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REVIEW

The American Society of Pain and Neuroscience (ASPN) Guidelines and Consensus on the Definition, Current Evidence, Clinical Use and Future Applications for Physiologic Closed-Loop Controlled Neuromodulation in Chronic Pain: A NEURON Group Project

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Introduction: Neuromodulation has been a staple of treatment for moderate-to-severe chronic refractory pain since the introduction of the first spinal cord stimulator by Norman Shealy in 1967. Appreciating the dynamic nature of electrical modulation of the nervous system from the epidural space, the goal has been consistent, reliable, and therapeutic neural activation of the spinal cord. This has proven to be extremely difficult. Recently, the Food and Drug Administration (FDA) released a guidance on physiologic closed loop controlled (PCLC) devices, highlighting the potential for these therapies to deliver accurate, consistent, real-time therapy, enhancing medical care and reducing variability. Because of the growing neuromodulation market focus on PCLC strategies, the American

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Society of Pain and Neuroscience (ASPN) sought to develop guidance on safety and efficacy, along with a taxonomy surrounding PCLC systems (PCLCSs) and to develop an evidence-based best practice review.

Methods: A librarian-assisted literature search was performed to identify manuscripts relevant to the topic of PCLC stimulation for management of chronic pain. Initial literature search was performed utilizing MEDLINE, EMBASE, Cochrane database, BioMed Central, and Web of Science. Included manuscripts encompassed meta-analyses, systematic reviews, randomized controlled trials (RCTs), prospective or retrospective studies with follow-up to 12 months, limited to the English language. MESH terms utilized included "closed-loop", "physiologic closed loop controlled", "spinal cord stimulation", "closed loop feedback", "feedback controlled", "neuromodulation", "pain", "persistent pain", "neuropathic pain", and "chronic pain". The modified USPSTF evidence and recommendation grading strategy previously utilized was again employed.

Results: Four studies were identified for review, 2 prospective, one retrospective, and one randomized controlled study with at least 12-month follow-up.

Conclusion: PCLC neuromodulation is an innovation that requires a responsible introduction. As commercial access grows, there is a responsibility that requires consistency with definition, evidence generation, focused on safety and efficacy.

Keywords: spinal cord stimulation, closed loop stimulation, physiologic closed loop stimulation, clinical evidence review, neuropathic pain, chronic pain, neuromodulation

Introduction

The field of neuromodulation has witnessed rapid advancements in recent years, offering hope and relief to individuals suffering from various chronic pain-related conditions, with label expansions of spinal cord stimulation (SCS) from persistent spinal pain syndrome type 2 (PSPS-T2) and complex regional pain syndrome (CRPS), to include painful diabetic neuropathy and non-surgical refractory back pain. Traditional electrical neuromodulation techniques, ie, fixed-output stimulation, have long been used to provide therapeutic relief to patients. Fixed-output (or open-loop systems) deliver pre-set, and unless intervened, fixed patterns of electrical stimulation. A new type of SCS system that uses a physiologic closed-loop feedback mechanism based on physiologic neural activation measurements has been recently developed. The increased interest in this novel technology has led to a need to define what constitutes a physiologic closed-loop controlled system (PCLCS). The recent Food and Drug Administration (FDA) guidance defines PCLCS as

> …a system consisting of sensors, actuators, and control algorithms that adjusts or maintains a physiologic variable through automatic adjustments to delivery or removal of energy or article (e.g., drugs, or liquid or gas regulated as a medical device) using feedback from a physiologic-measuring sensor(s).[1]

PCLCSs can benefit patients by facilitating safe, effective, consistent, accurate, real-time adjusted delivery of stimulation therapy, reducing the risk of under- or over-stimulation.[1] PCLCSs facilitate reduction of measurement error and guesswork, dependence on experienced programming technicians, and cognitive overload in programmers through standardization of programming based on patient's neural signature.

The Historical Roots of Closed-Loop Neuromodulation

Medical devices for blood sugar control, deep brain stimulation (DBS), and cardiac arrhythmia management have experimented with PCLCSs. A review of PCLC function in the diabetic literature highlighted the unique considerations and challenges for PCLC use. With the ability to monitor glucose continuously, care needs to be taken to determine the appropriate target for glycemic control to avoid incidences of severe hypoglycemia or diabetic ketoacidosis due to the variability seen between patient physiology.[2] This difficulty in bridging clinical algorithms with biophysiological variations can be seen in pacemaker technology as well, as efforts are currently being made to develop computational models to improve closed physiologic loop cardiac electrical device systems testing.[3] This complexity in algorithm is further reflected in DBS literature as it is suggested that feedback control may require the use of new closed control loop algorithms to ensure safe and effective disease management.[4]

In the early 1970s, Dr. William F. House, an otolaryngologist, and Dr Jack Urban, an engineer, achieved a groundbreaking milestone with the development of cochlear implants.[5] These implants marked one of the earliest successful implementations of the concept of a closed-loop system.[6] Cochlear implants utilize electrodes to directly

stimulate the auditory nerve in response to sound signals detected by an external microphone.[7] This remarkable innovation transformed the lives of individuals with severe-to-profound hearing loss or deafness, allowing them to perceive sound and significantly improve their ability to comprehend speech.

Translating this to the spinal cord, Parker et al introduced physiologic closed loop controlled (PCLC) technology to SCS, leveraging measurements of evoked compound action potentials (ECAPs) to create automated systems capable of maintaining optimal dorsal column fiber recruitment levels despite the dynamic environment between the stimulating electrodes and spinal cord.[8,9] These developments paved the way for landmark studies and further advancements in the field.

As this technologic innovation continues to be applied to spinal cord and specifically electrical neuromodulation for pain treatment, clear guidance is needed to shepherd the application and evidence generation responsibly.

Definition and Need for Guidance, Methods of Review and Evidence Synthesis, Faculty Selection, Bias Control

Definition and Scientific Rationale: What is Physiologic Closed-Loop Controlled Spinal Cord Stimulation (PCLC SCS)?

The United States Food and Drug Administration (FDA) has proposed technical considerations for the development of medical devices utilizing PCLC technology to ensure safe and effective use in the patient population.[1] The recent focus of PCLCSs has been on reducing risks seen in other industries where automation resulted in new problems including control system failure, automation bias, and increased system complexity.[10]

PCLC devices include five key components: a control algorithm, sensor, actuator, systems safety features, and a user interface. Closed-loop algorithms process data, and, based on predetermined principles, control adjustments to delivered energy to meet clinically pre-defined parameters, which include response time, steady state-deviation, and switching between therapy modes. A sensor's properties may directly impact treatment efficacy by improving accuracy and reliability of physiologic measurements across a multitude of variables (eg, environmental factors, timing, and interference).[1]

SCS is a type of neuromodulation that utilizes the application of electrical impulses to the spinal cord to reduce the chronic pain experience by providing pain relief and improvements in other domains affected by chronic pain. Traditionally, SCS systems are open-loop, fixed-output systems, delivering fixed, predetermined, preset patterns of electrical output to the spinal cord.

In traditional fixed-output systems, stimulation can be adjusted manually, usually by the representative of the company under the direction of the health care team as a "reprogramming". The patient can the alter the program by using the patient remote control (switching programs or adjusting the amplitude), or by algorithmic adjustment of the delivered program based on predetermined metrics and preset programs. During reprogramming, different patterns of stimulation can be utilized and factors such as amplitude, pulse width, and frequency can be adjusted to try to capture the intended target neural elements of the spinal cord for a therapeutic effect. Ultimately, fixed-output systems stimulate the spinal cord based on predetermined output, regardless of its impact on neural activation that can be affected by positionality or by physiological functions, such as breathing, heartbeat, and changing posture, all of which alter the distance between the spinal cord target fibers and epidural SCS electrodes.

PCLCSs require the identification of a physiologic measurement that is directly related to the intended therapy and is titrated directly. This physiologic measurement may have been identified. The ECAP is an extracellular measurement of the spinal cord's physiologic response to stimulation, ie, neural activation, and serves as a biomarker.[11] The amplitude of the ECAP corresponds to the number of axonal action potentials being generated by a given stimulus. Recent advances in technology allow us to measure ECAPs in real-time, both stimulating and sensing. PCLCSs should therefore capitalize on ECAP measurement by incorporating feedback control systems to automatically adjust the next stimulus amplitude to maintain the desired level of neural activation. Because a patient's requirements for neural activation may vary based on their activities at any given time, this may allow for dynamic, individualized therapy that can provide more optimized and consistent pain relief.

Therefore, PCLC SCS is SCS that is required to have a direct physiologic objective measurement of neural activation that directly, and in real-time, automatically adjusts the electrical output of the device to maintain a prescribed dose.

Need for Guidance

While potentially improving performance, automated processes require greater attention to training, improved interface design, and interaction design.[10] Due to the complex control algorithms, measurement and delivery devices, user interface, and article delivery characteristics, multiple opportunities exist for errors to occur. This could be related to device component failure, inter-device communication failure, software failure, erroneous algorithm, use error, or patient aberrant physiology. As such, the FDA recommends that device manufacturers maintain and document design control activities including risk identification and evaluation as well as monitoring efficacy throughout the lifecycle of the device for the entire device and not just the PCLC function.[1] As part of the system design process, manufacturers should collect data on device operations and user responses during clinical studies to understand the human factors and human engineering components that influence fault conditions and trigger fallback modes. Human factors and usability engineering should be applied to ensure the device is suitable for use with end users. System safety features must include fallback modes, transparent entrance and exit criteria, constraints on delivered energy, data logging, and alarms.[1]

PCLC technology has recently been introduced to the field of pain medicine, and it is the purpose of this American Society of Pain and Neuroscience (ASPN) NEURON (neuroscience, education, utilization, risk mitigation, optimal outcomes, and neuromodulation) endeavor. One SCS device has FDA approval for treatment of chronic intractable pain with 3-year follow-up safety and effectiveness data.[11–13] Closed-loop stimulation may provide additional benefits to concurrent neuromodulation therapies such as intrathecal drug delivery systems (IDDSs) by maintaining therapeutic cerebrospinal fluid (CSF) drug levels. This technology promises to improve outcomes, reduce human error, automate precise neural activation, and enhance our understanding of neural tissue electrical stimulation. See Figure 1.

As the headwinds of spinal cord stimulation grow stronger with criticisms of lack of efficacy for low back pain treatment in a Cochrane review, no statistical difference as compared to placebo, poor longevity, and bias, innovation in spinal cord stimulation needs to be met with careful, precise, balanced and deliberate rigor evaluating the scientific merit.[15–17]

Methods of Evidence Review and Evidence Synthesis

Due to the rate of new information within scientific literature, a systematic review was needed to synthesize the most relevant and salient information available to help relay key information.[18–20] A review performed to determine the time from publication of a protocol for a Cochrane review and the time to publication revealed a median publication time of 2 years.[21] To maintain relevant information within, the structure utilized here will be implemented into a living guideline allowing for more current information. With ongoing review of new literature, the goal would be to have biannual updates to ensure that the recommendations remain relevant integrating quantitative and qualitative evidence.[22]

A librarian-assisted literature search was performed from January 2023 to January 2024 to identify manuscripts relevant to the topic of PCLC stimulation for management of chronic pain, yielding articles from 2020 to 2023. Initial

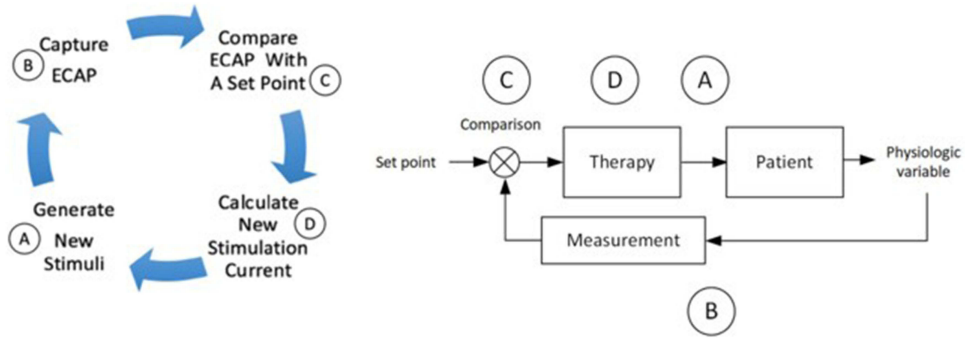

Figure 1 Phases of an ECAP-based spinal cord stimulation physiologic closed-loop control system.
Notes: Reprinted from Su PYP, Arle J, Poree L. Closing the loop and raising the bar: Automated control systems in neuromodulation. *Pain Pract*. 2024;24(1):177–185.[14]

Table 1 Quality of Evidence Ranking Using United States Preventative Services Task Force Criteria Modified for Therapy for Consensus Ranking

Grade	Definition	Suggestions for Practice
A	ASPN recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	ASPN recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	ASPN recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	ASPN recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I	ASPN concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

Notes: Modified from USPTF; adapted from Deer TR, Grider JS, Pope JE et al. Best Practices for Minimally Invasive Lumbar Spinal Stenosis Treatment 2.0 (MIST): Consensus Guidance from the American Society of Pain and Neuroscience (ASPN). *J Pain Res*. 2022;15:1325–1354.[24]
Abbreviations: ASPN, American Society of Pain and Neuroscience; USPSTF, United States Preventative Services Task Force.

literature search was performed utilizing MEDLINE, EMBASE, Google Scholar, Cochrane database, BioMed Central, and Web of Science. Included manuscripts encompassed meta-analyses, systematic reviews, RCTs, prospective studies, retrospective studies, case reports, and case series limited to the English language. Medical subject headlines (MESH) terms utilized included "closed-loop", "spinal cord stimulation", "closed loop feedback", "feedback controlled", "physiologic closed loop stimulation", "physiologic closed loop controlled stimulation", "neuromodulation", "pain", "persistent pain", "neuropathic pain", and "chronic pain".

Similar to other peer-reviewed, published consensus and guideline approaches taken in the pain literature,[23] including prior use within ASPN published guidance, the cumulative peer-reviewed literature evaluated utilizing modified USPSTF criteria for quality evidence and defined by level of certainty (see Tables 1 and 2, both reprinted from the original[24]). Each consensus point is described with grade of recommendation, level of evidence, and level of certainty.

An important note for the reader: these consensus points should always be considered as a guide. The consensus points are meant to assist in the assimilation of the current body of evidence and expert opinion. Individualized patient treatment should always be based on clinical judgment and the individual patient's need. This guideline is not intended to be used as the sole reason for denial or approval of treatment or services.

Faculty Selection

With the advent of PCLCS, ASPN determined evidence review and guidance was needed to explore and verify the utilization of this novel treatment modality as these PCLC devices are introduced to the SCS chronic pain treatment space. Using a multidisciplinary specialty approach, a panel of pain medicine specialists, including neurosurgeon, anesthesiology, physical medicine and rehabilitation, orthopedic surgery, and neurological surgery were selected to review the available literature regarding closed-loop stimulation and provide an evidence-based practice guideline, utilizing the modified United States Preventive Services Task Force (USPSTF) criteria,[25] as outlined. Committee members were selected based on clinical experience, previous research, and publication history.

Table 2 Levels of Certainty Regarding Net Benefit

Level of Certainty	Description
High	The available evidence includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies. **Evidence Level: I-A** - At least one controlled and randomized clinical trial, properly designed
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: • The number, size, or quality of individual studies. • Inconsistency of findings across individual studies. • Limited generalizability of findings to routine primary care practice. • Lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion. **Evidence Level I-B**- Well-designed, controlled, non-randomized clinical trials (prospective observational studies conforming to STROBE criteria) or **Evidence Level I-C** – Retrospective cohort or large case studies (>20 subjects)
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: • The limited number or size of studies. • Important flaws in study design or methods. • Inconsistency of findings across individual studies. • Gaps in the chain of evidence. • Findings not generalizable to routine primary care practice. • Lack of information on important health outcome **Evidence Level II**- Expert opinion based of risk:benefit or based upon case reports

Notes: Adapted from Deer TR, Grider JS, Pope JE et al. Best Practices for Minimally Invasive Lumbar Spinal Stenosis Treatment 2.0 (MIST): Consensus Guidance from the American Society of Pain and Neuroscience (ASPN). *J Pain Res*. 2022;15:1325–1354.[24]
Abbreviation: STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

Bias Control

All of the selected participants were invited by the executive board of ASPN. All were required to disclose all potential conflicts of interest, financial or otherwise, per the society's conflict of interest policy, and by the USPSTF criteria for conflict of interest (COI) disclosure.[26] All consensus statements, consensus grade, evidence level and level of certainty were finalized by nonbiased committee members.

Results

After the development of the working group and division of labor based on previous ASPN best practice and publication efforts, following the previously defined and modified USPSTF criteria for chronic pain treatments, a librarian-assisted literature search was performed to identify manuscripts relevant to the topic of PCLC stimulation for management of chronic pain. Initial literature search was performed utilizing MEDLINE, EMBASE, Cochrane database, BioMed Central, and Web of Science. Included manuscripts encompassed meta-analyses, systematic reviews, randomized controlled trials (RCTs), prospective or retrospective studies with follow-up to 12 months, limited to the English language. MESH (medical subject headings) terms utilized included "physiologic closed loop controlled", "closed-loop", "spinal cord stimulation", "closed loop feedback", "feedback controlled", "neuromodulation", "pain", "persistent pain", "neuropathic pain", and "chronic pain". The only prospective multicenter RCT published is the EVOKE study, with publications at 12, 24, and 36 months. The only prospective multicenter study with at least 12-month outcomes was the AVALON study, with publication at 12 and 24 months. Summarily, 2 prospective, one retrospective, and one randomized controlled study with at least 12-month follow-up. See Table 3.

Table 3 RCT Evidence Summary for Closed-Loop SCS

Author (Year)	Primary Aim	N, Sex, Mean Age ± SD	Follow-up	Outcomes	Findings
Mekhail 2020[11]	To evaluate back and leg pain, in double blinded fashion using closed loop fixed output versus closed loop SCS	n = 134. Closed loop: n=67, 33 women and 34 men, 54.6 ± 9.7 years old. Open loop: n=67, 32 women and 35 men, 55.9 ± 11.6 years old.	36 months, reporting at 12 months.	Neurophysiological data, pain intensity reduction as a VAS, ODI, SF-36, Pittsburg sleep scale, EQ-5D	134 patients, (67 to each treatment group). The intention-to-treat analysis of 125 patients at 3 months (62 in the closed-loop group and 63 in the open-loop group) and 118 patients at 12 months (59 in the closed-loop group and 59 in the open-loop group). The primary outcome in the closed-loop group was higher than in the open-loop group at 3 months (51 [82·3%] of 62 patients vs 38 [60·3%] of 63 patients; difference 21·9%, 95% CI 6·6–37·3; p=0·0052) and at 12 months (49 [83·1%] of 59 patients vs 36 [61·0%] of 59 patients; difference 22·0%, 6·3–37·7; p=0·0060). No differences in safety.
Mekhail et al 2022[12]	To evaluate back and leg pain, in double blinded fashion using closed loop fixed output versus closed loop SCS	n = 134. Closed loop: n=67, 33 women and 34 men, 54.6 ± 9.7 years old. Open loop: n=67, 32 women and 35 men, 55.9 ± 11.6 years old.	36 months, reporting at 24 months.	Neurophysiological data, pain intensity reduction as a VAS, ODI, SF-36, Pittsburg sleep scale, EQ5D	At 24 months, more closed-loop than open-loop patients were responders (≥50% reduction) in overall pain (53 of 67 [79.1%] in the closed-loop group; 36 of 67 [53.7%] in the open-loop group; difference, 25.4% [95% CI, 10.0%-40.8%]; P =.001). No difference in safety (difference in rate of study-related adverse events: 6.0 [95% CI, −7.8 to 19.7]). Improvements were also observed in secondary measures.
Mekhail et al 2023[13]	To evaluate back and leg pain, in double blinded fashion using closed loop fixed output versus closed loop SCS	n = 134. Closed loop: n=67, 33 women and 34 men, 54.6 ± 9.7 years old. Open loop: n=67, 32 women and 35 men, 55.9 ± 11.6 years old.	36 months, reporting at 36 months.	Neurophysiological data, pain intensity reduction as a VAS, ODI, SF-36, Pittsburg sleep scale, EQ-5D	More CL-SCS than OL-SCS participants reported ≥50% reduction (CL-SCS=77.6%, OL-SCS=49.3%; difference: 28.4%, 95% CI 12.8% to 43.9%, p<0.001) and ≥80% reduction (CL-SCS=49.3%, OL-SCS=31.3%; difference: 17.9, 95% CI 1.6% to 34.2%, p=0.032) in overall back and leg pain intensity. MCID from baseline were observed at 36 months in both CL-SCS and OL-SCS groups in all measurements, with greater levels of improvement with CL-SCS.

Abbreviations: CL-SCS, closed loop spinal cord stimulation; OL-SCS, open loop spinal cord stimulation; SF-36, Short Form health questionnaire (36-item); EQ-5D, EuroQOL 5-dimension questionnaire; ODI, Oswestry Disability Index; PCLC, physiological closed-loop controlled; PGIC, Patient Global Impression of Change; PSQI, Pittsburgh Sleep Quality Index; SCS, spinal cord stimulation; SD, standard deviation; SEM, standard error of mean; VAS, visual analogue scale.

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Current Evidence and Studies Using Physiologic Closed-Loop Stimulation for Chronic Pain

Randomized Controlled Trials

The EVOKE study was a pivotal, multicenter, double-blinded, randomized, parallel arm, self-selected cross over RCT comparing ECAP-controlled, closed-loop SCS and fixed-output, open-loop SCS for the treatment of chronic, intractable pain of the trunk and/or limbs for the back and leg. The primary outcome was defined as an improvement of >50% in overall back and leg pain intensity with no increase in baseline pain medication. Participants were randomized 1:1 to receive ECAP-controlled closed-loop SCS or the control open-loop SCS. Patients, investigators, and site staff were blinded to the treatment allocation. Notable inclusion criteria included intractable pain with functional limitations evidenced by VAS and ODI, a failure of conservative management, and no prior exposure to SCS. Each subject was permitted to self-select to crossover to the other therapy arm at 24 months. Non-inferiority followed by superiority were tested in the intention-to-treat population at 3, 12, 24, and 36 months.[11]

In the EVOKE study, 134 patients were randomized with 67 patients in the CL and 67 patients in the open-loop SCS (OL-SCS) arms proceeding to trial. Fifty-nine patients from the CL-SCS group and 54 patients from the OL-SCS group went on to receive an implant. Forty-four patients completed the final visit in the CL-SCS group and 42 patients in the OL-SCS group at 36-months follow-up. Using intention-to-treat analysis and last value carried forward, data from the patients randomized to each group was included in the primary analysis.

The results of the primary composite endpoint, which evaluated pain relief in combination with no increase in baseline pain medication, successfully demonstrated both non-inferiority ($p < 0.001$) and superiority (3-months: $p = 0.005$; 12-months: p-value=0.006) of CL-SCS to OL-SCS. In total, greater than 82% (3-months: 82.3%; 12-months: 83.1%) of CL-SCS patients met the primary endpoint individual success criteria compared to approximately 60% (3-months: 60.3%, 12-months: 61.0%) of OL-SCS patients. Additionally, the analysis of the primary endpoint was performed in the subset of subjects in the intention-to-treat population with a permanent implant, and demonstrated both non-inferiority ($p < 0.001$) and superiority (3-months: $p = 0.031$; 12-months: $p = 0.039$) of CL-SCS (3-months: 87.9%; 12-months: 89.1%) to OL-SCS (3-months: 71.7%; 12-months: 73.5%), confirming the robustness of the study conclusions. Thus, regardless of the methodology used to analyze the primary endpoint, the results consistently demonstrated superiority in clinical outcomes associated with CL-SCS compared to OL-SCS.

Non-inferiority was demonstrated across all the hierarchical secondary endpoints ($p \leq 0.002$). In addition, numerically better improvement was consistently observed, with statistical superiority of CL-SCS to OL-SCS in the percentage change in VAS average back pain (3-months: 72.1% CL-SCS vs 57.5% OL-SCS, $p = 0.015$; 12-months: 69.4% CL-SCS vs 54.0% OL-SCS, $p = 0.020$) and incidence of ≥50% reduction in VAS average back pain (3-months: 80.6% CL-SCS vs 57.1% OL-SCS, $p = 0.003$; 12-months: 79.7% CL-SCS vs 57.6% OL-SCS, $p = 0.008$) at 3 and 12-months. Statistical superiority of CL-SCS to OL-SCS was also observed in the incidence of high responders, (≥80% reduction) in VAS average overall trunk and limb pain at 12-months (12-months: 55.9% CL-SCS vs 37.3% OL-SCS, $p = 0.039$). Results at 24-, and 36-months confirmed the durable effects of EVOKE CL-SCS and OL-SCS. The ITT analysis at 36-month follow-up, showed that a significantly greater proportion of CL-SCS patients obtained ≥50% reduction (CL-SCS = 77.6%, OL-SCS = 49.3%, $p < 0.001$) and ≥80% reduction (CL-SCS = 49.3%, OL-SCS = 31.3%, $p = 0.032$) in overall back and leg pain.

As pain intensity only partially represents the impact that a therapy has on a patient's life, a recent study re-examined the 24-month, individual-level data from the EVOKE clinical trial to determine if there was a difference in a holistic treatment response when comparing CL-SCS to OL-SCS. The primary domains included pain intensity (via visual analog scale [VAS]), physical function (Oswestry Disability Index [ODI]), health-related quality of life (EuroQOL 5-dimension questionnaire [EQ-5D]), sleep (Pittsburgh Sleep Quality Index [PSQI]), and emotional function (Profile of Moods Scale [POMS]). Validated thresholds to achieve one or more minimal clinical important differences (MCIDs) were used for each domain, and cumulative holistic responder scores were calculated. An improvement by at least one MCID in at least two impaired domains constituted a multimodal treatment response. The same methods were applied to evaluate 36-months outcomes. Finally, neural activation (ECAP), neural activation accuracy (deviation of the elicited neural response

from the target neural response determined using root mean square error [RMSE]), and system utilization that produced the outcomes observed were also reported.

Responders in multiple domains were observed as early as 3-months following SCS therapy and sustained through end-of-study at 36-months.[13,27] For pain intensity, 82% CL-SCS versus 73% OL-SCS patients improved by at least one MCID. A greater proportion of CL-SCS patients (44.8%) compared to OL-SCS patients (28.4%) were categorized as holistic treatment responders achieving at least one MCID in all their baseline impaired domains at 36-months. Both arms of the study demonstrated high system utilization 77.6% vs 75.5% at 36-months for CL-SCS and OL-SCS, respectively. Notably, neural activation was two times greater in CL-SCS and neural activation accuracy was three times more accurate in the CL-SCS group vs OL-SCS group at 36-months follow-up.

Fifty-five percent of CL-SCS subjects voluntarily reduced or eliminated their opioid use at a clinically meaningful level.[12] CL-SCS provided statistically greater neural activation and accuracy at all time points. Moreover, both arms continued to demonstrate high system utilization greater than 75% through end-of-study. Importantly, given the consistent level of neural activation with CL-SCS, improvements observed in this group were greater and durable over the study period. Conversely, some of the initial improvements reported with OL-SCS lessened over time.

Other Evidence

Multiple studies have investigated the PCLCS in other study designs, including a large prospective single arm study with follow-up to 6, 12 and 24 months, the AVALON study, sub-analysis of the EVOKE study on sleep quality, cost-effectiveness and a real-world study on evidence of effectiveness and patient satisfaction in a single site (see Tables 4 and 5). Recent device reviews have assessed the safety, efficacy and characteristics of PCLC SCS. There are several ongoing studies that will add to the knowledge base of PCLC SCS (see Poree et al 2023[28] for a list of ongoing studies).

Appropriateness & Consensus on Current Use of Closed-Loop

Patient Selection

The patient selection process when considering a PCLC SCS does not conceptually differ from the patient selection process when considering any other SCS system, although it should be noted that the EVOKE study did not include, for example, patients with painful diabetic neuropathy, meaning that there is no direct evidence for PCLC SCS in this patient group and was only for patients with back and leg pain. However, the ECAP study, which enrolled 132 patients, included all comers and sought a commercial approval as a contingency for enrollment.[36,37]

Patient selection is a process whereby physicians try to match the patient's clinical picture, diagnosis to the appropriate treatment and assumes that such treatment and overall clinical care can be delivered in an effective and safe fashion.[38]

It is widely accepted that an appropriate patient selection process is one of the crucial factors that determines the multidimensional outcomes of SCS, both during the stimulation trial and long term. Evidence-based consensus guidelines on patient selection and trial stimulation for SCS have been published, with limited definitive guidance.[39]

Without a validated specific biomarker for either the efficacy of the SCS or pain felt by the patient, a rigorous and pragmatic multidisciplinary approach is required for the patient selection process. It must encompass the principles of appropriate patient's evaluation to obtain a precise pain diagnosis and provide a treatment as specific as possible for such diagnosis and take into consideration the specific pathology and the patient's psychosocial factors.[40] It should be noted, though, the potential to use PCLC SCS and more specifically ECAPs to guide patient selection during the trial period.[41] As aforementioned, PCLCS used during the trial period of the EVOKE study resulted in fewer patients having an unsuccessful trial.

Indication Recommendations

Patient selection for PCLC SCS is very similar to fixed output, historical SCS, with the additional confidence of the trial to serve as a predictor for long-term efficacy. Pope et al investigated the predictability of a PCLC SCS trial on Day 0 versus at the conclusion of the trial at Day 7, with PPV (positive predictive value) of 98.4% when ECAP generation, stability and maintenance is present at least 50% reduction of pain intensity and improvement in function is present.[41]

Table 4 Additional Evidence on PCLC SCS for Chronic Pain

Author (Year)	Primary Aim	N, Sex, Mean Age ± SD	Follow-up	Outcomes	Findings
Single-arm prospective study					
Russo (2018)[9] Russo (2020)[29] Brooker (2021)[30]	To evaluate the safety and performance of PCLC SCS for the treatment of chronic, intractable pain of the trunk and/or limbs	N=50 (with implanted device) F=26 (54%), 56.7±12.2y	24-months	Pain intensity (VAS, BPI) % reduction in pain Disability (ODI) HRQoL (EQ-5D-5L, EQ-VAS) Sleep quality (PSQI) Impression of change (PGIC) Satisfaction Opioid use Neurophysiological data	Statistically significant and clinically meaningful improvements with respect to baseline were observed in pain (VAS, BPI), physical function (ODI), sleep quality (PSQI), and quality of life (EQ-5D). High rates (>88%) of subject satisfaction with the therapy. The majority of subjects (>94%) perceived their overall status to be very much or much improved. Voluntary opioid reduction or elimination was observed in 83% of patients at 24-months. The most frequent (mode) ECAP amplitude was ~25 μV and activation was within the patients' therapeutic window >90% of the time.
Pope (2024)	To evaluate the immediate post operative treatment response employing PCLC SCS during trial and feasibility of early trial SCS responder prediction	N =132 (ECAP study enrollment) N=61	12 months, days (trial duration)	Day 0 success defined as > 50% improvement on pain intensity reduction of NRS (numerical rating scale), functional improvement (validated walking test), ECAP measurement and stability assessment	The high positive predictive value (PPV) (98.4%) and low false-positive rate (FPR) (5.6%) of the Day 0 evaluation provide confidence in predicting trial outcomes as early as the day of the procedure. Day 0 trials may be beneficial for reducing patient burden and complication rates associated with extended trials. ECAP dose controlledCL-SCS therapy may provide objective data and rapid-onset pain relief to improve prognostic ability of SCS trials in predicting outcomes.

(*Continued*)

Table 4 (Continued).

Author (Year)	Primary Aim	N, Sex, Mean Age ± SD	Follow-up	Outcomes	Findings
Real-world evidence study					
Nijhuis (2023)[31]	To evaluate the performance of PCLC SCS in a 'real-world' setting under normal conditions of use in a single European center, CRPS	N=22 (with implanted device) F=14 (64%), 54.8±2.0y (SEM)	12-months	Pain intensity (VNRS) % reduction in pain Satisfaction Neurophysiological data	Statistically significant and clinically meaningful improvements in pain intensity. 90% and 60% of patients obtained ≥50% and ≥80% pain reduction, respectively. At 12-months, 85% of the patients were very satisfied, satisfied, or quite satisfied. The mode ECAP was 11.7 μV at 12-months. Patients used their patient controller to adjust stimulation or program once (median) every three days.
Health economic evaluation					
Duarte (2023)[32]	To estimate the cost-effectiveness of PCLC SCS when compared with open-loop SCS for the management of people with chronic back and leg pain with or without prior spinal surgery	EVOKE study population	Time horizon of 15 years	Incremental cost-utility ratio	PCLC SCS was dominant (ie, cost-saving and provided additional health benefits) when compared to open-loop SCS. The results were robust to a range of deterministic and probabilistic sensitivity analyses.
Sub-analysis of the EVOKE study					
Duarte (2021)[33]	To estimate health-related utility scores associated with different health-states based on response to PCLC SCS measured as pain reduction	EVOKE study population	12-months	Pain intensity (VAS) HRQoL (EQ-5D-5L)	The improvement in HRQoL utility scores of people with chronic pain treated with PCLC SCS is directly associated with their level of pain
Taylor (2023)[34]	To estimate the health-related utility values associated with different levels of functional disability	EVOKE study population	12-months	Disability (ODI) HRQoL (EQ-5D-5L)	The HRQoL utility of people with chronic pain before and after treatment with PCLC SCS is associated with their level of disability
Costandi (2023)[35]	To investigate the impact of PCLC SCS on the sleep scales' component scores in patients with chronic pain	EVOKE study population	12-months	Sleep quality (PSQI)	Statistically and clinically significant long-term improvements in sleep quality with PCLC SCS compared to baseline

(*Continued*)

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Table 4 (Continued).

Author (Year)	Primary Aim	N, Sex, Mean Age ± SD	Follow-up	Outcomes	Findings
Levy (2024)	To investigate differences in outcomes and physiologic dose metrics observed between 1) a randomized controlled trial (RCT) and real-world SCS use, and 2) temporary SCS trial phase and post-implant SCS therapy.	EVOKE, AVALON, DURABILITY N = 130	12 month	VAS, ODI, HRQoL, PROMIS 10 Global Health, EQ-5D	Neural dose regimen with a high neural dose accuracy of 2.8 μV and dose ratio of 1.4 significant clinical benefit (MAE of 79 ± 1% for pain reduction and 12.5 ± 0.4 MCIDs). No differences were observed for MAE or neurophysiological dose metrics between the trial phase and post-implant MAE visit.
Mueller (2024)	To investigate the PCLC SCS and neurophysiological indicator metrics of therapy dose, usage above neural activation threshold, and accuracy of SCS therapy were assessed for relationship with pain reduction in over 600 SCS patients.	EVOKE, ECAP, AVALON study populations N = 600	12 months	ECAP, pain intensity reduction as VAS	Higher dose, time over ECAP threshold, and higher dosing accuracy are associated with better outcomes across patients as represented by VAS

Abbreviations: BPI, Brief Pain Inventory; CL-SCS, closed-loop spinal cord stimulation; CRPS, complex regional pain syndrome; ECAP, evoked compound action potential; EQ-5D, EuroQol-5 dimension; FPR, false-positive rate; HRQoL, health-related quality of life; MAE, maximal analgesic effect; MCID, minimal clinically important difference; NRS, numeric rating scale; ODI, Oswestry Disability Index; PCLC, physiological closed-loop controlled; PGIC, Patient Global Impression of Change; PPV, positive predictive value; PROMIS, Patient-Reported Outcomes Measurement Information System; PSQI, Pittsburgh Sleep Quality Index; RCT, randomized controlled trial; SCS, spinal cord stimulation; SD, standard deviation; SEM, standard error of mean; VAS, visual analogue scale; VNRS, verbal numerical rating score.

Table 5 Consensus Statement on PCLC SCS

Consensus Statement	Grade	Evidence Level	Level of Certainty Net Benefit
PCLC SCS is defined by a SCS system consisting of sensors, actuators, and control algorithms that adjusts or maintains a physiologic variable of neural activation through automatic adjustments to delivery or removal of electrical energy using feedback from the physiologic-measuring sensor	A	I-A	High
PCLC SCS is safe in the treatment of back and leg pain	A	I-A	High
PCLC SCS is efficacious in the treatment of back and leg pain	A	I-A	High
PCLC SCS is safe and efficacious in treatment of neuropathic pain from other sources, including CRPS, peripheral neuropathy	B	II-A	High
PCLC SCS is superior to OL-SCS in the treatment of back and leg pain	A	I-A	High
PCLC SCS improves sleep, quality of life, function and mood for patients with back and leg pain	A	I-A	High

Abbreviations: PCLC, physiological closed-loop controlled; SCS, spinal cord stimulation; CRPS, complex regional pain syndrome; OL-SCS, open-loop SCS.

Table 6 Consensus Statement on PCLC SCS Indications

Consensus Statement	Grade	Evidence Level	Level of Certainty Net Benefit
PCLC SCS should be considered in the treatment of chronic moderate to severe neuropathic pain	A	I-A	High

Abbreviations: PCLC, physiological closed-loop controlled; SCS, spinal cord stimulation.

Pain treatment follows a continuum of care. When all conservative treatments fail (eg, physiotherapy, oral medications, cognitive behavioral therapy, injections and radiofrequency therapy), SCS is an effective treatment for relieving a variety of pain conditions, including PSPS-T2, CRPS I and II, pain secondary to peripheral vascular disease (PVD), angina, multiple sclerosis, and peripheral neuropathy.[42–47] Studies have concluded that SCS provide significant long-term pain relief and improved quality of life in patients with neuropathic pain, including increases in social interactions, mood elevation, and improvement in activities of daily living.

Overall, the indication for PCLC SCS is omnipresent, as it serves as a technology innovation. As measurement of the ECAP can allow for a biomarker driven dosing strategy, device optimization is tailored to the individual patient sensitivity. This allows for the opportunity for success when population based, fixed output dosing would fail. Regarding activation of the dorsal column for pain relief, the Aβ nociceptor hypothesis posits that very short-term large-magnitude stimulation can activate Aβ nociceptors (which are present but only fire at multiples of stimulation intensity to Aβ sensory fibers) which can then cumulatively reverse analgesia and lead to loss of pain relief and so-called SCS habituation (refractoriness is a more correct term).[48] In the self-selected crossover double blinded EVOKE study mentioned previously, comparing open loop, fixed output to PCLCS, there were no explants in the PCLCS group due to loss of efficacy and had improved neural activation, as compared to the open loop/fixed output group (see Table 6).

Moreover, utilizing neurophysiologic biomarker driven PCLC SCS dosing allows for a deeper understanding of dosing accuracy, dosing consistency (therapy utilization) and use (device utilization), providing a level of granularity that was unavailable previously.

Surgical Technique

The surgical technique for the placement of PCLC neuromodulation devices is largely similar to the approach used by physicians for traditional SCS. There are, however, a few technique distinctions to consider. First, the SCS lead needs to be placed where activation mapping is performed, confirming sidedness. Traditional paresthesia or dermatomal mapping is not required. Although anatomic placement of leads has been performed commercially, it is recommended to confirm neural activation sidedness and testing. Second, if two leads are placed within the epidural space, it is necessary to ensure the leads are not touching, as this may affect the electrical field and identification of the ECAP and stability of the closed loop. This is oftentimes accomplished by placing both needles first and then "stair stepping" the lead to the final position, maintaining equidistance between the leads (see Table 7).

Programming

With ECAP controlled measurements occurring in real time, PCLC SCS can detect changes in ECAPs that may indicate a change in the patient's position or subtle shifts in anatomy, which enables prompt and adaptive modulation of stimulation parameters. This increased accuracy and consistent dosing leads to better pain control, significantly reduces

Table 7 Consensus Statement on PCLC SCS Lead Placement

Consensus Statement	Grade	Evidence Level	Level of Certainty Net Benefit
PCLC SCS placement is similar to traditional OL-SCS with more attention directed to lead spacing to optimize measurement and stimulation of the spinal cord	A	I-A	High

Abbreviations: PCLC, physiological closed-loop controlled; SCS, spinal cord stimulation; OL-SCS, open-loop SCS.

the need for manual re-adjustments or reprogramming visits, improves functional outcomes, and enhances quality of life for individuals.[12,30,31,49,50] Without this ability, SCS therapy invariably fluctuates and requires several manual adjustments by the patient throughout the day and frequent reprogramming visits to maintain the therapeutic benefit.[28,51]

The ECAP is a physiologic measurement or neural response elicited by electrical stimulation of the dorsal column. A summation ECAP response of the dorsal column after electrical stimulation is an indicator of neural activation.[52] Consistent neural activation at a determined therapeutic target is the goal of effective programming using PCLC stimulation. The dose response curve of each individual patient is central to a therapeutic neural activation target. The sensitivity of neural activation to increasing amplitudes creates a dose response curve specific to each patient. Patient comfort level regarding amplitude, frequency and pulse width is combined with objective information from the activation plot to set a therapeutic neural activation target, reported in microvolts. More precise than a therapeutic window, effective programming with PCLC stimulation sets a patient specific therapeutic target which the device auto-adjusts to maintain (see Table 8).

Intraoperative programming and testing is recommended, as with any SCS therapy. For fixed output systems, this is achieved by testing impedance or "paresthesia mapping". Contrastingly, with PCLC SCS, neural activation mapping and sidedness is recommended to ensure appropriate placement of the electrode within the epidural space. Objectively, ECAP threshold can be detected, and upper limits of stimulation are set initially subjectively, with defining output tolerance.

For the first time in the neuromodulation space for pain, we have the capacity for neurophysiologic biomarker driven neural dosing using the ECAP amplitude to measure neural activation, Retrospectively, Mueller et al investigated 600 patients and concluded that a higher dose of therapy utilization above ECAP threshold, and higher dose accuracy of 5 microvolts or less improves patient outcomes in validated assessments including pain intensity reduction, improved function, sleep and mood, representing the first evidence of a dose-response relationship in SCS.[53]

Further, Levy et al described in 180 patients the maximal analgesic benefit of SCS for the treatment of chronic pain patient using a dose regimen of 1.4 dose ratio above ECAP threshold and a dose accuracy of less than 5 microvolts (2.8 microvolts). This represents the first application of an evidence based neural dosing regimen to optimize clinical benefit.[54]

Clinical Utility of Objective Neurophysiological Measurements

Fixed-output SCS is a widely accepted form of therapy for chronic neuropathic pain. A serious challenge that fixed-output SCS therapy had since inception is the inability to provide effectively consistent pain relief regardless of body position.[51,55] Changes in distance or orientation of the spinal cord in regard to the position of the SCS stimulating electrodes could lead to either over-stimulation or under-stimulation and thus inconsistent and suboptimal pain control. In contrast, PCLC SCS uses real-time neurophysiologic feedback from the patient's own neural activity. The ability of PCLC SCS to measure amplitude, in the form of an ECAP, as data to be entered into a feedback loop allows for consistent activation of neural tissue and creation of a target ECAP.[12,30,49,50] Once a target ECAP has been established, this feedback loop allows for dynamic adjustments in the amplitude of SCS ensuring optimized therapy regardless of physiological or postural changes.[12,30,49,50]

Table 8 Consensus Statement on PCLC SCS Neural Activation

Consensus Statement	Grade	Evidence Level	Level of Certainty Net Benefit
PCLC SCS dorsal column stimulation requires sidedness for neural mapping for optimal placement of the electrode	A	I-A	High
PCLC SCS dorsal column stimulation does not require paresthesia overlap mapping for optimal placement of the electrode	B	I-A	High
PCLC SCS appears to require adjustment at each impulse and subsequent adjustment and feedback for the next stimulus for clinically relevant PCLC stimulation for SCS	A	I-A	High

Abbreviations: PCLC, physiological closed-loop controlled; SCS, spinal cord stimulation.

Neurophysiologic biomarker driven PCLC SCS provides invaluable insights that were never achieved before. Not only can you precisely neural dose SCS for each individual patient, but one also has the capacity to deliver the dose over the lifetime of the device and the pain complaint. This may offer solutions for failed SCS due to loss of efficacy, whether because over-stimulation or under-stimulation. Further, by precisely delivering the appropriate therapeutic neural dose on a pulse-to-pulse basis, with measurement and response in real-time, it allows for the potential for reduction of habituation and tolerance, suggested by the longevity of the EVOKE study cohort to 36 months. In addition, this may reduce and eliminate the placebo effect, guaranteeing neural activation. In addition, biometrically driven neurophysiologic dosing allows to gain more confidence in the differential diagnosis. For example, if a patient maintains therapeutic neural dosing and device utilization is consistent, and an increase or onset of pain occurs, this scenario may suggest a pain target that would not be treated by neuromodulation, requiring further nociceptive pain generator investigation. The integration of objective neurophysiological measurements utilized by PCLCSs such as ECAPs provides the clinician a powerful tool to optimize therapy, enhance patient outcomes, and develop insight into mechanisms driving chronic pain.

SCS technologies are advancing at a rapid pace.[55] As device technology moves forward, PCLC SCS could engage the trillions of ECAPs measured and recorded to uncover patterns, correlations, and predictors of treatment response. By measuring ECAPs clinicians potentially gain insight into difficult physiologic and pathologic issues such as: pain processing, neural plasticity, effects of PCLC SCS on the central nervous system, etc. The findings could guide the development of better PCLC SCS algorithms, help refine patient selection criteria, and drive future neuromodulation therapies. Through the evaluation of ECAP feedback loops in real time, PCLC SCS has the ability to provide precise, personalized pain relief (see Table 9).

Discussion

Continuous PCLC SCS has a growing body of evidence on safety and efficacy, highlighting different patient populations that may be served by the use of this innovative technology. To date, one large RCT, representing the only double blinded study prospective, self-selected crossover designed study, with long-term follow-up, is present in our space. Large observational studies with mirrored results exist, while a large single arm prospective study representing use in the real work population.[31] It is clear PCLC SCS represents a new technology that may continue to improve outcomes and reduce habituation and tolerance, remedying the headwinds of traditional open loop, fixed output systems.

Strengths and Limitations

The evidence for continuous PCLC SCS is supported by a 2-year multicenter observational study (AVALON), a one-year multicenter observational study (ECAP) and a three-year randomized, multicenter double-blinded, self-selected crossover RCT (EVOKE). This represents Level 1A evidence and a high degree of certainty, yielding a GRADE A consensus for improvement in pain intensity, sleep, function, mood, and quality of life. Currently, there is only one FDA-approved SCS therapy that offers closed loop stimulation with published 12-month data. The patient population most studied, with published results, is for back and leg pain. More research is needed on different chronic pain indications.

Table 9 Consensus Statement on PCLC SCS Dosing

Consensus Statement	Grade	Evidence Level	Level of Certainty Net Benefit
ECAP measurement is a measure of neural activation	A	I-A	High
PCLC SCS with the use of ECAPs allows for dose response titration with pulse-to-pulse adjustment, improving outcomes	A	I-A	High

Abbreviations: ECAP, evoked compound action potential; PCLC, physiological closed-loop controlled; SCS, spinal cord stimulation.

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Current Research Needs and Future Advancements

PCLC SCS represents a revolutionary advancement in neuromodulation with the potential to have immense impact on patient outcomes and healthcare. To understand and maximize the full potential of this new technology, additional research and innovation are necessary. These include, but are not limited to:

1. Knowledge gaps: a deeper understanding of the complex interplay between patient characteristics, stimulation, and outcomes needs to be achieved. Understanding how individual patient factors such as age, disease co-morbidities, gender, medications, etc., impact stimulation can help practitioners identify patterns, optimize therapy, and predict outcomes by confidence in stimulating the spinal cord with a predictable and reproducible physiologic response, as defined by an ECAP, allowing for improved patient selection and care.
2. Procedural enhancements: comprehension of the significance of physiologic signals like ECAPs and their relationship to certain outcomes could alter the way we approach trialing, trial objective endpoints, trial duration, and implantation.
3. Expanding indications: exploring novel applications of PCLC SCS can potentially provide relief to a wider range of neurological and neuromuscular conditions. Cervical, high thoracic and lower thoracic areas affected by the constant change of distance from leads to the spinal cord can be mapped to other pain etiologies, eg, upper extremity CRPS.
4. Continuous safety and efficacy monitoring: the substantial physiologic and objective data collected through PCLC SCS could potentially be utilized to monitor patients, track outcomes, refine and optimize treatment protocols.
5. Implications on access and healthcare burden: as new technology is introduced and indications are expanded, it is imperative to consider its implication on healthcare costs and the potential burden to the healthcare system. Cost-effectiveness of PCLC SCS when compared to fixed-output SCS has been demonstrated which further substantiates the value of this therapy to payors and perhaps improve access to care.[32]
6. Advancing technology: potential areas of development include PCLCS for sub-perception therapy, adding modalities that can improve ease of use and access for patients and practitioners such as remote monitoring, remote or autonomous/self-programming. These advances in programming can minimize human bias/error and allow for enhanced utilization of therapy.
7. Interdisciplinary collaboration: fostering collaboration amongst various specialties can maximize the impact of neurostimulation and allow for the exploration of ways to address more complex neurological diseases.
8. PCLCS may enable the development of prescription guidelines for SCS. These have the potential to optimize treatment effectiveness and is only possible to establish with PCLC SCS.

PCLCS begins a new chapter in neuromodulation therapy. Research and innovation can further drive this therapy beyond current understanding. By actively addressing knowledge gaps, expanding indications, considering healthcare implications, exploring how this technology can be advanced, and fostering interdisciplinary collaboration PCLCS has the potential to change the way we utilize SCS therapy.

Living Guidelines: Going Forward

Neuromodulation has quickly become a staple of chronic pain management with great advancements in hardware and software since its conceptualization and use in 1967.[56,57] Consensus guidelines have historically provided guidance for its evidence-based practice recommendations and use.[43,58–60] With the pace of technological breakthroughs and improved disease state understanding, regular validated relevant guidelines become necessary. It generally takes over a year before new publications are incorporated in a systematic review, thus intermittent updating may leave gaps when new important research discoveries are made. Living systematic review (LSR) is a concept pioneered in 2014 to help meet the needs for high quality, contemporary summaries synthesizing new research to provide up-to-date recommendations with adherence to rigorous academic standards.[61]

The International Living Systematic Review Network, a group funded by Cochrane and the Australian National Health and Medical Research Council, has outlined recommendations for maintaining a LSR.[62–65] Among the recommendations for conducting a LSR, having a strong baseline systematic review to build on with clearly delineated inclusion criteria is paramount. Once established, the updating and searching protocol are specific to each study with a peer review process catered to the prevalence of new evidence when available.[62] It is feasible to have a quarterly or biannual literature search to include any new evidence for inclusion and review with a formal editorial and peer review every 1–2 years regardless of whether new information is available.[62,66] Once the parameters have been set, the literature review procedure can be performed by humans or machine technologies to streamline the process.[63] As with all meta-analysis, with increased sample size, there is an increase in type I error and the statistical analysis needs to be modified to account for this.[64]

Based on these recommendations, utilizing this systematic review as the baseline to transitioning this manuscript into an LSR, the authors recommend a literature review utilizing the protocols detailed within to be updated in a peer reviewed fashion at a minimum of every other year. When research is available, the data within will be analyzed, and the recommendations will be updated before a peer review process is initiated. If no new relevant evidence is available, an expedited non peer reviewed update will be produced. Every two years, a formal re-evaluation of the literature for an updated systematic review will be performed to improve the fidelity of the information and to evaluate the integrity of the review process within.

Conclusion

PCLC systems are being incorporated innovatively to manage diseases that historically have been overly burdensome, and although technological advancements in open loop, fixed output systems have improved safety and efficacy, represents the only path that allows for the objective measurement of neural activation to refine and physiologically phenotype stimulation to develop and deliver optimal therapy. PCLC SCS has high-quality evidence for back and leg pain management, with the development of more research to manage different pain populations and indications, including movement disorders, ASPN is committed to survey the safety, efficacy, and evidence of PCLC neuromodulation, with periodic updates planned to update this live document.

Abbreviations

ASPN, American Society of Pain and Neuroscience; BPI, Brief Pain Inventory; CE (Mark), Conformité Européenne; CL, Closed-loop; CL-SCS, Closed-loop spinal cord stimulation; COI, Conflict of interest; CRPS, Complex regional pain syndrome; CSF, Cerebrospinal fluid; DBS, Deep brain stimulation; ECAP, Evoked compound action potential; EQ-5D, EuroQOL 5-dimension questionnaire; FBSS, Failed back surgery syndrome; FDA, Food and Drug Administration (the United States); HRQoL, Health-related quality of life; IDDS, Intrathecal drug delivery system; IPG, Implanted pulse generator; LSR, Living systematic reviews; MCID, Minimal clinically important difference; MESH, Medical subject headlines; the vocabulary thesaurus used for indexing articles by the National Library of Medicine; ODI, Oswestry Disability Index; OL, Open-loop; OL-SCS, Open-loop SCS; PCLC, Physiologic closed-loop controlled; PCLCS, Physiologic closed-loop controlled system; PGIC, Patient Global Impression of Change; POMS, Profile of Moods Scale; PPV, Positive predictive value; PSPS-T2, Persistent spinal pain syndrome type 2; PSQI, Pittsburgh Sleep Quality Index; PVD, Peripheral vascular disease; RCT, Randomized controlled trial; RMSE, Root mean square error; SCS, Spinal cord stimulation; SD, Standard deviation; SEM, Standard error of mean; SF-36, Short Form health questionnaire (36-item); STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; USPSTF, United States Preventive Services Task Force; VAS, Visual analog scale; VNRS, Verbal numerical rating score.

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PSS has received research funding from Saluda and Nalu, is co-founder of electroCore, and is a research advisor for SPR, Biotronik, Nalu, and AIS Healthcare; in addition, Dr Peter Staats has a patent for High Dose Capsaicin with royalties paid to Averitas, and a patent for vagus nerve stimulation licensed to electroCore. PV is a consultant to for Saluda and Presidio and has received research funding from Saluda, Presidio, and Biotronik. CMV is a consultant for Saluda Medical and PainTEQ. RML is an unpaid consultant for Abbott, Biotronik, Nalu, and Saluda and holds stock options with Nalu and Saluda. NM functioned as

the independent Medical Monitor of Saluda's EVOKE study. JMH, CWH, CML, BM, SMR, and JMS report no competing interests.

References

1. United States Food and Drug Administration (FDA), Health and Human Services. Technical Considerations for Medical Devices With Physiologic Closed-Loop Control Technology; Guidance for Industry and Food and Drug Administration Staff. 2023. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/technical-considerations-medical-devices-physiologic-closed-loop-control-technology. Accessed December 27, 2024.
2. Clarke WL, Renard E. Clinical requirements for closed-loop control systems. *J Diabetes Sci Technol*. 2012;6(2):444–452. doi:10.1177/193229681200600233
3. Ai W, Patel ND, Roop PS, Malik A, Trew ML. Cardiac electrical modeling for closed-loop validation of implantable devices. *IEEE Trans Biomed Eng*. 2020;67(2):536–544. doi:10.1109/TBME.2019.2917212
4. Krauss JK, Lipsman N, Aziz T, et al. Technology of deep brain stimulation: current status and future directions. *Nat Rev Neurol*. 2021;17(2):75–87. doi:10.1038/s41582-020-00426-z
5. House WF, Urban J. Long term results of electrode implantation and electronic stimulation of the cochlea in man. *Ann Otol Rhinol Laryngol*. 1973;82(4):504–517. doi:10.1177/000348947308200408
6. Klop WMC, Hartlooper A, Briare JJ, Frijns JHM. A new method for dealing with the stimulus artefact in electrically evoked compound action potential measurements. *Acta Otolaryngol*. 2004;124(2):137–143. doi:10.1080/00016480310016901
7. House LR. Cochlear implant: the beginning. *Laryngoscope*. 1987;97(8 Pt 1):996–997. doi:10.1288/00005537-198708000-00023
8. Parker JL, Karantonis DM, Single PS, Obradovic M, Cousins MJ. Compound action potentials recorded in the human spinal cord during neurostimulation for pain relief. *Pain*. 2012;153(3):593–601. doi:10.1016/j.pain.2011.11.023
9. Russo M, Cousins MJ, Brooker C, et al. Effective relief of pain and associated symptoms with closed-loop spinal cord stimulation system: preliminary results of the Avalon study. *Neuromodulation*. 2018;21(1):38–47. doi:10.1111/ner.12684
10. Lee JD. Review of a pivotal human factors article: "Humans and automation: use, misuse, disuse, abuse". *Hum Fact*. 2008;50(3):404–410. doi:10.1518/001872008X288547
11. Mekhail N, Levy RM, Deer TR, et al. Long-term safety and efficacy of closed-loop spinal cord stimulation to treat chronic back and leg pain (Evoke): a double-blind, randomised, controlled trial. *Lancet Neurol*. 2020;19(2):123–134. doi:10.1016/S1474-4422(19)30414-4
12. Mekhail N, Levy RM, Deer TR, et al. Durability of clinical and quality-of-life outcomes of closed-loop spinal cord stimulation for chronic back and leg pain: a secondary analysis of the evoke randomized clinical trial. *JAMA Neurol*. 2022;79(3):251–260. doi:10.1001/jamaneurol.2021.4998
13. Mekhail NA, Levy RM, Deer TR, et al. ECAP-controlled closed-loop versus open-loop SCS for the treatment of chronic pain: 36-month results of the EVOKE blinded randomized clinical trial. *Reg Anesth Pain Med*. 2024;49(5):346–354. doi:10.1136/rapm-2023-104751
14. PYP Su, Arle J, Poree L. Closing the loop and raising the bar: automated control systems in neuromodulation. *Pain Pract*. 2024;24(1):177–185. doi:10.1111/papr.13290
15. D'Souza RS, Klasova J, Hussain N. Behind the curtain: conflicts of interest in spinal cord stimulation trials—an infographic. *Reg Anesth Pain Med*. 2024. doi:10.1136/rapm-2024-106069
16. Traeger AC, Gilbert SE, Harris IA, Maher CG. Spinal cord stimulation for low back pain. *Cochrane Database Syst Rev*. 2023;3(3):CD014789. doi:10.1002/14651858.CD014789.pub2
17. Hara S, Andresen H, Solheim O, et al. Effect of spinal cord burst stimulation vs placebo stimulation on disability in patients with chronic radicular pain after lumbar spine surgery: a randomized clinical trial. *JAMA*. 2022;328(15):1506–1514. doi:10.1001/jama.2022.18231
18. Linares-Espinós E, Hernández V, Domínguez-Escrig JL, et al. Methodology of a systematic review. *Actas Urol Esp*. 2018;42(8):499–506. doi:10.1016/j.acuro.2018.01.010
19. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71
20. Koslosky E, Gendelberg D, Zhu J. Guidelines on how to perform a systematic review in spine surgery. *Clin Spine Surg*. 2021;34(3):107–108. doi:10.1097/BSD.0000000000001088
21. Andersen MZ, Gülen S, Fonnes S, Andresen K, Rosenberg J. Half of Cochrane reviews were published more than 2 years after the protocol. *J Clin Epidemiol*. 2020;124:85–93. doi:10.1016/j.jclinepi.2020.05.011
22. Lizarondo L, Stern C, Apostolo J, et al. Five common pitfalls in mixed methods systematic reviews: lessons learned. *J Clin Epidemiol*. 2022;148:178–183. doi:10.1016/j.jclinepi.2022.03.014
23. Sayed D, Grider J, Strand N, et al. The American society of pain and neuroscience (ASPN) evidence-based clinical guideline of interventional treatments for low back pain. *J Pain Res*. 2022;15:3729–3832. doi:10.2147/JPR.S386879
24. Deer TR, Grider JS, Pope JE, et al. Best practices for minimally invasive lumbar spinal stenosis treatment 2.0 (MIST): consensus guidance from the American society of pain and neuroscience (ASPN). *J Pain Res*. 2022;15:1325–1354. doi:10.2147/JPR.S355285
25. Harris RP, Helfand M, Woolf SH, et al. Current methods of the U.S. preventive services task force: a review of the process. *Am J Preventive Med*. 2001;20(3 SUPPL):21–35. doi:10.1016/S0749-3797(01)00261-6
26. Conflict of interest disclosures | United States preventive services taskforce. Available from: https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/conflict-interest-disclosures. Accessed December 27, 2024.
27. Kapural L, Mekhail NA, Costandi S, et al. Durable multimodal and holistic response for physiologic closed-loop spinal cord stimulation supported by objective evidence from the EVOKE double-blind randomized controlled trial. *Reg Anesth Pain Med*. 2024;49(4):233–240. doi:10.1136/rapm-2023-104639
28. Poree L, Foster A, Staats PS. Device profile of the Evoke physiologic closed-loop spinal cord stimulation system for the treatment of chronic intractable pain: overview of its safety and efficacy. *Expert Rev Med Devices*. 2023;20(11):885–898. doi:10.1080/17434440.2023.2255520
29. Russo M, Verrills P, Santarelli D, Gupta S, Martin J, Hershey B. A novel composite metric for predicting patient satisfaction with spinal cord stimulation. *Neuromodulation*. 2020;23(5):687–697. doi:10.1111/ner.13072

30. Brooker C, Russo M, Cousins MJ, et al. ECAP-controlled closed-loop spinal cord stimulation efficacy and opioid reduction over 24-months: final results of the prospective, multicenter, open-label Avalon study. *Pain Pract*. 2021;21(6):680–691. doi:10.1111/papr.13008
31. Nijhuis HJA, Hofsté WJ, Krabbenbos IP, Dietz BE, Mugan D, Huygen F. First report on real-world outcomes with evoked compound action potential (ECAP)-controlled closed-loop spinal cord stimulation for treatment of chronic pain. *Pain Ther*. 2023;12(5):1221–1233. doi:10.1007/s40122-023-00540-y
32. Duarte RV, Bentley A, Soliday N, et al. Cost-utility analysis of evoke closed-loop spinal cord stimulation for chronic back and leg pain. *Clin J Pain*. 2023;39(10):551–559. doi:10.1097/AJP.0000000000001146
33. Duarte RV, Soliday N, Leitner A, Taylor RS. Health-Related Quality of Life Associated With Pain Health States in Spinal Cord Stimulation for Chronic Neuropathic Pain. *Neuromodulation*. 2021;24(1):142–149. doi:10.1111/ner.13267
34. Taylor RS, Soliday N, Leitner A, et al. Association between levels of functional disability and health-related quality of life with spinal cord stimulation for chronic pain. *Neuromodulation*. 2023;26(6):1039–1046. doi:10.1016/j.neurom.2022.04.039
35. Costandi S, Kapural L, Mekhail NA, et al. Impact of long-term evoked compound action potential controlled closed-loop spinal cord stimulation on sleep quality in patients with chronic pain: an EVOKE randomized controlled trial study subanalysis. *Neuromodulation*. 2023;26(5):1030–1038. doi:10.1016/j.neurom.2022.10.050
36. Pope JE. on behalf of the ECAP study investigators. ECAP study: evaluating holistic response & disease-related neurophysiology in real-world chronic pain using ECAP-controlled closed-loop SCS. *North American Neuromodulation Society (NANS) Annual Meeting*. 2023.
37. Petersen EA, on behalf of the ECAP study investigators. ECAP study: evaluating holistic response in real-world chronic pain using ECAP-controlled closed-loop SCS. In: *American Society of Pain and Neuroscience (ASPN) Annual Conference*; 2023.
38. McCurry TM, Kasdan ML. Patient selection. *Clin Occup Environ Med*. 2006;5(2):217–223. doi:10.1016/j.coem.2005.11.009
39. Shanthanna H, Eldabe S, Provenzano DA, et al. Evidence-based consensus guidelines on patient selection and trial stimulation for spinal cord stimulation therapy for chronic non-cancer pain. *Reg Anesth Pain Med*. 2023;48(6):273–287. doi:10.1136/rapm-2022-104097
40. Chadwick A, Frazier A, Khan TW, Young E. Understanding the psychological, physiological, and genetic factors affecting precision pain medicine: a narrative review. *J Pain Res*. 2021;14:3145–3161. doi:10.2147/JPR.S320863
41. Pope JE, Antony A, Petersen EA, et al. Identifying SCS trial responders immediately after postoperative programming with ECAP dose-controlled closed-loop therapy. *Pain Ther*. 2024;13:1173–1185. doi:10.1007/s40122-024-00631-4
42. Cameron T. Safety and efficacy of spinal cord stimulation for the treatment of chronic pain: a 20-year literature review. *J Neurosurg*. 2004;100(3 Suppl Spine):254–267. doi:10.3171/spi.2004.100.3.0254
43. Deer TR, Krames E, Mekhail N, et al. The appropriate use of neurostimulation: new and evolving neurostimulation therapies and applicable treatment for chronic pain and selected disease states. *Neuromodulation*. 2014;17(6):599–615. doi:10.1111/ner.12204
44. Frey ME, Manchikanti L, Benyamin RM, Schultz DM, Smith HS, Cohen SP. Spinal cord stimulation for patients with failed back surgery syndrome: a systematic review. *Pain Physician*. 2009;12(2):379–397. doi:10.36076/ppj.2009/12/379
45. Kumar K, Hunter G, Demeria D. Spinal cord stimulation in treatment of chronic benign pain: challenges in treatment planning and present status, a 22-year experience. *Neurosurgery*. 2006;58(3):481–496; discussion 481–96. doi:10.1227/01.NEU.0000192162.99567.96
46. Taylor RS, Van Buyten JP, Buchser E, et al. Spinal cord stimulation for chronic back and leg pain and failed back surgery syndrome: a systematic review and analysis of prognostic factors. *Spine*. 2005;30(1):152–160. doi:10.1097/01.brs.0000149199.68381.fe
47. Turner JA, Loeser JD, Deyo RA, Sanders SB. Spinal cord stimulation for patients with failed back surgery syndrome or complex regional pain syndrome: a systematic review of effectiveness and complications. *Pain*. 2004;108(1–2):137–147. doi:10.1016/j.pain.2003.12.016
48. Russo M Recognising and shutting down A-Beta Nociceptor activation. In: *Neuromodulation Society of Australia and New Zealand 13th Annual Scientific Meeting*; 2018:Sydney, NSW, Australia.
49. Levy R, Deer TR, Poree L, et al. Multicenter, randomized, double-blind study protocol using human spinal cord recording comparing safety, efficacy, and neurophysiological responses between patients being treated with evoked compound action potential-controlled closed-loop spinal cord stimulation or open-loop spinal cord stimulation (the evoke study). *Neuromodulation*. 2019;22(3):317–326. doi:10.1111/ner.12932
50. Sun FT, Morrell MJ. Closed-loop neurostimulation: the clinical experience. *Neurotherapeutics*. 2014;11(3):553–563. doi:10.1007/s13311-014-0280-3
51. Vallejo R, Chakravarthy K, Will A, Trutnau K, Dinsmoor D. A new direction for closed-loop spinal cord stimulation: combining contemporary therapy paradigms with evoked compound action potential sensing. *J Pain Res*. 2021;14:3909–3918. doi:10.2147/JPR.S344568
52. Parker JL, Karantonis DM, Single PS, et al. Electrically evoked compound action potentials recorded from the sheep spinal cord. *Neuromodulation*. 2013;16(4):295–303. doi:10.1111/ner.12053
53. Muller L, Pope J, Verrills P, et al. First evidence of a biomarker-based dose-response relationship in chronic pain using physiological closed-loop spinal cord stimulation. *Reg Anesth Pain Med*. 2024. doi:10.1136/rapm-2024-105346
54. Levy RM, Mekhail NA, Kapural L, et al. Maximal analgesic effect attained by the use of objective neurophysiological measurements with closed-loop spinal cord stimulation. *Neuromodulation*. 2024:S1094–7159(24)00655–X. doi:10.1016/j.neurom.2024.07.003
55. Verrills P, Sinclair C, Barnard A. A review of spinal cord stimulation systems for chronic pain. *J Pain Res*. 2016;9:481–492. doi:10.2147/JPR.S108884
56. Gildenberg PL. History of electrical neuromodulation for chronic pain. *Pain Med*. 2006;7(s1):S7–S13. doi:10.1111/j.1526-4637.2006.00118.x
57. Lam CM, Latif U, Sack A, et al. Advances in spinal cord stimulation. *Bioengineering*. 2023;10(2):185. doi:10.3390/bioengineering10020185
58. Deer TR, Mekhail N, Provenzano D, et al. The appropriate use of neurostimulation of the spinal cord and peripheral nervous system for the treatment of chronic pain and ischemic diseases: the neuromodulation appropriateness consensus committee. *Neuromodulation*. 2014;17(6):515–550. doi:10.1111/ner.12208
59. Deer TR, Mekhail N, Provenzano D, et al. The appropriate use of neurostimulation: avoidance and treatment of complications of neurostimulation therapies for the treatment of chronic pain. *Neuromodulation*. 2014;17(6):571–598. doi:10.1111/ner.12206
60. Deer TR, Russo M, Grider JS, et al. The Neurostimulation Appropriateness Consensus Committee (NACC): recommendations on best practices for cervical neurostimulation. *Neuromodulation*. 2022;25(1):35–52. doi:10.1016/j.neurom.2021.10.013
61. Elliott JH, Turner T, Clavisi O, et al. Living systematic reviews: an emerging opportunity to narrow the evidence-practice gap. *PLoS Med*. 2014;11(2):e1001603. doi:10.1371/journal.pmed.1001603

62. Elliott JH, Synnot A, Turner T, et al. Living systematic review: 1. Introduction-The why, what, when, and how. *J Clin Epidemiol*. 2017;91:23–30. doi:10.1016/j.jclinepi.2017.08.010
63. Thomas J, Noel-Storr A, Marshall I, et al. Living systematic reviews: 2. Combining human and machine effort. *J Clin Epidemiol*. 2017;91:31–37. doi:10.1016/j.jclinepi.2017.08.011
64. Simmonds M, Salanti G, McKenzie J, Elliott J. Living systematic review network. Living systematic reviews: 3. Statistical methods for updating meta-analyses. *J Clin Epidemiol*. 2017;91:38–46. doi:10.1016/j.jclinepi.2017.08.008
65. Akl EA, Meerpohl JJ, Elliott J, Kahale LA, Schünemann HJ. Living Systematic Review Network. Living systematic reviews: 4. Living guideline recommendations. *J Clin Epidemiol*. 2017;91:47–53. doi:10.1016/j.jclinepi.2017.08.009
66. Turner T, McDonald S, Wiles L, English C, Hill K. How frequently should "living" guidelines be updated? Insights from the Australian living stroke guidelines. *Health Res Policy Syst*. 2022;20(1):73. doi:10.1186/s12961-022-00866-7