2.02.33	Phrenic Nerve Stimulation for Central Sleep Apnea		
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Section:	2.0 Medicine	**Page:**	Page 1 of 13

Policy Statement

The use of phrenic nerve stimulation for central sleep apnea is considered **investigational** in all situations.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Coding

The following CPT codes are specific for the remedē® System (Respicardia®, Inc; Minnetonka, MN) and may be used for this procedure:

- **0424T**: Insertion or replacement of neurostimulator system for treatment of central sleep apnea; complete system (transvenous placement of right or left stimulation lead, sensing lead, implantable pulse generator)
- **0425T:** Insertion or replacement of neurostimulator system for treatment of central sleep apnea; sensing lead only
- **0426T:** Insertion or replacement of neurostimulator system for treatment of central sleep apnea; stimulation lead only
- **0427T:** Insertion or replacement of neurostimulator system for treatment of central sleep apnea; pulse generator only
- **0428T:** Removal of neurostimulator system for treatment of central sleep apnea; pulse generator only
- **0429T:** Removal of neurostimulator system for treatment of central sleep apnea; sensing lead only
- **0430T:** Removal of neurostimulator system for treatment of central sleep apnea; stimulation lead only
- **0431T:** Removal and replacement of neurostimulator system for treatment of central sleep apnea, pulse generator only
- **0432T:** Repositioning of neurostimulator system for treatment of central sleep apnea; stimulation lead only
- **0433T**: Repositioning of neurostimulator system for treatment of central sleep apnea; sensing lead only
- **0434T**: Interrogation device evaluation implanted neurostimulator pulse generator system for central sleep apnea
- **0435T**: Programming device evaluation of implanted neurostimulator pulse generator system for central sleep apnea; single session
- **0436T**: Programming device evaluation of implanted neurostimulator pulse generator system for central sleep apnea; during sleep study

The following HCPCS code may be used for this procedure:

- **C1823**: Generator, neurostimulator (implantable), non-rechargeable, with transvenous sensing and stimulation leads

Description

Central sleep apnea (CSA) is characterized by sleep-disordered breathing due to diminished or absent respiratory effort. Central sleep apnea may be idiopathic or secondary (associated with a medical condition, drugs, or high altitude breathing). The use of positive airway pressure devices is currently the most common form of therapy for CSA. An implantable device that stimulates the phrenic nerve in the chest is a potential alternative treatment. The battery-

powered device sends signals to the diaphragm in order to stimulate breathing and normalize sleep-related breathing patterns.

Related Policies

- Diagnosis and Medical Management of Obstructive Sleep Apnea Syndrome
- Surgical Treatment of Snoring and Obstructive Sleep Apnea Syndrome

Benefit Application

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

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

Regulatory Status

In October 2017, the FDA approved the remede System (Respicardia, Inc; Minnetonka, MN) through the premarket approval application process. The approved indication is for treatment of moderate to severe CSA in adults. Follow-up will continue for 5 years in the post-approval study. FDA product code: PSR.

Rationale

Background

Central Sleep Apnea

Central sleep apnea (CSA) is characterized by repetitive cessation or decrease in both airflow and ventilatory effort during sleep. Central sleep apnea may be idiopathic or secondary (associated with a medical condition such as congestive heart failure, drugs, or high altitude breathing). Apneas associated with Cheyne-Stokes respiration are common among patients with heart failure (HF) or who have had strokes, and account for about half of the population with CSA. Central sleep apnea is less common than obstructive sleep apnea. Based on analyses of a large community-based cohort of participants 40 years of age and older in the Sleep Heart Health Study, the estimated prevalence of CSA and obstructive sleep apnea are 0.9% and 47.6%, respectively.[1] Risk factors for CSA include age (>65 years), male gender, history of HF, history of stroke, other medical conditions (acromegaly, renal failure, atrial fibrillation, low cervical tetraplegia, and primary mitochondrial diseases), and opioid use. Individuals with CSA have difficulty maintaining sleep and therefore experience excessive daytime sleepiness, poor concentration, and morning headaches, and are at higher risk for accidents and injuries.

Treatment

The goal of treatment is to normalize sleep-related breathing patterns. Because most cases of CSA are secondary to an underlying condition, central nervous system pathology, or medication side effects, treatment of the underlying condition or removal of the medication may improve CSA. Treatment recommendations differ depending on the classification of CSA as either hyperventilation-related (most common, including primary CSA and those relating to HF or high altitude breathing) or hypoventilation-related (less common, relating to central nervous system diseases or use of nervous system suppressing drugs such as opioids).

For patients with hyperventilation-related CSA, continuous positive airway pressure (CPAP) is considered first-line therapy. Due to CPAP discomfort, patient compliance may become an issue. Supplemental oxygen during sleep may be considered for patients experiencing hypoxia during sleep or who cannot tolerate CPAP. Patients with CSA due to HF with an ejection fraction >45%, and who are not responding with CPAP and oxygen therapy, may consider bilevel positive airway pressure or adaptive servo-ventilation (ASV) as second-line therapy. Bilevel positive airway pressure devices have 2 pressure settings, 1 for inhalation and 1 for exhalation. Adaptive servo-ventilation uses both inspiratory and expiratory pressure, and titrates the pressure to maintain adequate air movement. However, a clinical trial reported increased cardiovascular mortality with ASV in patients with CSA due to HF and with an ejection fraction <45%,[2,] and therefore, ASV is not recommended for this group.

For patients with hypoventilation-related CSA, first-line therapy is bilevel positive airway pressure.

Pharmacologic therapy with a respiratory stimulant may be recommended to patients with hyper- or hypoventilation CSA who do not benefit from positive airway pressure devices, though close monitoring is necessary due to the potential for adverse effects such as rapid heart rate, high blood pressure, and panic attacks.

Phrenic Nerve Stimulation

Several phrenic nerve stimulation systems are available for patients who are ventilator dependent. These systems stimulate the phrenic nerve in the chest, which sends signals to the diaphragm to restore a normal breathing pattern. Currently, there is 1 phrenic nerve stimulation device approved by the U.S. Food and Drug Administration (FDA) for CSA, the remede System (Respicardia, Inc.). A cardiologist implants the battery powered device under the skin in the right or left pectoral region using local anesthesia. The device has 2 leads, 1 to stimulate a phrenic nerve (either the left pericardiophrenic or right brachiocephalic vein) and 1 to sense breathing. The device runs on an algorithm that activates automatically at night when the patient is in a sleeping position, and suspends therapy when the patient sits up. Patient-specific changes in programming can be conducted externally by a programmer.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Phrenic Nerve Stimulation for Central Sleep Apnea

Clinical Context and Therapy Purpose

The purpose of phrenic nerve stimulation (PNS) in patients who have central sleep apnea (CSA) is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of PNS improve the net health outcome in patients with CSA compared with positive airway pressure or respiratory stimulation medication?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with CSA. Central sleep apnea is characterized by repetitive cessation or decrease in both airflow and ventilatory effort during sleep. Individuals with CSA have difficulty maintaining sleep and therefore experience excessive daytime sleepiness, poor concentration, and morning headaches, and are at higher risk for accidents and injuries.

Interventions

The therapy being considered is PNS. This system stimulates the phrenic nerve in the chest, which sends signals to the diaphragm to restore a normal breathing pattern. The device activates automatically when the patient is in a sleeping position and suspends therapy when the patient sits up.

Comparators

The current first-line therapy is positive airway pressure. There are several devices providing positive airway pressure (Table 1).

Table 1: Description of Positive Airway Pressure Devices

Device	Description	Comments
CPAP	continuous positive airway pressure	Considered first-line therapy for patients with hyperventilation-related CSA
BPAP	bilevel positive airway pressure (2 pressure settings - 1 for inhalation and 1 for exhalation)	Considered first-line therapy for patients with hypoventilation-related CSA
ASV	adaptive servo-ventilation (titrates the inspiratory and expiratory pressure)	Not recommended for patients with CSA with HF and a left ventricular ejection fraction <45%

CSA: central sleep apnea; HF: heart failure.

For patients who do not benefit from positive airway pressure devices, pharmacologic therapy with a respiratory stimulant may be recommended. Close monitoring is necessary due to the potential of adverse effects such as rapid heart rate, high blood pressure, and panic attacks.

Outcomes

Outcomes of interest include sleep quality metrics and quality of life measures. The Apnea-Hypopnea Index (AHI) is the number of apnea and hypopnea (events per hour of sleep, in which the apnea events last at least 10 seconds and are associated with decreased blood oxygenation. In adults, the AHI scale is: <5 AHI (normal); 5≥AHI<15 (mild); 15≥ AHI<30 (moderate); and ≥30 AHI (severe) per hour of sleep. Additional sleep metrics include the central apnea index (CAI, number of central apnea events per hour of sleep) and obstructive apnea index (OAI, number of obstructive apnea events per hour of sleep).

Subjective sleepiness can be measured by the Epworth Sleepiness Scale (ESS). The ESS is a short self-administered questionnaire that asks patients how likely they are to fall asleep (0="no chance" to 3="high chance") in 8 different situations (e.g., watching TV, sitting quietly in a car, or sitting and talking to someone). The scores are added, ranging from 0 to 24, with scores over 10 indicating excessive sleepiness and recommendation to seek medical attention. Quality of life

can be measured by Patient Global Assessment, which consists of a 7-point scale (1="markedly improved" to 7="markedly worsened").

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Randomized Controlled Trial

Costanzo et al (2015) provided background and methodologic details of the remedē System Pivotal Trial.[3] The trial is a prospective, multicenter, randomized, open-label controlled trial comparing transvenous unilateral phrenic nerve stimulation with no stimulation in patients with CSA of various etiologies (Table 2). All patients received implantation of the phrenic nerve stimulation system, with activation of the system after 1 month in the intervention group (n=73) and activation after 6 months in the control group (n=78). Activation is delayed 1 month after implantation to allow for lead healing. The primary efficacy endpoint was the percentage of patients achieving a reduction in AHI of 50%, as interpreted from polysomnography by an assessor blinded to the treatment arm. The reduction of 50% was based on assessments showing that a 50% reduction in AHI is associated with reduced mortality risk and is therefore clinically meaningful. Secondary endpoints include mean reductions in CAI, AHI, arousal index, oxygen desaturation index, and ESS. Of the 151 patients in the trial, 64% had heart failure (HF), 42% had atrial fibrillation, with a mean left ventricular ejection fraction of 39.6%.

Costanzo et al (2016) reported the 6-month per-protocol comparative results for the treatment and control groups (Table 3).[4] Twelve, 24-, and 36-month results for the intervention group are shown in Table 4. Adverse events were reported in 9% of the intervention group and 8% of the control group (for example, implant site infection, implant site hematoma, and lead dislodgement). Non-serious therapy-related discomfort was reported in 27 (37%) of the intervention group, with all but 1 case resolved by system reprogramming. At 6 months follow-up, 15 of the 73 (21%) patients in the treatment group were excluded due to no 6-month data: unrelated death, device explant, missed visit, and study exit (n=9), failed inclusion criteria (n=3), unsuccessful implant (n=2), and therapy programmed off (n=1).

At the 12-month follow-up, an additional 4 patients were lost due to unrelated death, device explant, patient refusal, and missed visits. Results from the remaining 54 patients in the intervention group at 12 months are summarized in Table 4.[5] Subgroup analyses showed consistent improvements in the percent experiencing more than 50% AHI reductions from treatment across all of the following subgroups: age (<65, 65 to <75, and >75), gender, HF (yes/no), defibrillator (yes/no), AHI severity (moderate/severe), and atrial fibrillation (yes/no). Follow-up at 24 months was available for 42 patients in the treatment group, while 22 patients in the treatment group and 28 patients in the control arm reached 36 month follow-up at the time of study closure.[6] Central apnea events remained low throughout follow-up with a median time to battery depletion of 39.4 months. Serious adverse events related to the implant procedure, device, or delivered therapy occurred in 10% of patients through the 24-month visit. All were reported to be resolved with remedē System revisions or programming. At the 5-year follow-up (N=52), AHI events remained low (median=17 events/hour) and ESS improved by a median of 3 points.[7] A total of 14% of patients reported a serious adverse event, but no long-term harm or device-related death occurred.

Table 2. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Intervention	**Control**
Costanzo (2015) [3,]	Germany, Poland, United States	31	2013-2015	Adult patients with moderate to severe CSA of various etiologies confirmed by PSG[a] and medically stable[b]	Implanted phrenic nerve stimulator (remedē system) activated at 1 month postprocedure (n=73, 58 analyzed)	Implanted phrenic nerve stimulator (remedē system) activated at 6 months postprocedure (n=78, 73 analyzed)

AHI: apnea-hypopnea index; CAI: central apnea index; CSA: central sleep apnea; OAI: obstructive apnea index; PSG: polysomnography; RCT: randomized controlled trial.
[a] AHI >20 events/hr; CAI >50% of all apneas, with >30 central apnea events; OAI <20% of all AHI.
[b] For 30 days prior to baseline testing: no hospitalizations for illness, no breathing mask-based therapy, and on stable medications and therapies.

Table 3. Summary of Key RCT Results[a]

Study	Baseline	6-Month	Change from Baseline	Between Group Difference
Costanzo (2015, 2016)[3,4,]				
>50% AHI reduction				
Treatment	NA	51% (39% to 64%)	NA	
Control	NA	11% (5% to 20%)	NA	41% (25% to 54%)
AHI				
Treatment	49.7 ± 18.9	25.9 ± 20.5	-23.9 ± 18.6	
Control	43.9 ± 17.3	45.0 ± 20.3	1.1 ± 17.6	-25.0 ± 18.1
CAI				
Treatment	31.7 ± 18.6	6.0 ± 9.2	-25.7 ± 18.0	
Control	26.2 ± 16.2	23.3 ± 17.4	-2.9 ± 17.7	-22.8 ± 17.8
PGA[b]				
Treatment	NA	60% (47% to 73%)	NA	
Control	NA	6% (2% to 14%)	NA	55% (40% to 68%)
ESS				
Treatment	10.7 ± 5.3	7.1 ± 4.1	-3.6 ± 5.6	
Control	9.3 ± 5.7	9.4 ± 6.1	0.1 ± 4.5	-3.7 ± 5.0

AHI: Apnea-Hypopnea Index; CAI: central apnea index; CI: confidence interval; ESS: Epworth Sleepiness Scale; NA: not applicable; PGA: Patient Global Assessment; RCT: randomized controlled trial.
[a] Data are presented as either % (95% CIs) or mean (standard deviation).
[b] Patients with marked or moderate improvement in 7-point quality of life scale.

Costanzo et al (2018) provided 12-month follow-up results for the subgroup of patients in the Pivotal Trial who had HF.[8,] Pooling of results was possible by using 6 and 12-month data from the intervention group and 12 and 18-month data from the control group (the phrenic nerve stimulator was activated in the control group 6 months after implantation). At baseline, 96 of the patients in the trial had HF. By the 6 month follow-up, there had been 4 deaths, 1 explant, and 5 withdrew from the study. By the 12-month follow-up, there had been an additional 5 deaths, 1 ex plant, and 1 withdrawal, as well as 4 missing the final visit. Results at 6 and 12 months follow-up for the subgroup of patients with HF are summarized in Table 4.

Table 4. Summary of Treatment Arm Results at Follow-up

	Baseline	6-Month	12-Month	24-Month Median [IQR]	36-Month Median [IQR]	Paired Change, Baseline to 12-Month Mean (95% CI)
Costanzo (2018)[5,6,]						

	Baseline	6-Month	12-Month	24-Month Median [IQR]	36-Month Median [IQR]	Paired Change, Baseline to 12-Month Mean (95% CI)
Treatment arm alone, N	58	58	54	42	22[a]	54
AHI	49.7 ± 18.9	25.9 ± 20.5	23.0 ± 21.9	16 [7, 37]	13 [8, 37]	-25.4 (-44.4 to -11.4)
CAI	31.7 ± 18.6	6.0 ± 9.2	3.4 ± 6.9	0 [0, 3]	1 [0, 3]	-26.0 (-40.2 to -14.6)
OAI	2.1 ± 2.2	6.3 ± 7.0	4.5 ± 5.1	3 [0, 8]	4 [1, 11]	0.9 (-0.5 to 4.4)
PGA[b]	NA	60% (47% to 72%)	60% (47% to 72%)			NA
ESS	10.7 ± 5.3	7.1 ± 4.1	6.5 ± 3.5			-4.0 (-7.0 to -1.0)
Costanzo (2018)[8],						
Pooled HF subgroup, N	96	86	75			79
>50% AHI reduction	NA	53% (42% to 64%)	57% (45% to 68%)			NA
AHI	47.1 ± 18.5	25.2 ± 14.2	3.5 ± 6.5			-19.9 (-34.6 to -11.8)
CAI	26.2 ± 17.7	4.1 ± 6.0	3.4 ± 6.9			-26.0 (-40.2 to -14.6)
PGA[b]	NA	58% (NR)	55% (NR)			NA
ESS	8.9 ± 5.1	6.2 ± 4.1	6.1 ± 3.7			-2.0 (-5.0 to 0.0)

AHI: Apnea-Hypopnea Index; CAI: central apnea index; CI: confidence interval; ESS: Epworth Sleepiness Scale; HF: heart failure; IQR; interquartile range; NA: not applicable; NR: not reported; OAI: obstructive apnea index; PGA: Patient Global Assessment.
[a] Patients in the treatment group who had reached 36 months of follow-up prior to study closure.
[b] Patients with marked or moderate improvement in 7-point quality of life scale.

Non-Comparative Studies

Abraham et al (2015)[9], and Jagielski et al (2016)[10], presented 6-month and 12-month results from a U.S. Food and Drug Administration regulated feasibility study of 47 patients with CSA of various etiologies who received phrenic nerve stimulation with the remedē system (Table 5). Sleep disorder parameters were measured by polysomnography, through 12 months, with optional sleep testing at 18 months. Quality of life was measured on a 7-point scale, with patients answering the question, "How do you feel today compared with how you felt before having your device implanted?" Central sleep apnea etiologies included HF (79%), other cardiac (13%), and opiate use (4%). Three deaths occurred during the study period, none attributed to the intervention. Five experienced serious adverse events, 3 at the beginning of the study (2 [hematoma, migraine] due to implantation procedure and 1 chest pain), and 2 during 12-months of follow-up (pocket perforation and lead failure). A summary of sleep metric and quality of life results are presented in Table 6.

Table 5. Summary of Non-Comparative Study Characteristics

Study	Country	Participants	Follow-Up
Abraham (2015)[9], and Jagielski (2016)[10],	Germany, Italy, Poland, United States	Adult patients with a history of sleep apnea, predominantly CSA rather than OSA, and AHI >20 events/hour	12 months (optional 18 months)

AHI: Apnea-Hypopnea Index; CSA: central sleep apnea; OSA: obstructive sleep apnea.

Table 6. Summary of Non-Comparative Study Results[9,10,]

Outcome	Baseline (N =47) mean SD	3 months (N =47) mean SD	6 months (N =41) mean SD	12 months (N =41) mean SD	18 months (N =17) mean SD
AHI, events/hour	49.9 ± 14.6	22.4 ± 13.6	23.8 ± 13.1	27.5 ± 18.3[b]	24.9 ± 13.5[b]
CAI, events/hour	28.0 ± 14.2	4.7 ± 8.6	4.6 ± 7.4	6.0 ± 9.2[b]	4.8 ± 5.8[b]
OAI, events/hour	3.0 ± 2.9	3.9 ± 4.7	3.9 ± 5.4	4.5 ± 6.0	5.6 ± 6.2
4% ODI, events/hour	45.2 ± 18.7	21.6 ± 13.7	23.1 ± 13.1	26.9 ± 18.0[b]	25.2 ± 13.7[b]
Arousal index, events/hour	36.2 ± 18.8	23.7 ± 10.6	25.1 ± 12.5	32.1 ± 15.2	26.8 ± 9.2
QOL, % improvement from baseline[a]	NA	70.8%	75.6%	83.0%	NR

AHI: Apnea-Hypopnea Index; CAI: central apnea index; NA: not applicable; NR: not reported; OAI: obstructive apnea index; ODI: oxygen desaturation index; QOL: quality of life; SD: standard deviation.
a Patients with marked or moderate improvement in 7-point quality of life scale.
b p<.006 compared to baseline.

Fox et al (2017) presented data on the long-term durability of the remedē System, measuring battery lifetime, device exchangeability, lead position stability, and surgical accessibility.[11,] Three consecutive patients, mean age 75.7 years, with CSA and HF with preserved ejection fraction were implanted with the remedē phrenic nerve stimulation device due to intolerability of conventional mask therapy. Implantation occurred in 2011 and the patients were followed for 4 years. Mean battery life duration was 4.2 ± 0.2 years. Therapy was well tolerated by the patients, with improvements sustained in AHI, oxygen desaturation index, and quality of life (measured by ESS). Mean device replacement procedure time was 23 minutes, under local anesthesia, with a 2-day hospital stay.

Section Summary: Phrenic Nerve Stimulation for Central Sleep Apnea
Evidence for the use of phrenic nerve stimulation therapy for the treatment of CSA consists of 1 RCT and observational studies. In the RCT, all patients were implanted with the phrenic nerve stimulation device, with the device activated in the intervention group at 1 month postimplantation and activated in the control group at 6 months postimplantation. The RCT provided 6 month comparative analyses showing significant improvements in sleep metrics as well as quality of life measures among patients with the activated stimulation device compared with patients receiving the inactivated device. Patients in the activated device arm were followed for 12 months, with analyses showing sustained significant improvements from baseline in sleep metrics and quality of life. A subgroup analysis was conducted on the subgroup of patients with HF, combining 6- and 12-month data from patients in the intervention group and 12 and 18-month data from the control group. Results from the subgroup analysis of patients with HF showed significant improvements in sleep metrics and quality of life at 12 months. An invasive procedure would typically be considered appropriate only if non-surgical treatments had failed, but there is very limited data in which phrenic nerve stimulation was evaluated in patients who had failed the current standard of care, positive airway pressure, or respiratory stimulant medication.

Summary of Evidence
For individuals with CSA who receive phrenic nerve stimulation, the evidence includes 1 RCT and observational studies. Relevant outcomes are change in disease status, functional outcomes, and quality of life. The RCT compared the use of phrenic nerve stimulation to no treatment among patients with CSA of various etiologies. All patients received implantation of the phrenic nerve stimulation system, with activation of the system after 1 month in the intervention group and activation after 6 months in the control group. Activation is delayed 1 month after implantation to allow for lead healing. At 6 months follow-up, the patients with the activated device experienced significant improvements in several sleep metrics and quality of life measures. At 12 months follow-up, patients in the activated device arm showed sustained significant improvements from baseline in sleep metrics and quality of life. A subgroup analysis of

patients with HF combined 6- and 12-month data from patients in the intervention group and 12- and 18-month data from the control group. Results from this subgroup analysis showed significant improvements in sleep metrics and quality of life at 12 months compared with baseline. Results from observational studies supported the results of the RCT. An invasive procedure would typically be considered only if non-surgical treatments had failed, but there is limited data in which phrenic nerve stimulation was evaluated in patients who had failed the current standard of care, positive airway pressure, or respiratory stimulant medication. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' 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 Sleep Medicine
The American Academy of Sleep Medicine (2012) published a guideline on the treatment of central sleep apnea (CSA), based on the results of a literature review and meta-analysis.[12,] Moderate evidence supported the use of continuous positive airway pressure or adaptive servo-ventilation to treat CSA related to congestive heart failure. Limited evidence was available for the use of positive airway pressure therapy (continuous positive airway pressure, bilevel positive airway pressure, adaptive servo-ventilation) to treat primary CSA; however, there is a potential for ameliorating central respiratory events, the risks are low, and the therapies are readily available. The use of phrenic nerve stimulation devices were not discussed in the guideline. An update to the guideline, published in 2016,[13,] adjusted the previous guideline, to warn that adaptive servo-ventilation is not recommended for individuals with CSA related to congestive heart failure with an ejection fraction <45%. The use of phrenic nerve stimulation as a treatment option was not addressed in the guideline.

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

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers. A 2019 review by National Government Services, Inc concluded that there is insufficient evidence to show that transvenous phrenic neurostimulation is reasonable and necessary for the treatment of CSA in the Medicare population (L37929).[14,] This policy was retired on January 27, 2022.
Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in March 2022 did not identify any ongoing or unpublished trials that would likely influence this review.

References

1. Donovan LM, Kapur VK. Prevalence and Characteristics of Central Compared to Obstructive Sleep Apnea: Analyses from the Sleep Heart Health Study Cohort. Sleep. Jul 01 2016; 39(7): 1353-9. PMID 27166235

2. Cowie MR, Woehrle H, Wegscheider K, et al. Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure. N Engl J Med. Sep 17 2015; 373(12): 1095-105. PMID 26323938
3. Costanzo MR, Augostini R, Goldberg LR, et al. Design of the remede System Pivotal Trial: A Prospective, Randomized Study in the Use of Respiratory Rhythm Management to Treat Central Sleep Apnea. J Card Fail. Nov 2015; 21(11): 892-902. PMID 26432647
4. Costanzo MR, Ponikowski P, Javaheri S, et al. Transvenous neurostimulation for central sleep apnoea: a randomised controlled trial. Lancet. Sep 03 2016; 388(10048): 974-82. PMID 27598679
5. Costanzo MR, Ponikowski P, Javaheri S, et al. Sustained 12 Month Benefit of Phrenic Nerve Stimulation for Central Sleep Apnea. Am J Cardiol. Jun 01 2018; 121(11): 1400-1408. PMID 29735217
6. Fox H, Oldenburg O, Javaheri S, et al. Long-term efficacy and safety of phrenic nerve stimulation for the treatment of central sleep apnea. Sleep. Oct 21 2019; 42(11). PMID 31634407
7. Costanzo MR, Javaheri S, Ponikowski P, et al. Transvenous Phrenic Nerve Stimulation for Treatment of Central Sleep Apnea: Five-Year Safety and Efficacy Outcomes. Nat Sci Sleep. 2021; 13: 515-526. PMID 33953626
8. Costanzo MR, Ponikowski P, Coats A, et al. Phrenic nerve stimulation to treat patients with central sleep apnoea and heart failure. Eur J Heart Fail. Dec 2018; 20(12): 1746-1754. PMID 30303611
9. Abraham WT, Jagielski D, Oldenburg O, et al. Phrenic nerve stimulation for the treatment of central sleep apnea. JACC Heart Fail. May 2015; 3(5): 360-369. PMID 25770408
10. Jagielski D, Ponikowski P, Augostini R, et al. Transvenous stimulation of the phrenic nerve for the treatment of central sleep apnoea: 12 months' experience with the remede (R) System. Eur J Heart Fail. Nov 2016; 18(11): 1386-1393. PMID 27373452
11. Fox H, Bitter T, Horstkotte D, et al. Long-Term Experience with First-Generation Implantable Neurostimulation Device in Central Sleep Apnea Treatment. Pacing Clin Electrophysiol. May 2017; 40(5): 498-503. PMID 28211952
12. Aurora RN, Chowdhuri S, Ramar K, et al. The treatment of central sleep apnea syndromes in adults: practice parameters with an evidence-based literature review and meta-analyses. Sleep. Jan 01 2012; 35(1): 17-40. PMID 22215916
13. Aurora RN, Bista SR, Casey KR, et al. Updated Adaptive Servo-Ventilation Recommendations for the 2012 AASM Guideline: "The Treatment of Central Sleep Apnea Syndromes in Adults: Practice Parameters with an Evidence-Based Literature Review and Meta-Analyses". J Clin Sleep Med. May 15 2016; 12(5): 757-61. PMID 27092695
14. Centers for Medicare and Medicaid Services. Local Coverage Determination: Transvenous Phrenic Nerve Stimulation in the Treatment of Central Sleep Apnea (A57548) 2019 https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=37929. Last Accessed March 21, 2022.

Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide

additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0424T	Insertion or replacement of neurostimulator system for treatment of central sleep apnea; complete system (transvenous placement of right or left stimulation lead, sensing lead, implantable pulse generator)
	0425T	Insertion or replacement of neurostimulator system for treatment of central sleep apnea; sensing lead only
	0426T	Insertion or replacement of neurostimulator system for treatment of central sleep apnea; stimulation lead only
	0427T	Insertion or replacement of neurostimulator system for treatment of central sleep apnea; pulse generator only
	0428T	Removal of neurostimulator system for treatment of central sleep apnea; pulse generator only
	0429T	Removal of neurostimulator system for treatment of central sleep apnea; sensing lead only
	0430T	Removal of neurostimulator system for treatment of central sleep apnea; stimulation lead only
	0431T	Removal and replacement of neurostimulator system for treatment of central sleep apnea, pulse generator only
	0432T	Repositioning of neurostimulator system for treatment of central sleep apnea; stimulation lead only
	0433T	Repositioning of neurostimulator system for treatment of central sleep apnea; sensing lead only
	0434T	Interrogation device evaluation implanted neurostimulator pulse generator system for central sleep apnea
	0435T	Programming device evaluation of implanted neurostimulator pulse generator system for central sleep apnea; single session
	0436T	Programming device evaluation of implanted neurostimulator pulse generator system for central sleep apnea; during sleep study
HCPCS	C1823	Generator, neurostimulator (implantable), non-rechargeable, with transvenous sensing and stimulation leads

Policy History

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

Effective Date	Action
07/01/2019	BCBSA Medical Policy adoption
07/01/2020	Annual review. No change to policy statement. Literature review updated.
07/01/2021	Annual review. No change to policy statement. Literature review updated.
07/01/2022	Annual review. No change to policy statement. Literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and

effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

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

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

Prior Authorization Requirements (as applicable to your plan)

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

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

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

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Phrenic Nerve Stimulation for Central Sleep Apnea 2.02.33 **Policy Statement:** The use of phrenic nerve stimulation for central sleep apnea is considered **investigational** in all situations.	**Phrenic Nerve Stimulation for Central Sleep Apnea 2.02.33** **Policy Statement:** The use of phrenic nerve stimulation for central sleep apnea is considered **investigational** in all situations.