomitant VNS and electroconvulsive therapy (ECT) in the 14 participants in the Rush RCT who received both treatments. This was a descriptive analysis of a small number of individuals and does not aid our understanding of the effectiveness of VNS. The third new empirical study was a case series (n=74) conducted in Europe. This study was critically appraised. A Blue Cross Blue Shield technology assessment report, used for the first MTAC review, has not been updated since August 2006. No additional published articles were identified on the Cyberonics website. The citation for the new European study is as follows:

Schlaepfer TE, Frick C, Zobel A et al. Vagus nerve stimulation for depression: efficacy and safety in a European study. Psychol Med 2008; 38: 651-661. See Evidence Table.

The use of Vagus Nerve Stimulation in the treatment of treatment-resistant depression does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

10/12/2020: MTAC REVIEW
gammaCore Sapphire non-invasive vagus nerve stimulator
Evidence Conclusion:

- Cluster headache
  - Although results are promising, there is insufficient evidence to determine the efficacy of nVNS for the acute treatment of patients with cluster headache.
  - Results are promising from one RCT. More studies are needed. There is insufficient evidence to determine the efficacy of nVNS as prophylactic treatment for the prevention of episodic or chronic cluster headache.
- Migraine
  - Acute treatment of migraine: A randomized controlled trial with moderate quality shows that nVNS was effective for aborting migraine attacks at 30 and 60 minutes after treatment and for relieving pain 2 hours after treatment. More studies are warranted to confirm these findings.
  - Prevention of migraine: there is insufficient evidence to determine the efficacy of nVNS in preventing migraine with or without aura.

Articles: PubMed was searched through August 2020 with the search terms (gammaCore Sapphire OR non-invasive vagus nerve stimulator) AND (cluster headache OR episodic cluster headache OR chronic cluster headache OR migraine) with variations. The search was limited to English language publications and human populations. The reference lists of relevant studies were reviewed to identify additional publications. Only RCTs were included in the search. Studies with no comparison group were not reviewed. Key trials were selected and reviewed.

Responsive Neurostimulation, (NeuroPace RNS System) For The Treatment Of Adult Patients With Drug Resistant Focal Epilepsy

BACKGROUND

Epilepsy is a common chronic brain disorder that affects individuals of all ages, races, social classes, and geographic regions. It is characterized by recurrent unprovoked seizures resulting from excessive electrical discharges in a group of brain cells. The seizure episodes may involve only one part of the body (partial or focal seizure) or the entire body (generalized seizure) depending on when disturbance first starts in the brain and how far it spreads. Seizure episodes

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may also vary in severity, duration, and frequency (Asadi-Pooya, et al 2023, WHO 2024).

Epilepsy has many different causes, which can be complex and in sometimes hard to identify. These are largely divided into six categories: genetic, structural, metabolic, infectious, immune, and unknown (Thijs, et al, 2019).

07/08/2024: MTAC Review
Responsive Neurostimulation (RNS)
Evidence Conclusion:

- The limited quality and quantity of the published evidence does not provide sufficient evidence to support the use of active responsive neurostimulation (RNS) for the treatment of patients with focal drug resistant epilepsy (DRE).
  - There is insufficient evidence to determine the net health outcomes of RNS in patients with focal DRE.
  - There is no published evidence, to date, to determine that the safety, tolerability, and effectiveness of RNS is equivalent or superior to resective surgery, or other neuromodulation therapies approved for use in patients with focal drug resistant epilepsy.
  - Low-quality evidence from a single, industry funded, sham-controlled RCT with only 3 months randomized period suggests that active responsive neurostimulation may be more effective than no stimulation in reducing seizure frequency, but not in improving responder rates in adults with drug-resistant focal epilepsy. The study also showed that the implant may be associated with serious adverse events.
  - High-quality studies a with long follow-up duration are needed to determine the comparative effectiveness and safety of RNS to surgical intervention or other neurostimulation modalities.

Articles: The literature search for comparative studies on the safety and efficacy of responsive neurostimulation (RNS, NeuroPace, system) in patients with focal drug resistant epilepsy, did not identify any RCT or meta-analyses of RCTs that compared RNS head-to-head with surgical resection or other active neurostimulation modalities e.g., VNS, or DBS.

The published literature on the use of RNS for patients with focal DRE consisted of:

- One sham-controlled trial published in three articles (Morrel 2011, Heck, et al 2014, and Meador, et al 2015).
- An open -label long-term treatment (LTT) study of patients who completed either the feasibility or the pivotal trial (Bergey .et al 2015 and, et al 2020).
- An open label observational study evaluating RNS use in adults enrolled in the pivotal trial who had seizures of mesial temporal lobe origin. (Geller, et al,2017)
- A systematic review (SR) and meta-analysis (MA) of RNS for DRE (Kusyk, et al 2022)
- A SR with a MA (Skrehot, et al 2023) indirectly comparing different neurostimulation modalities (RNS, VNS, and DBS) used for the treatment of patients with focal DRE.
- A SR with MA (Tourma, et al 2022) published by The International League against Epilepsy (ILAE) that also indirectly compared different neurostimulation modalities, and included patients for patients with focal onset DRE as well as those with generalized onset epilepsy,
- A more recent retrospective meta-analysis (Bystrom, et al 2023) performed to determine whether thalamic RNS may be safe and effective in treating DRE.

The pivotal study, and two systematic reviews with meta-analyses of studies on RNS alone, and of studies on different neurostimulation therapies for drug resistant focal epilepsy were selected for critical appraisal.

The use of Responsive Neurostimulation in the treatment of treatment-resistant depression does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

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Thijs RD, Surges R, O'Brien TJ, et al. Epilepsy in adults. Lancet. 2019 Feb 16;393(10172):689-701. doi: 10.1016/S0140-6736(18)32596-0. Epub 2019 Jan 24. PMID: 30686584.

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Applicable Codes

Vagus Nerve Stimulation, Implantable
Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® or HCPC Codes	Description
61885	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array
61886	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to 2 or more electrode arrays
61888	Revision or removal of cranial neurostimulator pulse generator or rec
64553	Percutaneous implantation of neurostimulator electrode array; cranial nerve
64568	Incision for implantation of cranial nerve (eg, vagus nerve) neurostimulator electrode array and pulse generator
64569	Revision or replacement of cranial nerve (eg, vagus nerve) neurostimulator electrode array, including connection to existing pulse generator

Vagus Nerve Stimulation, Transcutaneous (gammaCore Sapphire non-invasive vagus nerve stimulator)
Considered Not Medically Necessary:

CPT® or HCPC Codes	Description
E1399	Durable medical equipment, miscellaneous

Responsive Neurostimulation (RNS)
Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® Codes	Description
61850	Twist drill or burr hole(s) for implantation of neurostimulator electrodes, cortical
61860	Craniectomy or craniotomy for implantation of neurostimulator electrodes, cerebral, cortical
61863	Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalamic nucleus,

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	periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; first array
61864	Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (eg, thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; each additional array (List separately in addition to primary procedure)
61889	Insertion of skull-mounted cranial neurostimulator pulse generator or receiver, including craniectomy or craniotomy, when performed, with direct or inductive coupling, with connection to depth and/or cortical strip electrode array(s)
61891	Revision or replacement of skull-mounted cranial neurostimulator pulse generator or receiver with connection to depth and/or cortical strip electrode array(s)
61892	Removal of skull-mounted cranial neurostimulator pulse generator or receiver with cranioplasty, when performed
61880	Revision or removal of intracranial neurostimulator electrodes

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

****To verify authorization requirements for a specific code by plan type, please use the **Pre-authorization Code Check**.

Date Created	Date Reviewed	Date Last Revised
10/08/1999	07/06/2010[MDCRPC], 05/03/2011[MDCRPC], 03/06/2012[MDCRPC], 01/08/2013[MDCRPC], 11/05/2013[MPC], 09/02/2014[MPC], 07/07/2015[MPC], 05/03/2016[MPC], 03/07/2017[MPC], 01/09/2018[MPC], 11/06/2018[MPC], 11/05/2019[MPC], 11/05/2019[MPC], 11/03/2020[MPC], 11/02/2021[MPC], 11/01/2022[MPC], 11/01/2022[MPC], 11/07/2023[MPC]	11/05/2024

[MDCRPC] Medical Director Clinical Review and Policy Committee
[MPC] Medical Policy Committee

Revision History	Description
11/03/2020	Added MTAC review for gammaCore Sapphire non-invasive vagus nerve stimulator
11/02/2021	MPC approved to adopt MCG* B-821-T criteria for medical necessity determinations for VNS for Mental Health Diagnoses. Requires 60-day notice, effective 04/01/2022.
11/05/2024	MPC approved to adopt clinical criteria for Responsive Neurostimulation (NeuroPace). Requires 60-day notice, effective April 1, 2025.

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