Sacral Nerve Stimulation for Urinary and Fecal Indications

Policy Number: 2023T0630C
Effective Date: October 1, 2023

➲ Instructions for Use

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- Gastrointestinal Motility Disorders, Diagnosis, and Treatment

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- Gastroesophageal and Gastrointestinal (GI) Services and Procedures

Application

UnitedHealthcare Commercial

This Medical Policy applies to all UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange

This Medical Policy applies to Individual Exchange benefit plans in all states except for Colorado.

Coverage Rationale

➲ See Benefit Considerations

Note: This policy applies to individuals ≥ 18 years of age.

Sacral nerve stimulation screening trial is proven and medically necessary for treating urinary voiding dysfunction when all the following criteria are met:

- Lower urinary tract symptoms, as indicated by one or more of the following:
  - Overactive bladder symptoms
  - Urge Incontinence
  - Nonobstructive urinary retention
- Bladder capacity of 100 ml or greater
- Urinary voiding dysfunction is not secondary to a neurologic disease origin
- No bladder outlet obstruction
- Symptoms refractory to conservative care (e.g., bladder training, pelvic floor rehabilitation, pharmacological therapy)
- Individual capable of operating sacral nerve stimulating device

Sacral nerve stimulation screening trial is proven and medically necessary for treating Fecal Incontinence when all the following criteria are met:

- Symptoms refractory to conservative care (e.g., bowel training, bulking agents, pelvic floor rehabilitation)
- Individual capable of operating sacral nerve stimulating device
- Fecal Incontinence is not secondary to a neurologic disease origin
- Fecal Incontinence is not secondary to Constipation

Sacral nerve stimulation permanent implantation for treating urinary voiding dysfunction and Fecal Incontinence is proven and medically necessary when all the following criteria are met:

- All criteria for sacral nerve stimulation screening trial have been met
- Improvement in reported symptoms of 50% or greater in response to a screening trial of sacral nerve stimulation

Sacral nerve stimulator replacement or revision is considered medically necessary when the individual has met all the above criteria and the existing device cannot be repaired or is no longer under warranty.

Removal of sacral nerve stimulator and all related components is proven and medically necessary.

Sacral nerve stimulation for the treatment of Constipation and Chronic Pelvic Pain is considered unproven and not medically necessary due to insufficient evidence of safety and/or efficacy.

Documentation Requirements

Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The documentation requirements outlined below are used to assess whether the member meets the clinical criteria for coverage but do not guarantee coverage of the service requested.

CPT/HCPCS Codes*	Required Clinical Information
Sacral Nerve Stimulation for Urinary and Fecal Indications	

64590
64595
L8679
L8680
L8682
L8685
L8686
L8687
L8688
	Medical notes documenting the following, when applicable:
	• Diagnosis
	• History of the medical condition(s) requiring treatment, including:
	  ○ Origin of the dysfunction
	  ○ Presence or absence of bladder outlet obstruction
	  ○ Presence or absence of constipation
	• Signs and symptoms
	• Treatments tried, failed, or contraindicated; include the dates, duration of treatment, and reason for discontinuation
	• Bladder capacity in milliliters
	• Individual's capacity to operate device
	• For permanent implantation, include percentage improvement of symptoms in response to a screening trail

*For code descriptions, refer to the Applicable Codes section.

Definitions

Chronic Pelvic Pain: Chronic Pelvic Pain is defined as persistent or recurrent episodic pelvic pain associated with symptoms suggesting lower urinary tract, sexual, bowel, or gynecological dysfunction with no proven infection or other obvious pathology (Fall et al., 2010).

Chronic Urinary Retention: Chronic Urinary Retention is diagnosed when an individual has a postvoid residual volume (PVR) ≥ 300 milliliters (mL) that persists for ≥ 6 months and is documented on ≥ 2 separate occasions (Stoffel et al., 2016).

Constipation: Constipation is a syndrome that is defined by bowel symptoms (difficult or infrequent passage of stool, hardness of stool, or a feeling of incomplete evacuation) that may occur either in isolation or secondary to another underlying disorder (Bharucha et al., 2013).

Fecal Incontinence: Fecal Incontinence is the involuntary passage of fecal matter through the anus or the inability to control the discharge of bowel contents. Its severity can range from an involuntary passage of flatus to complete evacuation of fecal matter (Shah & Villanueva Herrero, 2022).

Urge Incontinence: Urge Incontinence is a type of Urinary Incontinence in adults, which involves sudden compelling urges to void and results in involuntary leakage of urine (Nandy & Ranganathan, 2022).

Urinary Incontinence: Urinary Incontinence is known as the leakage of any volume of urine, which is mostly involuntary (Nandy & Ranganathan 2022).

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
64561	Percutaneous implantation of neurostimulator electrode array; sacral nerve (transforaminal placement) including image guidance, if performed
64581	Incision for 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
L8679	Implantable neurostimulator, pulse generator, any type
L8680	Implantable neurostimulator electrode, each
L8682	Implantable neurostimulator radiofrequency receiver
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

Description of Services

Sacral nerve stimulation (SNS), also referred to as sacral neuromodulation (SNM), is a safe, effective, and minimally invasive therapy to treat Urinary Incontinence, urinary retention, urgency, frequency, and Fecal Incontinence. Research suggests that placement of the SNM lead in the S3 region will cause stimulation of afferent fibers from the anal sphincter, rectum, and pelvic floor. SNM inhibits the guarding reflex and induces voiding in individuals with urinary retention. SNM appears to stimulate the relaxation of pelvic floor muscles and the urethra, which helps initiate micturition for individuals with impaired bladder pressure, retention, and incomplete emptying (Feloney et al., 2022).

Individuals first undergo a trial of 3 to 7 days to determine eligibility for a neurostimulator. Individuals who have had a successful test stimulation, usually defined as improvement in reported symptoms of 50% or greater in response to a screening trial of SNS, may undergo implantation of a permanent neurostimulator. Permanent SNS implantation is performed under general

anesthesia. Briefly, a midline sacral incision is made down to the level of the lumbodorsal fascia, which is opened about 1.5 centimeters from the midline. An insulated needle is placed into the appropriate foramen, and the motor responses are evaluated until the appropriate foramen is located. The connecting lead and neurostimulator are then connected. The incision is closed in layers usually, without drains. A confirmatory radiograph is obtained before discharge (Das et al., 2000).

Clinical Evidence

Urinary Indications

A 2022 Hayes Health Technology Assessment was conducted to evaluate the utilization of sacral nerve stimulation (SNS) in treating non-obstructive urinary retention (NOUR). The assessment consisted of evidence from six studies, including one randomized controlled trial (RCT), one pretest-posttest study, one repeated measures study, and three case series with follow-ups ranging from 10 months to 8 years. The evidence suggests that SNS improves outcomes for individuals who have NOUR; however, it cautions individuals who have chronic refractory NOUR as they are frequently not candidates for SNS therapy due to inadequate response during initial testing. Overall, the evidence evaluated in this assessment described SNS as a reasonable treatment option for individuals with intractable NOUR who are not responding to standard or alternative therapies and who meet the criteria for permanent implantation.

A Hayes Health Technology Assessment was conducted to analyze percutaneous tibial nerve stimulation (PTNS) for treating symptomatic neurogenic lower urinary tract dysfunction (nLUTD), and reports SNS as a proper clinical alternative to PTNS. The assessment describes PTNS and SNS as third-line treatments for individuals refractory to behavioral or pharmacologic therapy. Overall, the literature evaluated in this assessment designated PTNS as a minimally invasive alternative to SNS; however, studies comparing the two technologies are lacking (Hayes, 2019; updated 2022).

Tilborghs & Wachter (2022) conducted a systematic review of literature on sacral neuromodulation (SNM) for the treatment of overactive bladder (OAB). The comprehensive literature search for the collection of articles related to SNM for OAB was conducted utilizing the following databases: Pubmed/MEDLINE, Cochrane, and Scopus. Studies included were those with at least 50 individuals who received SNM therapy for OAB and had a follow-up of at least 12 months to evaluate the safety and efficacy of SNM. The literature review uncovered no life-threatening or major irreversible complications. According to the authors, SNM proved to be a safe and effective therapy for OAB for the short, medium, and long term without precluding any other treatment options.

A 2021 Hayes Evolving Evidence Review on Axonics® Sacral Neuromodulation (Axonics Inc) for managing urinary dysfunction investigated full-text studies, systematic reviews, clinical practice guidelines, and position statement's support of the technology. The review of clinical studies suggested minimal support for using Axonics SNM for treating lower urinary tract dysfunction and no support from systematic reviews. The evolving evidence review found strong support for using Axonics SNM in managing urinary dysfunction in full-text clinical practice guidelines and position statements.

A Hayes Health Technology Assessment compared the effectiveness of PTNS to onabotulinumtoxinA (BTX) and SNS for treating symptomatic non-neurogenic OAB. The assessment describes SNS, transcutaneous tibial nerve stimulation, and transvaginal pelvic floor electrostimulation as alternative treatments for OAB. Additionally, the evidence shows that treatment options such as BTX or neuromodulation, including SNS or PTNS, are proper treatment options when an individual has failed behavioral and pharmacologic therapies. Overall, there is a necessity for further research into the use of PTNS for maintenance therapy of OAB syndrome. Well-designed comparative or controlled studies on the efficacy and safety of maintenance therapy past the initial treatment course with PTNS are lacking (Hayes, 2018; updated 2021).

InterStim™ was the subject of an ECRI Clinical Evidence Assessment that evaluated implantable SNS for treating urinary incontinence (UI). The assessment used data from two systematic reviews, two extensive before-and-after studies, two large case series, and one RCT. Evidence limitations included the risk of bias in the RCT due to lack of outcome assessor blinding, the retrospective design of the case series, and lack of parallel controls in the before-and-after studies. The RCT included in the assessment suggests InterStim works as well as other treatments such as botulinum toxin (Botox®) for decreasing UI. The authors concluded that InterStim is safe and effective in relieving UI and urinary frequency symptoms in most individuals with UI (ECRI, 2012; updated April 2021).

An ECRI Clinical Evidence Assessment evaluated Axonics rechargeable SNM (Axonics Modulation Technologies, Inc.) for treating UI. The assessment indicated that SNM is generally a safe and effective treatment option for specific individuals with UI; however, the evidence is limited to two small sample sized before-and-after studies. Limitations to the literature include a considerable risk of bias, a small sample size, and a lack of comparison of Axonics to other therapies. Overall, additional studies such as RCTs that report long-term outcomes are necessary to assess the comparative safety and effectiveness of Axonics SNM to other treatments (ECRI, 2019; updated 2021).

Elterman et al. (2021) directed a prospective, multicenter, international RCT to explore the effects of InterStim's three different amplitude settings in female subjects with OAB symptoms such as urinary urge incontinence (UUI). The impact of sub-sensory amplitude settings on OAB symptoms was evaluated using voiding diaries at six and 12 weeks during SNM therapy. To be included in the trial, the participant must have a primary diagnosis of UUI, be female, 18 years of age or older, be a candidate for InterStim placement, and be willing to maintain a current regimen of OAB medication. Exclusion criteria prohibited individuals with neurological conditions, uncontrolled diabetes, urinary tract infection (UTI), stress incontinence, or those who received treatment with Botox in the past nine months. Subjects who completed enrollment/baseline visits, lead implant, therapy evaluation, and neurostimulator device implant were randomized in a 1:1 ratio to one of three amplitude settings (50% of sensory threshold [ST], 80% of ST, and ST). Individuals logged in the voiding diaries at baseline, therapy evaluation, and at the six and 12-week follow-up visits. Quality of life (QoL) was assessed using the validated international consultation on incontinence modular questionnaire—overactive bladder symptoms quality of life (ICIQ-OABqol) at baseline and 12 weeks. Subjects' feeling of improvement was evaluated using the patient global impression of improvement (PGI-I) questionnaire at six and 12-week follow-up visits. Successful test stimulation was defined as ≥ 50% improvement in UI or urinary frequency voiding symptoms or return to normal voiding of fewer than eight voids per day for subjects with urinary frequency. Successful test stimulation was demonstrated in 48 individuals; 46 were implanted with a neurostimulator device, and 43 completed the 12-week follow-up visit. The UI outcomes were as follows; the change from baseline to 12 weeks was −3.0 UI episodes/day (95% CI: −4.4 to−1.7) for the 50% of ST group, −2.9 UI episodes/day (95% CI: −4.7 to−1.2) for 80% of ST group, and−3.6 UI episodes/day (95% CI: −5.2 to−1.9) for the ST group. Post-hoc analyses indicated a significant decrease in UI episodes at all three amplitude settings at six and 12 weeks compared to baseline (all $p < .004$). Regarding QoL, the PGI-I questionnaire showed that subjects across all three randomized groups reported improvement in their bladder condition at 12 weeks compared to before treatment with InterStim therapy (PGI-I questionnaire responses 82.4%, 92.3%, and 92.3% for the 50%, 80%, and ST groups, respectively). According to the researchers, this study proved that individuals with sub-sensory amplitude settings at 50%, 80%, and ST experienced reduced UI episodes. The authors conclude that the outcomes of the trial show possible advancements in the post-implantation phase of InterStim therapy with improved comfort for individuals suffering from OAB symptoms.

van Ophoven et al. (2021) conducted a systematic literature review and meta-analysis on SNM in individuals with nLUTD, NOUR, or a combination of both. Authors searched the literature between 1998 and March 2020 using the Preferred Reporting Items for systematic reviews and Meta-Analyses (PRISMA) statement. The systematic literature review yielded 47 studies; 21 (887 individuals) were included in the meta-analysis of test SNM, and 24 (428 individuals) in the meta-analysis of permanent SNM. The level of evidence was assessed using the Oxford Centre for Evidence-Based Medicine and ranged from 3 to 4. Individuals with nLUTD who received SNM were divided into three subgroups: neurogenic detrusor overactivity (nDO), neurogenic NOUR, or a combination of both; resulting in test SNM success rates for nDO 61%, 52% for neurogenic NOUR, and 69% for a combination of both. Meta-analyses were conducted to generate pooled estimates for test and permanent SNM success rates. Test success rates varied significantly depending on neurogenic conditions; however, the pooled success rate of SNM test stimulation was 66.2%. The meta-analysis of permanent SNM resulted in a pooled success rate of 84.2%. The pooled success rates for test and permanent SNM were 64.2% and 82.9%, respectively. Adverse events (AEs) were reported in less than 25% of 494 individuals, with the most common being loss of effectiveness (4.7%), infection (3.6%), pain at the implant site (3.2%), and lead migration (3.2%). Limitations include the risk of bias; in some studies, there were small sample sizes, retrospective case series included, heterogeneous populations, lack of disease classification, and variations in terms of outcome parameters along with techniques. The systematic reviews and meta-analysis support the high overall success rates and the benefits of permanent SNM for various nLUTDs.

Lo et al. (2020) compared the efficacy of BTX, SNM, and PTNS as a third-line treatment for the management of OAB symptoms in adults through a systematic review and network meta-analysis. Utilizing the PRISMA flow diagram, the search was conducted from January 1995 to September 2019, resulting in 20 articles. The studies all met the qualitative inclusion criteria, including 17 RCTs (3,038 individuals) that compared any dose of BTX, SNM, and PTNS with each other or a placebo for the management of adult OAB. The results were reported as an average number of episodes at baseline for each trial outcome. The efficacy of

treatments for urinary frequency from nine studies showed a more significant reduction in micturition per day for those treated with SNM compared with the placebo PTNS and BTX. To compare the efficacy of the three modalities on the number of incontinence episodes per day at 12 weeks of follow-up, seven studies were used revealing that all three modalities were more efficacious than the placebo. However, the network meta-analysis showed SNM demonstrated a more significant reduction in the total number of incontinences per day compared to placebo, PTNS, and BTX. From 10 studies, the treatment effects on UTIs were evaluated, revealing that BTX was associated with a higher incidence of UTIs compared with placebo SNM and PTNS. In 11 studies, authors found the impact of treatments with BTX on post-management urine retention was associated with a higher occurrence of post-treatment urine retention needing catheterization compared to placebo, SNM, and PTNS. Limitations included the lack of studies using standardized questionnaires and parameters to assess the long-term effectiveness of the three treatment options. Overall, this systematic review and meta-analysis showed that all three treatments were more efficacious in managing adult OAB syndrome than the placebo. BTX resulted in more complications such as UTI and urine retention. At the 12-week follow-up, SNM resulted in the most significant reduction in UI episodes and voiding frequency compared with BTX and PTNS.

Yang et al. (2020) systematically reviewed the literature on individuals with refractory OAB who chose SNM therapy after failed BTX treatment and performed a meta-analysis of the collected data. To assess the quality of the literature, the authors employed the Newcastle-Ottawa Scale (NOS) along with two independent reviewers who screened the studies and extracted data. The exploration resulted in seven studies comprising 319 individuals meeting the inclusion criteria. The authors discovered a 58.5% success rate in individuals with refractory OAB utilizing SNM therapy after failed BTX therapy, and no significant difference between individuals with refractory OAB who chose SNM as a first choice (RR = 0.96, 95% CI [0.72–1.26], p = 0.735). Limitations to the study include limited pertinent research, small research samples, scarcity of RCTs, homogeneity, sensitivity, and linguistic constraints. The authors concluded that in treating OAB, SNM therapy has long-term and stable healing effects with a significant overall success rate for individuals with OAB who chose SNM after failed BTX or as a first-choice therapy.

In a prospective, multicenter study (Siegel et al., 2018, included in the 2012 ECRI report) on subjects with OAB and treated with SNM, five-year follow-up results were evaluated. The authors assessed the therapeutic success rates, QoL, and safety of SNM after five years of having InterStim implantation. The prospective, multicenter study resulted in 340 individuals completing the test stimulation and 272 implanted. The study's outcome showed a five-year success rate of 67% utilizing modified completer analysis and 82% using completers analysis. Participants with UUI and urinary frequency showed a mean reduction from baseline of 2.0 ±2.2 leaks per day and 5.4 ±4.3 voids per day, respectively. All ICIQ-OABgol measures demonstrated improvement in QoL ($p < 0.0001$), AEs consisted of a change in stimulation (22%), site pain (15%), and therapeutic product ineffectiveness (13%). The authors concluded that SNM has an acceptable safety profile through five years, sustained efficacy, and QoL improvements for individuals with OAB. In Siegel et al. (2016)'s three-year follow-up of the same prospective, multicenter study on SNM treatment for individuals with OAB, the authors also concluded that at 36 months, the data demonstrated sustained safety, efficacy, and improved QoL. Siegel et al. (2015) similarly conducted a prospective, randomized, multicenter study evaluating SNM with InterStim therapy compared to standard medical therapy (SMT) at a six-month follow-up in subjects with mild symptoms of OAB. Before and during baseline data collection, enrolled subjects discontinued OAB medications. Individuals included in the study had symptoms of OAB, including UUI (≥ 2 leaks/72 hr.) and/or urinary frequency ≥ eight voids/day), failed at least one anticholinergic medication, and had at least one drug not yet tried. Individuals were randomized 1:1 into two groups; 70 to SNM and 77 to SMT. The primary outcome of OAB therapeutic success was measured using voiding diaries collected at the six-month visit. Individuals with both UI and urinary frequency had to display a ≥ 50% improvement in average leaks/day or voids/day from baseline or return to regular voiding frequency (< 8 voids/day) to be considered a success. The primary intent-to-treat analysis showed that OAB therapeutic success was significantly more in the SNM group (61%) than in the SMT group (42%). In the as-treated analysis, OAB therapeutic success was 76% for SNM and 49% for SMT. The group receiving SNM showed significant improvements in QoL versus the group receiving SMT, and 86% of SNM subjects reported improved or greatly improved urinary symptom interference scores at six months, compared to 44% for SMT subjects. The device-related AE rate was 30.5%, and the medication-related AE rate was 27.3%. The authors concluded that the study demonstrated superior objective and subjective success of SNM compared to SMT, indicating SNM is a safe and effective treatment for individuals suffering from mild to moderate symptoms of OAB.

In a multicenter, open-labeled, randomized extension trial (Amundsen et al., 2018, included in the 2012 ECRI report), the authors compared two-year outcomes of SNM to BTX for individuals with refractory UUI. The trial began in February 2012 and ended in July 2016. In nine US medical centers, 386 women with ≥ six urinary urge incontinence episodes (UUIE) were assessed. Individuals were randomized to SNM (n = 194) or BTX 200 U (n = 192) and were followed to assess AEs. Participants

of the trial were considered clinical responders (CR) to treatment if they demonstrated ≥ 50% reduction in UUIEs after placement of SNM or after one month of BTX treatment. Reprogramming was allowed during the two years for SNM, after six months; two more BTX injections were permitted. The primary outcome was the change in mean daily UUIE over the two years, and secondary outcomes were results of no UUIE, ≥ 75%, and ≥ 50% UUI reduction. The Overactive Bladder Questionnaire Short Form, Urinary Distress Inventory short form, Incontinence Impact Questionnaire, Patient Global Impression of Improvement, Over-active Bladder Satisfaction of Treatment Questionnaire, and AEs were also utilized to assess outcomes. Over the two years, 58% of the SNM cohort required reprogramming, and 17% required three or more reprogramming. The SNM revisions rate was 3% at the two-year interval due to decreased efficacy. No difference in decreased mean UUIE for both groups over two years (-3.88 vs -3.50 episodes/d; mean difference = 0.38; 95% CI= -0.14–0.89; p = 0.2) was reported. The BTX group was more likely to experience complete resolution of UUI at the six-month mark (treatment difference = -18%; 95% CI= -29-6; p < 0.0001) and ≥ 75% reduction, treatment difference = -20%; 95% CI = -31- –8; p=0.001). The differences between the groups decreased over time, with comparable rates of complete resolution (5% each) and 75% reduction (22% for BTX and 21% for SNM) at the two-year mark. Higher treatment satisfaction, and treatment endorsement was demonstrated in the BTX group (treatment satisfaction mean difference = -9.1, 95% CI = -14.4, -3.9; p < 0.001) (treatment endorsement mean difference = -12.2, 95% CI = -17.7 - -6.6; p < 0.001) according to OAB-SATq subscales. AE data was available for 328 out of 369 participants, with only UTI rates being clinically different between groups as the BTX group experienced more UTIs. The authors found no significant difference in symptoms specific to QoL measures, global improvement assessment, or AE subscales. The trial results demonstrated how both treatments evaluated had continued UUI improvement over two years, with reductions in average daily UUIE.

Fecal Incontinence

An ECRI Clinical Evidence Assessment evaluated InterStim II System (Medtronic plc.) on its effectiveness in restoring bowel control for individuals with chronic fecal incontinence (FI). The evidence assessment consisted of a technology assessment, five RCTs, one systematic review, and two pre/post-treatment studies. Of the five RCTs included, four compared InterStim with sham and optimal medical therapy for individuals with varying disease severity. The technology assessment and systematic review are at risk for bias due to the small sample size, single-center study design, retrospective data, lack of randomization, and blinding. RCTs that compare InterStim with other treatments would be necessary to provide comparative data. However, the clinical evidence assessment concluded that InterStim is safe and effective, appearing to improve continence for up to five years in those individuals with chronic FI (ECRI, 2020; updated 2021).

The 2021 ECRI Clinical Evidence Assessment evaluated Axonics rechargeable SNM system (Axonics Modulation Technologies, Inc.) for treating FI. The assessment uncovered evidence indicating SNM is a generally safe and effective treatment option for some individuals with FI. The literature supporting SNM derives from two before and after studies, creating limitations of the evidence such as small sample size, lack of parallel controls, and risk for bias. Overall, RCTs comparing long-term individualized outcomes of Axonics r-SNM with other treatments for FI are necessary to accurately assess Axonics safety and efficacy.

Ram et al. (2020) conducted a systematic review and meta-analysis to evaluate the efficacy of SNM in treating low anterior resection syndrome (LARS). During study screening, the articles were assessed using the New-castle Ottawa Score. The primary outcome measure was the number of individuals in each group with successful treatment. Out of 434 publications specific to the efficacy of SNM for the treatment of LARS discovered, 13 studies were included in the final analysis. All sacral nerve implantations were achieved in two stages, beginning with an initial temporary peripheral nerve evaluation (PNE) before implantation, resulting in 114 individuals receiving PNE test stimulation. Individuals achieved a successful decrease in FI in 87/114 (76.3%) subjects who underwent PNE test stimulation. Additionally, improvements in anal continence were seen in several clinical and functional parameters demonstrated by the following results: Wexner Score 10.78 points (95% CI 8.55-13.02, p < 0.0001), manometric maximum resting pressure mean improvement of 6.37 mm/Hg (95% CI 2.67-10.07, p = 0.0007), maximum squeeze pressure mean improvement of 17.99 mm/Hg (95% CI 17.42-18.56, p < 0.0001), and maximum tolerated volume mean improvement of 22.74 ml (95% CI 10.65-34.83, p = 0.0002). The overall success rate excluding study heterogeneity resulted in 83.30% (95% CI 71.33-95.26%, p < 0.0001). In the quality-of-life questionnaires, significant advances were also demonstrated, although the study included a small group of individuals. Limitations include retrospective studies, bias, and lack of a control group. The authors concluded that improvements in symptoms and QoL demonstrate a clear benefit of SNM for individuals suffering from FI following low anterior resection. Furthermore, the authors determined SNM is a valuable therapeutic option for refractory FI following rectal resection.

Tan et al. (2020) conducted a systematic review and meta-analysis to quantify placebo effects and responses following sham electrical nerve stimulation for individuals with FI and constipation. The literature search was conducted from inception until April 2017 through Ovid MEDLINE, PubMed, EMBASE, and Cochrane databases. Excluded from the review were any pediatric individuals and non-sham-controlled trials. After meeting inclusion and exclusion criteria, ten randomized sham-controlled trials were utilized to investigate the effect of lower gastrointestinal electrical nerve stimulation for treating FI and constipation. The results of the sham stimulation showed improvements in FI episodes by 13 episodes a week (95% CI -2.53 to -0.01, p = 0.05), fecal urgency improved by 1.5 episodes a week (CI −3.32 to 0.25, p = 0.09), and Cleveland Clinic Severity scores by 2.2 points (CI 1.01 to 3.36, p = 0.0003). Improved symptoms of constipation were also seen with the sham stimulation consisting of improved stool frequency (1.3 episodes per week, CI 1.16 to 1.42, p < 0.00001), Wexner Constipation scores (5.0 points, CI −7.45 to −2.54 p < 0.0001), and Gastrointestinal Quality of Life scores (7.9 points, CI −0.46 to 16.18, p = 0.06). The authors conclude that sham stimulation is associated with clinical and statistically meaningful improvements in symptoms of incontinence and constipation.

Ramage et al. (2015) conducted a systematic review on the efficacy of SNS for individuals with LARS. The authors undertook the review following the PRISMA guidelines, and two reviewers performed the literature search and data extraction separately. To be considered for the review, studies must have evaluated the use of SNS following rectal resection and assessed at least one of the following endpoints: bowel function, QoL, or ano-neorectal physiology. The search yielded 189 articles; authors excluded 156 due to lack of full text resulting in 27 full-text articles, with seven related to SNS for FI. Included in the seven articles chosen were one case report and six prospective case series. The studies included 43 individuals, 42 of whom had a resection due to rectal cancer, one due to Crohn's disease, and 39 receiving neoadjuvant chemoradiotherapy. The average follow-up for these individuals was 15 months. Definitive implantation was conducted in 34 individuals, with 32 out of the 34 experiencing improvements in symptoms. Limitations included heterogeneity of data and a small number of non-controlled studies available. The overall efficacy of treatment based on the intention to treat analysis was 74%, comparable with results found in the adult population after SNS for all causes of FI. The authors concluded that SNS for FI in LARS is worth attempting for individuals with LARS not responding to medical treatment.

A systematic review (Thaha et al., 2015, included in the 2021 ECRI report) published in the Cochrane database assessed the effects of SNS using implanted electrodes for treating FI and constipation in adults. Inclusion criteria consisted of all randomized or quasi-randomized trials assessing the effects of SNS on FI or constipation in adults. The data collected was analyzed by two review authors independently, and the authors assessed the methodological quality of the included trials. Results of the search yielded six cross-over trials and two parallel-group trials. The randomized, controlled parallel-group trial (Tjandra et al., 2008, included in the 2021 ECRI report) consisted of 53 individuals with severe FI receiving SNS who revealed decreased episodes of FI compared to the control group receiving optimal medical therapy (mean difference (MD) −5.20, 95% confidence interval (CI) −9.15 to −1.25 at three months; MD −6.30, 95% CI −10.34 to −2.26 at 12 months). The second randomized parallel-group trial by Thin et al. (2015) consisted of 15 individuals with FI receiving SNS who experienced decreased episodes of FI compared to PTNS (MD −3.00, 95% CI −6.61 to 0.61 at three months; MD −3.20, 95% CI −7.14 to 0.74 at 12 months). The multicenter, double-blind cross-over trial by Leroi et al. (2005) yielded 24 blinded individuals studied during 'on' and 'off' stimulation periods. The trial's results showed that 19 participants had their average FI episodes per week fall from 1.7 during the 'off' period to 0.7 during the 'on' period. The remaining group of five showed an average rise of FI from 1.7 during the 'off' period to 3.7 during the 'on' period. In the cross-over trial by Sørensen & Thomsen (2010), individuals had no FI episodes in either the one-week 'on' or 'off' stimulator periods. In the cross-over trial by Vaizey (2014), two individuals with FI demonstrated an average of six FI episodes per week during the 'off' period and one during the 'on' stimulator period. Kahlke et al. (2015)'s prospective single-center randomized cross-over trial consisted of 14 individuals with FI who experienced significantly lower episodes of FI each week during the 'on' stimulator period compared to the 'off' stimulator period. The double-blind placebo-controlled cross-over study by Kenefick et al. (2002) demonstrated how two participants with idiopathic constipation experienced an average of two bowel movements per week during the 'off' stimulator cross-over period and five during the 'on' period. AEs such as bloating occurred in 79% of individuals during the 'off' stimulator period compared to 33% during the 'on' stimulator period. The two-phase, double-blind, randomized controlled cross-over study by Dinning et al. (2015) consisted of 59 individuals suffering from constipation who did not have any improvement in frequency of bowel movements with SNS, and 73 AEs were reported. The AE included pain at the site of the implant, wound infection, and urological events. The authors conclude that SNS can improve continence in most individuals with FI, but SNS did not improve symptoms for those with constipation.

In an investigator-blinded randomized parallel-arm trial (Thin et al., 2015, included in the Thaha et al. [2015] systematic review) the authors compared PTNS to SNS to demonstrate both treatments' short-term effectiveness and acceptability for individuals

with FI. Recruitment took place over 12 months from Royal London Hospital and University College London Hospitals NHS Foundation Trust for specialist investigation and treatment for FI. To be eligible for the trial, individuals needed to meet the National Institute for Health and Care Excellence (NICE) criteria for symptom severity and failure of previous conservative treatments; if individuals had specific contraindications to either therapy, they were excluded. Subjects were placed in an SNS or PTNS group with restricted randomization. Of 40 individuals, 23 were randomized to receive SNS and 17 to receive PTNS. The quantitative endpoints were assessed 2-4 weeks before intervention and at three and six months following completed treatment. Bowel diaries recorded the number and type of incontinence episodes over two weeks to determine the number of FI episodes per week. Success was defined as a reduction of ≥ 50% in FI weekly episodes. The outcomes were measured utilizing quantitative outcome questionnaires, which included symptom severity scores, Cleveland Clinic Incontinence Score (CCIS), Faecal Incontinence Quality of Life Scale (FIQL), generic Short Form 36 (SF-36®; QualityMetric), and EQ-5D™ (EuroQol Group) quality-of-life measures. Results of the trial showed that within-group effect estimates for SNS were more significant than those for PTNS, especially in individuals who progressed to permanent implantation. In the available-case analysis of the SNS group, FI episodes per week enhanced from a mean (s.d.) of 11.4 (12.0) at baseline to 4.0 (4.0) and 4.9 (6.9) at 3- and 6-month follow-up, respectively. The results of the PTNS group showed improvement from 10.6 (11.2) to 5.8 (6.9) and 6.3 (6.9), respectively. The CCIS outcomes showed improvements in the SNS group from a mean (s.d.) baseline of 16.2 (3.0) to 11.1 (5.2) at three months and 10.4 (5.6) at six months, and the PTNS group scored 15.1 (2.7) to 11.7 (4.4) and 12.1 (5.2) respectively. Clinical success (reduction of ≥ 50% in FI episodes a week) was achieved in nine (47%) of 19 participants at three months and 11 (61%) of 18 participants at six months. The SNS group demonstrated more significant effect estimates across all domains when compared to the PTNS group. SF-36 and EQ-5D scores exhibited slight improvement after treatment. Changes in scores for EQ-5D (0 represents death and 10 indicates perfect health) varied between zero and 0.11 with no noteworthy in-group changes. In the SF-36 scale subscales (0 stands for death and 100 indicates perfect health), increases in the physical role were seen in the SNS group, predominantly after permanent implantation; modest increases were detected in the emotional role and social functioning for both SNS and PTNS. The implanted SNS group confirmed a greater treatment effect than was seen with the presence of all available cases. This pattern was sustained for most of the key measures and led to a reduction in FI episodes of ≥ 50% (53%) and 10 (67%) of 15 participants at 3 and 6 months, respectively. The qualitative study suggested that SNS and PTNS had similar, very high acceptability levels. Limitations to the trial include pilot design, a small number of subjects, and short follow-up. The trial demonstrated that both SNS and PTNS offer clinical benefits to individuals with FI in the short term and are both highly acceptable.

Worsøe et al. (2013) conducted a systematic review on the efficacy of sacral anterior root stimulation (SARS), SNS, PNS, magnetic stimulation, and nerve re-routing for neurogenic bowel dysfunction (NBD). NBD includes a combination of FI, constipation, abdominal pain, and bloating. The review discovered evidence that neurostimulation has been investigated for NBD, but no consensus has been proven regarding the efficacy or clinical use. Studies showed that SNS affects individuals with incomplete but not those with complete spinal cord injury (SCI), showing that further studies are necessary to clarify which spinal pathways are required for the clinically significant effects of SNS. The authors conclude that numerous neurostimulation methods for treating NBD have been investigated however, the articles are limited to retrospective and pilot designs. Further large, controlled trials with well-defined inclusion criteria and endpoints are necessary to determine the efficacy of the technologies for NBD.

Chronic Pelvic Pain

There is insufficient evidence to support sacral nerve stimulation for treating chronic pelvic pain. Additional high-quality studies are required to demonstrate clinical efficacy and utility and compare this technology to other treatments.

Hernández-Hernández et al. (2021) analyzed the records of 105 individuals to determine the long-term outcomes of SNS in both idiopathic and neurogenic pelvic floor disorders. The authors evaluated efficacy using the Global Response Assessment (range, 0%-100%) and, depending on the clinical indication used the International Consultation on Incontinence Questionnaire-short form, number of catheterizations or pads a day, and the numerical pain scale. The authors evaluated safety by analyzing complications, reinterventions, and explants; QoL was assessed through phone interviews. The clinical indications were OAB (36 individuals), urinary retention (37 individuals), bladder pain syndrome/interstitial cystitis (BPS/IC) (19 individuals), FI (8 individuals), and double incontinence (DI) (6 individuals). The implant rates according to the clinical indication were as follows: OAB, 55.6%; urinary retention, 56.8%; BPS/IC, 63.15%; FI, 87.5%; and DI, 66.7%. Results after observing clinical and/or statistically significant improvements in all efficacy variables were as follows: In 34% of individuals, loss of therapeutic effect at 75-month follow-up, in 39% (25 individuals), device-related pain appeared; for 20 of those participants the pain was resolved by reprogramming, and five individuals required removal. The QoL results showed a high level of satisfaction, with more than 90% of individuals stating they would recommend SNS. The authors concluded that SNS offers an alternative for individuals with

refractory pelvic floor dysfunction, and pain, possessing a favorable profile and providing long-lasting improvements in symptoms and QoL. However, there was a loss of effect, particularly within the first two years, with SNS becoming ineffective in 20% of individuals. Additionally, limitations of the study include small sample size, retrospective nature of the study, and risk of bias.

In 2019, Mahran and colleagues conducted a systematic review and meta-analysis of the literature on the use of SNM to improve chronic pelvic pain symptoms. Overall, fourteen studies were included in the analyses. The primary outcome measure was an improvement in the Visual Analog Scale (VAS) for individuals with chronic pelvic pain compared to different subgroups. Secondary outcome measures compared the effectiveness of SNM in the subgroups based on the SNM approach and etiology of chronic pelvic pain. The authors utilized seven studies, which included 105 individuals with chronic pelvic pain, and pure BPS/IC etiology, then compared them with 34 individuals with chronic pelvic pain due to other etiologies. The results demonstrated significantly more improvement in pain scores in the non- BPS/IC group (WMD = −5.72, CI 95% = −6.18 to −5.27), than in the BPS/IC group (WMD = −4.13, CI 95% = −5.36 to −2.90). Seven studies showed significant improvement in urinary frequency (WMD = −8.72, 95% CI = −10.85 to −6.59 p < 0.001). Five studies revealed significant overall improvement in urgency (WMD = −1.2, 95% CI = −1.9, to − p < 0.001), nocturia (WMD = −2.31, 95% CI = −3.81 to −0.81 p = 0.003), and voided volume (WMD = 109.61, 95% CI = 57.79–161.43, p < 0.001). The authors concluded that SNM is a promising treatment option for refractory chronic pelvic pain with better effects in treating individuals with etiologies other than BPS/IC. Added higher quality randomized prospective studies are necessary to compare SNM to other modalities for treating chronic pelvic pain.

Tutolo et al. (2018) conducted a systematic review of the literature on the efficacy and safety of SNM and PTNS in non-neurogenic LUTDs and chronic pelvic pain not responsive to conservative treatments. In total, twenty-one studies were identified, met inclusion criteria, and were analyzed. The search demonstrated that neuromodulation is a practical method for decreasing incontinence episodes, pad use, voiding frequency, and improving bladder capacity and voiding volume, with an overall success rate ranging from 61% to 90% for SNM and 54% to 79% for PTNS. Additionally, SNM demonstrated high long-term efficacy rates for individuals with urgency incontinence, urgency frequency syndrome, and idiopathic retention refractory to conservative treatment. A low level of evidence was uncovered for IC/BPS, and the authors concluded it is impossible to give clinically compelling evidence for treating IC/BPS with SNM.

In 2017, Wang et al. led a global systematic review and meta-analysis to evaluate available literature on the efficacy and safety of SNM for refractory BPS/IC. In total, seventeen studies were identified and included, including 583 individuals who had failed conservative management and had a BPS/IC duration ranging from 3 to 9.1 years. The primary outcome measures were the 0-10 VAS, the Interstitial Cystitis Problem Index (ICPI), the Interstitial Cystitis Symptom Index (ICSI), and success rate. The secondary outcomes measured included daytime frequency, nocturia, voids per 24 hours, urgency, average voided volume, complication rate, and explanation rate. The results of the pooled analysis showed that SNM was associated with a reduction of pelvic pain (weighted mean difference [WMD] −3.99; 95% [CI] −5.22 to −2.76; p < 0.00001). The ICPI and ICSI results were also successful (WMD −6.34; 95% CI −9.57 to −3.10; p = 0.0001; and WMD −7.17; 95% CI −9.90 to −4.45; p < 0.00001, respectively). The secondary outcome results were as follows: daytime frequency (WMD −7.45; 95% CI −9.68 to −5.22; p < 0.00001), nocturia (WMD −3.01; 95% CI −3.56 to −2.45; p < 0.00001), voids per 24 hours (WMD −9.32; 95% CI −10.90 to −7.74; p < 0.00001), voids per 24 hours (WMD −9.32; 95% CI −10.90 to −7.74; p < 0.00001), urgency (WMD −1.08; 95% CI −1.79 to −0.37; p = 0.003), and average voided volume (WMD 95.16 ml; 95% CI 63.64 to 126.69; p < 0.0001). The results showed a pooled treatment success rate of 84% (95% CI 76% to 91%). The current evidence uncovered in this review indicates that SNM may be effective and safe for treating refractory BPS/IC. However, likely the long-term efficacy of SNM for treating BPS/IC decreases significantly. The limitations of the study consisted of a small sample size, some studies that were retrospective case series prone to increased risk of bias, substantial heterogeneity between studies, and scarcity of data that made subgroup analyses of bilateral vs. unilateral stimulation and stimulation parameters impossible. Given the overall low quality of included studies, additional well-designed, large-volume RCTs are essential to reach definitive conclusions.

Constipation

There is insufficient evidence to support sacral nerve stimulation for treating constipation. More high-quality studies are required to demonstrate clinical efficacy and utility and compare this technology to other treatments.

Pauwels et al. (2021) conducted a systematic overview of the current literature regarding neurostimulation modalities and the effects on chronic functional constipation in adults. The search produced seventeen studies deemed eligible for inclusion. The exploration uncovered several double-blinded cross-over RCTs demonstrating no significant impact of neurostimulation compared to sham stimulation for refractory constipation. Additionally, no significant improvement in constipation-related

symptoms and QoL was uncovered in the review, suggesting the need for more powerful studies to decide the benefits of neurostimulation for constipation. The authors concluded that neurostimulation has not demonstrated benefits in filling the treatment gap for chronic functional constipation.

In 2017, Zerbib and colleagues led a multicenter, randomized, double-blinded, placebo-controlled, cross-over study (n = 36 individuals) to determine the efficacy of SNM for severe refractory constipation. Individuals selected were those with chronic constipation for more than a year defined by two or fewer complete bowel movements per week, straining to evacuate at > 25% of attempts, or sensation of incomplete evacuation after defecation on > 25% of attempts. Participants were also included if they had no symptomatic response to standard therapies for at least three months. Of the 36 participants, 20 were offered permanent pulse generator implantation and assigned randomly in a cross-over design to active or sham stimulation at two eight-week intervals. A 2-week wash-out period separated the two trial stages. In random order, individuals were randomized to the two-interval cross-over with eight weeks of stimulation (on) and sham stimulation (off). After the second period, all individuals began the study's second phase and received active stimulation until week 50 after randomization. The primary outcome measured was the number of individuals who responded during the 'on' and 'off' stimulation periods. To consider the individual a responder to therapy, one had to achieve at least three bowel movements per week and/or > 50% improvement of symptoms. Secondary outcomes measured were the percentage of individuals with a response at one year, short- and long-term clinical and physiological factors associated with response to temporary and permanent SNM, the effects of SNM on an individual's daily bowel diary, Wexner score, QoL, VAS score, anorectal manometry parameters, and colonic transit time. No statistically significant difference between 'on' and 'off' periods was demonstrated in the stool diaries or by the Wexner, VAS, or QoL score. A total of eleven individuals had sustained clinical response at one-year follow-up. Active stimulation had no significant effect compared with sham stimulation in both intention-to-treat (response in 12 of 20 *vs.* 11 of 20 participants, respectively) and per-protocol analyses. This randomized cross-over study did not show an effect of active stimulation compared with the absence of stimulation for individuals with refractory constipation who responded to PNE. Although the authors concluded that SNM is associated with improved QoL symptoms, the results do not support the recommendations of permanent implantation for individuals with refractory constipation who initially responded to temporary nerve stimulation.

In a prospective, double-blind, randomized, placebo-controlled, two-phase, cross-over study (Dinning et al., 2015, included in the Thaha et al. [2015] systematic review) the authors evaluated the efficacy of treatment with SNS for slow transit constipation. To carry out the analysis, three weeks of PNE were started in all individuals; out of the 59 individuals eligible for the study, 55 received permanent SNS implantation. After permanent implantation, participants were randomized to a sub-sensory/sham group for three weeks each, then randomized again to the suprasensory/sham group for three weeks each. A 2- week washout period took place between each arm. The primary outcome measure was the number of individuals who reported a bowel movement associated with a feeling of complete evacuation on more than two days a week for at least two of three weeks. Additionally, stool diaries were kept, and QoL was measured after each arm. The study resulted in no significant changes in QoL scores, and the number of individuals who satisfied the primary outcome measure did not differ between suprasensory (30%) and sham (21%) stimulations. Comparable results were seen between sub-sensory (25%) and sham (25%) stimulations. The authors concluded that SNS did not improve the frequency of complete bowel movements over the three-week active period for individuals with refractory slow transit constipation.

An extensive review regarding the efficacy of SNS for individuals with constipation (Thomas et al., 2013, included in Pauwels et al. [2021] systematic review) resulted in the evaluation of 13 published studies. Included in the review were those studies reporting the clinical outcome of SNS for constipation. Of the thirteen studies, 10 involved adult subjects and included two double-blind crossover studies and three retrospective reviews. The authors discovered in the evidence reviewed that the research has been primarily small, low-level evidence studies with short follow-ups. Additionally, the studies' size and the reported inconsistent outcomes pose difficulty in performing meaningful summative data analysis. From the review, the authors concluded that SNS might be an effective treatment for constipation; however, more extensive clinical and cost-effectiveness studies which compare SNS to alternative treatments are required to determine its efficacy for constipation.

Clinical Practice Guidelines

American College of Gastroenterology (ACG)

In 2021, the ACG supplied recommendations for managing benign anorectal disorders. The recommendations for SNS in treating constipation are derived from three RCTs. According to the ACG, the trials have shown no benefit of SNS in constipation (regardless of type). In addition, the long-term complication rate is considerable, with 61% reporting device-related

AEs in a long-term (60 months) follow-up study. Therefore, the ACG concedes that this procedure cannot be recommended for individuals with constipation (Wald et al., 2021).

The ACG utilized the pivotal North American multicenter controlled study to develop guideline recommendations regarding FI. The guideline states that individuals whose symptoms respond to temporary SNS for 2–3 weeks are eligible for permanent implantation. The ACG recommends SNS for individuals with FI whose symptoms are refractory to medical therapy (Wald et al., 2021).

American Gastroenterological Association (AGA)

The AGA researched publications, including systematic reviews and expert opinions, to define the fundamental principles for surgical intervention and device-aided therapy for managing FI and defecatory disorders (DD). The AGA developed best practice advice #4, saying: SNS should be considered for individuals with moderate or severe FI in those whose symptoms have not responded after a three-month or longer trial of conservative measures, biofeedback therapy, and who do not have contraindications to these procedures. The AGA concluded that although small studies advocate that SNS may improve rectal sensation for individuals with DD, rectal hyposensitivity, and tempt colonic propagating sequences, there is no evidence that SNS improves bowel symptoms or rectal evacuation in DD. From this evidence, the AGA developed best practice advice #13, stating: based on limited evidence, SNS should not be used for managing DD in clinical practice (Bharucha et al., 2017).

American Urological Association (AUA)/Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction (SUFU)

In 2012 the AUA/SUFU sought to provide a clinical framework for diagnosing and treating non-neurogenic OAB. The guideline's primary evidence source is the systematic review performed by the Agency for Healthcare Research and Quality (AHRQ) Evidence Report/Technology Assessment titled 'Treatment of Overactive Bladder in Women' (Hartmann et al., 2009). The following guidance was offered: In individuals with signs and symptoms consistent with an OAB diagnosis, clinicians may offer SNS as third-line treatment in a carefully selected population characterized by severe refractory OAB symptoms or those not candidates for second-line therapy and are willing to undergo a surgical procedure. The authors found that SNS is a suitable therapy with long-lasting treatment effects but is counterbalanced by frequent and moderately severe AEs, including pain at the stimulator and lead sites, lead migration, infection/irritation, electric shock, the need for additional surgeries (a side effect occurring in greater than 30% of individuals), and periodic battery replacement. Additionally, individuals should be cognitively capable of operating the device and compliant with long-term treatment protocols. The authors note that given the adverse effects on QoL associated with severe OAB, the benefits of SNS appear to outweigh the risks and burdens. This guideline was updated by Lightner et al. (2019) with no change to the statement regarding SNS (Gormley et al., 2012, included in the 2019 Hayes report).

European Association of Urology (EAU)

In 2022 the EAU developed guidelines for diagnosing and managing non-neurogenic female lower urinary tract symptoms (LUTS). Part 1 of the guidelines addresses diagnostics, OAB, stress UI, and mixed UI. Updated literature searches were conducted in September 2021, and evidence synthesis was carried out using the modified GRADE criteria outlined for all EAU guidelines. This report covers recommendations associated with LUTS and the treatment of OAB, stress UI, and mixed UI. The recommendations outlined in this guideline related to SNS for treatment of LUTS are: Offer SNS to individuals who have OAB/UUI refractory to anticholinergic therapy, and life-long surveillance to women with an SNS implant to monitor for lead displacement, malfunction, and battery wear. This guideline was developed with the grade of recommendation: strong recommendation based on moderate-quality evidence, 1B (Nambiar et al., 2022).

International Continence Society (ICS)

The ICS produced a best practice statement for the use of SNM authored by Goldman et al. (2018). A panel of urology, gynecology, and colorectal surgery experts describe SNM as an accepted therapy for refractory urinary urgency and frequency, UUI, NOUR, and FI. Per the expert panel members of the ICS, guidelines for urinary indications are as follows:

- SNM can be offered to individuals with OAB with or without incontinence who fail to respond to or are intolerant of conservative and medical therapies (Level of Evidence: I; Grade of Recommendation: A).
- SNM is an effective treatment for Fowler's Syndrome, voiding dysfunction, and NOUR (Level of Evidence: I; Grade of Recommendation: A).

- There is limited evidence supporting the role of SNM for individuals with interstitial cystitis (IC)/bladder pain syndrome (BPS). SNM is a choice for IC/BPS non-responsive to conservative therapies after appropriate assessment (Level of Evidence: III; Grade of Recommendation: C).
- There is a lack of evidence supporting SNM as a treatment choice for individuals with non-IC/BPS chronic pelvic pain (Level of Evidence: III; Grade of Recommendation: C).
- SNM is an option for symptom control for individuals with nLUTD who are at low risk of upper urinary tract deterioration (Level of Evidence: III; Grade of Recommendation: C).
- There is a lack of evidence to suggest that urodynamic testing can predict SNM outcomes (Level of Evidence: III; Grade of Recommendation C).
- The trial phase of SNM is the most valued tool for predicting the potential therapeutic success of SNM for urinary indications (Level of Evidence: II; Grade of Recommendation: B).
- In cases where SNM has been tried and failed, UDS may be considered to define further the underlying disorder (Expert Opinion).

Per the expert panel members of the ICS, guidelines for FI are as follows:

- SNM should be considered a second-line treatment possibility for bothersome FI for individuals who have failed conservative measures (Level of Evidence: II; Grade of Recommendation: B).
- An anal sphincter muscle defect is not a contraindication for SNM (Level of Evidence: III; Grade of Recommendation: C).
- Individuals with FI after Low Anterior Resection for rectal cancer may be candidates for SNM test lead implantation if conservative treatment fails (Level of Evidence: III; Grade of Recommendation: D).
- SNM is the preferred therapy for a proper individual with combined urinary and bowel symptoms (Level of Evidence: III; Grade of Recommendation: C).
- SNM for constipation should only be considered for individuals who have had symptoms for more than one year and have failed conservative treatment. No mechanically correct cause should exist (Level of Evidence: IV; Grade of Recommendation: D).
- A 2-3-week bowel diary is needed before the SNM test for bowel dysfunction. Anorectal physiology testing (manometry, anorectal sensation, volume tolerance, compliance) can be considered to help outline the elements of dysfunction and guide management (Level of Evidence: IV; Grade of Recommendation: C).

Absolute contraindications for SNM include:

- Insufficient clinical response to a therapeutic trial, incapability to operate the device with a absence of supportive caregivers who could otherwise offer assistance, and individuals who are pregnant (Level of Evidence: IV; Grade of Recommendation: C).

Relative contraindications for SNM include:

- Individuals with severe or rapidly progressive neurologic disease, individuals with established complete SCI, individuals with a known expected need for magnetic resonance imaging (MRI) of body parts below the head, and those with abnormal sacral anatomy (Level of Evidence: III; Grade of Recommendation: C).

Tips for the introduction of SNM to Individuals:

- SNM therapy should be discussed with all individuals as part of their bowel or bladder control treatment pathway (Level of Evidence: IV; Grade of Recommendation: C).
- Surgeons should evaluate the necessity for life-long follow-up, subsequent battery replacement, complications, and anticipated symptom improvement (Level of Evidence: IV; Grade of Recommendation: C).
- Preoperative counseling before SNM should consist of a discussion of risks, including implant site pain, infection, paresthesia, leg pain, and/or need for reprogramming or for device revision (Level of Evidence: 3; Grade of Recommendation: C).

Screening for success during the test period:

- Individuals who achieve 50% improvement in one or more of their troublesome urinary or bowel parameters during the PNE or Stage 1 test period may be offered complete system implantation.
- PNE test stimulation period is typically seven days for bladder and 10-21 days for bowel indications (Level of Evidence: III; Grade of Recommendation: 3).
- Stage 1 test period duration is typically 2-3 weeks. Stage 1 testing can be tried if PNE is questionable, particularly if a lengthier test period is required for screening. A repeat stage 1 test may be performed at the physician's discretion.

- The clinician should consider both sensory and motor responses important for success (Level of Evidence: IV; Grade of Recommendation: C).

Successful outcome – bladder and bowel:
- An individual who is satisfied with the treatment is considered to have a successful treatment outcome (Level of Evidence: III; Grade of Recommendation: C).
- For individuals with voiding dysfunction or nLUTD, further evaluations may be necessary to ensure the long-term safety of the urologic tract (Level of Evidence: III; Grade of Recommendation: C).

National Institute for Health and Care Excellence (NICE)

The 2020 NICE guideline recommendations for the Axonics SNM system for treating refractory OAB are as follows:
- Evidence supports the case for adopting the Axonics SNM system for treating refractory OAB in the NHS. Axonics SNM system improves symptoms and QoL. It has a longer battery life than the non-rechargeable system used in NHS clinical practice.
- Axonics SNM system should be considered as an option for individuals with refractory OAB, that is, when conservative treatment or treatment with medicine has not worked, in line with NICE's guidelines on urinary incontinence and pelvic organ prolapse and LUTS. Axonics SNM system is small and does not need to be removed for most MRI scans, so it may be useful for those with a low body mass index (BMI) or when an MRI is likely.
- Cost modeling estimates that over 15 years, the Axonics SNM system is cost saving compared with the non-rechargeable system by about £6,025 per person. Cost savings are calculated to begin six years after implant. This is because the device needs to be replaced less frequently than the non-rechargeable system, assuming Axonics has a life span of at least 15 years. For more details, refer to the NICE resource impact statement.

In the 2019 NICE guideline for assessing and managing UI and pelvic organ prolapse in women aged 18 and over, recommendations regarding SNS are as follows: offer percutaneous SNM to women after local or regional multidisciplinary teams (MDT) review of their OAB has not responded to non-surgical management including medications and:
- Symptoms have not responded to botulinum toxin (BTX) type A or,
- Individuals are unprepared to accept the risks of needing catheterization associated with BTX type A.

Additionally, NICE recommends discussing the long-term implications of percutaneous SNS with women, including:
- The need for test stimulation and probability of the test's success.
- The risk of failure.
- The long-term commitment.
- The need for surgical revision.
- The adverse effects.

The NICE guideline also recommends telling women how to self-refer for prompt specialist review if symptoms return following a percutaneous SNS procedure.

Recommendations on clinical management of lower urinary tract symptoms in men from NICE (2015a) include:
- Consider offering implanted SNS to manage detrusor overactivity only to men whose symptoms have not responded to conservative management and drug treatments.
- Consider offering urinary diversion to manage intractable urinary tract symptoms only to men whose symptoms have not responded to conservative management and drug treatments, and if cystoplasty or SNS is not clinically appropriate or is unacceptable to the individual.

NICE (2015b) produced interventional procedure guidance on SNS for idiopathic chronic NOUR, saying:
- Current evidence on the safety and efficacy of SNS for idiopathic chronic NOUR is adequate to support this procedure, provided those standard arrangements are in place for clinical governance, consent, and audit.
- During the consent process, clinicians should ensure that individuals understand the risk of complications, the need for further surgery, and the possible need for device removal and provide them with clear written information. In addition, the use of NICE's information for the public is recommended.
- Patient selection and treatment should be made in specialist units by clinical teams experienced in assessing, treating, and long-term care of individuals with bladder dysfunction and using SNS.
- NICE encourages the audit and reporting of long-term safety outcomes.

In the 2011 NICE interventional procedures guidance on Endoscopic Radiofrequency Therapy of The Anal Sphincter for Fecal Incontinence, NICE offered the following guidance regarding SNS:

- If conservative treatments have been unsuccessful, surgical options include sphincter repair, SNS, stimulated graciloplasty (creation of a new sphincter from other suitable muscles), anorectal or transabdominal implantation of an artificial anal sphincter, or permanent colostomy.

In the 2008 NICE interventional procedures guidance on Transabdominal Artificial Bowel Sphincter Implantation for Fecal Incontinence, the following guidance addressed SNS:

- First-line treatment for FI is usually conservative and includes dietary management and an antidiarrheal medication. This may be followed by pelvic floor muscle training, biofeedback therapy, and electrical stimulation. Local surgery to repair the sphincter may be recommended if conservative treatments fail. If local surgery proves inadequate, alternatives include:
  - SNS,
  - graciloplasty (creation of a new sphincter from other suitable muscles);or
  - implantation of an artificial anal sphincter (anorectal or transabdominal).
- The most severe cases may require a permanent colostomy.

In the 2007 NICE clinical guideline for the management of fecal incontinence in adults' recommendations regarding SNS is as follows:

- A temporary SNS trial should be considered for individuals with FI in whom sphincter surgery is deemed inappropriate. Refer to the NICE interventional procedures guidance on SNS for FI. These may be individuals with intact anal sphincters or those with sphincter disruption. In those with a defect, contraindications to direct repair may include atrophy, denervation, a minor flaw, absence of voluntary contraction, fragmentation of the sphincter, or a poor-quality muscle.
- All individuals should be informed of this procedure's potential benefits and limitations and undergo a trial stimulation period of at least two weeks to decide if they are likely to benefit. Individuals with FI should be offered SNS based on their response to percutaneous nerve evaluation during a specialist assessment, which is predictive of therapy success. Individuals being considered for SNS should be assessed and managed at a specialist center with experience in performing this procedure.
- If a trial of SNS is unsuccessful, an individual can be considered for a neo sphincter, for which the two options are a stimulated graciloplasty or an artificial anal sphincter. See also the NICE interventional procedures guidance on stimulated graciloplasty for FI. Individuals should be informed of the potential benefits and limitations of both procedures. Those offered these procedures should be advised that they may experience evacuatory disorders and/or severe infection, which may necessitate the removal of the device. Individuals being considered for either procedure should be assessed and managed at a specialist center with experience in performing these procedures. If an artificial anal sphincter is to be used, special arrangements should be followed, as shown in the NICE interventional procedure's guidance on artificial anal sphincter implantation.
- Individuals who have an implanted SNS device stimulated graciloplasty, or an artificial anal sphincter should be offered training and ongoing support at a specialist center. These individuals should be monitored, have regular reviews, and be given a point of contact.

The 2006 NICE interventional procedures guideline for Stimulated gracilopasty for fecal incontinence offers the following guidance regarding SNS:

- Stimulated graciloplasty is used to treat refractory FI (for example, anorectal atresia) as an alternative to colostomy. Other approaches to establishing continence are the insertion of an artificial anal sphincter and SNS.
- The Specialist Advisors suggested that this procedure has been superseded by SNS.

The 2004b NICE interventional procedures guidelines on SNS for fecal incontinence state:

- Current evidence on the safety and efficacy of SNS for FI appears adequate to support the use of this procedure, provided that the standard arrangements are in place for consent, audit, and clinical governance.
- The procedure should only be performed in specialist units by clinicians with a particular interest in assessing and treating FI.

The 2004a NICE interventional procedure guidelines on SNS for urge incontinence and urgency-frequency are as follows:

- Current evidence on the safety and efficacy of SNS for urge incontinence and urgency-frequency appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit, and clinical governance.

- Patient selection is important. The diagnosis should be defined as clearly as possible and the procedure limited to individuals who have not responded to conservative treatments such as lifestyle modifications, behavioral techniques, and drug therapy. individuals should be selected based on their response to PNE.
- SNS is used to treat the symptoms of an OAB, including UUI and/or urgency frequency in individuals who have failed or cannot tolerate conventional treatments.
- In individuals for whom conservative treatments have been unsuccessful, the standard alternatives include bladder reconstruction (such as augmentation and cystoplasty) and urinary diversion.

Further recommendations have been made as part of the clinical guideline on lower urinary tract symptoms published in May 2010, as follows:

- Consider offering implanted SNS to manage detrusor overactivity only to men whose symptoms have not responded to conservative management and drug treatments.

Royal College of Obstetricians & Gynaecologists (RCOG)

In 2015 the RCOG published Scientific Impact Paper No. 46, which stated: The role of neuromodulation in managing chronic pelvic pain syndromes is yet to be fully determined. Its part in OAB and FI, however, is better established. While there is rising evidence of efficacy in pelvic pain from small case series or pilot studies, higher quality studies such as RCTs are essential. Currently, it is generally agreed that specialists should only consider neuromodulation in pelvic pain management within the setting of a broader pain management plan. Methods available include PNS (e.g., PTNS, sacral nerve/root stimulation, and pudendal nerve stimulation) and spinal cord stimulation.

The American Society of Colon and Rectal Surgeons (ASCRS)

The ASCRS Surgeons developed clinical practice guidelines titled 'Evaluation and Management of Constipation'. The Clinical Practice Guidelines Committee state that although the existing evidence advocates for SNM as an effective treatment for chronic constipation, most published reports were uncontrolled, with no evaluation of any other treatment modality. There was also no consistent definition of constipation or uniform technique to measure improvement in these studies. The committee suggests additional evidence is required to determine which measures should be used to evaluate success with test stimulation, whether individuals who fail test implantation should be implanted with a permanent stimulator, which criteria ought to be used to govern the success of permanent stimulation and to delineate which individuals may profit from this treatment as opposed to other modalities. The ASCRS guideline regarding SNM for individuals with constipation reads as follows: SNM may be an effective treatment for individuals with chronic constipation and successful PNE 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 recommendation based on moderate-quality evidence, 2B (Paquette et al., 2016).

The ASCRS formed clinical practice guidelines based on a review of published evidence for evaluating and managing individuals with FI. Authors reviewed all manuscripts, studies in adults, systematic reviews, and meta-analyses to develop the recommendations of these clinical practice guidelines, which the entire Clinical Practice Guidelines Committee reviewed. The GRADE system was utilized for the final grade of recommendation and approved by the Committee. The ASCRS state SNM may be considered a first-line surgical option for incontinence for individuals with and without sphincter defects. This guideline was developed with the grade of recommendation: strong recommendation based on moderate-quality evidence, 1B (Paquette et al., 2015).

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

FDA granted Premarket Approval (PMA) for InterStim in September 1997 (P970004) to treat OAB. FDA approved InterStim to treat urinary retention in April 1999 (S004). FDA approved the most recent InterStim device, InterStim Micro, in July 2020 (S302). InterStim's labeled indication reads as follows: [SNM] delivered by the InterStim™ system for Urinary Control is indicated for the treatment of urinary retention and the symptoms of overactive bladder, including urinary urge incontinence and significant symptoms of urgency-frequency alone or in combination, in individuals who have failed or could not tolerate more conservative treatments. Medtronic InterStim Micro rechargeable sacral neuromodulation (SNM) system is the most recent model cleared and received FDA clearance in 2020. Refer to the following website for additional information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P970004. (Accessed July 6, 2022)

On September 6, 2019, the FDA granted PMA for the Axonics r-SNM® System (P190006). The Axonics r-SNM System is a rechargeable SNM system approved for sale in the United States, Europe, Canada, and Australia. This device is indicated for "The treatment of chronic fecal incontinence for individuals who have failed or are not candidates for more conservative treatments." This approval is contingent upon submissions of annual safety reports, including any adverse events associated with the device. Refer to the following website for additional information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P190006. (Accessed July 6, 2022)

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Policy History/Revision Information

Date	Summary of Changes
10/01/2023	**Application** ***Individual Exchange Plans*** • Removed language indicating this Medical Policy does not apply to Individual Exchange benefit plans in the states of Massachusetts, Nevada, and New York **Supporting Information** • Archived previous policy version 2023T0630B

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.