LifeWise
Health Plan of Washington

MEDICAL POLICY – 7.01.593
Vagus Nerve Stimulation

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RELATED MEDICAL POLICIES:

2.01.526	Transcranial Magnetic Stimulation as a Treatment of Depression and Other Psychiatric/Neurologic Disorders
7.01.516	Bariatric Surgery
7.01.522	Gastric Electrical Stimulation
7.01.546	Spinal Cord and Dorsal Root Ganglion Stimulation

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | DOCUMENTATION REQUIREMENTS | CODING
RELATED INFORMATION | EVIDENCE REVIEW | REFERENCES | HISTORY

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Introduction

The vagus nerve starts in the brain stem and runs down the neck, into the chest, and then down to the stomach area. Stimulating this nerve has been studied as a way to treat several different types of conditions. A small device that generates electricity is surgically placed in a person's chest. A thin wire leads from the device to the vagus nerve. Vagus nerve stimulation may be used to treat seizures that don't respond to medication. Vagus nerve stimulation may also be used to treat depression that doesn't respond to medications and certain other treatments. However, for other conditions it's considered investigational (unproven). There is not yet enough information in published medical studies to show how well it works for other conditions. Similarly, non-implanted devices to stimulate the vagus nerve for treatment of any condition are also investigational due to lack of evidence that they improve one's health.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Service	Medical Necessity
Vagus nerve stimulation e.g., NeuroCybernetic Prosthesis (NCP) (Cyberonics) for refractory seizures	**Vagus nerve stimulation may be considered medically necessary as a treatment of medically refractory seizures*.** **Note:** *Medically refractory seizures are defined as seizures that occur despite therapeutic levels of antiepileptic drugs or seizures that cannot be treated with therapeutic levels of antiepileptic drugs because of intolerable adverse events of these drugs. This indication is applicable for both pediatric and adult individuals.

Vagus nerve stimulation for Major Depressive Disorder (unipolar depression)	**Vagus nerve stimulation, including surgical implantation, and including electronic analysis and reprogramming, may be considered medically necessary for the treatment of Major Depressive Disorder (unipolar depression, not bipolar depression) without psychotic features when:**
	• The individual is aged 18 years old and older
	• Is experiencing a current episode of moderate to severe depression as demonstrated by documentation of the individual's symptoms and their severity or by one or more standardized depression rating scales
	• No acute or chronic psychotic symptoms
	• One of the following criteria are met:
	  ○ Failure of at least 3 antidepressant medications from at least 2 different classes in separate trials
	  OR
	  ○ Failure of at least 2 different antidepressant medications from at least 2 different classes in separate trials, plus failure with the addition of an augmenting agent to at least one of the failed antidepressants
	• Depression continued to be moderate or severe after a course of transcranial magnetic stimulation (TMS), or TMS was stopped due to intolerable or incapacitating or dangerous side effects, or a contraindication to transcranial magnetic stimulation
	• Depression continued to be moderate or severe after a course of electroconvulsive therapy (ECT), or ECT was stopped due to

Service	Medical Necessity
	intolerable or incapacitating or dangerous side effects, or a contraindication to electroconvulsive therapy **Note:** Concerns about possible side effects of TMS or ECT or desire to not undergo TMS or ECT are not considered to be contraindications.
Contraindications	**Vagus nerve stimulation is considered not medically necessary when either of the following contraindications are present:** • A history of left vagotomy or bilateral vagotomy • Current or planned therapeutic short-wave diathermy, therapeutic microwave diathermy, therapeutic ultrasound diathermy (this does not include diagnostic ultrasound) or surgical diathermy on any body location
Vagus nerve stimulation in conjunction with other neuromodulation modalities for the treatment of psychiatric or substance use disorders	**Use of vagus nerve stimulation (VNS) in conjunction with transcranial magnetic stimulation (TMS) may be considered medically necessary for 3 months after vagus nerve stimulator implantation for Major Depressive Disorder, while waiting for VNS to become effective, if the individual has just completed a full or brief intensive course of TMS and is transitioning to maintenance TMS, or is undergoing maintenance TMS, and TMS has been partially but inadequately effective. Use of TMS in conjunction with VNS may be considered medically necessary for a maximum of 3 additional 3-month intervals if, at the completion of each interval, VNS has not resulted in improvement of depression to mild or remission based on a standardized rating scale. Continued TMS in conjunction with VNS is considered not medically necessary when either depression has improved to mild or remission based on a standardized rating scale, or 12 months have elapsed since vagus nerve stimulator implantation.** **Any other use of VNS in conjunction with transcranial magnetic stimulation (TMS) for the treatment of psychiatric disorders or substance use disorders is considered not medically necessary.**

Service	Medical Necessity
	Use of VNS in conjunction with any other modality of neuromodulation for the treatment of psychiatric disorders or substance use disorders, including but not limited to electroconvulsive therapy (ECT), deep brain stimulation (DBS), or cranial electrotherapy stimulation (CES), is considered not medically necessary.
Vagus nerve stimulation in conjunction with Spravato (esketamine) or any other formulation of ketamine or with any psychedelic drug	**Use of vagus nerve stimulation (VNS) in conjunction with Spravato (esketamine) or with any other formulation of ketamine or with any psychedelic drug is considered investigational.**

Service	Investigational
Vagus nerve stimulation	**Vagus nerve stimulation is considered investigational as a treatment of other conditions, including but not limited to:** • Essential tremor • Fibromyalgia • Headaches • Heart failure • Obesity (see Related Policy **7.01.516**) • Tinnitus • Traumatic brain injury • Upper-limb impairment due to stroke • Psychiatric conditions other than Major Depressive Disorder • Substance use disorders
Non-implantable vagus nerve stimulation devices e.g., gammaCore (ElectroCore); transcutaneous auricular vagus nerve stimulation devices	**Non-implantable (transcutaneous) vagus nerve stimulation devices are considered investigational for all indications.**

Additional Information

For Major Depressive Disorder

- A diagnosis code that includes a numeral for severity, or a diagnosis with the descriptor moderate or severe, is not sufficient to establish severity; documentation of symptoms and their severity or score on a standardized rating scale is required.
- Standardized rating scale scores of moderately severe are considered to be equivalent to severe.
- Failure of a medication trial means that medication was not effective, was partially but inadequately effective, was effective for some period but then lost effectiveness, had to be stopped due to adverse effects, or doses could not be increased to potentially therapeutic levels due to adverse effects.
- Each medication that failed must be individually identified, and the reason or reasons for failure must be specified for each medication.
- Unless stopped because of intolerable adverse effects, a minimum of thirty continuous days with no or inadequate improvement is required before a medication trial is considered to be a failed trial.
- Second generation antipsychotics, lithium, and anticonvulsants that are utilized as mood stabilizers are considered to be augmenting agents, not antidepressants.
- Trials of antidepressants that are commonly used for insomnia are considered to be failed trials only if the dose was at minimum antidepressant dose (amitriptyline: 150 mg; doxepin: 150 mg; mirtazapine: 15 mg; trazodone: 150 mg), not at lower doses that are used for insomnia, or, if titration up to an antidepressant dose was planned but could not be done due to intolerable adverse effects.

Documentation Requirements

The medical records submitted for review should document that medical necessity criteria are met. For seizures the record should include documentation that member has medically refractory seizures as evidenced by:

- Persistent seizures in spite of therapeutic levels of antiepileptic medications

OR

- Member has intolerable side effects of drug therapy

For depression, the record should include the following:

- Diagnosis
- Severity of symptoms
- Brief history of the diagnosis

Documentation Requirements

- Medication trials, including the outcome of the trial for each medication
- The outcome of treatment with TMS and ECT or contraindications

Vagus nerve stimulation has been evaluated for the treatment of obesity. This indication is addressed in a separate policy (see **Related Policies**).

Coding

Code	Description
CPT	
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
64553	Percutaneous implantation of neurostimulator electrodes; cranial nerve
64568	Open implantation of cranial nerve (e.g., vagus nerve) neurostimulator electrode array and pulse generator
64569	Revision or replacement of cranial nerve (e.g., vagus nerve) neurostimulator electrode array, including connection to existing pulse generator
95970	Electronic analysis of implanted neurostimulator pulse generator/ transmitter (e.g., contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain, cranial nerve, spinal cord, peripheral nerve, or sacral nerve, neurostimulator pulse generator/ transmitter, without programming
95976	Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g., contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with simple cranial nerve neurostimulator pulse generator / transmitter programming by physician or other qualified health care professional
95977	Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g., contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive

Code	Description
	neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with complex cranial nerve neurostimulator pulse generator / transmitter programming by physician or other qualified health care professional
HCPCS	
C1767	Generator, neurostimulator (implantable), nonrechargeable
C1778	Lead, neurostimulator (implantable)
E0735	Noninvasive vagus nerve stimulator (new code effective 1/1/2024)
K1020	Non-invasive vagus nerve stimulator (code termed 1/1/2024)
L8680	Implantable neurostimulator electrode, each
L8681	Patient programmer (external) for use with implantable programmable neurostimulator pulse generator
L8682	Implantable neurostimulator radiofrequency receiver
L8683	Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver
L8684	Radiofrequency transmitter (external) for use with implantable sacral root neurostimulator receiver for bowel and bladder management, replacement
L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
L8686	Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension
L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
L8688	Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension
L8689	External recharging system for battery (internal) for use with implantable neurostimulator

Related Information

Definition of Terms

Medically refractory seizures are defined as:

- Seizures that occur in spite of therapeutic levels of antiepileptic drugs or
- Seizures that cannot be treated with therapeutic levels of antiepileptic drugs because of intolerable adverse effects of these drugs.

Evidence Review

Description

Stimulation of the vagus nerve can be performed by using a pulsed electrical stimulator implanted within the carotid artery sheath. This technique has been proposed as a treatment for refractory seizures, depression, and other disorders. There are also devices available that are implanted at different areas of the vagus nerve. This policy also addresses devices that stimulate the vagus nerve transcutaneously.

Background

Vagus nerve stimulation (VNS) was initially investigated as a treatment alternative in individuals with medically refractory partial-onset seizures for whom surgery is not recommended or for whom surgery has failed. Over time, the use of VNS has expanded to include generalized seizures, and it has been investigated for a range of other conditions.

While the mechanisms for the therapeutic effects of VNS are not fully understood, the basic premise of VNS in the treatment of various conditions is that vagal visceral afferents have a diffuse central nervous system projection, and activation of these pathways has a widespread effect on neuronal excitability. An electrical stimulus is applied to axons of the vagus nerve, which have their cell bodies in the nodose and junctional ganglia and synapse on the nucleus of the solitary tract in the brainstem. From the solitary tract nucleus, vagal afferent pathways project to multiple areas of the brain. VNS may also stimulate vagal efferent pathways that innervate the heart, vocal cords, and other laryngeal and pharyngeal muscles, and provide parasympathetic innervation to the gastrointestinal tract.

Other types of implantable vagus nerve stimulators that are placed in contact with the trunks of the vagus nerve at the gastroesophageal junction are not addressed in this policy.

Summary of Evidence

Vagus Nerve Stimulation

For individuals who have seizures refractory to medical treatment who receive VNS, the evidence includes randomized controlled trials (RCTs) and multiple observational studies. The relevant outcomes are symptoms, change in disease status, and functional outcomes. The RCTs have reported significant reductions in seizure frequency for individuals with partial-onset seizures. The uncontrolled studies have consistently reported large reductions in a broader range of seizure types in both adults and children. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have treatment-resistant depression who receive VNS, the evidence includes two RCTs evaluating the efficacy of implanted VNS for treatment-resistant depression compared to sham, one RCT comparing therapeutic to low-dose implanted VNS, nonrandomized comparative studies, and case series. The relevant outcomes are symptoms, change in disease status, and functional outcomes. The sham-controlled RCTs only reported short-term results and found no significant improvement in the primary outcome. The low-dose VNS controlled trial reported no statistically significant differences between the dose groups for change in depression symptom score from baseline. Other available studies are limited by small sample sizes, potential selection bias, and confounding biases, and lack of a control group in the case series. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have chronic heart failure who receive VNS, the evidence includes a systematic review including four RCTs and case series. The relevant outcomes are symptoms, change in disease status, and functional outcomes. Meta-analyses of the RCTs evaluating chronic heart failure found significant improvements in New York Heart Association functional class, quality of life, 6-minute walk-test, and N-terminal-pro brain natriuretic peptide levels in individuals treated with VNS compared to control. An analysis of the ANTHEM-HF uncontrolled trial evaluated longer-term outcomes of VNS use in chronic heart failure. They found that left ventricular (LV) ejection fraction improved by 18.7%, 19.3%, and 34.4% at 12, 24, and 36 months, respectively, with high-intensity VNS. Individuals with low-intensity VNS only had significant improvement in LV ejection fraction at 24 months (12.3%). The ANTHEM-HFpEF trial found improvements in New York Heart Association functional class, quality of life, and 6-minute walk

test distances in patients with preserved ejection fraction and implanted VNS. Although this data is promising, a lack of a no-VNS comparator group precludes drawing conclusions based on findings from the uncontrolled studies. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have upper-limb impairment due to stroke who receive VNS, the evidence includes three pilot RCTs. The relevant outcomes are symptoms, change in disease status, and functional outcomes. Two RCTs compared VNS plus rehabilitation to rehabilitation alone; one failed to show significant improvements for the VNS group on response and function outcomes, but the other, which had a larger patient population, found a significant difference in response and function outcomes. The other RCT compared VNS to sham and found that although VNS significantly improved response rate, there were three serious adverse events related to surgery. A systematic review pooling these data found that implanted VNS improved upper limb motor function based on Fugl-Meyer Assessment-Upper Extremity score when compared to control. Longer-term follow-up studies are needed to evaluate long-term efficacy and safety. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have other neurologic conditions (e.g., essential tremor, headache, fibromyalgia, tinnitus, or autism) who receive VNS, the evidence includes case series. The relevant outcomes are symptoms, change in disease status, and functional outcomes. Case series are insufficient to draw conclusions regarding efficacy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Transcutaneous Vagus Nerve Stimulation

For individuals with cluster headaches who receive transcutaneous VNS (tVNS; also referred to as noninvasive VNS [nVNS]) to prevent cluster headache, the evidence includes one RCT. The relevant outcomes are symptoms, change in disease status, quality of life, and functional outcomes. One RCT for prevention of cluster headache showed a reduction in headache frequency but did not include a sham treatment group. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with cluster headache who receive nVNS to treat acute cluster headache, the evidence includes RCTs. The relevant outcomes are symptoms, change in disease status, quality of life and functional outcomes. The Non-invasive Neurostimulation of the Vagus Nerve with the GammaCore Device for the Treatment of Cluster Headache (ACT1) and A Randomized, Multicentre, Double-blind, Parallel, Sham-controlled Study of GammaCore, a Non-invasive

Neurostimulator Device for the Acute Relief of Episodic and Chronic Cluster Headache (ACT2) RCTs compared nVNS to sham for treatment of acute cluster headache in individuals including both chronic and episodic cluster headache. In ACT1, there was no statistically significant difference in the overall population in the proportion of individuals with pain score of 0 or 1 at 15 minutes into the first attack and no difference in the proportion of individuals who were pain-free at 15 minutes in 50% or more of the attacks. In the episodic cluster headache subgroup (n=85) both outcomes were statistically significant favoring nVNS although the interaction p-value was not reported. In ACT2, the proportion of attacks with pain intensity score of 0 or 1 at 30 minutes was higher for nVNS in the overall population (43% vs. 28%, p=0.05) while the proportion of attacks that were pain-free at 15 minutes was similar in the 2 treatment groups in the overall population (14% vs. 12%). However, a statistically significantly higher proportion of attacks in the episodic subgroup (n=27) were pain-free at 15 minutes in the nNVS group compared to sham (48% vs. 6%, p<0.01). These studies suggest that people with episodic and chronic cluster headaches may respond differently to acute treatment with nVNS. Studies designed to focus on episodic cluster headache are needed. Quality of life and functional outcomes have not been reported. Treatment periods ranged from only two weeks to one month with extended open-label follow-up of up to three months. There are few adverse events of nVNS and they are mild and transient. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with migraine headache who receive nVNS to treat acute migraine headache, the evidence includes one RCT. The relevant outcomes are symptoms, change in disease status, quality of life and functional outcomes. One RCT has evaluated nVNS for acute treatment of migraine with nVNS in 248 individuals with episodic migraine with/without aura. There was not a statistically significant difference in the primary outcome of the proportion of participants who were pain-free without using rescue medication at 120 minutes (30% vs 20%; p = 0.07). However, the nVNS group had a higher proportion of individuals with decrease in pain from moderate or severe to mild or no pain at 120 minutes (41% vs 28%; p=0.03) and a higher proportion of individuals who were pain-free at 120 for 50% or more of their attacks (32% vs 18%; p=0.02). There are few adverse events of nVNS and they are mild and transient. Quality of life and functional outcomes were not reported, and the double-blind treatment period was four weeks with an additional four weeks of open-label treatment. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with chronic migraine headache who receive nVNS to prevent migraine headache, the evidence includes three RCTs. The relevant outcomes are symptoms, change in disease status, quality of life and functional outcomes. The Non-Invasive Neurostimulation of the Vagus Nerve with the GammaCore Device for the Prevention of Chronic Migraine; nVNS: noninvasive transcutaneous vagus nerve stimulation (EVENT) RCT was a feasibility study of

prevention of migraine that was not powered to detect differences in efficacy outcomes. It does not demonstrate the efficacy of nVNS for prevention of migraine. The Randomized, Multicentre, Double-blind, Parallel, Sham-controlled Study of gammaCore, a Non-invasive Vagal Nerve Stimulator (nVNS), for Prevention of Episodic Migraine (PREMIUM) RCT was a phase 3, multicenter, sham-controlled RCT including 341 randomized participants with a 12-week double-blind treatment period. The results of PREMIUM demonstrated that nVNS was not statistically significantly superior to sham with respect to the outcomes of reduction of at least 50% in migraine days from baseline to the last four weeks, reduction in number of migraine days from baseline to the last four weeks, or acute medication days. The PREMIUM II trial was a multicenter, sham-controlled RCT including 231 randomized participants with a 12-week double-blind treatment period. The trial was terminated early due to the COVID-19 pandemic and results were based on a intention to treat (mITT) population that included 113 total participants. Results demonstrated that treatment with nVNS was not statistically significantly superior to sham with respect to the primary outcome of reduction in the number of migraine days per month during weeks 9 through 12, nor other outcomes such as mean change in the number of headache days or acute medication days. However, the percentage of individuals with at least a 50% reduction in the number of migraine days was significantly greater in the nVNS group than in the sham group. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have other neurologic, psychiatric, or metabolic disorders (e.g., epilepsy, depression, schizophrenia, noncluster headache, impaired glucose tolerance, fibromyalgia, stroke) who receive tVNS, the evidence includes RCTs and case series for some of the conditions. The relevant outcomes are symptoms, change in disease status, and functional outcomes. The RCTs are all small and have various methodologic problems. None showed definitive efficacy of tVNS in improving patient outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in **Table 1.**

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03320304[a]	A Global Prospective, Multi-cEnter, ObServational Post-market Study to Assess short, Mid and Long-term Effectiveness and Efficiency of VNS Therapy as Adjunctive Therapy in real-world patients with difficult to Treat dEpression	500	Dec 2028
NCT03887715	A Prospective, Multi-center, Randomized Controlled Blinded Trial Demonstrating the Safety and Effectiveness of VNS Therapy System as Adjunctive Therapy Versus a No Stimulation Control in Subjects With Treatment-Resistant Depression (RECOVER)	6800	Dec 2030
NCT04935567	PRediction of Vagal Nerve Stimulation EfficaCy In Drug-reSistant Epilepsy: Prospective Study for Pre-implantation Prediction	120	Dec 2026
NCT04777500	Applying Transcutaneous Auricular Vagus Nerve Stimulation to Treat Fibromyalgia	60	Mar 2023
NCT04534556	Wireless Nerve Stimulation Device To Enhance Recovery After Stroke	20	Jan 2024
NCT04448327	Sex-Dependent Impact of Transcutaneous Vagal Nerve Stimulation on the Stress Response Circuitry and Autonomic Dysregulation in Major Depression	80	Nov 2024
NCT04539964	Vagus Nerve Stimulation Using the SetPoint System for Moderate to Severe Rheumatoid Arthritis: The RESET-RA Study	250	May 2027
Unpublished			
NCT02562703	Transcutaneous Vagus Nerve Stimulation for Treating Major Depressive Disorder: a Phase II, Randomized, Double-blind Clinical Trial	40	Jul 2016 (unknown)
NCT02089243	Prospective Randomized Controlled Study of Vagus Nerve Stimulation Therapy in the Patients With Medically Refractory Medial Temporal Lobe Epilepsy; Controlled Randomized Vagus Nerve Stimulation Versus Resection (CoRaVNStiR)	40	Jul 2017 (unknown)
NCT01281293[a]	A Post Market, Long Term, Observational, Multi-site Outcome Study to Follow the Clinical Course and Seizure	124	Aug 2018

NCT No.	Trial Name	Planned Enrollment	Completion Date
	Reduction of Patients With Refractory Seizures Who Are Being Treated With Adjunctive VNS Therapy		
NCT03380156	Effect of Transcutaneous Vagal Stimulation (TVS) on Endothelial Function and Arterial Stiffness in Patients With Heart Failure With Reduced Ejection Fraction	50	May 2020
NCT04926415	Effects of Transcutaneous Auricular Vagus Nerve Stimulation on Obesity and Insulin Resistance	30	Apr 2022

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

Practice Guidelines and Position Statements

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the policy conclusions.

Guidelines or position statements will be considered for inclusion if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Academy of Neurology

In 1999, the American Academy of Neurology released a consensus statement on the use of VNS in adults, which stated: "VNS is indicated for adults and adolescents over 12 years of age with medically intractable partial seizures who are not candidates for potentially curative surgical resections, such as lesionectomies or mesial temporal lobectomies."[87] The guidelines were updated in 2013 and reaffirmed in 2019, stating: "VNS may be considered for seizures in children, for LGS [Lennox-Gastaut syndrome]-associated seizures, and for improving mood in adults with epilepsy (Level C). VNS may be considered to have improved efficacy over time (Level C)."[88]

American Psychiatric Association

Updated in 2010, the American Psychiatric Association guidelines for the treatment of major depressive disorder in adults included the following statement on the use of VNS: "Vagus nerve stimulation (VNS) may be an additional option for individuals who have not responded to at least four adequate trials of antidepressant treatment, including ECT [electroconvulsive therapy]," with a level of evidence III (may be recommended on the basis of individual circumstances).[89]

National Institute for Health and Care Excellence

In 2016, the NICE issued guidance on use of transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine (IPG552).[90] The guidance states: "Current evidence on the safety of transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine raises no major concerns. The evidence on efficacy is limited in quantity and quality." The guidance also comments that further research is needed to clarify whether the procedure is used for treatment or prevention, for cluster headache or migraine, appropriate patient selection, and treatment regimen and suggests that outcome measures should include changes in the number and severity of cluster headache or migraine episodes, medication use, quality of life in the short and long term, side effects, acceptability, and device durability.

In 2018, the NICE also published a Medtech innovation briefing on nVNS for cluster headache (MIB162).[91] The briefing states that the "intended place in therapy would be as well as standard care, most likely where standard treatments for cluster headache are ineffective, not tolerated or contraindicated" and that key uncertainties around the evidence are that "people with episodic and chronic cluster headaches respond differently to treatment with gammaCore. The optimal use of gammaCore in the different populations is unclear. The NICE published a Medical technologies guidance [MTG46] on gammaCore for cluster headache in December 2019[92]. The recommendations state that evidence supports using gammaCore to treat cluster headache and that gammaCore is not effective in everyone with cluster headache.

In 2020, the NICE published an Interventional Procedure Overview on implanted vagus nerve stimulation for treatment-resistant depression (IPG679).[93] The guidance states: "Evidence on the safety of implanted vagus nerve stimulation for treatment-resistant depression raises no major safety concerns, but there are frequent, well-recognized side effects. Evidence on its efficacy is limited in quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research." The guidance further states that "NICE

encourages further research into implanted vagus nerve stimulation for treatment-resistant depression, in the form of randomized controlled trials with a placebo or sham stimulation arm. Studies should report details of patient selection. Outcomes should include validated depression rating scales, patient-reported quality of life, time to onset of effect and duration of effect, and any changes in concurrent treatment."

Medicare National Coverage

Medicare has a national coverage determination for VNS. Medicare coverage policy notes that "Clinical evidence has shown that vagus nerve stimulation is safe and effective treatment for patients with medically refractory partial onset seizures, for whom surgery is not recommended or for whom surgery has failed. Vagus nerve stimulation is not covered for patients with other types of seizure disorders that are medically refractory and for whom surgery is not recommended or for whom surgery has failed."[94]

In response to a request from LivaNova, on May 30, 2018, the Centers for Medicare & Medicaid Services (CMS) initiated its second reconsideration of its national coverage decision on VNS for Treatment Resistant Depression (TRD). Based on an internal literature review (search dates unspecified), CMS concluded that although the published evidence suggests that VNS is a promising treatment for patients with treatment resistant depression, the reviewed studies have important flaws that leave uncertainty about its true benefits and harms.[95] Thus, effective February 15, 2019, the CMS expanded Medicare coverage to "cover US Food and Drug Administration approved vagus nerve stimulation devices for TRD through Coverage with Evidence Development when offered in a CMS approved, double-blind, randomized, placebo-controlled trial with a follow-up duration of at least one year with the possibility of extending the study to a prospective longitudinal study when the CMS approved, double-blind, randomized placebo-controlled trial has completed enrollment, and there are positive interim findings." CMS approval of a Coverage with Evidence Development study requires answering nine research questions specifying measurement of response, remission, harms and other health outcome variables, use of specific eligibility criteria for TRD diagnosis as described in an Agency for Healthcare Research and Quality Technology Assessment conducted by Gaynes et al (2018),96 as well and 13 additional operational criteria. CMS has approved one ongoing study for Coverage with Evidence Development - A Prospective, Multi-center, Randomized Controlled Blinded Trial Demonstrating the Safety and Effectiveness of VNS Therapy System as Adjunctive Therapy Versus a No Stimulation Control in Subjects With Treatment-Resistant Depression (RECOVER) (NCT03887715).97 Conway et al (2020) have published a detailed description of the RECOVER study rationale and design.[98]

Update 2024

Although vagus nerve stimulation (VNS) for treatment-resistant depression was approved by the FDA in 2005, VNS for depression was previously considered to be investigational due to significant methodological limitations in earlier published studies, plus failure to recognize the length of time often required after implantation before VNS demonstrated initial effect and subsequent maximum effect. Two large trials failed to reach their primary outcome measure, likely in part because of the period of 3 to 12 months generally required to achieve initial response and maximum response after implantation, and because of inadequate strength of stimulation that produced some but insufficient positive effect. More recent studies and meta-analyses allowing for adequate periods for clinical effect after implantation, with large sample sizes, done at multiple sites, and with follow-up post-implantation up to 5 years, have demonstrated a greater likelihood of achieving response and remission[99-102]., including among ECT non-responders. Studies have examined reduction in or remission of symptoms of depression, and improvements in quality of life.

Studies have been open-label non-randomized observational trials, likely due to the challenges of having sufficient numbers of participants agree to be randomized to surgery or no surgery, or agree to be randomized to implantation of an actual vagus nerve stimulator or surgical implantation of a sham device (which would then later have to be removed), in addition to impediments to true blinding. However, the large numbers of participants tend to reduce the likelihood of placebo effect.

In one of the largest studies (795 participants), response rates among participants who had failed four or more depression treatments (medications, or medications and ECT) varied from 43.3% to 67.6%[100]. Even at the lower end of the range of response rates, an important consideration is that as the most invasive treatment modality for Major Depressive Disorder, vagus nerve stimulation is most often the only remaining option for attempting to treat major depression that has failed to respond to medication, transcranial magnetic stimulation, and ECT.

Recent studies have also clarified the length of time required for vagus nerve stimulation (VNS) to demonstrate a positive response for Major Depressive Disorder. Studies have evaluated results at 3, 6, 9, and 12 months after implantation. On average, VNS does not begin to demonstrate a positive response until 3 months after implantation. Maximum response is generally not demonstrated until 6, 9, or 12 months after implantation[99, 103-106]. For individuals who have been receiving transcranial magnetic stimulation (TMS) up to the time of implantation, and for whom TMS has been partially but inadequately effective, continuing TMS on a

maintenance schedule during the time required for VNS to become effective, and assessing at 3-month intervals, can reduce the likelihood of clinical regression while waiting for VNS to become effective. Further improvement from VNS after 12 months is unlikely, and a positive response from VNS is unlikely if there has not been a positive response by 12 months.

Although several studies have been published regarding a non-surgical VNS modality, transcutaneous auricular VNS, for the treatment of Major Depressive Disorder and other psychiatric disorders, definitive conclusions about supposed positive results cannot be made due to problematic methodological limitations of the studies.[107].

Regulatory Status

Table 2 includes updates on the US Food and Drug Administration (FDA) approval and clearance for VNS devices pertinent to this policy.

Table 2. FDA-Approved or FDA-Cleared Vagus Nerve Stimulators

Device Name	Manufacturer	Approved/ Cleared	PMA / 510(k)	Product Code(s)	Indications
NeuroCybernetic Prosthesis (NCP)/VNS Therapy	LIvaNov (Cyberonics)	1997	P970003	LYJ, MUZ	Indicated or adjunctive treatment of adults and adolescents >12 years of age with medically refractory partial onset seizures
		2005	P970003 / S50		Expanded indication for adjunctive long-term treatment of chronic or recurrent depression for patients ≥18 years of age experiencing a major depressive episode and have not had an adequate response to ≥4 adequate antidepressant treatments
		2017	P970003 / S207		Expanded indicated use as adjunctive therapy for seizures in patients ≥4 years

Device Name	Manufacturer	Approved/ Cleared	PMA / 510(k)	Product Code(s)	Indications
					of age with partial-onset seizures that are refractory to antiepileptic medications
gammaCore	ElectroCore	2017/2018	DEN150048 / K171306 / K173442	PKR, QAK	Indicated for acute treatment of pain associated with episodic cluster and migraine headache in adults using noninvasive VNS on the side of the neck
gammaCore-2,gammaCore-Sapphire	ElectroCore	2017/2018 /2021	K172270 / K180538 / K182369 / K191830/ K203456 / K211856	PKR	Indicated for: Adjunctive use for the preventive treatment of cluster headache in adult patients. The acute treatment of pain associated with episodic cluster headache in adult patients. The acute treatment of pain associated with migraine headache in adult individuals. The preventive treatment of migraine headache in adult individuals.
SYMMETRY	LivaNova	2019	P970003	MUZ	Adjunctive long-term treatment of chronic or recurrent depression for patients ≥18 years of age experiencing a major depressive episode and have not had an adequate response to ≥4 adequate antidepressant treatments.

FDA: US Food and Drug Administration; PMA: premarket approval; VNS: vagus nerve stimulation.

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History

Date	Comments
06/25/98	Add to Surgery Section - New Policy - 7.01.20 Vagus Nerve Stimulation
01/07/99	Coding Update - 1999 CPT coding release.
06/02/00	Replace Policy - Added cross-references to other stimulation policies.
01/08/02	Replace Policy - Title change; revised new indication for children, investigational as a treatment for depression. Held for notification, published 4/15/02.
09/12/03	Replace Policy - Information update; policy statement unchanged.
10/12/04	Replace Policy - Policy reviewed with literature search. FDA information and a reference added. Statement on investigational status of VNS treatment for essential tremor added.
09/13/05	Replace Policy - Policy updated with literature review and FDA approval of VNS for depression. Added headaches and essential tremor as investigational in the policy statement; remaining policy statements unchanged.
02/06/06	Codes updated - No other changes.
06/09/06	Disclaimer and Scope update - No other changes.
09/12/06	Replace Policy - Policy updated with June 2006 TEC Assessment (treatment-resistant depression) and literature review for other indications; policy statement unchanged; references added.
01/08/08	Replace Policy - Policy updated with literature search; no change in policy statement. References and codes added.
10/14/08	Replace Policy - Policy updated with literature search; no change in policy statement. References and codes added.

Date	Comments
01/13/09	Replace Policy - Policy updated with literature search. Policy statement revised to indicate the VNS may be considered medically necessary in refractory seizures (both partial and generalized) and is investigational in treatment of obesity. References added.
01/12/10	Replace Policy - Policy updated with literature search; no change to the policy statements. Rationale extensively reorganized and condensed. References added.
03/08/11	Replace Policy - Policy updated with literature search; references 30-32 have been added. No change to policy statements. ICD-10 codes added.
01/03/12	Deleted codes 64568, 64569, 64570 and 64573 removed.
06/26/12	Replace policy. Policy updated with literature search, references 26-28, 33, 34 added. Policy statement updated to include the addition of heart failure and fibromyalgia to the list of investigational conditions.
08/27/12	Update Related Policy – Add 2.01.50. Update coding section – ICD-10 codes are now effective 10/01/2014.
01/10/13	Coding update. New CPT codes 0312T – 0318T, effective 1/1/13, added to policy.
01/22/13	Update Related Policies. 2.01.50 replaced with 2.01.526.
02/15/13	Update Related Policies. Change title to policy 2.01.526.
05/28/13	Replace policy. Policy reviewed. Rationale section reformatted for readability, references renumbered to match the changes. A literature search through January 2013 did not prompt additions to the reference list. Vagus nerve blocking therapy codes (0312T-03127T) removed as inappropriate for this policy. Policy statement unchanged.
06/13/14	Annual Review. Policy updated with literature review through February 5, 2014. References 7, 13-17, 29-31, and 41-44 added. Policy statement updated to include the addition of tinnitus and traumatic brain injury to the list of investigational conditions. Rationale section reorganized.
01/26/15	Update Related Policy. Add 7.01.143.
03/13/15	Update Related Policies. Add 7.01.522.
05/27/15	Annual Review. Policy updated with literature review through January 27, 2015. Added vBloc Maestro system to Regulatory Status section. References 2, 14-17, 35, 40, 45-46, 51, 54-58, 62 added; others renumbered. Policy statements unchanged. Coding update: ICD-9 and ICD-10 diagnosis codes removed; ICD-9 procedure codes 02.93, 86.96, 86.97, and 86.98 removed; ICD-10 codes added for purposes of remediation.
09/01/15	Update Related Policies. Add 7.01.150.
05/01/16	Annual Review, approved April 12, 2016. Policy updated with literature review through January 20, 2016; references 44, 55, and 57 added. Regulatory Status section revised with device information. Policy statements unchanged.

Date	Comments
03/01/17	Coding Update. Removed CPT code 95973 as it was deleted as of 01/01/2016.
08/25/17	Coding Update, removed CPT codes 95971, 95972, 95974, and 95975. Policy moved to new format, no changes to policy statement.
12/01/17	Annual Review, approved November 9, 2017. Policy updated with literature review through August 31, 2017. Multiple references added. Policy statements edited for clarity. The intent of policy statements unchanged. Removed CPT codes 61888 and 64570.
05/01/18	Annual Review, approved April 3, 2018. Policy updated with literature review through December 2017; references 2, 67-68, 77 and 84 added; reference 44 updated. Added information regarding transcutaneous device for treatment of migraine headache pain. Added note that VNS medical necessity criteria statement applies to both pediatric and adult patients. Policy statements unchanged.
05/01/19	Annual Review, approved April 2, 2019. Policy updated with literature review through December 2018; several references added. Indications 7 and 8 added. Policy statements unchanged.
04/01/20	Delete policy, approved March 10, 2020. This policy will be deleted effective July 2, 2020, and replaced with InterQual criteria for dates of service on or after July 2, 2020.
07/02/20	Delete policy.
11/01/20	Policy reinstated effective February 5, 2021, approved October 13, 2020. Policy updated with literature review through December 2019; references added. Policy statements unchanged.
05/01/21	Annual Review, approved April 1, 2021. Policy updated with literature review through December 17, 2020; references added. Policy statements unchanged. Related policies updated. Update Related Policies, removed policy 7.01.150 as it was archived.
06/01/21	Coding update. Added HCPC codes C1767 and C1778.
01/01/22	Coding update, updated code description for CPT 64568.
05/01/22	Annual Review, approved April 11, 2022. Policy updated with literature review through January 3, 2022; references added. Policy statements unchanged. Added HCPCS code K1020.
05/01/23	Annual Review, approved April 10, 2023. Policy updated with literature review through December 22, 2022; references added. Policy statements unchanged. Changed the wording from "patient" to "individual" throughout the policy for standardization.
01/01/24	Coding update. Added new HCPCS code E0735 and added term date to HCPCS code K1020.
05/01/24	Annual Review, approved April 8, 2024. Policy updated with literature review through December 21, 2023; references added. Policy statements unchanged.
08/01/24	Interim Review, approved July 9, 2024. Policy updated with criteria for when VNS may be considered medically necessary for the treatment of Major Depressive Disorder,

Date	Comments
	and with criteria for when VNS may be considered medically necessary in conjunction with transcranial magnetic stimulation (TMS) for the treatment of Major Depressive Disorder. Policy stipulations added that VNS is considered investigational for the treatment of any other psychiatric disorders (other than Major Depressive Disorder) or any substance use disorders, and that transcutaneous auricular VNS is considered investigational. Policy statements added that TMS may be considered medically necessary in conjunction with VNS specifically when being continued as maintenance TMS, if TMS has been partially but inadequately effective, to prevent regression during the time between VNS implantation and VNS becoming effective; that VNS in conjunction with any other neuromodulation modality for the treatment of psychiatric disorders or substance use disorders is not medically necessary; and that VNS in conjunction with Spravato or with any other formulation of ketamine or with any psychedelic drug is considered investigational. Added CPT codes 95970, 95976, and 95977. Added a 2024 Update to the Evidence Review section. Added SYMMETRY by LivaNova (an FDA approved VNS device for depression) to the Regulatory Status section. Added eight additional citations to the References section.
09/01/24	Policy renumbered from 7.01.20 Vagus Nerve Stimulation to 7.01.593 Vagus Nerve Stimulation, approved August 28, 2024. Added "not bipolar depression" to the criteria for vagus nerve stimulation for Major Depressive Disorder for additional clarification. Added "No acute or chronic psychosis" to the criteria for vagus nerve stimulation for Major Depressive Disorder for additional clarification. Added cessation of transcranial magnetic stimulation due to intolerable or incapacitating or dangerous side effects as an additional option for satisfying the requirement regarding a trial of transcranial magnetic stimulation for vagus nerve stimulation for Major Depressive Disorder. Added cessation of electroconvulsive therapy due to intolerable or incapacitating or potentially dangerous side effects as an additional option for satisfying the requirement regarding a trail of electroconvulsive therapy for vagus nerve stimulation for Major Depressive Disorder.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.