Medical Policy Manual Surgery, Policy No. 212

Phrenic Nerve Stimulation for Central Sleep Apnea

Effective: August 1, 2025

Next Review: June 2026
Last Review: June 2025

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Central sleep apnea (CSA) is characterized by repetitive cessation or decrease in both airflow and ventilatory effort during sleep. The goal of phrenic nerve stimulation treatment is to normalize sleep-related breathing patterns.

MEDICAL POLICY CRITERIA

Note: This policy only addresses phrenic nerve stimulation for *central* sleep apnea (CSA). It does not address hypoglossal nerve stimulation for *obstructive* sleep apnea (OSA). See Cross References section below.

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

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Noninvasive Ventilators in the Home Setting, Durable Medical Equipment, Policy No. 87
2. Surgeries for Snoring, Obstructive Sleep Apnea Syndrome, and Upper Airway Resistance Syndrome, Surgery, Policy No. 166
3. Hypoglossal Nerve Stimulation, Surgery, Policy No.215

BACKGROUND

CENTRAL SLEEP APNEA

Central sleep apnea (CSA) is characterized by repetitive cessation or decrease in both airflow and ventilatory effort during sleep. CSA may be idiopathic or secondary (associated with Cheyne-Stokes breathing, a medical condition, drugs, or high altitude breathing. Cheyne-Stokes breathing is common among patients with heart failure or who have had strokes, and accounts for about half of the population with CSA. CSA is less common than obstructive sleep apnea (OSA). Based on analyses of a large community-based cohort in the Sleep Heart Health Study, the estimated prevalences of CSA and OSA are 0.9% and 47.6%, respectively.[1] Risk factors for CSA include age (>65 years), male gender, history of heart failure, 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, 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 heart failure 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 heart failure and with an ejection fraction >45% and who are not responding with CPAP and oxygen therapy, may consider bilevel positive airway pressure (BPAP) or adaptive servo-ventilation (ASV) as second-line therapy. BPAP devices have two pressure settings, one for inhalation and one for exhalation. ASV 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 heart failure 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 BPAP.

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

Currently, there is one phrenic nerve stimulation device approved by the Food and Drug Administration (FDA), the remedē System (Respicardia, Inc.). The remedē System is an

implantable device that stimulates the phrenic nerve in the chest which sends signals to the diaphragm to restore a normal breathing pattern. A cardiologist implants the battery powered device under the skin in the right or left pectoral region. The procedure is conducted using local anesthesia. The device has two leads, one to stimulate a phrenic nerve (either the left pericardiophrenic or right brachiocephalic vein) and one 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.

REGULATORY STATUS

In October 2017, the FDA granted approval for the remedē System (Respicardia, Inc; Minnetonka, MN) through the premarket approval application process. The approved indication is for treatment of moderate to severe central sleep apnea in adults. Product code: PSR.

EVIDENCE SUMMARY

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). Additional sleep metrics include 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).

Quality of life outcomes can be measured by the Epworth Sleepiness Scale (ESS) or a Patient Global Assessment. 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.

SYSTEMATIC REVIEWS

Luni (2020) reported a meta-analysis of five studies (n=204) evaluating the efficacy of transvenous neurostimulation of the phrenic nerve for central sleep apnea.[3] An analysis of the pooled data demonstrated a reduction of mean AHI in the stimulation group compared to the control group by 26.7 events/hour (95% CI -31.99 to -21.46, p 0.00), and a mean AHI difference of -22.47. Compared with the control group, the mean reduction in the oxygen desaturation index of 4% or more was decreased in the stimulation group by -24.16 events/hour (95% CI -26.20 to -22.12, p 0.00).

RANDOMIZED CONTROLLED TRIAL

Costanzo (2015) provided background and methodologic details of the remedē System Pivotal Trial.[4] 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 1). All patients received implantation of the phrenic nerve stimulation system, with activation of the system after one month in the intervention group (n=73) and activation after six months in the control group (n=78). Activation is delayed one month after implantation to allow for lead healing. The primary efficacy endpoint is percentage of patients

achieving a reduction in Apnea-Hypopnea Index (AHI) of 50%, as interpreted from polysomnography by an assessor blinded to 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, OD14, and Epworth Sleepiness Scale. Quality of life is measured by Patient Global Assessment (PGA), which consists of a 7-point scale (1="markedly improved" to 7="markedly worsened"). Of the 151 patients in the trial, 64% had heart failure, 42% had atrial fibrillation, and a mean left ventricular ejection fraction of 39.6. Six-month per protocol comparative results for the treatment and control groups were published in 2016 by Costanzo .[5] 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 one case resolved by system reprogramming.

Costanzo (2018) provided 12 months followup results for the intervention arm.[6] At six months followup, 15 of the 73 (21%) in the treatment group were excluded due to no six-month data (n=9: unrelated death, device explant, missed visit, study exit), failed inclusion criteria (n=3), unsuccessful implant (n=2), therapy programmed off (n=1). At 12 months followup, an additional four patients were lost due to unrelated death, device explant, patient refusal, and missed visit. Results from the remaining 54 patients in the intervention group are summarized in Table 3. Subgroup analyses showed consistent improvements in percent experiencing >50% AHI reductions from treatment across all of the following subgroups: age (<65, 65 to <75, and >75), gender, heart failure (yes/no), defibrillator (yes/no), AHI severity (moderate/severe), and atrial fibrillation (yes/no).

Another publication by Costanzo in 2018 provided 12-months follow-up results for the subgroup of patients in the Pivotal Trial who had heart failure.[7] 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 six months after implantation). At baseline, 96 of the patients in the trial had heart failure. By the six-month followup, there had been four deaths, one explant, and five withdrew from the study. By the 12-month followup, there had been an additional five deaths, one implant, and one withdrawal, as well as four missing the final visit. Results at 6 and 12 months followup for the subgroup of patients with heart failure are summarized in Table 2.

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 had reached 36 month follow-up at the time of study closure.[8] Central apnea events remained low throughout follow-up with a median time to battery depletion of 39.4 months. Median AHI at 24 months and 36 months was 16 and 13, respectively. 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.

Five-year outcomes of the Pivotal Trial were published in 2021.[9] Patients in the treatment group and those in the control group, who had therapy activated after the primary endpoint assessment at the six-month visit, were pooled. The 42 patients evaluated for five-year outcomes had a change from baseline of -22 for AHI ($p<0.001$), -23 for CAI ($p<0.001$), 1 for OAI ($p=0.003$), and -5 for ESS ($p=0.008$). Serious adverse events related to the implant procedure, device, or delivered therapy occurred in 15% of patients through the five-year visit, none of which caused long-term harm.

An analysis of the pivotal trial data for safety and efficacy of TPNS in patients with concomitant cardiovascular implantable electronic devices (CIEDs) was reported by Nayak (2020).[10] Of the 151 initially enrolled patients, 64 had a concomitant CIED. There was no difference in safety or efficacy between patients with and without CIEDs.

Table 1. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Intervention	Control
Costanzo (2015)[4]	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 (remede system) activated at 1 month postprocedure (n=73)	Implanted phrenic nerve stimulator (remede system) activated at 6 months postprocedure (N=78)

[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.
AHI: apnea-hypopnea index; CSA: central sleep apnea; PSG: polysomnography.

Table 2. Summary of Key RCT Results

Study	Baseline	6-Month	Change from Baseline	Between Group Difference
Costanzo (2018)[5]				
>50% AHI reduction				
Treatment, n=58	NA	51% (39% to 64%)	NA	
Control, n=73	NA	11% (5% to 20%)	NA	41% (25% to 54%)
AHI				
Treatment, n=58	49.7 ± 18.9	25.9 ± 20.5	-23.9 ± 18.6	
Control, n=73	43.9 ± 17.3	45.0 ± 20.3	1.1 ± 17.6	-25.0 ± 18.1
CAI				
Treatment, n=58	31.7 ± 18.6	6.0 ± 9.2	-25.7 ± 18.0	
Control, n=73	26.2 ± 16.2	23.3 ± 17.4	-2.9 ± 17.7	-22.8 ± 17.8
PGA				
Treatment, n=58	NA	60% (47% to 73%)	NA	
Control, n=73	NA	6% (2% to 14%)	NA	55% (40% to 68%)
ESS				
Treatment, n=58	10.7 ± 5.3	7.1 ± 4.1	-3.6 ± 5.6	
Control, n=73	9.3 ± 5.7	9.4 ± 6.1	0.1 ± 4.5	-3.7 ± 5.0
	Baseline	**6-Month**	**12-Month**	**Paired Change, Baseline to 12-Month Mean (95% CI)**
Costanzo (2018)[6]				
Treatment arm alone, N	58	58	54	54
AHI	49.7 ± 18.9	25.9 ± 20.5	23.0 ± 21.9	-25.4 (-44.4 to -11.4)
CAI	31.7 ± 18.6	6.0 ± 9.2	3.4 ± 6.9	-26.0 (-40.2 to -14.6)
OAI	2.1 + 2.2	6.3 + 7.0	4.5 + 5.1	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)

Study	Baseline	6-Month	Change from Baseline	Between Group Difference
Costanzo (2018)[7]				
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)

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

An analysis of the Pivotal Trial data to compare PAP-naïve and prior PAP-treated patients was completed by Schwartz (2021).[11] At baseline, CSA was more severe and symptomatic in the PAP-treated vs. PAP-naïve group (median AHI 52/h vs. 38, central apnea index (CAI) 32/h vs. 18, ESS 13 vs. 10, fatigue severity scale 5.2 vs. 4.5). Active therapy resulted in statistically significant improvements in polysomnographic metrics ($p<0.001$ for AHI, 4% ODI, arousal index, and CAI), with little or no change in the inactive control group. Of PAP-treated and PAP-naïve patients, 98% and 94% indicated they would undergo the implant again.

Baumert (2023) published an analysis of effect of transvenous phrenic nerve stimulation (TPNS) on the composition of the nocturnal hypoxemic burden in patients with CSA using data from the Pivotal Trial.[12] TPNS titrated to reduce respiratory events significantly reduced the ODI in the treatment group more than the control group (-15.85 h-1 ± 1.99, +1.32 h-1 ± 1.85; $p < 0001$) and shortened the relative T90 duration by -3.81 percentage points ± 1.23 vs. 0.49 percentage points ± 1.14 increase ($p = 0.012$). This shortening of T90 was primarily accomplished by reducing the brief cyclic desaturations (T90desaturation: -4.32 percentage points ± 0.98 vs. 0.52 percentage points ± 0.91, $p = 0.0004$) while notable non-specific drifts in SpO2 remained unchanged (T90 non-specific: 0.18 percentage points ± 0.62 vs. -0.13 percentage points ± 0.57; $p = 0.72$). The authors conclude that TPNS reduces the nocturnal hypoxemic burden due to sleep-disordered breathing, and that a considerable nocturnal hypoxemic burden from other sources remains.

Baumert (2023) also published a separate analysis of effect of transvenous phrenic nerve stimulation (TPNS) on nocturnal heart rate perturbations in patients with CSA using data from the Pivotal Trial.[13] TPNS titrated to reduce respiratory events is associated with reduced cyclical heart rate variations in the very low-frequency domain across REM (VLFI: 4.12 ±0.79 % vs. 6.87 ± 0.82 %, $p = 0.02$) and NREM sleep (VLFI: 5.05 ± 0.68 % vs. 6.74 ± 0.70 %, $p = 0.08$) compared to the control group. Low-frequency oscillations were reduced in the treatment arm in REM ($p=0.02$) and NREM sleep ($p=0.03$). The authors concluded that long-term follow-up studies are needed to determine if the reduction in heart rate perturbation by TPNS translates to cardiovascular mortality reduction.

Hill (2023) conducted a subgroup analysis in individuals with CSA and HF (n=75) from the Pivotal Trial, investigating the effect of treatment on sleep, quality of life, and symptoms between baseline and 12 months using self-reported questionnaires.[14] Improvements were

seen in 69% of individuals in ESS scores, 60% of individuals in Minnesota Living with Heart Failure Questionnaire (MLHFQ) scores, and 53% of individuals in Fatigue Severity Score (FSS) scores.

Samii (2024) published a post hoc analysis of the remedē System Pivotal Trial aimed to determine sex-specific differences in the safety and effectiveness of treating moderate to severe CSA in adults with transvenous phrenic nerve stimulation (TPNS).[15] Women (n = 16) experienced improvement in CSA metrics that were comparable to the benefits experienced by men (n = 135), with central apneas being practically eliminated post TPNS. Women experienced improvement in sleep quality and architecture that was comparable to men post TPNS. While women had lower baseline apnea hypopnea index than men, their quality of life was worse at baseline. Additionally, women reported a 25-percentage point greater improvement in quality of life compared to men after 12 months of TPNS therapy. TPNS was found to be safe in women, with no related serious adverse events through 12 months post-implant, while men had a low rate of 10%. The women in this study had less prevalent and less severe CSA than men and they were more likely to report reduced quality of life.

Abraham (2024) conducted a post hoc, retrospective, subgroup analysis of patients with heart failure from remedē System Pivotal Trial (n=96).[16] The analysis used the win ratio (WR) hierarchy to compare all patients in the treatment group (n=48) to the control group (n=48). Five subjects in the treatment group exited the trial prior to therapy initiation and were excluded from the WR analysis. The WR hierarchy included three components: longest survival, lowest heart failure (HF) hospitalization rate, and a ≥2-category difference in Patient Global Assessment (PGA) at 6 months. They found that more patients in the treatment group experienced clinical benefit compared with the control group (WR: 4.92; 95% CI: 2.27 to 10.63; p<.0001). The authors noted limitations including the retrospective nature of the analysis, the small number of subjects, and the potential impact of new HF treatments on the applicability of the results.

NON-COMPARATIVE STUDIES

Fox (2017) presented data on long term durability of the remedē System, measuring battery lifetime, device exchangeability, lead position stability, and surgical accessibility.[17] Three consecutive patients, mean age 75.7 years, with CSA and HF with preserved ejection fraction were implanted with the remede phrenic nerve stimulation device due to intolerability of conventional mask therapy. Implantation occurred in 2011 and the patients were followed for four 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 two-day hospital stay.

Abraham (2015)[18] and Jagielski (2016)[19] presented 6-month and 12-month results from a cohort of 47 patients with CSA of various etiologies who received phrenic nerve stimulation with the remedē system. Sleep disorder parameters were measured by polysomnography, through 12 months, with an optional sleep testing at 18 months. . Quality of life was measured on a seven-point scale, with patients answering the question, "How do you feel today compared with how you felt before having your device implanted?" CSA etiologies included heart failure (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, three at the beginning of the study (two [hematoma, migraine] due to implantation procedure

and one chest pain), and two during 12-month followup (pocket perforation and lead failure). A summary of sleep metric and quality of life results are presented in Table 3.

Table 3. Summary of Non-Comparative Study Results[18, 19]

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 baselinea	NA	70.8%	75.6%	83.0%	NR

[a] Patients with marked or moderate improvement in 7-point quality of life scale
[b] p<0.006 compared to baseline
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; RCT: randomized controlled trial; SD: standard deviation.

SUMMARY OF EVIDENCE

For individuals with central sleep apnea who receive phrenic nerve stimulation, the evidence includes one randomized controlled trial (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 central sleep apnea of various etiologies. All patients received implantation of the phrenic nerve stimulation system, with activation of the system after one month in the intervention group and activation after six months in the control group. Activation is delayed one month after implantation to allow for lead healing. At six months follow-up, the patients with the activated device experienced significant improvements in several sleep metrics and quality of life measures. At 12 months followup, 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 heart failure 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 analyses 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. No RCTs were identified in which phrenic nerve stimulation was compared with the current standard of care, positive airway pressure or respiratory stimulant medication. 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

PRACTICE GUIDELINE SUMMARY

No evidence-based clinical practice guidelines were identified with recommendations regarding the use of phrenic nerve stimulation for central sleep apnea.

SUMMARY

There is not enough research to know if or how well phrenic nerve stimulation works to treat central sleep apnea. This does not mean that it does not work, but more research is needed to know. There are no clinical practice guidelines based on research that recommend phrenic nerve stimulation for this population. Therefore, the use of phrenic nerve stimulation for the treatment of central sleep apnea is considered investigational.

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.* 2016;39:1353-9. PMID: 27166235
2. Cowie MR, Woehrle H, Wegscheider K, et al. Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure. *The New England journal of medicine.* 2015;373(12):1095-105. PMID: 26323938
3. Luni FK, Daniels J, Link MS, et al. Meta-analysis of Usefulness of Phrenic Nerve Stimulation in Central Sleep Apnea. *The American journal of cardiology.* 2020;125(11):1738-44. PMID: 32295701
4. 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. *Journal of cardiac failure.* 2015;21(11):892-902. PMID: 26432647
5. Costanzo MR, Ponikowski P, Javaheri S, et al. Transvenous neurostimulation for central sleep apnoea: a randomised controlled trial. *Lancet.* 2016;388(10048):974-82. PMID: 27598679
6. Costanzo MR, Ponikowski P, Javaheri S, et al. Sustained 12 Month Benefit of Phrenic Nerve Stimulation for Central Sleep Apnea. *The American journal of cardiology.* 2018;121(11):1400-08. PMID: 29735217
7. Costanzo MR, Ponikowski P, Coats A, et al. Phrenic nerve stimulation to treat patients with central sleep apnoea and heart failure. *European journal of heart failure.* 2018;20(12):1746-54. PMID: 30303611
8. 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.* 2019;42(11). PMID: 31634407
9. 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;13:515-26. PMID: 33953626
10. Nayak HM, Patel R, McKane S, et al. Transvenous Phrenic Nerve Stimulation for Central Sleep Apnea is Safe and Effective in Patients with Concomitant Cardiac Devices. *Heart rhythm.* 2020. PMID: 32619739
11. Schwartz AR, Goldberg LR, McKane S, et al. Transvenous phrenic nerve stimulation improves central sleep apnea, sleep quality, and quality of life regardless of prior positive airway pressure treatment. *Sleep Breath.* 2021. PMID: 33745107
12. Baumert M, Immanuel S, McKane S, et al. Transvenous phrenic nerve stimulation for the treatment of central sleep apnea reduces episodic hypoxemic burden. *Int J Cardiol.* 2023;378:89-95. PMID: 36841294

13. Baumert M, Linz D, McKane S, et al. Transvenous phrenic nerve stimulation is associated with normalization of nocturnal heart rate perturbations in patients with central sleep apnea. *Sleep.* 2023. PMID: 37284759
14. Hill L, Meyer T, McKane S, et al. Transvenous phrenic nerve stimulation to treat central sleep apnoea in patients with heart failure may improve sleep, quality of life, and symptoms. *Eur J Cardiovasc Nurs.* 2023;22(5):489-97. PMID: 36125322
15. Samii S, McKane S, Meyer TE, et al. Analysis by sex of safety and effectiveness of transvenous phrenic nerve stimulation. *Sleep Breath.* 2024;28(1):165-71. PMID: 37436669
16. Abraham WT, Oldenburg O, Lainscak M, et al. Win ratio analysis of transvenous phrenic nerve stimulation to treat central sleep apnoea in heart failure. *ESC Heart Fail.* 2025;12(1):80-86. PMID: 39422417
17. Fox H, Bitter T, Horstkotte D, et al. Long-Term Experience with First-Generation Implantable Neurostimulation Device in Central Sleep Apnea Treatment. *Pacing and clinical electrophysiology : PACE.* 2017;40(5):498-503. PMID: 28211952
18. Abraham WT, Jagielski D, Oldenburg O, et al. Phrenic nerve stimulation for the treatment of central sleep apnea. *JACC Heart failure.* 2015;3(5):360-69. PMID: 25770408
19. 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. *European journal of heart failure.* 2016;18(11):1386-93. PMID: 27373452

CODES

Codes	Number	Description
CPT	33276	Insertion of phrenic nerve stimulator system (pulse generator and stimulating lead[s]), including vessel catheterization, all imaging guidance, and pulse generator initial analysis with diagnostic mode activation, when performed
	33277	Insertion of phrenic nerve stimulator transvenous sensing lead (List separately in addition to code for primary procedure)
	33278	Removal of phrenic nerve stimulator, including vessel catheterization, all imaging guidance, and interrogation and programming, when performed; system, including pulse generator and lead(s)
	33279	Removal of phrenic nerve stimulator, including vessel catheterization, all imaging guidance, and interrogation and programming, when performed; transvenous stimulation or sensing lead(s) only
	33280	Removal of phrenic nerve stimulator, including vessel catheterization, all imaging guidance, and interrogation and programming, when performed; pulse generator only
	33281	Repositioning of phrenic nerve stimulator transvenous lead(s)
	33287	Removal and replacement of phrenic nerve stimulator, including vessel catheterization, all imaging guidance, and interrogation and programming, when performed; pulse generator
	33288	Removal and replacement of phrenic nerve stimulator, including vessel catheterization, all imaging guidance, and interrogation and programming, when performed; transvenous stimulation or sensing lead(s)
	93150	Therapy activation of implanted phrenic nerve stimulator system, including all interrogation and programming
	93151	Interrogation and programming (minimum one parameter) of implanted phrenic nerve stimulator system

Codes	Number	Description
	93152	Interrogation and programming of implanted phrenic nerve stimulator system during polysomnography
	93153	Interrogation without programming of implanted phrenic nerve stimulator system
HCPCS	C1823	Generator, neurostimulator (implantable), non-rechargeable, with transvenous sensing and stimulation leads

Date of Origin: *June 2019*