7.01.69	Sacral Nerve Neuromodulation/Stimulation		
Original Policy Date:	June 10, 1998	**Effective Date:**	June 1, 2023
Section:	7.0 Surgery	**Page:**	Page 1 of 30

Policy Statement

Urinary Incontinence and Nonobstructive Retention
Criteria A

I. A trial period of sacral nerve neuromodulation with either percutaneous nerve stimulation or a temporarily implanted lead may be considered **medically necessary** in individuals who meet **all** of the following criteria:
   A. There is a diagnosis of at least **one** of the following:
      1. Urge incontinence
      2. Urgency-frequency syndrome
      3. Nonobstructive urinary retention
      4. Overactive bladder
   B. There is documented failure or intolerance to at least 2 conventional conservative therapies (e.g., behavioral training such as bladder training, prompted voiding, or pelvic muscle exercise training, pharmacologic treatment for at least a sufficient duration to fully assess its efficacy, and/or surgical corrective therapy).
      1. The individual is an appropriate surgical candidate
      2. Incontinence is not related to a neurologic condition

Criteria B

II. Permanent implantation of a sacral nerve neuromodulation device may be considered **medically necessary** in individuals who meet **all** of the following criteria:
   A. All of criteria A. A and B above are met
   B. A trial stimulation period demonstrates at least 50% improvement in symptoms over a period of at least 48 hours

III. Other urinary/voiding applications of sacral nerve neuromodulation are considered **investigational**, including but not limited to the treatment of stress incontinence or urge incontinence due to a neurologic condition (e.g., detrusor hyperreflexia, multiple sclerosis, spinal cord injury, other types of chronic voiding dysfunction).

Fecal Incontinence
Criteria A

IV. A trial period of sacral nerve neuromodulation with either percutaneous nerve stimulation or a temporarily implanted lead may be considered **medically necessary** in individuals who meet **all** of the following criteria:
   A. There is a diagnosis of chronic fecal incontinence of more than 2 incontinent episodes on average per week for more than 6 months or for more than 12 months after vaginal childbirth
   B. There is documented failure or intolerance to conventional conservative therapy (e.g., dietary modification, the addition of bulking and pharmacologic treatment) for at least a sufficient duration to fully assess its efficacy
   C. The individual is an appropriate surgical candidate
   D. The condition is not related to an anorectal malformation (e.g., congenital anorectal malformation; defects of the external anal sphincter over 60°; visible sequelae of pelvic radiation; active anal abscesses and fistulae) or chronic inflammatory bowel disease
   E. Incontinence is not related to a neurologic condition
   F. The individual has not had rectal surgery in the previous 12 months or, in the case of cancer, the individual has not had rectal surgery in the past 24 months

Criteria B

V. Permanent implantation of a sacral nerve neuromodulation device may be considered **medically necessary** in individuals who meet **all** of the following criteria:
   A. All of criteria A. A through F above are met
   B. A trial stimulation period demonstrates at least 50% improvement in symptoms over a period of at least 48 hours

VI. Sacral nerve neuromodulation is considered **investigational** in the treatment of chronic constipation or chronic pelvic pain.

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

Policy Guidelines

The International Continence Society has defined overactive bladder syndrome (OAB) as "urinary urgency, usually accompanied by increased daytime frequency and/or nocturia, with urinary incontinence (OAB-wet) or without (OAB-dry), in the absence of urinary tract infection or other detectable disease"

(available at https://www.ics.org/glossary/symptom/overactivebladderoaburgencysyndrome).

Coding
Sacral nerve neuromodulation involves several steps identified by the codes listed below.

Peripheral Nerve Evaluation
Peripheral nerve evaluation to determine candidacy for permanent implantation would be reported using the following codes:

- HCPCS Codes
  - **A4290**: Sacral nerve stimulation test lead, each
  - **E0745**: Neuromuscular stimulator, electronic shock unit
  - **E1399**: Durable medical equipment, miscellaneous
- CPT Code
  - **64561**: Percutaneous implantation of neurostimulator electrode array; sacral nerve (transforaminal placement) including image guidance, if performed

Open Implantation of the Electrode Array
Open implantation of the electrode array, whether as the first stage of the 2-stage implantation procedure, or as the final implantation of the electrode array after a positive percutaneous test, would be reported using the following codes:

- HCPCS Code
  - **L8680**: Implantable neurostimulator electrode, each
- CPT Code
  - **64581**: Open implantation of neurostimulator electrode array; sacral nerve (transforaminal placement)

Open Implantation of the Neurostimulator Pulse Generator
Open implantation of the neurostimulator pulse generator would be reported using the following codes:

- HCPCS Codes
  - **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
- **CPT Code**
  - **64590**: Insertion or replacement of peripheral or gastric neurostimulator pulse generator or receiver, direct or inductive coupling

Analysis and Reprogramming of the Implanted Device
Some patients will require analysis and reprogramming of the device once implanted. A site of service differential may apply. The following CPT code may be used:

- **CPT Code**
  - **95970**: Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g., contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain, cranial nerve, spinal cord, peripheral nerve, or sacral nerve, neurostimulator pulse generator/transmitter, without programming

Revision or Removal of the Implanted Electrodes or Stimulator
Some patients may require revision or removal of the implanted electrodes or pulse stimulator. The following CPT codes may be used:

- **CPT Codes**
  - **64585:** Revision or removal of peripheral neurostimulator electrode array
  - **64595**: Revision or removal of peripheral or gastric neurostimulator pulse generator or receiver

Note: HCPCS code L8680 is reported with 1 unit for each contact point on the implanted lead.

Description

Sacral nerve neuromodulation, also known as sacral nerve stimulation, involves the implantation of a permanent device that modulates the neural pathways controlling bladder or rectal function. This evidence review addresses the use of sacral nerve neuromodulation to treat urinary or fecal incontinence, fecal nonobstructive retention, and chronic pelvic pain in patients with intact neural innervation of the bladder and/or rectum.

Related Policies

- Biofeedback as a Treatment of Urinary Incontinence in Adults
- Pelvic Floor Stimulation as a Treatment of Urinary and Fecal Incontinence

Benefit Application

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

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these

instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

In 1997, the InterStim® Sacral Nerve Stimulation system (Medtronic) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process for the indication of urinary urge incontinence in patients who have failed or could not tolerate more conservative treatments. In 1999, the device received FDA approval for the additional indications of urgency-frequency and urinary retention in patients without mechanical obstruction. In 2006, the InterStim II System (Medtronic) was approved by the FDA through the premarket approval process for the treatment of intractable cases of overactive bladder and urinary retention. The new device is smaller and lighter than the original and is reported to be suited for those with lower energy requirements or small stature. The device also includes updated software and programming options.

In 2011, the InterStim System was approved by the FDA through the premarket approval process for both fecal incontinence, chronic fecal incontinence in patients who have failed or could not tolerate more conservative treatments.

In 2020, the InterStim X™ device was approved by the FDA. This latest generation of the InterStim device does not require recharging and has a battery life of at least 10 years and up to 15 years if used at a low-energy setting.

The InterStim device has not been specifically approved by the FDA for the treatment of chronic pelvic pain.

In 2019, the Axonics® Sacral Neuromodulation System (Axonics) received premarket approval from the FDA for both fecal incontinence and treatment of urinary retention and symptoms of overactive bladder. This system has a rechargeable battery that has a device life of 15 years after implantation.

In 2023, the Virtis™ Sacral Neuromodulation System (Nuvectra) was approved by the FDA for treatment of urinary retention and symptoms of overactive bladder, including urinary urge incontinence and significant symptoms of urgency-frequency in patients who have failed more conservative treatments.

FDA product code: EZW.

Rationale

Background

Treatment

Treatment using sacral nerve neuromodulation, also known as indirect sacral nerve stimulation, is 1 of several alternative modalities for individuals with urinary or fecal incontinence (urge incontinence, significant symptoms of urgency-frequency, nonobstructive urinary retention) who have failed behavioral (e.g., prompted voiding) and/or pharmacologic therapies.

The sacral nerve neuromodulation device consists of an implantable pulse generator that delivers controlled electrical impulses. This pulse generator is attached to wire leads that connect to the sacral nerves, most commonly the S3 nerve root. Two external components of the system help control the electrical stimulation. A control magnet, kept by the individuals , is used to turn the device on or off. A console programmer is kept by the physician and used to adjust the settings of the pulse generator.

Before implantation of the permanent device, individuals undergo an initial testing phase to estimate potential response to treatment. The first type of testing developed was percutaneous nerve evaluation. This procedure is done with the patient under local anesthesia, using a test needle to identify the appropriate sacral nerve(s). Once identified, a temporary wire lead is inserted through the test needle and left in place for 4 to 7 days. This lead is connected to an external stimulator, which is carried by patients in their pocket or on their belt. The results of this test phase are used to determine whether individuals are appropriate candidates for the permanent device. If individuals show a 50% or greater reduction in symptom frequency, they are deemed eligible for the permanent device

The second type of testing is a 2 stage surgical procedure. In the first stage, a quadripolar-tined lead is implanted (stage 1). The testing phase can last as long as several weeks, and if individuals show a 50% or greater reduction in symptom frequency, they can proceed to stage 2 of the surgery, which is permanent implantation of the neuromodulation device. The 2 stage surgical procedure has been used in various ways. They include its use instead of percutaneous nerve evaluation, for individuals who failed percutaneous nerve evaluation, for with an inconclusive percutaneous nerve evaluation, or for individuals who had a successful percutaneous nerve evaluation to refine individual selection further.

The permanent device is implanted with the individuals under general anesthesia. The electrical leads are placed in contact with the sacral nerve root(s) via an incision in the lower back, and the wire leads are extended through a second incision underneath the skin, across the flank to the lower abdomen. Finally, a third incision is made in the lower abdomen where the pulse generator is inserted and connected to the wire leads. Following implantation, the physician programs the pulse generator to the optimal settings for that individual. The individual can switch the pulse generator on and off by placing the control magnet over the area of the pulse generator for 1 to 2 seconds.

This evidence review does not address pelvic floor stimulation, which refers to electrical stimulation of the pudendal nerve. Pelvic floor stimulation is addressed separately (see evidence review 1.01.17). Also, this review does not address devices that provide direct sacral nerve stimulation in individuals with spinal cord injuries.

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are 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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA

(Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Urinary Incontinence

Clinical Context and Therapy Purpose

Urge incontinence is defined as leakage of urine when there is a strong urge to void. Urgency-frequency is an uncontrollable urge to urinate, resulting in very frequent, small volumes and is a prominent symptom of interstitial cystitis (also called bladder pain syndrome). Urinary retention is the inability to empty the bladder of urine completely.

The purpose of sacral nerve neuromodulation in individuals with urinary incontinence 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 urinary incontinence.

Interventions

The treatment being considered is sacral nerve neuromodulation.

Comparators

The comparator of interest is pharmacologic treatment.

Outcomes

The outcomes of interest are symptoms, morbid events, and treatment-related morbidity. Positive outcomes include reduction or elimination of episodes of incontinence without complications from the device or implantation procedure.

Negative outcomes would be infection, bleeding, pain, and lead breakages, and lack of improvement in incontinence.

Although no set standard for length of follow-up has been established, the existing literature evaluating sacral nerve neuromodulation for urinary incontinence has lengths of follow-up ranging from 6 months to 5 years. Follow-up of at least 1 year would be preferred.

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 events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Randomized Controlled Trials

Several RCTs on sacral nerve neuromodulation for urinary incontinence have been conducted. One was sponsored by Medtronic and submitted to the U.S. Food and Drug Administration (FDA) as part of the device approval process.[1,] Findings have not otherwise been published. In this RCT, 177 of 581

patients had urinary retention. Patients with urinary retention reported significant improvements regarding volume per catheterization, a decrease in the number of catheterizations per day, and increased total voided volume per day. At 12 months post-implant, 61% of patients had ceased use of catheterization. At baseline, 220 (38%) of 581 had significant urgency-frequency symptoms. After 6 months, 83% of patients with urgency-frequency symptoms reported increased voiding volumes with the same or reduced degree of frequency. At 12 months, 81% of patients had reached normal voiding frequency. Compared with a control group, patients with implants reported significant improvements in quality of life, as evaluated by the 36-Item Short-Form Health Survey. The trial was well-designed, using standardized clinical and functional status outcomes measurements, and enrolled patients with severe urge incontinence who had failed extensive prior treatments. The magnitude of effect (approximately one-half of patients became dry, three-quarters experienced at least 50% reduction in incontinence) was fairly large, probably at least as great as with surgical procedures, and larger than expected from a placebo effect or conservative measures such as behavioral therapy or drugs. The therapy evaluation test, in which the device was turned off (i.e., sham treatment was provided) and patients thus served as their controls, provided further evidence that the effect on incontinence was due to electrical stimulation and demonstrated that the effect of sacral nerve neuromodulation is reversible. The cohort analysis of the clinical trial provided some evidence that the effect of sacral nerve neuromodulation could be maintained for up to 2 years. There was a high rate of adverse events reported in this trial. Most were minor and reversible; however, approximately one-third of patients required surgical revision for pain at the operative sites or migration of the leads.

An additional prospective RCT of 44 patients with urge incontinence was published by Weil et al (2000).[2,] At 6 months, the implant group showed significantly greater improvements in standardized clinical outcomes, compared with those receiving conservative therapy. The magnitude of effect was substantial.

Siegel et al (2015) published results of an industry-sponsored, FDA-mandated, post-approval study known as the InSite (InSite for Over Active Bladder) trial. This RCT compared sacral nerve neuromodulation using a 2-stage surgical procedure with standard medical therapy.[3,] Study inclusion criteria were a diagnosis of overactive bladder (at least 8 voids per day and/or at least 2 involuntary leaking episodes in 72 hours) and a failed trial of at least 1 anticholinergic or antimuscarinic medication. Also, there needed to be at least 1 such medication that had not yet been prescribed. Patients with neurologic diseases and with primary stress incontinence were excluded. Seventy patients were allocated to sacral nerve neuromodulation and 77 to standard medical therapy. Of the 70 patients in the sacral nerve neuromodulation group, 11 elected not to receive test stimulation with the tined lead, and 8 received the lead but did not receive a full system implant due to lack of response to a 14-day test stimulation period (response was defined as ≥50% reduction in average leaks and/or voids). Patients in the medical treatment group tried the next recommended medication or restarted a discontinued medication. Therapeutic success was defined as at least a 50% improvement in average leaks per day or at least a 50% improvement in the number of voids per day or a return to fewer than 8 voids per day. In the intention-to-treat (ITT) analysis, the therapeutic success rate at 6 months was 61% in the sacral nerve neuromodulation group and 42% in the standard treatment group; the difference between groups was statistically significant (p=.02). Quality of life at 6 months was a secondary outcome. Several validated quality-of-life scales were used, and all favored the sacral nerve neuromodulation group compared with the standard treatment group (p<.002 for all comparisons).

A 12-month follow-up of the InSite trial was published by Noblett et al (2016).[4,] They analyzed patients from the sacral nerve stimulation group of initial RCT plus additional patients enrolled and implanted in the interim. A total of 340 patients underwent test stimulation, 272 underwent implantation, and 255 completed 12 months of follow-up. In a modified completers' analysis, the therapeutic success rate was 82%. This modified completers' analysis included patients who were implanted and had either a baseline or 12-month evaluation or withdrew from the trial due to a device-related adverse event or lack of efficacy. In an analysis limited to study completers, the therapeutic response rate was

85%. The Noblett et al (2016) analysis did not include data from the control group of patients receiving only standard medical therapy.

Amundsen et al (2016) reported on an RCT comparing intradetrusor injection of onabotulinumtoxinA (n=192) with sacral nerve neuromodulation (n=189) in women with refractory urgency urinary incontinence, defined as at least 1 supervised behavioral or physical therapy intervention and the use of a minimum of 2 anticholinergics (or inability to tolerate or contraindications to the medication).[5,] In the ITT analysis, patients in the onabotulinumtoxinA-treated group had greater reductions in urge incontinence per day (3.9 per day) than in the sacral nerve neuromodulation treated group (3.3 per day; mean difference, 0.63; 95% confidence interval [CI], 0.13 to 1.14; p=.01). OnabotulinumtoxinA-treated patients had greater reductions in some overactive bladder-related quality of life questionnaire-related measures, although the clinical meaningfulness of the changes was uncertain. Patients in the onabotulinumtoxinA-treated group were more likely to have urinary tract infections (35% vs. 11%; risk difference, -23%; 95% CI, -33% to -13%; p<.001).

Observational Studies

Chartier-Kastler et al (2022) published 3-year results from a prospective, observational, multicenter study from France (SOUNDS).[6,] Patients with overactive bladder (N=229) underwent InterStim implantation (either a first device or a replacement) and were followed for a mean of 33.7 ± 3.7 months. During the 3-year follow-up, average daily voids and leaks were significantly reduced (all p<.05) and response (defined as ≥50% reduction in voids per day or return to normal voiding frequency) ranged from 72% to 86%. Quality of life scores were improved at all study visits. About half of the patients experienced adverse events, which were mostly minor, but surgical revision was required in 33% of patients. Lack of a control arm may limit the clinical applicability of these results.

Pezella et al (2021) published an observational, single-arm, multicenter study (ARTISAN-SNM) of the Axonics system in 129 patients with urinary urgency incontinence.[7,] After 2 years, 93% of the 121 patients that remained in the study met the criteria for response, which was defined as a ≥50% reduction in urge incontinence episodes. Freedom from urge incontinence episodes (100% reduction) occurred in 37% of patients. Average number of incontinence episodes per day decreased from 5.6 ± 0.3 at baseline to 1.0 ± 0.3 at 2 years (p<.0001). No serious device-related adverse events occurred.

Similarly, Blok et al (2020) reported 2-year results of the prospective RELAX-OAB study that evaluated the Axonics system in 51 patients with overactive bladder.[8,] Response to treatment was defined as a ≥50% reduction in voids or leaks or a return to normal voiding frequency (<8 voids per day), and was assessed 1 month after implantation. Forty patients were followed for the full 2 years. Of these, 30 patients had met the criteria for response at 1 month and 27 were still responders after 2 years. No serious device-related adverse events occurred.

Case Series

Case series have provided longer follow-up data than the RCTs. For example, a series by Groen et al (2011) in the Netherlands reported the longest follow-up.[9,] Sixty patients had at least 5 years of follow-up after sacral nerve neuromodulation for refractory idiopathic urge urinary incontinence. Success was defined as at least a 50% decrease in the number of incontinent episodes or pads used per day. The success rate was 52 (87%) of 60 at 1 month and gradually decreased to 37 (62%) at 5 years. The number of women who were completely continent was 15 (25%) at 1 month and 9 (15%) at 5 years. At the 5-year follow-up, sacral nerve neuromodulation was still used by 48 (80%) of 60 women. Fifty-seven adverse events were reported in 32 (53%) of 60 patients. The most frequent were hardware-related or pain or discomfort. There were 23 reoperations in 15 patients. In most cases, the pain was managed conservatively.

Findings from a large prospective series were reported by White et al (2009).[10,] The series focused on complications associated with sacral nerve neuromodulation in 202 patients with urge incontinence, urinary urgency, or urinary retention. At a mean follow-up of 37 months (range, 7 to 84 months), 67

(30%) patients had experienced adverse events that required either lead or implantable pulse generator revisions. Complications included pain (3%), device malfunction secondary to trauma (9%), infection (4%), postoperative hematoma (2%), and lead migration (6%). Also, 5% of patients underwent elective removal, 4% had device removal due to lack of efficacy, and 2% required removal due to battery expiration. At the last follow-up, 172 (85%) patients had functional implanted units.

Section Summary: Urinary Incontinence

Data from RCTs, observational studies, and case series with long-term follow-up have suggested that sacral nerve neuromodulation reduces symptoms of urge incontinence, urgency-frequency syndrome, nonobstructive urinary retention, and overactive bladder in selected patients.

Fecal Incontinence

Clinical Context and Therapy Purpose

Fecal incontinence can arise from a variety of mechanisms, including rectal wall compliance, efferent and afferent neural pathways, central and peripheral nervous systems, and voluntary and involuntary muscles. Fecal incontinence is more common in women (female assigned at birth), due mainly to muscular and neural damage that may occur during vaginal delivery.

The purpose of sacral nerve neuromodulation in individuals with fecal incontinence 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 fecal incontinence.

Interventions

The treatment being considered is sacral nerve neuromodulation.

Comparators

The comparator of interest is continued conservative therapy, such as dietary modification, bulking, or pharmacologic treatment.

Outcomes

The outcomes of interest are symptoms, morbid events, and treatment-related morbidity. Positive outcomes include reduction or elimination of episodes of incontinence without complications from the device or implantation procedure.

Negative outcomes would be infection, bleeding, pain, and lead breakages, and lack of improvement in incontinence.

Although no set standard for length of follow-up has been established, the existing literature evaluating sacral nerve neuromodulation for fecal incontinence has lengths of follow-up ranging from 2 weeks to 84 months. Follow-up of at least 1 year would be preferred.

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 events, 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

Thaha et al (2015) conducted a Cochrane review assessing sacral nerve stimulation for fecal incontinence and constipation in adults, which included randomized, quasi-randomized, and crossover trials.[11,] For fecal incontinence, reviewers included 6 trials of sacral nerve neuromodulation (N=219 patients), 2 of which used parallel-group designs (Thin et al [2015], Tjandra et al [2008]; the latter described below); the others used crossover designs. The primary methodologic quality issue noted was a lack of clarity involving randomization techniques and allocation concealment. Reviewers concluded: "The limited evidence from the included trials suggests that sacral nerve stimulation can improve continence in a proportion of patients with fecal incontinence."
Thin et al (2013) published a systematic review of randomized trials and observational studies evaluating sacral nerve neuromodulation for treating fecal incontinence.[12,] Sixty-one studies met the following eligibility criteria: assessed at least 10 patients, had a clear follow-up interval, and reported the success rate of therapy based on a 50% or greater reduction in fecal incontinence episodes. Only 2 studies were RCTs (Tjandra et al [2008], Leroi et al [2005]; described next) and 50 were prospective case series. Data from 2 studies with long-term follow-up were pooled to calculate median success rates using ITT analysis. These median success rates were 63% in the short term (≤12 months of follow-up), 58% in the medium term (12 to 36 months), and 54% in the long term (>36 months). The per-protocol short-, medium-, and long-term success rates were 79%, 80%, and 84%, respectively.

Previously, Tan et al (2011) published a meta-analysis of studies evaluating sacral nerve neuromodulation for treating fecal incontinence.[13,] They identified 34 studies that reported on at least 1 of their outcomes of interest and documented how many patients underwent temporary and permanent sacral nerve neuromodulation. Only 1 study was an RCT (Tjandra et al [2008], described below). In the 34 studies, 944 patients underwent temporary sacral nerve stimulation, and 665 subsequently underwent permanent sacral nerve stimulation implantation. There were 279 patients who did not receive permanent implantation, and 154 of them were lost to follow-up. Follow-up in the studies ranged from 2 to 35 weeks. In a pooled analysis of findings of 28 studies, there was a statistically significant decrease in the number of incontinence episodes per week with sacral nerve neuromodulation compared with maximal conservative therapy (weighted mean difference, -6.83; 95% CI, -8.05 to -5.60; p<.001). Fourteen studies reported incontinence scores, and when these results were pooled, there was also a significantly greater improvement in scores with sacral nerve stimulation than with conservative therapy (weighted mean difference, -10.57; 95% CI, -11.89 to -9.24; p<.001).

Maeda et al (2011) published a systematic review of studies on complications following permanent implantation of a sacral nerve stimulation device for fecal incontinence and constipation.[14,] Reviewers identified 94 articles. Most addressed fecal incontinence. A combined analysis of data from 31 studies on sacral nerve stimulation for fecal incontinence reported a 12% suboptimal response to therapy (149/1232 patients). A review of complications reported in the studies found that the most commonly reported complication was pain around the site of implantation, with a pooled rate of 13% (81/621 patients). The most common response to this complication was repositioning the stimulator, followed by device explantation and reprogramming. The second most common adverse event was an infection, with a pooled rate of 4% (40/1025 patients). Twenty-five (63%) of the 40 infections led to device explantation.

Randomized Controlled Trials

Tjandra et al (2008) published an RCT assessing 120 patients with severe fecal incontinence.[15,] Patients were randomized to sacral nerve stimulation or best supportive therapy, consisting of pelvic floor exercises with biofeedback, bulking agents, and dietary management with a team of dieticians. Exclusion criteria included neurologic disorders and external anal sphincter defects of more than 120° of the circumference, although a "high proportion" of the patients had pudendal neuropathy. The trial was not blinded. Of the 60 patients randomized to sacral nerve stimulation, 54 (90%) had successful test stimulation and 53 proceeded with the implant of the pulse generator. At baseline, the

sacral nerve stimulation group had an average of 9.5 incontinent episodes per week, and the controls had 9.2. Both groups had an average of 3.3 days per week with incontinence. At 12-month follow-up, episodes had decreased to 1 day per week, with 3.1 episodes in the sacral nerve stimulation group, but no change in the control group (mean, 3.1 days/week), with 9.4 episodes. Complete continence was achieved in 22 (42%) of the 53 sacral nerve stimulation patients and 13 (24%) patients improved by 75% to 99%. None of the patients had worsening of fecal continence. Adverse events included pain at implant site (6%), seroma (2%), and excessive tingling in the vaginal region (9%).

Leroi et al (2005) in France published an industry-supported, double-blind, randomized crossover study.[16,] Thirty-four patients had successful temporary percutaneous stimulation and underwent permanent implantation of a sacral nerve neuromodulation device. Following a 1 to 3 month postimplantation period in which the device was turned on, patients had their device turned on for 1 month and off for 1 month, in random order. Twenty-four (71%) randomized patients completed the trial. There was a statistically significant greater decrease in fecal incontinence episodes with the device turned on (p=.03). However, there was also a large decrease in incontinent episodes for the placebo group. The median frequency of fecal incontinence episodes decreased by 90% when the device was in the on position; it decreased by 76% when the device was in the off position.

Prospective Noncomparative Studies

A key multicenter prospective trial is the 16-site multicenter FDA investigational device exemption study of sacral nerve stimulation in 120 patients with fecal incontinence. Findings were initially reported by Wexner et al (2010).[17,] To be included, patients had to have chronic fecal incontinence for more than 6 months or more than 12 months after vaginal childbirth, defined as more than 2 incontinent episodes on average per week. All patients had failed or were not candidates for more conservative treatments. Exclusion criteria included congenital anorectal malformation; previous rectal surgery if performed within the last 12 months (or 24 months in case of cancer); defects of the external anal sphincter over 60°; chronic inflammatory bowel disease; visible sequelae of pelvic radiotherapy; active anal abscesses and fistulae; neurologic diseases such as clinically significant peripheral neuropathy or complete spinal cord injury; and anatomic limitations preventing the successful placement of an electrode. A total of 285 patients were screened; 133 were enrolled and underwent acute test stimulation, and 120 showed at least 50% improvement during the test phase and received a permanent stimulator. Thirty-four of the 120 patients exited the study for various reasons both related (i.e., lack of efficacy in 6 patients, implant site infection or skin irritation in 5 patients) and unrelated to the implant (i.e., the death of a local principal investigator). Analysis based on the initial 133 patients showed a 66% success rate (≥50% improvement), while analysis based on 106 patients considered completed cases at 12 months showed an 83% success rate. The success rate based on the 120 patients who received a permanently implanted stimulator would fall between these 2 rates. Of 106 cases included in the 12-month results, perfect continence (100% improvement) was reported in approximately 40%, while an additional 30% of patients achieved 75% or greater reduction in incontinent episodes. Success was lower in patients with an internal anal sphincter defect (65% [n=20]) than in patients without a defect (87% [n=86]).

Three and 5-year findings were subsequently published. Mellgren et al (2011) reported on the 120 patients who received a permanently implanted stimulator.[18,] Mean length of follow-up was 3.1 years, and 83 (69%) completed at least part of the 3-year follow-up assessment. In ITT analysis using the last observation carried forward, 79% of patients experienced at least a 50% reduction in the number of incontinent episodes per week compared with baseline, and 74% experienced at least a 50% reduction in the number of incontinent days per week. In a per-protocol analysis at 3 years, 86% of patients experienced at least a 50% reduction in the number of incontinent episodes per week, and 78% experienced at least a 50% reduction in the number of incontinent days per week. By the 3-year follow-up, 334 adverse events considered potentially device-related had been reported in 99 patients; 67% of these occurred within the first year. The most frequently reported adverse events among the 120 patients were implant site pain (28%), paresthesia (15%), implant site infection (10%), diarrhea (6%), and extremity pain (6%). Six infections required surgical intervention (5 device

removals, 1 device replacement). Hull et al (2013) reported on outcomes in 72 patients (60% of the 120 implanted patients) who had completed a 5-year follow-up visit.[19,] Sixty-four (89%) of the patients who contributed bowel diary data at 5 years had at least a 50% improvement from baseline in weekly incontinent episodes, and 26 (36%) of the 72 patients had achieved total continence. It is uncertain whether outcomes differed in the 40% of patients missing from the 5-year analysis.

A study by Altomare et al (2015) also reported on long-term outcomes (minimum, 60-month follow-up; median, 84-month follow-up) in patients implanted with a sacral nerve stimulator for fecal incontinence.[20,] Patients were identified from a European registry and surveyed. Long-term success was defined as maintaining the temporary stimulation success criteria, i.e., at least 50% reduction in the number of fecal incontinence episodes (or fecal incontinence symptom score) at last follow-up, compared with baseline. A total of 272 patients underwent permanent implantation of a sacral nerve stimulation device, and 228 were available for follow-up. A total of 194 (71.3%) of the 272 patients with implants, maintained improvement in the long-term.

A study by Leo et al (2020) prospectively evaluated long-term function with sacral nerve stimulation for fecal incontinence (N=256).[21,] The median incontinence score improved from 19/24 at baseline to 7/24 at the 6-month follow-up. Of the total cohort, 235 patients were followed for a median of 110 months (range, 12 to 270) with a median continence score of 10/24; this score was confirmed at longer-term follow-up (132 months ; range, 60 to 276) of 185 patients.

A French study by Desprez et al (2020) that retrospectively analyzed prospectively collected data found that long-term efficacy with sacral nerve stimulation was maintained for at least 10 years post-implantation in approximately half of the patients treated for fecal incontinence.[22,] A similarly designed study by De Meyere et al (2020) in a single-center in Belgium demonstrated that the efficacy of sacral nerve stimulation in patients with fecal incontinence or low anterior resection syndrome was maintained for at least 5 years.[23,] A study by Picciariello et al (2022) identified patients who had a sacral nerve modulation implantation procedure more than 10 years earlier for fecal incontinence to assess long-term functional outcomes and quality of life.[24,] They found that only 17 (27%) of 58 patients originally identified are still experiencing efficacy with sacral nerve modulation, after a median follow-up of 13 years.

Jottard et al (2021) prospectively studied the Axonics system in 15 patients with fecal incontinence.[25,] The primary outcome was fecal incontinence episodes at 4 weeks according to self-recorded stool diaries. Response (defined as ≥50% improvement in fecal incontinence episodes) occurred in 87% of patients. The median number of incontinence episodes decreased from 8 at baseline to 1.5 at both 4 weeks and 6 months (both p=.001).

Section Summary: Fecal Incontinence

The evidence base consists of 2 RCTs, observational studies including several with long-term follow-up, and systematic reviews of RCTs and uncontrolled studies. Collectively, findings from these studies have suggested that sacral nerve neuromodulation and sacral nerve stimulation improve outcomes when used to treat chronic fecal incontinence in well-selected patients who have failed conservative therapy.

Constipation

Clinical Context and Therapy Purpose

The purpose of sacral nerve neuromodulation in individuals with constipation who have failed conservative treatment 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 constipation who have failed conservative treatment.

Interventions
The treatment being considered is sacral nerve neuromodulation.

Comparators
The comparator of interest is continued conservative therapy, such as dietary modification or pharmacologic treatment.

Outcomes
The outcomes of interest are symptoms, morbid events, and treatment-related morbidity. Positive outcomes include regular bowel movements without complications from the device or implantation procedure.

Negative outcomes would be infection, bleeding, pain, and lead breakages, and lack of improvement in constipation.

Although no set standard for length of follow-up has been established, the existing literature evaluating sacral nerve neuromodulation for constipation has lengths of follow-up ranging from 3 weeks to 55 months.

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 events, 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
A systematic review by Pauwels et al (2021) assessed the role of neuromodulation for treatment in chronic constipation.[26,] Seventeen studies on sacral nerve modulation were included. Although multiple uncontrolled retrospective and prospective studies included in the analysis demonstrated positive results on the effect of sacral nerve modulation in constipation, the 3 RCTs that were identified (Dinning et al [2015] and Zerbib et al [2017], described below, and Thomas et al [2015]) demonstrated no significant improvements in outcomes. The RCT by Thomas et al (2015) only included 11 patients.

In 2017, the Pelvic Floor Society, an affiliate of the Association of Coloproctology of Great Britain and Ireland, conducted a systematic review as the basis for practice recommendations on the use of sacral nerve stimulation for the treatment of constipation.[27,] The systematic review assessed 7 observational studies, all generally of poor quality due to inadequate description of methods. Due to inconsistent reporting on harms and treatment success, and heterogeneity in the patient populations, the Society could not recommend sacral nerve stimulation.

The Cochrane review by Thaha et al (2015) assessed sacral nerve stimulation for constipation and fecal incontinence in adults.[11,] Two trials on sacral nerve neuromodulation for constipation were included, Dinning et al (2015) and another very small crossover trial. In the smaller trial (Kenefick et al [2002]; n=2), the time with abdominal pain and bloating decreased during the "on" period from 79%

to 33%. However, in the larger Dinning et al (2015) trial (discussed below), there was no improvement with sacral nerve neuromodulation during the "on" period. Reviewers concluded: "sacral nerve stimulation did not improve symptoms in patients with constipation."

Thomas et al (2013) published a systematic review of controlled and uncontrolled studies evaluating sacral nerve stimulation for the treatment of chronic constipation.[28,] Reviewers identified 11 case series and 2 blinded crossover studies. Sample sizes for the case series ranged from 4 to 68 patients implanted with a permanent sacral nerve stimulation device; in 7 of the 11 studies, fewer than 25 patients underwent sacral nerve stimulation implantation. Among the 2 crossover studies, 1 study, already mentioned above, included 2 patients implanted with a sacral nerve stimulation device (Kenefick et al [2002]). The other, a study by Knowles et al (2012),[29,] evaluated temporary stimulation in only 14 patients (see below).

Randomized Controlled Trials

Knowles et al (2012) reported on a randomized, double-blind, crossover RCT of sacral nerve stimulation in 14 women.[29,] Patients were included if they were diagnosed with evacuatory dysfunction and rectal hyposensitivity and had failed maximal conservative treatment. They were randomized to 2 weeks of stimulation with the sacral nerve stimulation device turned on and 2 weeks with the sacral nerve stimulation device turned off, in random order. There was no washout period between treatments. The primary efficacy outcome was change in rectal sensitivity, which was assessed using 3 measures of rectal sensory thresholds. The trial found a statistically significantly greater increase in rectal sensitivity with the device turned on for 2 of the 3 measures. Among the secondary outcome measures, there was a significantly greater benefit of active treatment on the percentage of successful bowel movements per week and the percentage of episodes with a sense of complete evacuation. In addition to its small sample size, the trial lacked a washout period between treatments (i.e., there could have been a carryover effect when the device was used first in the on position). Moreover, the patients were highly selected; only 14 of the approximately 1800 patients approached met the eligibility criteria and agreed to participate in the study.

Zerbib et al (2017) reported on a double-blind crossover RCT of sacral nerve stimulation in 36 women with refractory constipation.[30,] Subjects were eligible if they had chronic constipation (>1 year), with 2 or fewer bowel movements per week, straining to evacuate with more than 25% of attempts, or sensation of incomplete evacuation with more than 25% of attempts, with lack of response to standard therapies. Thirty-six subjects meeting inclusion criteria underwent an initial peripheral nerve evaluation; those who had adequate symptom improvement to a predefined level were offered a permanent sacral nerve stimulation implant. After a 2-week washout, subjects were randomized to "on" or "off" for 8 weeks, followed by a 2-week washout, when the groups crossed over. Of the 36 patients enrolled, 20 responded and underwent randomization. Four were excluded (2 due to wound infection, 1 each due to the withdrawal of consent and lack of compliance). At 1 year follow-up, a positive response was observed in 12 of 20 and 11 of 20 patients after active and sham stimulation periods, respectively (p=.746).

A larger randomized crossover trial was published by Dinning et al (2015).[31,] The trial included patients (age range, 18 to 75 years) with slow transit constipation. Potentially eligible patients completed a 3-week stool diary and, in order to continue participating, they had to indicate in the diary that they had complete bowel movements less than 3 days per week for at least 2 of the 3 weeks. Patients with metabolic, neurogenic, or endocrine disorders known to cause constipation were excluded. Fifty-seven met eligibility criteria and had temporary percutaneous nerve evaluation, and 55 underwent permanent implantation. In random order, patients received active stimulation (subsensory in phase 1, suprasensory in phase 2) or sham stimulation (the device was on but pulse width and frequency were set to zero). The primary outcome measure, determined by stool diaries, was a bowel movement with feelings of complete evacuation more than 2 days per week for at least 2 of 3 weeks; it was only assessed in phase 2. Compared with sham stimulation, 16 (29.6%) of 54 patients met the primary outcome during suprasensory stimulation, and 11 (20.8%) of 53 patients met it during sham

stimulation; the difference was not statistically significant (p=.23). Other outcomes did not differ significantly with suprastimulation versus sham stimulation and outcomes did not differ in the phase 1 comparison of subsensory versus sham stimulation.

Case Series

One of the larger case series was published by Kamm et al (2010).[32,] This prospective study was conducted at multiple sites in Europe. It included 62 patients who had idiopathic chronic constipation lasting at least 1 year and who had failed medical and behavioral treatments. Constipation was defined as at least 1 of the following: fewer than 2 bowel movements per week, straining to evacuate in at least 25% of attempts, or a sensation of incomplete evacuation on at least 25% of occasions. Forty-five (73%) of the 62 patients met criteria for permanent implantation during the 3-week trial period. Criteria included an increase in evacuation frequency to at least 3 per week or a 50% reduction in either frequency of straining during evacuation or in episodes with the sensation of incomplete evacuation. After a median follow-up of 28 months (range, 1 to 55 months) after permanent implantation, 39 (87%) of 45 patients were classified as treatment successes (ie, met the same improvement criteria as used to evaluate temporary stimulation). There was a significant increase in the frequency of bowel movements from a median of 2.3 per week at baseline to 6.6 per week at the latest follow-up (p<.001). The frequency of spontaneous bowel movements (ie, without laxatives or other stimulation) increased from a median of 1.7 per week at baseline to 4.3 per week at the last follow-up (p=.001). A total of 101 adverse events were reported; 40 (40%) of these were attributed to underlying constipation or an unrelated diagnosis. Eleven serious adverse events related to treatment were reported (the authors did not specify whether any patients experienced >1 serious event). The serious adverse events included deep postoperative infection (n=2), superficial erosion of lead through the skin (n=1), persistent postoperative pain at the site of implantation (n=2), conditions leading to lead revision (n=4), and device failure (n=2). The study was criticized for including a large number of patients who had more than 2 bowel movements per week at study entry.

Another study, published by Maeda et al (2010), focused on adverse events.[33,] This chart review included 38 patients with constipation who received permanent sacral nerve stimulation after a successful trial period. When charts were reviewed, a mean of 25.7 months had elapsed since implantation. A total of 58 reportable events were identified in 22 (58%) of the 38 patients. A median of 2 (range, 1 to 9) events per patient was reported; 26 (45%) of 58 events were reported in the first 6 months after device implantation. The most common reportable events were lack or loss of efficacy (26/58 [45%] events) and pain (16 [28%] events). Twenty-eight (48%) of the events were resolved by reprogramming. Surgical interventions were required for 19 (33%) of the events, most commonly permanent electrode replacement (14 events). Three (8%) of 38 patients discontinued device use due to reportable events.

Section Summary: Constipation

Systematic reviews that include 3 randomized crossover studies along with other studies are available; 1 of the 3 RCTs had a sample size of 2, and the other 2 RCTs reported mixed outcomes when active sacral nerve stimulation was compared with sham stimulation. Results of an additional RCT did not support permanent implantation of a sacral nerve stimulator in patients with refractory constipation who initially responded to temporary stimulation. There are also several, mainly small, case series, some of which were included as part of the systematic reviews. Collectively, available data are insufficient to permit scientific conclusions about the effect of sacral nerve neuromodulation or sacral nerve stimulation on health outcomes in patients with constipation.

Chronic Pelvic Pain

Clinical Context and Therapy Purpose

The purpose of sacral nerve neuromodulation in individuals with chronic pelvic pain 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 chronic pelvic pain.

Interventions
The treatment being considered is sacral nerve neuromodulation.

Comparators
The comparator of interest is continued conservative therapy, such as cognitive behavioral therapy or pharmacologic treatment.

Outcomes
The outcomes of interest are symptoms, morbid events, and treatment-related morbidity. Positive outcomes include relief from chronic pelvic pain without complications from the device or implantation procedure.

Negative outcomes would be infection, bleeding, pain, and lead breakages, and lack of improvement in constipation.

Although no set standard for length of follow-up has been established, the existing literature evaluating sacral nerve neuromodulation for chronic pelvic pain has a length of follow-up of 1 year.

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 events, 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
Case series
A systematic review by Tirlapur et al (2013), evaluating studies on nerve stimulation for chronic pelvic pain, did not identify any RCTs on sacral nerve stimulation for treatment of chronic pelvic pain or bladder pain.[34,] The published evidence was limited to case series. For example, Martellucci et al (2012) reported on 27 patients with chronic pelvic pain (at least 6 months) who underwent testing for sacral nerve neuromodulation implantation.[35,] After a 4-week temporary stimulation phase, 16 (59%) of 27 patients underwent implantation of an InterStim device. In the 16 implanted patients, mean pain on a visual analog scale was 8.1 before implantation and 2.1 at the 6- and 12-month follow-ups. An earlier study by Siegel et al (2001) reported on 10 patients and reported that 9 of them experienced a decrease in pain with sacral nerve stimulation.[36,]

Section Summary: Chronic Pelvic Pain
Data from several small case series with heterogeneous patient samples represent insufficient evidence on the effect of sacral nerve neuromodulation and sacral nerve stimulation on health outcomes in patients with chronic pelvic pain. RCTs are needed, especially with sham controls, reporting pain as the primary outcome.

Trial Stimulation Techniques
As described in the Background section, there are 2 types of trial stimulation before permanent implantation of a neuromodulation device. They are percutaneous nerve evaluation and stage 1 (lead

implantation) of a 2 stage surgical procedure. Percutaneous nerve evaluation was the initial method of trial stimulation and has been the standard of care before permanent implantation of the device. In review articles like that by Baxter and Kim (2010), lead migration was described as a potential problem with the percutaneous nerve evaluation technique but no studies were identified that quantified the rate of lead migration in large numbers of patients.[37,] The 2-stage surgical procedure is an alternative trial stimulation modality.

Comparative rates of lead migration and rates of progressing to permanent implantation are useful outcomes in that there may be reduced sensitivity of the percutaneous nerve evaluation test due to lead dislodgement. However, due to the potential placebo effect of testing, it is also important to compare the long-term efficacy of sacral nerve neuromodulation after these 2 trial stimulation techniques. Also, it would be useful to have data on the optimal approach to using the 2-stage surgical procedure. As noted in the Background section of this evidence review, the 2-stage surgical procedure has been used in various ways, including for patients who failed percutaneous nerve evaluation, for patients with an inconclusive percutaneous nerve evaluation, and for patients who had a successful percutaneous nerve evaluation to further refine patient selection.

No RCTs were identified that evaluated long-term health outcomes (e.g., reduction in incontinence symptoms) after trial stimulation with percutaneous nerve evaluation versus stage-1 lead implantation. There are limited data on the rates of failure after sacral nerve neuromodulation in patients selected using the 2-stage test. Leong et al (2011), in a single-center prospective study, evaluated 100 urge incontinence patients with both percutaneous nerve evaluation and the first stage of the 2-stage technique (i.e., patients served as their own controls).[38,] Patients were first screened with the percutaneous nerve evaluation and, afterward, with lead implantation. Response to testing was based on diary data for 3 consecutive days after receiving each type of lead. In the test phase, 47 (47%) patients had a positive response to percutaneous nerve evaluation, and 69 (69%) had a positive response to the first-stage lead placement test. All patients who responded to percutaneous nerve evaluation also responded to stage-1 testing. The 69 patients who responded to stage-1 testing underwent implantation. They were then followed for a mean of 26 months, and 2 patients (3% of those with a positive test) failed therapy. Although this study showed a low failure rate, only 22 subjects had a successful test with the stage-1 technique but not with percutaneous nerve evaluation. This is a small number of patients on which to base conclusions about the comparative efficacy of the 2 techniques. Also, the order of testing could have biased findings. All patients had percutaneous nerve evaluation testing before the first-stage lead implantation and could have been biased by their first test. Stronger study designs would require randomizing the order of testing or randomizing patients to receive 1 type of testing or the other.

Scheepens et al (2002) analyzed 15 patients with urinary incontinence or retention who had a good initial response to percutaneous nerve evaluation but then failed percutaneous nerve evaluation in the longer term (i.e., days 4 to 7 of testing).[39,] These 15 patients underwent stage 1 of the 2-stage technique. One patient failed the first stage and was explanted. Of the remaining 14 patients, 2 were explanted later due to lack of efficacy of sacral nerve neuromodulation. The other 12 patients were followed for a mean of 4.9 years and voiding diary data showed improvement in nearly all incontinence symptoms. There was a low failure rate after stage-1 testing but this is a small sample size, and stage-1 testing was not compared with another trial stimulation method (e.g., percutaneous nerve evaluation).

Marcelissen et al (2010) published findings in 92 patients with urinary symptoms who underwent trial evaluation for sacral nerve neuromodulation treatment.[40,] Patients initially underwent percutaneous nerve evaluation (n=76) or stage-1 surgery (n=16). Patients who had a negative percutaneous nerve evaluation (n=41) then underwent stage-1 evaluation. Eleven (63%) of 16 patients had a positive initial stage-1 test and were implanted with a sacral nerve neuromodulation device. Thirty-five (46%) of 76 patients had a positive initial percutaneous nerve evaluation test and underwent permanent implantation. Forty-one (54% of those undergoing percutaneous nerve evaluation) patients had a

negative test and then had stage-1 surgical evaluation. Eighteen (44%) of 41 had a positive stage-1 test and underwent implantation. Altogether 64 patients underwent implantation of a sacral nerve neuromodulation device. Mean follow-up was 51 months. Thirty-eight (59%) of 64 patients implanted experienced clinical success at last follow-up, defined as more than 50% improvement in symptoms reported in a voiding diary. The clinical success rate was not reported separately by trial stimulation method.

Several studies (e.g., Borawski et al [2007][41,] and Bannowsky et al [2008][42,]) compared response rates during the test phase in patients with urinary incontinence symptoms; both found higher response rates with the stage-1 test than with percutaneous nerve evaluation. In these studies, more people who received the stage-1 test went on to undergo implantation. The Borawski et al (2007) study was an RCT with 30 patients (13 received percutaneous nerve evaluation, 17 received the stage- 1 test). The Bannowsky et al (2008) study was not randomized; 42 patients received a percutaneous nerve evaluation, and 11 patients received a stage-1 test. Neither followed patients once devices were implanted, so neither provided data on the relative success rates of sacral nerve neuromodulation after these 2 test procedures. Without follow-up after implantation, it is not possible to determine whether the 2-stage procedure reduced false negatives (i.e., selected more people who might benefit) or increased false negatives (i.e., selected more people who might go on to fail).

No published studies were identified that compared different trial stimulation techniques in patients with nonurinary conditions (e.g., fecal incontinence or chronic pelvic pain).

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.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2012 Input

In response to requests, input was received from 4 physician specialty societies and 2 academic medical centers while this policy was under review in 2012. Reviewers from 2 specialty societies and 2 academic medical centers provided opinions on the possible medical necessity of implantable leads for test stimulation, as part of a 2-stage process for device implantation. All 4 respondents supported the use of implantable leads for test stimulation as an alternative to percutaneous test stimulation, for patients who had failed percutaneous test stimulation and/or for patients with inconclusive percutaneous test stimulation. Reasons for support included a longer period of interrupted treatment with stage-1 stimulation due to less lead migration and a higher rate of positive tests compared with percutaneous test stimulation.

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.

Urinary Disorders

American Urological Association

In 2019, the American Urological Association updated its guidelines on the diagnosis and treatment of overactive bladder.[43,] The guidelines stated that sacral neuromodulation may be offered as a

third-line treatment in carefully selected patients with severe refractory symptoms or in those who are not candidates for second-line therapy (e.g., oral antimuscarinics, oral β3-adrenoceptor agonists, transdermal oxybutynin) and are willing to undergo surgery (recommendation, evidence strength Grade C).

American College of Obstetricians and Gynecologists

A 2015 practice bulletin on urinary incontinence (replaced practice bulletin number 63, 2005; reaffirmed in 2019) from the College stated, "sacral neuromodulation may be considered for patients with recalcitrant urinary urge incontinence who have failed other conservative measures, including bladder training, pelvic floor physical therapy with biofeedback, and pharmacologic treatment."[44,]

International Continence Society

In 2018, the International Continence Society published a best practice statement on the use of sacral neuromodulation.[45,] The authors specified that the guideline recommendations applied primarily to the Interstim device and may or may not be applicable to future devices that have become available since that time. For both urinary and bowel disorders, first-line interventions include behavioral therapy, physical therapy, and medical management. Sacral neuromodulation can be offered to patients who fail or have an intolerance to first-line interventions. The guideline also states that sacral neuromodulation is appropriate for interstitial cystitis, bladder pain syndrome, Fowler's syndrome, voiding dysfunction, and nonobstructive urinary retention. However, there was a lack of evidence supporting the use of sacral neuromodulation for chronic pelvic pain unrelated to any of the aforementioned etiologies. For constipation, sacral neuromodulation should only be considered for patients who have had symptoms for at least 1 year, whose symptoms cannot be attributed to a mechanically correctable cause, and when conservative treatment has failed. Contraindications to sacral neuromodulation include lack of response during a therapeutic trial and pregnancy. Relative contraindications may include severe or rapidly progressive neurologic disease, abnormal sacral anatomy, anticipated need for magnetic resonance imaging below the head, and spinal cord injury.

National Institute for Health and Care Excellence

In 2020, NICE issued guidance on the Axonics sacral neuromodulation system for treating refractory overactive bladder.[46,] The guidance states that the Axonics system should be considered an option for people with refractory overactive bladder. Similarly, 2004 guidance states that use of sacral nerve stimulation for urge incontinence and symptoms of urgency/frequency is supported by evidence of efficacy and safety.[47,]

Fecal Disorders

National Institute for Health and Care Excellence

In 2007, NICE issued guidance on the management of fecal incontinence. The guidance was reviewed in 2014 and 2018, and no changes were made. The guidance has recommended:

> "a trial of temporary sacral nerve stimulation should be considered for people with faecal incontinence in whom sphincter surgery is deemed inappropriate.... All individuals should be informed of the potential benefits and limitations of this procedure and should undergo a trial stimulation period of at least 2 weeks to determine if they are likely to benefit. People with faecal incontinence should be offered sacral nerve stimulation on the basis of their response to percutaneous nerve evaluation during specialist assessment, which is predictive of therapy success."[48,]

American College of Gastroenterology

In its 2014 clinical guideline on the management of benign anorectal disorders, including fecal incontinence, the American College of Gastroenterology (ACG) found that "sacral nerve stimulation should be considered in [fecal incontinence] who do not respond to conservative therapy (strong recommendation, moderate quality of evidence)."[49,] The 2021 update of these guidelines keep the recommendation for sacral nerve stimulation in patients with fecal incontinence refractory to medical therapy the same as in the 2014 version.[50,] Additionally, due to a lack of evidence supporting

efficacy and the risk of adverse events and complications, the 2021 ACG Panel makes a statement stating that sacral nerve stimulation "cannot be recommended in patients with constipation of any type."

American College of Obstetricians and Gynecologists

A 2019 practice bulletin (reaffirmed 2021) on fecal incontinence from the American College of Obstetricians and Gynecologists (ACOG) stated, "Sacral nerve stimulation can be considered as a surgical treatment option for women with fecal incontinence with or without anal sphincter disruption who have failed conservative treatments."[51,]

American Society of Colon and Rectal Surgeons

In 2015, the American Society of Colon and Rectal Surgeons released a clinical practice guideline for the treatment of fecal incontinence.[52,] They stated that "sacral neuromodulation may be considered as a first-line surgical option for incontinent patients with and without sphincter defects (Grade of Recommendation: Strong, based on moderate-quality evidence, 1B)."

In 2016, the Society released a clinical practice guideline for the management of constipation.[53,] In this guideline, they stated "sacral neuromodulation may be an effective treatment for patients with chronic constipation and successful peripheral nerve evaluation test when conservative measures have failed; however, it is not currently approved by the US Food and Drug Administration for this condition in the United States (Grade of Recommendation: Weak, based on moderate quality evidence, 2B)."

Chronic Pelvic Pain

American College of Obstetricians and Gynecologists

A 2020 practice bulletin (reaffirmed 2023) on chronic pelvic pain from ACOG does not mention sacral nerve stimulation or modulation.[54,]

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

Since 2002, the Centers for Medicare & Medicaid Services has covered sacral nerve stimulation for the "treatment of urinary urge incontinence, urgency-frequency syndrome, and urinary retention."[55,] Sacral nerve stimulation "involves both a temporary test stimulation to determine if an implantable stimulator would be effective and a permanent implantation in appropriate candidates. Both the test and the permanent implantation are covered."
"The following limitations for coverage apply to all three indications:

- Patients must be refractory to conventional therapy … and be appropriate surgical candidates such that implantation with anesthesia can occur.
- Patients with stress incontinence, urinary obstruction, and specific neurologic diseases … that are associated with secondary manifestations … are excluded.
- Patients must have had successful test stimulation in order to support subsequent implantation. Before patients are eligible for permanent implantation, they must demonstrate a 50% or greater improvement through test stimulation. Improvement is measured through voiding diaries."

Ongoing and Unpublished Clinical Trials

Some currently ongoing trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03139734	Sacral Neuromodulation for Pelvic Pain Associated with Endometriosis	50	May 2022
NCT03811821	Comparative Effects of Biofeedback, Sacral Nerve Stimulation, and Injectable Bulking Agents for Treatment of Fecal Incontinence: The Fecal Incontinence Treatment Study (FIT) Study	285	Dec 2025
NCT04506866[a]	Evaluation of InterStim Micro System Performance and Safety (ELITE) to Confirm Long-Term Outcomes - Post Market Clinical Follow-Up Study	148	Nov 2024
NCT04713085	Sacral Nerve Stimulation in Children and Adolescents With Chronic Constipation: a Case-control Study on Invasive and Non-invasive Neuromodulatory Treatment	30	Dec 2023
NCT04232696[a]	Clinical Study of Neuaspera's Implantable Sacral Nerve Stimulation (SNS) System in Patients With Symptoms of Overactive Bladder (OAB)	310	April 2024
NCT02577302[a]	Multi-center, Prospective, Randomized, Controlled, Non-Inferiority, Clinical Trial of Chronic Afferent Nerve Stimulation (CAN-Stim) of the Tibial Nerve Versus Sacral Nerve Stimulation (SNS) in the Treatment of Urinary Urgency Incontinence Resulting From Refractory Overactive Bladder (OAB)	200	Oct 2024
NCT05543382[a]	Cycling Study With the Axonics System	60	Jun 2023
NCT05064384[a]	Axonics SacRal NeuromodulaTIon System RegisTRY Study : ARTISTRY	300	Nov 2023
NCT03327948[a]	Axonics SacRal NeuromodulaTIon System for Urinary Urgency Incontinence TreatmeNt (ARTISAN-SNM)	145	Jun 2020 (active, not recruiting)
Unpublished			
NCT04710433	Non-invasive Sacral Nerve Stimulation in Children and Adolescents With Chronic Constipation: a Case-control Study on External Neuromodulatory Treatment	59	Dec 2021

[a] denotes an industry-sponsored trial
NCT: national clinical trial.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Diagnosis of type of incontinence, frequency and duration
  - Other pertinent diagnoses or comorbidities (e.g., neurologic conditions, malformations, prior radiation therapy, infections, etc.) or documentation of the absence of them
  - Documented trial stimulation period demonstrating at least 50% improvement in symptoms (for permanent implant)
  - Prior trial of conservative therapies and patient response
- Make and model of device being requested (if applicable)
- Multidisciplinary evaluation notes if applicable

Post Service (in addition to the above, please include the following):

- Operative report(s)

Coding

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

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

Type	Code	Description
CPT®	64561	Percutaneous implantation of neurostimulator electrode array; sacral nerve (transforaminal placement) including image guidance, if performed
	64581	Open implantation of neurostimulator electrode array; sacral nerve (transforaminal placement)
	64585	Revision or removal of peripheral neurostimulator electrode array
	64590	Insertion or replacement of peripheral or gastric neurostimulator pulse generator or receiver, direct or inductive coupling
	64595	Revision or removal of peripheral or gastric neurostimulator pulse generator or receiver
	95970	Electronic analysis of implanted neurostimulator pulse generator/ transmitter (e.g., contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with brain, cranial nerve, spinal cord, peripheral nerve, or sacral nerve, neurostimulator pulse generator/transmitter, without programming
	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
HCPCS	A4290	Sacral nerve stimulation test lead, each
	E0745	Neuromuscular stimulator, electronic shock unit
	E1399	Durable medical equipment, miscellaneous
	L8680	Implantable neurostimulator electrode, each
	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

Policy History

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

Effective Date	Action
06/10/1998	New Policy Adoption
10/20/1999	Policy Review
01/11/2008	Policy Revision Title change. Prior policy title: Implantable Unilateral Sacral Nerve Stimulation for Urinary Incontinence. Code Revision.
09/25/2009	Policy Title Revision, criteria revised
10/29/2010	Coding Update
04/01/2011	Policy revision with position change
08/29/2014	Policy revision with position change
04/30/2015	Sacral Anterior Root Stimulation for Neurogenic Bladder (Policy statement indication) has been merged to this policy from Neuromuscular, Functional, and Threshold Electrical Stimulation Policy revision without position change
07/31/2015	Coding Update
02/01/2016	Coding update
03/01/2017	Policy revision without position change
07/01/2018	Policy revision without position change
06/01/2019	Policy revision without position change
06/01/2023	Policy reactivated. Previously archived from 06/01/2020 to 05/31/2023.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

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

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

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an

authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

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

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

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

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** Blue font: Verbiage Changes/Additions
Reactivated Policy **Policy Statement:** N/A	**Sacral Nerve Neuromodulation/Stimulation 7.01.69** **Policy Statement:** **Urinary Incontinence and Nonobstructive Retention** **Criteria A** I. A trial period of sacral nerve neuromodulation with either percutaneous nerve stimulation or a temporarily implanted lead may be considered **medically necessary** in individuals who meet **all** of the following criteria: A. There is a diagnosis of at least **one** of the following: 1. Urge incontinence 2. Urgency-frequency syndrome 3. Nonobstructive urinary retention 4. Overactive bladder B. There is documented failure or intolerance to at least 2 conventional conservative therapies (e.g., behavioral training such as bladder training, prompted voiding, or pelvic muscle exercise training, pharmacologic treatment for at least a sufficient duration to fully assess its efficacy, and/or surgical corrective therapy). 1. The individual is an appropriate surgical candidate 2. Incontinence is not related to a neurologic condition **Criteria B** II. Permanent implantation of a sacral nerve neuromodulation device may be considered **medically necessary** in individuals who meet **all** of the following criteria: A. All of criteria A. A and B above are met B. A trial stimulation period demonstrates at least 50% improvement in symptoms over a period of at least 48 hours III. Other urinary/voiding applications of sacral nerve neuromodulation are considered **investigational**, including but not limited to the treatment of stress incontinence or urge incontinence due to a

POLICY STATEMENT	
BEFORE	AFTER Blue font: Verbiage Changes/Additions
	neurologic condition (e.g., detrusor hyperreflexia, multiple sclerosis, spinal cord injury, other types of chronic voiding dysfunction). **Fecal Incontinence** **Criteria A** IV. A trial period of sacral nerve neuromodulation with either percutaneous nerve stimulation or a temporarily implanted lead may be considered **medically necessary** in individuals who meet **all** of the following criteria: A. There is a diagnosis of chronic fecal incontinence of more than 2 incontinent episodes on average per week for more than 6 months or for more than 12 months after vaginal childbirth B. There is documented failure or intolerance to conventional conservative therapy (e.g., dietary modification, the addition of bulking and pharmacologic treatment) for at least a sufficient duration to fully assess its efficacy C. The individual is an appropriate surgical candidate D. The condition is not related to an anorectal malformation (e.g., congenital anorectal malformation; defects of the external anal sphincter over 60°; visible sequelae of pelvic radiation; active anal abscesses and fistulae) or chronic inflammatory bowel disease E. Incontinence is not related to a neurologic condition F. The individual has not had rectal surgery in the previous 12 months or, in the case of cancer, the individual has not had rectal surgery in the past 24 months **Criteria B** V. Permanent implantation of a sacral nerve neuromodulation device may be considered **medically necessary** in individuals who meet **all** of the following criteria: A. All of criteria A. A through F above are met B. A trial stimulation period demonstrates at least 50% improvement in symptoms over a period of at least 48 hours

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
	VI. Sacral nerve neuromodulation is considered **investigational** in the treatment of chronic constipation or chronic pelvic pain.