# 07.01.77 Diaphragmatic / Phrenic Nerve Stimulation and Diaphragm Pacing Systems



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### Summary

### Description

Diaphragmatic/phrenic nerve stimulation, also referred to phrenic pacing, phrenic nerve stimulation, diaphragm pacing, or electrophrenic respiration, is the electrical stimulation of the diaphragm via the phrenic nerve, the major nerve supply to the diaphragm that controls breathing and is a purposed treatment for a number of conditions including central sleep apnea (CSA), central alveolar hypoventilation syndrome/congenital central hypoventilation syndrome, and high quadriplegia at or above C-3. The battery-powered device sends signals to the diaphragm in order to stimulate breathing.

## Summary of Evidence

### Central alveolar hypoventilation syndrome/central hypoventilation syndrome and spinal cord injuries

For adults with central alveolar hypoventilation syndrome/central hypoventilation syndrome, and ventilatory failure from stable spinal cord injuries C3 and above, who receive diaphragmatic/phrenic nerve stimulation the evidence includes systematic reviews of comparative and noncomparative observational studies. No published randomized controlled trials were identified. Relevant outcomes are change in disease status, functional outcomes, and quality of life (QOL). Comparative observational studies reported inconsistent mortality findings. When compared with mechanical ventilation, survival was longer with phrenic nerve pacing when adjusted for age in 1 study of 126 individuals. However, no statistically significant differences in hospital length of stay or mortality were found in another study that used a risk-adjusted multivariate model that included admission year. Thus, the evidence is insufficient to determine that the technology results in an improvement in the net health outcome. However, for certain carefully selected individuals aged 18 years and older with intact and functional use of the bilateral phrenic nerve, lung, and diaphragm, diaphragmatic/phrenic nerve stimulation will be considered medically necessary for the treatment of chronic central alveolar hypoventilation syndrome/central hypoventilation syndrome, ventilatory failure from stable spinal cord injury at or above C3 when policy criteria have been met.

### Central Sleep Apnea (CSA)

For adults with CSA who receive phrenic nerve stimulation, the evidence includes a systematic review, 1 randomized controlled trial (RCT), and observational studies. Relevant outcomes are change in disease status, functional outcomes, and QOL. 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 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 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.

### Other Indications

For individuals who receive diaphragmatic/phrenic nerve stimulation devices for the treatment of other indications, including but not limited to, individuals with motor neuron disease, (i.e., amyotrophic lateral sclerosis (ALS), when respiratory insufficiency is temporary and the management of heart failure, the evidence includes a systematic review, 2 RCTs, and observational studies. Relevant outcomes are change in disease status, functional outcomes, and QOL. For individuals with ALS, a systematic review that included 2 RCTs found shorter survival with diaphragm pacing systems than with either sham stimulation or non-invasive ventilation and higher complication rates compared with non-invasive

ventilation. No studies were identified that were adequately powered that have directly evaluated whether using diaphragmatic / phrenic nerve stimulation or diaphragm pacing systems in the pediatric population. Further large, randomized, comparative, controlled studies are needed to determine the safety and efficacy. The studies need to help define optimal patient selection and assess-long term outcomes. The evidence is insufficient to determine the effects of the technology on net health outcomes.

### Additional Information

Not applicable

## OBJECTIVE

The objective of this evidence review is to determine whether the use of diaphragmatic/phrenic nerve stimulation and diaphragm pacing systems improves the net health outcome.

## PRIOR APPROVAL

Not applicable.

## POLICY

### Medically Necessary: Mark IV System or NeuRx Diaphragm Pacing System (DPS)

Diaphragmatic/phrenic nerve stimulation as an alternative to mechanical ventilation is considered **medically necessary** when the individual meets **all of the following** criteria:

- Has chronic central alveolar hypoventilation syndrome/central hypoventilation syndrome; **OR** ventilatory failure from stable spinal cord injury at or above C3; **and**
- 18 years and older;
- Diaphragm movement with stimulation visible under fluoroscopy or ultrasound;
- Has intact and functional use of the bilateral phrenic nerve, lung, and diaphragm;
- Diaphragmatic/phrenic nerve stimulation will allow the individual to breath without the assistance of a mechanical ventilator for at least 4 continuous hours a day;
- Has normal chest anatomy, a normal level of consciousness, and the ability to participate in and complete the training and rehabilitation associated with the use of the device;
- The device has received premarket approved by the U.S. Food and Drug Administration.

### Investigational

Diaphragm/phrenic nerve stimulation are considered **investigational** for all other indications including but not limited to the following because the evidence is insufficient to determine the technology results in an improvement in the net health outcomes:

- When the above criteria is not met
- Central sleep apnea (i.e., remedē System)

- Management of heart failure
- Motor neuron disease, (i.e., amyotrophic lateral sclerosis (ALS)) (i.e, NeuRx DPS)
- When respiratory insufficiency is temporary

### Replacement and Revisions

Replacement or revisions of diaphragm/phrenic nerve stimulation and diaphragm pacing systems (generator and/or leads) is considered **medically necessary** if the individual meets the above criteria and is no longer under warranty or cannot be repaired.

## POLICY GUIDELINES

- A provider may utilize electromyography (EMG) or nerve conduction studies to assess phrenic nerve function.
- **Diaphragm Fluoroscopy (Sniff Test):** a diaphragm fluoroscopy (sniff test) checks how the diaphragm (the muscle that controls breathing) moves when an individual breathes normally and when they inhale quickly. The diaphragm normally moves down when a person inhales, and up when a person exhales. Both the right and left sides of the diaphragm should move in the same direction at the same time. This test shows if there are problems with the phrenic nerve, which controls movement of the diaphragm.
  - Normal Diaphragmatic Motion:
    - The diaphragm contracts during inspiration: moves downward
    - The diaphragm relaxes during expiration: moves upwards
    - Both hemi-diaphragms move together
  - Abnormal Diaphragmatic Motion
    - The affected hemi-diaphragm does not move downwards during inspiration
    - Paradoxical motion can occur (diaphragm moves opposite to the normal direction of its movements)
    - Weak response to phrenic nerve stimulation or there is unilateral movements

### Coding

See the Codes table for details.

## BACKGROUND

### Diaphragmatic/Phrenic Nerve Stimulators for Ventilator-Dependent Conditions in Adults

### Amyotrophic Lateral Sclerosis

The hallmark of ALS is the combination of upper and lower motor neuron weakness. Respiratory muscle dysfunction impacts on quality of life and survival. With disease progression, the lower motor neurons that innervate the diaphragm via the phrenic nerve degenerate, resulting in muscle denervation and diaphragmatic paresis and paralysis. Neuromuscular respiratory failure is the cause of death in the majority of individuals with amyotrophic lateral sclerosis (ALS).

## Central Sleep Apnea (CSA)

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.

## Central Sleep Apnea 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 individuals with hyperventilation-related CSA, continuous positive airway pressure (CPAP) is considered first-line therapy. Due to CPAP discomfort, compliance may become an issue. Supplemental oxygen during sleep may be considered for individuals experiencing hypoxia during sleep or who cannot tolerate CPAP. Individuals with CSA due to heart failure 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 two pressure settings, one for inhalation and one 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 individuals with CSA due to heart failure and with an ejection fraction <45%, and therefore, ASV is not recommended for this group.

For individuals 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 for Central Sleep Apnea

Several phrenic nerve stimulation systems are available for individuals 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 remedē System (Zoll Medical). 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.

### Spinal Cord Injury

Diaphragmatic/phrenic nerve stimulation is an alternative to mechanical ventilation for a select subgroup of individuals. Common indications include individuals with high quadriplegia/spinal cord injury at or above C-3 and chronic central alveolar hypoventilation syndrome. These individuals typically experience respiratory muscle paralysis leading to chronic ventilatory insufficiency. The standard therapy is chronic mechanical ventilation via tracheostomy.

Individuals with partial or complete respiratory insufficiency who have an intact phrenic nerve and diaphragm may be eligible for diaphragmatic/phrenic nerve stimulation Prior to implantation individuals may undergo diaphragm electromyography, pulmonary function studies and/or polysomnography (i.e., sleep study). They should be alert, mentally competent, motivated, and able to complete the training and rehabilitation needed for a successful outcome.

## Regulatory Status

### Mark IV System

The Avery Breathing Pacemaker System (that is, the Mark IV™ Avery Biomedical Device, Inc., Commack, NY): This device is surgically implanted (e.g., thoracotomy approach) by placing an electrode behind the phrenic nerve, either in the neck or in the chest. The electrode is connected to a radiofrequency receiving (generator) which is implanted just under the skin which are connected to an external transmitter and antennas to send radiofrequency energy to the implanted receivers. The receivers then convert the radio waves into stimulation pulses. These pulses are then sent down the electrodes to the phrenic nerves, causing the diaphragm to contract. This contraction causes the individual to inhale. When the pulses stop, the diaphragm relaxes and the patient exhales. Repetition of this series of pulses produces a normal breathing pattern. For Mark IV pacing to be effective, candidates need to require at least 12 hours of mechanical ventilatory support daily and can gain freedom from the ventilator during the day; have a condition for which the device has been approved, they must have an intact phrenic nerve, a functional diaphragm, normal chest anatomy, and uncompromised lung function. The individual should be alert, mentally competent, motivated, and able to complete the training and rehabilitation needed for a successful outcome. The implantation procedure and management of the pacing system should be carried out by specialists with expertise in the intervention.

### remedē System

In October 2017, the remedē System (Respicardia, Inc [now Zoll Medical]; Minnetonka, MN) was approved by the FDA through the premarket approval application process (PMA #P160039). The approved indication is for the treatment of moderate to severe CSA in adults. A cardiologist implants the system which includes a battery powered pulse generator that is implanted under the skin in the upper chest and thin wire leads that are threaded through veins (transvenous) near the nerve that stimulates breathing (phrenic nerve). The system is programmed using an external system programmer and programming wand. The remedē System delivers a small electrical stimulus to the phrenic nerve while a

patient is asleep. This stimulus makes the diaphragm muscle contract, which causes the patient to take a breath. The remedē System has 2 modes, it can be set to generate pulses at a fixed rate (asynchronous therapy) or it can deliver a pulse only when it detects a pause in breathing (synchronous therapy). The physician is able to set the stimulator to deliver the most appropriate therapy for the individual. The system has safeguards to make sure that therapy is only delivered during sleep, for example it works only at the time of day when the individual is expected to be sleeping and it turns on only when the patient is inactive and lying down. Follow-up will continue for 5 years in the post-approval study. FDA product code: PSR.

### NeuRx Diaphragm Pacing System (DPS)

In September 2011 the NeuRx DPS (Synapse Biomedical Inc.; Oberlin, OH) was initially approved by the FDA with a humanitarian device exception (H100006) for use in individuals with amyotrophic lateral sclerosis (ALS). In March 2023, the FDA approved the NeuRx DPS through the premarket approval application process (P200018) for use in adults with stable high spinal cord injury (SCI) who can breathe without assistance of a mechanical ventilator for at least 4 hours a day. The NeuRx DPS is implanted using standard laparoscopic surgical technique in an outpatient procedure. The implanted intramuscular diaphragm electrodes are connected to a four channel external stimulator which is worn by the individual. The stimulator provides repetitive electrical stimulation to the implanted electrodes to cause the individual's diaphragm to contract and cause the individual to draw breath in a manner similar to natural breathing. A physician programs the stimulator to produce the right stimulation patterns.

FDA product code for SCI: OIR

## RATIONALE

This evidence review was created in October 2018 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through August 2025.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are 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. RCTs 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 Amyotrophic Lateral Sclerosis (ALS)

### *Clinical Context and Therapy Purpose*

The purpose of phrenic nerve stimulation (PNS) in ventilator-dependent conditions in adults who have to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

### *Populations*

The relevant population of interest is individuals with ventilator-dependent conditions in adults with ALS.

### *Interventions*

The therapy being considered is diaphragmatic/peripheral nerve stimulation (PNS). This system stimulates the phrenic nerve in the chest, which sends signals to the diaphragm to restore a normal breathing pattern.

### *Comparators*

Individuals with for Amyotrophic Lateral Sclerosis (ALS) typically experience respiratory muscle paralysis leading to chronic ventilatory insufficiency and the standard therapy for these individuals is chronic mechanical ventilation via tracheostomy.

### *Outcomes*

Diaphragm stimulation devices are intended to lessen dependence on mechanical ventilators, increase mobility and independence, improve speech and sense of taste and smell, and reduce secretions and risks of infection.

### 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

### Systematic Review

Woo et al (2020) completed a systematic review of studies that assessed phrenic nerve/ diaphragmatic stimulation. This review included 2 randomized controlled trials, 2 case-control studies, and 1 case report of individuals with ALS. Safety outcomes were rarely the primary outcome measure and were

inconsistently reported across studies. In the RCT's, compared to treatment without diaphragm pacing, individuals in the intervention group had shorter survival and similar quality of life. Compared to sham stimulation, serious adverse events and complications were similar in the diaphragm pacing group. When compared to non-invasive ventilation, the complication rates was higher with diaphragm pacing (78% versus 3%).

### Observational Studies

Kaufman et al (2021) conducted a review on the treatment for bilateral diaphragmatic dysfunction using phrenic nerve reconstruction and diaphragm pacemakers. Patients with bilateral diaphragmatic dysfunction were prospectively enrolled in the following treatment algorithm: Unilateral PR was performed on the more severely impacted side with bilateral DP implantation. Motor amplitudes, ultrasound measurements of diaphragm thickness, maximal inspiratory pressure, forced expiratory volume, forced vital capacity and subjective patient-reported outcomes were obtained for retrospective analysis following completion of the prospective database. Fourteen male patients with bilateral diaphragmatic dysfunction confirmed on chest fluoroscopy and electrodiagnostic testing were included. All 14 patients required nocturnal ventilator support, and 8/14 (57.1%) were oxygen dependent. All patients reported subjective improvement, and all 8 oxygen-dependent patients were able to discontinue oxygen therapy following treatment. Improvements in maximal inspiratory pressure, forced vital capacity and forced expiratory volume were 68%, 47% and 53%, respectively. There was an average improvement of 180% in motor amplitude and a 50% increase in muscle thickness. Comparison of motor amplitude changes revealed significantly greater functional recovery on the PR + DP side. The authors concluded PR and simultaneous implantation of a DP may restore functional activity and alleviate symptoms in patients with bilateral diaphragmatic dysfunction. PR plus diaphragm pacing appear to result in greater functional muscle recovery than pacing alone. This study is not adequately powered additional well-designed studies are needed.

Gonzalez-Bermejo et al (2011) described an ancillary study to a prospective, non-randomized trial (NCT00420719) assessing the effects of diaphragm pacing on forced vital capacity (FVC). Sleep-related disturbances being early clues to diaphragmatic dysfunction, we postulated that they would provide a sensitive marker. Stimulators were implanted laparoscopically in the diaphragm close to the phrenic motor point in 18 ALS patients for daily conditioning. ALS functioning score (ALSFRS), FVC, sniff nasal inspiratory pressure (SNIP), and polysomnographic recordings (PSG, performed with the stimulator turned off) were assessed before implantation and after four months of conditioning (n = 14). Sleep efficiency improved (69 ± 15% to 75 ± 11%, p = 0.0394) with fewer arousals and micro-arousals. This occurred against a background of deterioration as ALSFRS-R, FVC, and SNIP declined. There was, however, no change in NIV status or the ALSFRS respiratory subscore, and the FVC decline was mostly due to impaired expiration. Supporting a better diaphragm function, apneas and hypopneas during REM sleep decreased. In conclusion, in these severe patients not expected to experience spontaneous improvements, diaphragm conditioning improved sleep and there were hints at diaphragm function changes.

Onders et al (2009) summarized the complete worldwide multi-center review with diaphragm pacing stimulation (DPS) to maintain and provide diaphragm function in ventilator-dependent SCI patients and respiratory-compromised patients with ALS. It high-lighted the surgical experiences and the differences in diaphragm function in these 2 groups of patients. In prospective Food and Drug Administration (FDA) trials, patients underwent laparoscopic diaphragm motor point mapping with intra-muscular electrode implantation. Stimulation of the electrodes ensued to condition and strengthen the diaphragm. From March of 2000 to September of 2007, a total of 88 patients (50 SCI and 38 ALS) were implanted with DPS at 5 sites. Age of patients at implantation ranged from 18 to 74 years. Time from SCI to implantation

ranged from 3 months to 27 years. In 87 patients the diaphragm motor point was mapped with successful implantation of electrodes with the only failure the second SCI patient who had a false-positive phrenic nerve study. Patients with ALS had much weaker diaphragms identified surgically, requiring trains of stimulation during mapping to identify the motor point at times. There was no peri-operative mortality even in ALS patients with forced vital capacity (FVC) below 50 % predicted. There was no cardiac involvement from diaphragm pacing even when analyzed in 10 patients who had pre-existing cardiac pacemakers. No infections occurred even with simultaneous gastrostomy tube placements for ALS patients. In the SCI patients, 96 % were able to use DPS to provide ventilation replacing their mechanical ventilators; and in the ALS studies, patients have been able to delay the need for mechanical ventilation up to 24 months. The authors concluded that this multi-center experience has shown that laparoscopic diaphragm motor point mapping, electrode implantation, and pacing can be safely performed both in SCI and in ALS. In SCI patients it allows freedom from ventilator and in ALS patients it delays the need for ventilators, increasing survival.

### Section Summary: Phrenic Nerve Stimulation for Amyotrophic Lateral Sclerosis (ALS)

Evidence for the use of phrenic nerve stimulation therapy for the treatment of phrenic nerve stimulation for amyotrophic lateral sclerosis (ALS) consists of a systematic review that included 2 randomized controlled trials (RTCs) and observational studies. The systematic review reported that the 2 RCTs found shorter survival with diaphragm pacing systems than with either sham stimulation or non-invasive ventilation and higher complication rates compared with non-invasive ventilation.

## Phrenic Nerve Stimulation for Central Sleep Apnea

### *Clinical Context and Therapy Purpose*

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

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

### *Populations*

The relevant population of interest is individuals with CSA. CSA 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 individual is in a sleeping position and suspends therapy when the individual 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 individuals with hyperventilation-related CSA |
| BPAP | bilevel positive airway pressure (2 pressure settings - 1 for inhalation and 1 for exhalation) | Considered first-line therapy for individuals with hypoventilation-related CSA |
| ASV | adaptive servo-ventilation (titrates the inspiratory and expiratory pressure) | Not recommended for individuals with CSA with HF and a left ventricular ejection fraction <45% |

CSA: central sleep apnea; HF: heart failure.

For individuals 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 $\geq$ AHI<15 (mild); 15 $\geq$ AHI<30 (moderate); and $\geq$ 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 individuals 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

## Systematic Reviews

In April of 2022 Hayes completed a Health Technology Assessment on the phrenic nerve stimulation (remedē System) for central sleep apnea and was last updated May 27, 2025. The assessement rated phrenic nerve stimulation (PNS) with the remedē System for the treatment of central sleep apnea (CSA) in adults a $D^{2.}$ A $D^{2}$ rates indicates an "there is insufficient published evidence to assess the safety and/or impact on health outcomes or patient management." The assessment reported there is anoverall very low-quality body of evidence that is insufficient to draw conclusion about the efficacy and safety of PNS for CSA. It also reflects a sparse evidence base with a limited sample size and follow-up to adequately assess the clinical significance of PNS on CSA-related morbidity or mortality, especially compared with standard treatments for CSA.

Wang et al (2024) conducted a meta-analysis to evaluate the efficacy of PNS in individuals with CSA. They conducted a systematic review up to December of 2021 and included 10 publications of RCTs and observational studies. Nine studies (n=351) reported AHI before and after PNS with a standard mean difference of -2.24 (95% CI: -3.11 to -1.36; p<.00001). Seven studies (n=332) reported CAI with a standard mean difference of -2.32 (95% CI: -3.17 to -1.47; p<.00001). Six studies (n=281) reported arousal index with a standard mean difference of -1.79 (95% CI: -2.74 to -0.85; p<.00001). Four studies (n=173) reported T90 with a standard mean difference of -0.54 (95% CI: -1.26 to 0.19; p<.00001). Three studies (n=104) reported sleep efficiency with a standard mean difference of 0.22 (95% CI: -0.26 to 0.69; p=.07). And 4 studies (n=186) reported ESS with a standard mean difference of -0.73 (95% CI: -1.59 to 0.14; p<.00001). A limitation of the meta-analysis is 4 of the publications used the same study cohort and another 2 publications used the same study cohort. The authors conclude the results of the meta-analysis indicates PNS may improve CSA, however, larger randomized studies are needed to assess long-term effects of PNS. Details on the systematic review are in Tables 2 to 4.

**Table 2. Comparison of Studies Included in Systematic Reviews & Meta-Analyses**

| Study | Wang et al (2024) |
|---|---|
| Costanzo et al (2021) | ● |
| Oldenburg et al (2020) | ● |
| Costanzo et al (2018) | ● |
| Zhang et al (2017) | ● [a] |
| Fox et al (2017) | ● |
| Jagielski et al (2016) | ● |
| Costanzo et al (2016) | ● |
| Abraham et al (2015) | ● |
| Ponikowski et al (2012) | ● |
| Zhang et al (2012) | ● |

a. This study was identified in the systematic review, but was not included in the overall meta-analyses.

**Table 3. Systematic Reviews & Meta-Analyses Characteristics**

| Study | Dates | Trials | Participants[1] | N (Range) | Design | Duration |
|---|---|---|---|---|---|---|
| Wang et al (2024) | Up to December 2021 | 10 | Individuals with CSA | 580 (3 to 151) | RCTs and observational | 1 night to 5 years |

RCT: randomized controlled trial.

**Table 4. Systematic Reviews & Meta-Analyses Results**

| Study | AHI | CAI | Arousal Index | T90 | Sleep efficiency | ESS |
|---|---|---|---|---|---|---|
| Wang et al (2024) | | | | | | |
| Total N | 351 | 332 | 281 | 173 | 104 | 186 |
| Pooled effect (95% CI) | SMD, -2.24 (-3.11 to -1.36) | SMD, -2.32 (-3.17 to -1.47) | SMD, -1.79 (-2.74 to -0.85) | SMD, -0.54 (-1.26 to 0.19) | SMD, 0.22 (-0.26 to 0.69) | SMD, -0.73 (-1.59 to 0.14) |
| $I^2$ | 96% | 95% | 96% | 90% | 63% | 93% |

AHI: Apnea-Hypopnea Index; CAI: central apnea index; CI: confidence interval; ESS: Epworth Sleepiness Scale; T90: percent of sleep with O2 saturation <90%.

## Randomized Controlled Trials

Costanzo et al (2015) provided background and methodologic details of the remedē System Pivotal Trial. 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 (a table below) Twelve, 24 -, and 36-month results for the intervention group are shown in a table below. 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 a table below. 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. 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. A total of 14% of patients reported a serious adverse event, but no long-term harm or device-related death occurred.

Several post hoc analyses have been reported from the remedē System Pivotal Trial further investigating the effects of transvenous phrenic nerve stimulation. Baumert et al (2023) investigated treatment effect on the change in episodic hypoxemic burden between baseline and 6 months.1They found the treatment group (n=72) compared to the control group (n=62) had reduced oxygen desaturation index (ODI) (-15.85 ± 1.99 1/h vs. 1.32 ± 1.85 1/h; p<.0001) and shortened T90 (-3.81 ± 1.23 vs. 0.49 ± 1.14; p=.0121). In another paper by Baumert et al (2023) they investigated the effect of treatment on nocturnal heart rate perturbations between baseline and 6 months. They found the treatment group (n=22) compared to the control group (n=26) had reduced cyclical heart rate variations in the very low-frequency power index across rapid eye movement (REM) (4.12 ± 0.79% vs. 6.87 ± 0.82%; p=.02) and non-rapid eye movement (NREM) sleep (5.05 ± 0.68% vs. 6.74 ± 0.70%; p=.08). They also found normalized low-frequency power was reduced in the treatment arm in REM (0.67 ± 0.03 n.u. vs. 0.77 ± 0.03 n.u.; p=.02) and NREM sleep (0.70 ± 0.02 n.u. vs. 0.76 ± 0.02 n.u.; p=.03). Hartmann et al (2023) studied the effects of treatment on sleep microstructure. They analyzed polysomnography data from baseline and 6 months. The treatment group (n=57) compared to controls (n=64) showed a decrease in the frequency of A2+A3 phases (-5.86 ± 11.82 vs. 0.67 ± 15.25; p=.006) and an increase in frequency of A1 phases (2.57 ± 11.67 vs. -2.47 ± 10.60; p=.011). Change in cyclic alternating pattern (CAP) rate at follow-up was comparable between both groups. The authors concluded transvenous phrenic nerve stimulation may affect sleep microstructure, however, further studies are need to better the understand these mechanisms. Samii et al (2023) investigated sex differences in treatment effect over 12 months. They found females (n=16) and males (n=135) experienced comparable improvements in CSA metrics, including improved sleep quality and architecture. At 12 months compared to baseline, females had improved AHI (median (Q1, Q3): -21 (-24, -10) events/hour; p=.002), CAI (median (Q1, Q3): -14 (-21, -10) events/hour; p=.002), and ESS scores (median (Q1, Q3): -2 (-9, -1) points; p=.008), and males had improved AHI (median (Q1, Q3): -22 (-40, -6) events/hour; p<.001), CAI (median (Q1, Q3): -21 (-35, -12) events/hour; p<.001), and ESS scores (median (Q1, Q3): -3 (-7, 0) points; p<0.001). However, this study was limited by the small number of females and the study was not powered to detect sex-specific differences in outcomes. Abraham et al (2024) conducted a post hoc, retrospective, subgroup analysis of patients with heart failure from this

cohort (n=96).[21,] 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.

**Table 5: Summary of Key RCT Characteristics**

| Study; Trial | Countries | Sites | Dates | Participants | Interventions | |
|---|---|---|---|---|---|---|
| | | | | | **Intervention** | **Control** |
| Costanzo (2015) | 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) |
| Baumert et al (2023) | NR | 31 | NR | Adult patients with moderate to severe CSA of various etiologies confirmed by PSG[a] and who had PSG data at the visit of interest | Implanted phrenic nerve stimulator (remedē system) on (n=72) | Implanted phrenic nerve stimulator (remedē system) off (n=62) |

AHI: apnea-hypopnea index; CAI: central apnea index; CSA: central sleep apnea; NR: not reported; 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 6: Summary of Key RCT Results[a]**

| Study | Baseline | 6-Month | Change from Baseline | Between Group Difference |
|---|---|---|---|---|
| Costanzo (2015, 2016) | | | | |
| **>50% AHI reduction** | | | | |

| Study | Baseline | 6-Month | Change from Baseline | Between Group Difference |
|---|---|---|---|---|
| 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 |
| Baumert et al (2023) | | | | |
| ODI | | | | |
| Treatment | NA | 23.70 ± 1.99 | -15.85 ± 1.99 | NA |
| Control | NA | 40.87 ± 1.85 | 1.32 ± 1.85 | NA |
| T90 | | | | |
| Treatment | NA | 7.96 ± 1.23 | -3.81 ± 1.23 | NA |
| Control | NA | 12.26 ± 1.14 | 0.49 ± 1.14 | NA |

AHI: Apnea-Hypopnea Index; CAI: central apnea index; CI: confidence interval; ESS: Epworth Sleepiness Scale; NA: not applicable; ODI: oxygen desaturation index; PGA: Patient Global Assessment; RCT: randomized controlled trial T90: percent of sleep with O2 saturation <90%..

[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. 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 explant, 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 the table 7. Hill et al (2023) also 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. 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.

**Table 7: 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) | | | | | | |
| 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) | | | | | | |

| | Baseline | 6-Month | 12-Month | 24-Month Median [IQR] | 36-Month Median [IQR] | Paired Change, Baseline to 12-Month Mean (95% CI) |
|---|---|---|---|---|---|---|
| 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) and Jagielski et al (2016) 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 8). 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 9.

Wang et al (2023) conducted a prospective, non-randomized study in a small cohort who was enrolled in the Pivotal Trial. Individuals with CSA with HF (N=9) were enrolled. Comparing pre- and post-treatment, there was a reduction in AHI (41 ± 18 e/h vs. 29 ± 25 e/h; p=.02) and increase in mean arterial oxygen saturation (SaO2) (93 ± 1% vs. 95 ± 2%; p=.03). This study was limited because of its small sample size and it only investigated the effects of treatment over two nights of therapy. Randomized, long-term studies are necessary to better assess the effect of treatment on individuals with CSA and HF.

**Table 8: Summary of Non-Comparative Study Characteristics**

| Study | Country | Participants | Follow-Up |
|---|---|---|---|
| Abraham (2015) and Jagielski (2016) | 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 9. Summary of Non-Comparative Study Results**

| 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. 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 a systematic review, 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 post implantation and activated in the control group at 6 months post implantation. The RCT provided 6-month comparative analyses showing significant improvements in sleep metrics as well as quality of life

measures among individuals with the activated stimulation device compared with individuals receiving the inactivated device Individuals 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 individuals with heart failure, combining 6- and 12-month data from individuals in the intervention group and 12 and 18-month data from the control group. Results from the subgroup analysis of individuals with heart failure 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 individuals who had failed the current standard of care, positive airway pressure, or respiratory stimulant medication.

## Diaphragmatic/Phrenic Nerve Stimulation (PNS) in Stable Spinal Cord Injuries C3 and Above in Adults

### *Clinical Context and Therapy Purpose*

The purpose of phrenic nerve stimulation (PNS) in adults who have C3 and above stable spinal cord injuries is to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

### *Populations*

The relevant population of interest is adult individuals who have C3 and above stable spinal cord injuries.

### *Interventions*

The therapy being considered is diaphragmatic/peripheral nerve stimulation (PNS). This system stimulates the phrenic nerve in the chest, which sends signals to the diaphragm to restore a normal breathing pattern.

### *Comparators*

Individuals with high-level, C3 and above stable spinal cord injuries typically experience respiratory muscle paralysis leading to chronic ventilatory insufficiency and the standard therapy for these individuals is chronic mechanical ventilation via tracheostomy.

### *Outcomes*

Diaphragm stimulation devices are intended to lessen dependence on mechanical ventilators, increase mobility and independence, improve speech and sense of taste and smell, and reduce secretions and risks of infection.

### 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

## Systematic Reviews

Woo et al (2020) completed a systematic review of 10 studies (n = 281) assessed phrenic nerve/ diaphragmatic stimulation. Studies involving individuals with cervical spine injury included a cohort study, a case-control study and 3 case reports. Safety outcomes were rarely the primary outcome measure and were inconsistently reported across studies. In the only study of cervical spine injury (n = 55), that compared overall survival between diaphragm pacing and a control group rates were similar between groups across 3 subgroups based on age: 0-30 years (19.2 versus 17.4 months; *p*=.142), 30-45 years (3.2 versus 9.9 months; *p*=.129), 46+ years (10.3 versus 7.5 years; *p*=.860).

Sieg et al (2016) completed a systematic review of phrenic nerve/diaphragmatic stimulation for high spinal cord injuries and central hypoventilation syndromes dating back to the 1980s yielded 420 studies from the literature and concluded that the procedure was a safe and effective option for decreasing ventilator dependence in high spinal cord injuries and central hypoventilation. However, there were no Class I, II, or III studies, and just 18 relevant Class IV (lowest quality) articles. Authors assessed the quality of the studies as “very poor” and could not complete a meta-analysis of efficacy or safety.

## Observational Studies

Kerwin et al (2018) completed a retrospective review on the use of diaphragm pacing in the management of acute cervical spinal cord injury of 101 individuals, 40 of whom received diaphragm pacing and 61 who did not. Median time to liberation after DPS implantation was 7 days. Hospital length of stay and mortality were significantly lower on bivariate analysis in DPS patients. Diaphragm pacing system placement was not found to be associated with statistically significant differences in these outcomes on risk-adjusted multivariate models that included admission year. The authors concluded diaphragm pacing system implantation in patients with acute CSCI can be one part of a comprehensive critical care program to improve outcomes. However, the association of DPS with the marked improved mortality seen on bivariate analysis may be due solely to improvements in critical care throughout the study period. Further studies to define the benefits of DPS implantation are needed.

Posluszny (2014) provided results of a retrospective review were published describing a multicenter, nonrandomized treatment protocol using a D/P system during the initial hospitalization phase following high (cervical) spinal cord injury. A total of 14 inpatient sites in the U.S. were included in this analysis, all of which used the same database for data collection, which included age, sex, mechanism and level of injury, date of injury, date of D/P system surgery, surgical findings, and outcomes. Twenty-nine subjects with an average age of 31.4 years (range, 17-65 years) were identified for this review; however, 7 subjects were subsequently disqualified due to pre-procedural findings from diaphragm motor point mapping that showed non-stimulatable diaphragms from either phrenic nerve damage or infarct. All subjects had experienced a traumatic high spinal cord injury with an elapsed time from injury to surgery of 40 days (range of 3-112 days). The post-procedure outcomes following laparoscopic D/P system implantation showed that 72.7% (16 of 22) were completely free of ventilator support in an average of 10.2 days (mean SE of 10.2 ± 13.1 days [range, 1-45 days]). The remaining 6 subjects who had undergone D/P system implantation experienced delayed weaning of 180 days (in 2 trial participants), and partial weaning was achieved in 3 subjects, reflecting a total success rate of 82%. It was possible to

remove the D/P wires from 8 of the 22 implanted subjects due to complete respiratory recovery. The last subject needed transfer to a long-term acute care hospital and subsequently had life-prolonging measures withdrawn. The authors concluded that laparoscopic diaphragm motor point mapping early after traumatic cervical spinal cord injury can assist with diagnosing those with complete phrenic motor neuron loss or phrenic nerve injury for whom D/P system implantation is not indicated. Also, in those with intact phrenic nerve systems following injury, D/P system implantation can successfully wean them from ventilator support, although it is acknowledged that these individuals may have been successfully weaned from ventilator dependence over time during the course of their recovery without the use of DP.

Romero et al (2012) completed a retrospective review study of a prospectively collected database of patients with high cervical spinal cord injury on permanent respiratory support (n = 126) compared 38 on phrenic nerve pacing with 88 who were mechanically ventilated. Paced patients were younger (17.8 ± 11.1 CCP.1041 5 of 8 years versus 45.5 ± 21.9 years, P < .001) owing to device requirements but had a longer survival, even after adjustment for age (P < .04), and improved health-related quality of life using SF-36 scores.

### Section Summary: Diaphragmatic/Phrenic Nerve Stimulation (PNS) in Ventilator-Dependent C1-C3 Spinal Cord Injuries in Adults

A 2020 systematic review of observational studies found no difference in survival rates and mixed findings for complication rates. A previous systematic review described the quality of the studies as “very poor”. Single-arm observational studies reported mixed results in multivariate survival analyses, depending on risk adjustment. Well-designed and controlled prospective studies are still needed to further evaluate the improvement in net health outcome.

## Diaphragmatic/Phrenic Nerve Stimulation and Diaphragm Pacing Systems in the Pediatric Population

### *Clinical Context and Therapy Purpose*

The purpose of phrenic nerve stimulation (PNS) in ventilator-dependent conditions in children who have to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

### *Populations*

The relevant population of interest is individuals with ventilator-dependent conditions in children.

### *Interventions*

The therapy being considered is diaphragmatic/peripheral nerve stimulation (PNS). This system stimulates the phrenic nerve in the chest, which sends signals to the diaphragm to restore a normal breathing pattern.

### *Comparators*

Individuals less than 18 years of age with respiratory failure and the standard therapy for these individuals is chronic mechanical ventilation via tracheostomy.

### *Outcomes*

Diaphragm stimulation devices are intended to lessen dependence on mechanical ventilators, increase mobility and independence, improve speech and sense of taste and smell, and reduce secretions and risks of infection.

### 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

## Observational Studies

Ballard et al (2018) completed a retrospective chart review was performed of 14 children with Congenital Central Hypoventilation Syndrome and Rapid-Onset Obesity with Hypothalamic dysfunction, Hypoventilation, and Autonomic Dysregulation undergoing phrenic nerve-diaphragm pacemaker implantation at a single academic pediatric hospital between 2009 and 2017. Demographic information, intraoperative management, and perioperative complications were analyzed from patient records. Twelve of 14 patients (86%) underwent an inhalational induction via tracheostomy. Lung isolation was achieved via fiberoptic guidance of a single lumen endotracheal tube sequentially into the right or left mainstem bronchi for 12 patients (86%). Double lumen endotracheal tubes were utilized in two patients (7%) and bronchial blockers in two patients (7%) for lung isolation. Anesthesia was maintained using a balanced technique of volatile agents (sevoflurane/isoflurane) and opioids (fentanyl). Bradyarrhythmias developed in six patients (43%) during surgery, 5 (36%) responded to anticholinergics and one patient (7%) required backup cardiac pacing using a previously implanted bipolar cardiac pacemaker. Intraoperative hypothermia (<35.5°C) was present in five patients (36%) despite the use of warming devices. Hypercarbia (>50 mm Hg) during lung isolation was present in eight patients (57%) and hemoglobin desaturation (<90%) in four patients (29%). Postoperatively, oxygen desaturation was a common complication with nine patients (64%) requiring supplemental oxygen administration via mechanical ventilator or manual bag ventilation. Opioids via patient-controlled analgesia devices (12 patients, 86%) or intermittent injection (two patients, 14%) were administered to all patients for postoperative pain control. Phrenic nerve-diaphragm pacemaker placement was successful thoracoscopically in all patients with no perioperative mortality. The main anesthetic challenges in patients with Congenital Central Hypoventilation Syndrome and Rapid-Onset Obesity with Hypothalamic dysfunction, Hypoventilation, and Autonomic Dysregulation include hemodynamic instability, the propensity to develop hypothermia, hypercarbia/hypoxemia, and the need to perform bilateral sequential lung isolation requisite to the thoracoscopic implantation technique. Most anesthetic agents can be used safely in these patients; however, adequate knowledge of the susceptibility to complications, coupled with adequate preparation and understanding of the innate disease characteristics, are necessary to treat anticipated complications.

Nicholson et al (2015) completed a single-center retrospective review was performed of CCHS patients undergoing placement of phrenic nerve electrodes for diaphragm pacing between 2000 and 2012. Data abstracted from the medical record included operation duration, ventilation method, number of trocars required, and postoperative and pacing outcomes. Charts of eighteen patients were reviewed. Mean surgical time was 3.3±0.7 hours. In all cases except one, three trocars were utilized for each hemithorax, with no conversions to open procedures. Five patients (27.8%) experienced postoperative complications. The mean ICU stay was 4.3±0.5 days, and the mean hospital stay is 5.7±0.3days. Eleven patients (61.1%) achieved their daily goal pacing times within the follow-up period. The authors concluded thoracoscopic placement of phrenic nerve electrodes for diaphragmatic pacing is a safe and effective treatment modality for CCHS. Observed complications were temporary, and the majority of patients were able to achieve pacing goals. This study was not adequately powered, and further well-designed studies should be completed.

### Section Summary: Diaphragmatic/Phrenic Nerve Stimulation and Diaphragm Pacing Systems in the Pediatric Population

No studies were identified that were adequately powered that have directly evaluated whether using diaphragmatic / phrenic nerve stimulation or diaphragm pacing systems in the pediatric population improves the net health outcome such as change in disease status and morbid events.

## 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 Neurology (AAN)*

In 2009, the AAN published guidelines on the care of the patient with amyotrophic lateral sclerosis – Drug, nutritional, and respiratory therapies, and on the care of the patient with amyotrophic lateral sclerosis: multidisciplinary care, symptom management, and cognitive/behavioral impairment that was last reaffirmed in 2023. These guidelines do not include any recommendation applicable to this evidence review.

#### *American Academy of Sleep Medicine (AASM)*

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. 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, 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.

### *American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure Society of America (HFSA)*

In 2022 the AHA/ACC/HFSA published a guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. The guideline stated, “significant gaps exist despite evolving evidence and treatment strategies in patients with HF.” “Selected, common issues that should be addressed in future clinical research include the “efficacy and safety of transvenous stimulation of the phrenic nerve or role of nocturnal supplemental oxygen for treatment of central sleep apnea in patients with HF”.

### *National Institute for Health and Care Excellence (NICE)*

In 2024, NICE published an interventional procedure guidance [IPG792] on phrenic nerve pacing for ventilator-dependent high cervical spinal cord injury that recommends “The evidence for this procedure shows benefits, such as increased ventilator-free time, reduced respiratory infections and living longer. People with high cervical spinal cord injury have multiple comorbidities and their quality of life is often limited. This procedure only treats 1 part of a very complex condition, so the benefits of the procedure are limited. The evidence does not raise any major safety concerns. So, phrenic nerve pacing is recommended.”

In 2023, NICE published an interventional procedure guidance [IPG762] on intramuscular diaphragmatic stimulation for ventilator-dependent chronic respiratory failure from spinal cord injuries recommends, “the evidence for this procedure is limited because there is a lack of long-term data and no high-quality clinical trials. But the evidence does suggest that this procedure may improve quality of life and enable people to have some ventilator-free time each day. The evidence on safety includes reports of electrode insertion site infection and pneumonia, but it is not certain if pneumonia is directly caused by the procedure. More research will offer more evidence on safety and long-term outcomes. High spinal cord injury is severely disabling. For people who are dependent on mechanical ventilation, this procedure offers one of few options that could enable them to have some ventilator-free time. So, this procedure is recommended but only with special arrangements.”

In 2017, NICE published an interventional procedure guidance [IPG593] on intramuscular diaphragm stimulation for ventilator-dependent chronic respiratory failure caused by motor neurone disease that recommends, “current evidence on intramuscular diaphragm stimulation for ventilator dependent chronic respiratory failure caused by motor neurone disease suggests that there are serious long-term safety concerns. Evidence on efficacy is limited and therefore, this procedure should not be used to treat this condition.”

## Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review can be located at clinicaltrials.gov.

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## CODES

**To report provider services, use appropriate CPT codes, HCPCS codes, Revenue codes, and/or ICD diagnosis 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) |
| | 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) |

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|---|---|---|
| | 64575 | Open implantation of neurostimulator electrode array; peripheral nerve (excludes sacral nerve) |
| | 64580 | Open implantation of neurostimulator electrode array; neuromuscular |
| | 64585 | of peripheral neurostimulator electrode array |
| | 64590 | Insertion or replacement of peripheral, sacral, or gastric neurostimulator pulse generator or receiver, requiring pocket creation and connection between electrode array and pulse generator or receiver |
| | 64595 | Revision or removal of peripheral, sacral, or gastric neurostimulator pulse generator or receiver, with detachable connection to electrode array |
| | 64596 | Insertion or replacement of percutaneous electrode array, peripheral nerve, with integrated neurostimulator, including imaging guidance, when performed; initial electrode array |
| | 64597 | Insertion or replacement of percutaneous electrode array, peripheral nerve, with integrated neurostimulator, including imaging guidance, when performed; each additional electrode array (List separately in addition to code for primary procedure) |
| | 64598 | Revision or removal of neurostimulator electrode array, peripheral nerve, with integrated neurostimulator |
| | 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 |
| | 93152 | Interrogation and programming of implanted phrenic nerve stimulator system during polysomnography |
| | 93153 | Interrogation without programming of implanted phrenic nerve stimulator system |
| | 95970 | Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g. contact group(s), interleaving, amplitude, pulse width, frequency [Hz], on/off cycle, 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 |

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|---|---|---|
| | 95971 | 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 spinal cord or peripheral nerve (e.g. sacral nerve) neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional |
| | 95972 | 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 complex spinal cord or peripheral nerve (e.g. sacral nerve) neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional |
| **HCPCS** | | |
| | C1767 | Generator neurostimulator (implantable) non-rechargeable |
| | C1778 | Lead, neurostimulator (implantable) |
| | C1787 | Patient programmer, neurostimulator |
| | C1816 | Receiver and/or transmitter, neurostimulator (implantable) |
| | C1820 | Generator, neurostimulator (implantable), non-high-frequency with rechargeable battery and charging system |
| | C1822 | Generator, neurostimulator (implantable), high frequency, with rechargeable battery and charging system |
| | C1823 | Generator, neurostimulator (implantable), non-rechargeable, with transvenous sensing and stimulation |
| | C1883 | Adapter/extension, pacing lead or neurostimulator lead (implantable) |
| | C1897 | Lead, neurostimulator test kit (implantable) |
| | L8679 | Implantable neurostimulator, pulse generator any type |
| | L8680 | Implantable neurostimulator electrode, each |
| | L8681 | Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only |
| | L8682 | Implantable neurostimulator radiofrequency receiver |
| | L8683 | Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver |

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|---|---|---|
| | L8685 | Implantable neurostimulator pulse generator, single array, rechargeable includes extension |
| | L8686 | Implantable neurostimulator pulse generator, single array, nonrechargeable, includes extension |
| | L8687 | Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension |
| | L8688 | Implantable neurostimulator pulse generator, dual array, nonrechargeable, includes extension |
| | L8689 | External recharging system for battery (internal) for use with implantable neurostimulator, replacement only |
| | | |
| **Type of Service** | Medicine | |
| **Place of Service** | Inpatient / Outpatient | |

## POLICY HISTORY

| Date | Reason | Action |
|---|---|---|
| August 2025 | Annual Review | Policy Revision |
| August 2024 | Annual Review | Policy Renewed |
| August 2023 | Annual Review | Policy Revised |
| October 2022 | Annual Review | Policy Revised |
| October 2021 | Annual Review | Policy Renewed |
| October 2020 | Annual Review | Policy Renewed |
| October 2019 | Annual Review | Policy Renewed |
| October 2018 | | New Policy Created |

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

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