Pain Physician 2024; 27:129-139 • ISSN 1533-3159

Retrospective Analysis

Demographics and PainDETECT as Predictors of 24-Month Outcomes for 10 kHz SCS in Nonsurgical Refractory Back Pain

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Disclaimer: The study was funded by Nevro Corp.

Conflict of interest: See pg. 137 for this information.

Manuscript received: 06-30-2023
Revised manuscript received: 11-07-2023
Accepted for publication: 11-14-2023

Free full manuscript: www.painphysicianjournal.com

Background: Nonsurgical refractory back pain (NSRBP) is broadly defined as chronic refractory back pain in patients who have not had previous spine surgery and, because they are deemed inappropriate candidates for surgery, are reliant on conventional medical management (CMM), which often provides poor long-term outcomes. High-frequency spinal cord stimulation (10kHz SCS) has demonstrated high rates of pain relief and improvements in functioning in patients with NSRBP. However, despite the use of temporary trial stimulation to select patients who will respond to therapy, some patients fail to achieve long-term therapy response with permanent implants. Prediction analysis founded on patients' baseline characteristics may enrich the appropriate selection of patients for permanent implantation.

Objectives: To examine baseline patient characteristics to predict long-term pain and functional responses to treatment with 10 kHz SCS for NSRBP.

Study Design: A retrospective analysis of baseline patient characteristics as predictors of 24-month pain and functional outcomes from a previous multicenter randomized controlled trial of 10 kHz SCS in patients with NSRBP.

Patients: Patients diagnosed with chronic, neuropathic, axial, low back pain refractory to CMM who had had no previous spine surgery, were deemed unsuitable candidates for it according to a spine surgeon, were implanted with 10kHz SCS and continued with CMM for up to 24 months.

Methods: The baseline characteristics of and 24-month outcomes in the 125 implanted patients who participated in the NSRBP randomized controlled trial (RCT) were included in this analysis. The baseline characteristics included demographics, baseline pain on the visual analog scale (VAS), baseline function based on the Oswestry Disability Index (ODI), mental health according to the patient health questionnaire-9 (PHQ-9), neuropathic pain as measured by PainDETECT, and each patient's temporary trial response. Patient response at 24 months was defined as absolute change from the baseline on the VAS and ODI, and each patient was also classified as a pain responder (achieving at least a 50% decrease in VAS pain score from the baseline) and a function responder (at least a 10-point decrease in ODI or a 24-month score of no more than 20 points). Multivariate prediction models based on regression and classification and regression tree (CART) techniques were developed using the response variables discussed above as the dependent variables and the baseline characteristics as the independent variables.

Results: Different factors contributed to pain and functional outcomes. Patients presenting with neuropathic pain (PainDETECT ≥ 19) and female gender had higher odds of being pain responders to 10 kHz SCS therapy than did males and those without neuropathic pain. Both higher age and depression score (PHQ-9) independently reduced the odds that a patient would be an ODI responder. Years since diagnosis, the reason the patient was deemed unsuitable for spine surgery, and pain etiology were not predictive of pain or functional outcomes.

Limitations: A retrospective sub-analysis of a single pragmatic randomized controlled trial.

Conclusions: There may be an opportunity to increase pain relief and functional improvement if additional patient screening accompanies the temporary lead trial. The presence of neuropathic pain, female gender, age, and depression had some predictive value, but this analysis demonstrates the treatment efficacy of 10 kHz SCS across a wide range of patients with NSRBP.

Key words: Predictors of response, nonsurgical refractory back pain, biomarkers, pain management, spinal cord stimulation, 10 kHz SCS

IRB Approval Number: WIRB® Protocol #20181672

Clinical Trials Registration Number: NCT03680846

Pain Physician 2024: 27:129-139

Chronic low back pain is a prevalent and costly condition for people and communities if pain relief is not achieved and adequate quality of life or function is not restored (1,2). Variability in underlying etiologies makes pain relief challenging (3,4). Data that may help inform patient selection for a treatment is critical for informing treatment algorithms. The first line of treatment for chronic low back pain is conventional medical management (CMM), which includes medications, physical therapy, and interventional procedures such as radiofrequency ablation (RFA) and nerve blocks (5-8). Though some patients are effectively treated with CMM, many patients are unable to reach long-term pain relief (9).

For years, opioids were a frontline CMM treatment for chronic pain patients (10). Now, to avoid inappropriate use of opioids for chronic pain, other methods of pain relief have received more focus. Spinal cord stimulation (SCS) is a technology with a growing body of evidence supporting its use as a treatment for chronic back pain spanning the last three decades (11). Several novel SCS waveform technologies have emerged, including 10 kHz high-frequency SCS, which has applications for nociceptive, neuropathic, and other pain syndromes (12,13). For failed back surgical syndrome (FBSS), described more recently as persistent spinal pain syndrome type II (PSPS-T2), SCS is an effective approach, likely due to the predominance of neuropathic pain (14,15).

Nonspecific back pain is another term used for situations involving no clear underlying cause or surgical target for treatment (16). Here, nonsurgical refractory back pain (NSRBP) has been defined as a combination of these elements of chronic refractory back pain in patients who have not had previous spine surgery and who have been assessed by a spine surgeon and deemed inappropriate candidates for surgery (17).

Prior to the publication of the NSRBP RCT, there was limited evidence of the efficacy of SCS for the treatment of NSRBP (11,18). However, this pragmatic RCT compared 10 kHz SCS to CMM and found 10 kHz SCS produced a high response rate, with 81% of patients achieving more than 50% pain relief through 24 months, potentially indicating a cost-effective long-term management option (18-20). This benefit has also been demonstrated in a real-world retrospective analysis of patients receiving 10 kHz SCS for NSRBP, with reports of substantial improvement in pain, reduction in opioids and anticonvulsant medications, and a decrease in office visitations and procedures for chronic pain (21). Similarly, cost-effectiveness has been demonstrated separately to result in a significant decrease in total health care costs, offsetting device costs in 27 months (22).

The definition of NSRBP is broad and not specific to a particular low back pain etiology, which presents an opportunity to explore what characteristics or features may define subgroups within this heterogeneous population that are most responsive to 10 kHz SCS therapy. In the NSRBP RCT, approximately 20% of patients did not achieve at least 50% pain relief at 12- and 24-months post-implantation despite a successful trial (19,20). Given the considerable cost of implanting a stimulator via a procedure that is not without risk of complications, predictors of treatment success should be explored to allow for improved patient selection beyond standard temporary percutaneous lead testing (23-25). In previous reports, psychological condition and other biomarkers were used successfully to predict what pain relief SCS could provide (26,27). However, functional outcomes also play an important role in defining meaningful clinical improvement (4,28). If significant predictors are found, they may be useful for optimizing patient selection for SCS and improving long-term therapy response rates (29).

Here, we are the first to report on an analysis

examining the association between baseline patient characteristics and 24-month pain and functional outcomes obtained with 10 kHz SCS therapy in patients with NSRBP.

Methods

Pain outcomes at 12 and 24 months after the NSRBP RCT have been reported previously (19,20). Briefly, patients diagnosed with chronic, neuropathic, axial low back pain refractory to CMM who had had no previous spine surgery and were deemed unsuitable candidates for it according to a spine surgeon were eligible for inclusion. Patients with radiculopathy were not excluded, but inclusion required axial back pain to be predominant. Subjects were randomized 1:1 to receive either 10 kHz SCS plus CMM (the best standard of care as determined by the study investigator for each individual patient) or CMM alone. Patients randomized to high-frequency SCS underwent trial stimulation of up to 14 days at 10 kHz frequency with pulse width of 30 μsec and current amplitude adjusted to maximize pain relief. Patients with a successful trial (defined as ≥ 50% pain relief) were eligible for permanent SCS implantation. The primary endpoint was the proportion of subjects in each group achieving > 50% pain relief at 3 months compared to the baseline, and the 6-month secondary endpoints included pain relief on the visual analog scale (VAS), Oswestry disability index (ODI), and quality of life (EQ-5D-5L). Patients who consented to a study extension were followed to over 24 months. Last observation carried forward (LOCF) imputation was used for missing data.

In this analysis, we investigated predictors of the absolute change in pain (on the VAS) and function (on the ODI) as well as the classification variables of responder versus nonresponder for pain and function. For the ODI score, at least a 10-point reduction was considered clinically meaningful (30,31). The predictors evaluated are shown in Table 1. In addition to assessment of pain using the VAS, the PainDETECT questionnaire was used to assess neuropathic pain. Notably, since PainDETECT was not used to screen patients in the RCT, the baseline values were not limited in range (32). The calculated score of 0 to 12 means that a neuropathic component is unlikely, a score of 13 to 18 is ambiguous (meaning a neuropathic component could be present), and 19 to 38 means a neuropathic component is likely. The severity of depression in chronic pain was assessed using the Patient Health Questionnaire-9 (PHQ-9) (33). The maximum possible score is 27. Scores greater than 5, 10, 15, and 20 represent mild, moderate, moderately severe, and severe depression, respectively.

Univariate and multivariate regression was performed using absolute change in the VAS and absolute change in the ODI as the dependent variables and the predictors of response (Table 1) as the independent variables. Stepwise regression was used to select the best model. VAS responders were defined as patients with at least 50% decreases in their VAS pain scores from the baseline. ODI responders were defined as patients with at least 10-point decreases in ODI or 24-month scores of no more than 20 points. For the multivariate regression models, both forward and backward stepwise methods were tried. In addition, a classification and regression tree model with cross-validation pruning was analyzed.

Results

Table 1 presents the baseline characteristics of the 125 patients who underwent permanent implantations following a successful trial. The mean age was 55.4 ± 12.2 years, and the average number of years since the diagnosis of chronic back pain was 11. A majority of patients were female, had been living with their chronic pain diagnoses for more than four years, had BMIs of ≥ 30 kg/m^2, and were nonsurgical candidates due to presentation and underlying pathology. The most common underlying pathologies were degenerative disc disease and/or internal disc disruption and spondylosis and/or lumbar facet-mediated pain. Leg pain was less common, with 46% of patients reporting radiculopathy at the baseline. The VAS was 7.4 ± 1.1 at the baseline, and neuropathic pain was detected in 44% of patients according to PainDETECT, with a mean baseline score of 17.2 ± 6.7. The mean ODI score was 47.4 ± 10.6, suggestive of severe disability, and the PHQ-9 recorded mild-to-moderate depression present at the baseline (9.0 ± 5.6).

Overall, 93% (n = 134/145) of patients who underwent the trial achieved at least 50% pain relief, and 125 patients went forward with permanent implantations. The average pain relief achieved during the trial was 85% (95% CI 83 to 87%) in this permanent implantation (PI) group. At the 3-month follow-up, significantly more patients in the 10 kHz-SCS-plus-CMM arm (80.9% of patients in the per-protocol population) achieved at least 50% pain relief from the baseline (responders) compared to those who had received CMM alone (1.3%; $P < 0.001$). The results were 80.0% vs 2.7% at the 6-month follow-up for the 10 kHz-SCS-plus-CMM arm and CMM arm, respectively ($P < 0.001$).

Table 1. *Summary of the univariate regression models with baseline characteristics as predictors of 24 month change in VAS and change in ODI.*

Baseline Characteristics (n = 125)	% of Patients in first category (1)	*P* value (VAS)	*P* value (ODI)
Gender (1: Male, 0: Female)	42%	0.014*	0.24
Nonsurgical candidate due to presentation and underlying pathology (1: not acceptable surgical candidate due to pathology, 0: not surgical candidate due to comorbidities or refusing surgery)	81%	0.57	0.99
Obesity (1: BMI ≥ 30 kg/m^2, 0: BMI < 30kg/m^2)	57%	0.52	0.77
Years since diagnosis (1: ≥ 4 years, 0: 0–3 years)	74%	0.39	0.28
Degenerative disc disease and/or internal disc disruption/annular tear (1: yes, 0: no)	77%	0.41	0.56
Spondylosis and/or lumbar facet joint pain (1: yes, 0: no)	67%	0.44	0.38
Radiculopathy (1: yes, 0: no)	46%	0.44	0.36
Mild/moderate spinal stenosis (1: yes, 0: no)	34%	0.58	0.87
Spondylolisthesis (1: yes, 0: no)	12%	0.79	0.90
Sacroiliac dysfunction (1: yes, 0: no)	6%	0.45	0.98
Neuropathic pain (1: PainDETECT ≥ 19, 0: PainDETECT < 19)	44%	0.048*	0.003*
Nociceptive pain (1: PainDETECT ≤ 12, 0: PainDETECT > 12)	23%	0.15	0.17
	Mean (SD)		
Age	55.4 (12.2)	0.18	0.004*
PHQ-9	9.0 (5.6)	0.95	0.45
Pain Detect Score	17.2 (6.7)	0.003*	0.003*
Baseline ODI Score	47.4 (10.6)	0.52	0.021*
Baseline VAS (cm)	7.4 (1.1)	0.0002*	0.95
Change in VAS at end of trial	-6.3 (1.3)	< 0.0001*	0.23

As shown in Fig. 1, pain relief and improvement in disability were consistent at 24 months, with 82% (95% CI 74 to 87%) of patients considered pain relief responders and 58% (95% CI 50 to 67%) of patients considered profound responders. As far as disability was concerned, 75% (95% CI 68 to 83%) of patients continued to achieve at least a 10-point reduction in ODI or a 24-month score of no more than 20 points. Overlaying pain and ODI response, Fig. 1C shows that 87% of ODI responders also met the VAS response threshold. While there was a high correlation between pain and disability outcome (r = 0.613), there were patients who achieved a pain response but not a clinically meaningful improvement in disability and vice versa. Since the patients that responded to these two outcomes may represent different groups of patients, we performed a predictive analysis with each outcome to see if and how the predictors may differ.

Predicting Absolute Change in VAS

To determine the relationship between pain relief at 24 months and the baseline predictors, univariate regression between each predictor and the absolute change in VAS between the baseline and 24 months was performed, with the *P*-values for each regression model shown in Table 1. Statistically significant univariate predictors included gender, neuropathic pain (PainDETECT ≥ 19), total PainDETECT score, change in VAS at the end of the trial, and baseline VAS. A multivariate regression with an Akaike information criterion (AIC) stepwise selection procedure retained gender, total PainDETECT score, and change in VAS at the end of the trial as predictors (Table 2A). Women and those with higher total PainDETECT scores had larger decreases in VAS at 24 months (Fig. 2C). The relationship between the change in VAS at the end of the trial and the change in VAS at 24 months is shown in Fig. 2A. On average, a decrease of one point in VAS at the end of the trial corresponded to a decrease of 0.57 points at the end of 24 months.

Predicting Pain Responders

Logistic regression was performed to determine whether the same baseline characteristics could predict if a patient would be a responder (≥ 50% pain relief). When looking at this binary outcome (Table 2B), we saw that a change in VAS at the end of the trial was no longer predictive, but a higher PainDETECT score and

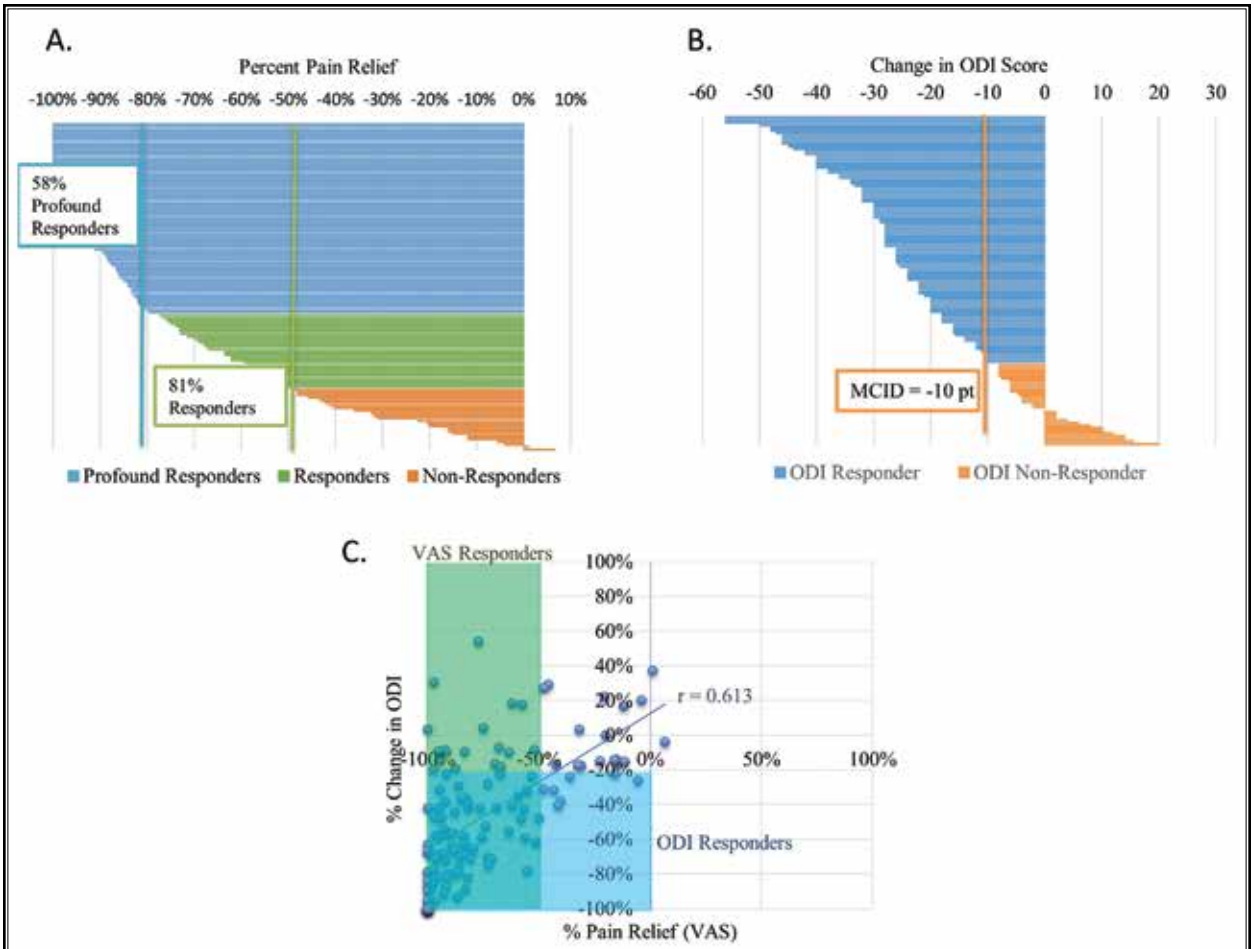

Fig. 1. *A) Individual pain response from baseline at 24 months, including responders (≥ 50% pain relief) and profound responders (≥ 80% pain relief). B) Individual change in ODI from baseline at 24 months. ODI responders achieved 10-pt reduction in ODI or a score below 20 points. C) Association between individual pain and ODI response from baseline at 24 months. ODI: Owestry Disability Index.*

female gender were weak predictors of success. The odds of therapy response increased by 8% (95% confidence interval [CI]; 0.6 to 17%) for every additional point on the PainDETECT questionnaire ($P = 0.037$), and females had 3.0 times the odds of being responders than did males ($P = 0.029$).

Finally, a classification and regression tree (CART) was also fit to the data, but no significant predictors remained after we pruned the tree with cross-validation (34).

Predicting Absolute Change in ODI

Absolute change in ODI from the baseline was used as the response variable representing change in function, and the same baseline parameters were investigated as predictors with univariate linear regression. Table 1 shows that age, neuropathic pain (PainDETECT ≥ 19), PainDETECT total score, and baseline ODI were significant univariate predictors of response. In a multivariate regression model with an AIC stepwise variable selection, age, radiculopathy, neuropathic pain (PainDETECT ≥ 19), change in VAS at the end of the trial, and baseline ODI, baseline VAS, and baseline PHQ-9 scores were included in the final model (Table 3A). Older patients had smaller decreases in ODI scores. With each additional 10 years of age at the baseline, the decrease in ODI score was lower by 3.6 points on average (Fig. 2B). Patients with neuropathic pain (PainDETECT ≥ 19) had greater reductions in ODI scores on average (Fig. 2D). Patients with higher PHQ-9 scores had smaller decreases in ODI scores—with each one-point increase in PHQ-9, the decrease in ODI score was reduced by

an average of 0.71 points. Patients with radiculopathy had a less of a decrease in their ODI scores, on average 5.7 points lower than those without radiculopathy. Patients with more pain at the baseline (higher baseline VAS scores) had smaller decreases in ODI scores, and patients with better pain response in the trial (larger end-of-trial VAS decreases) had larger ODI decreases.

Table 2A. *Predictors of patient's response, defined as point change in VAS*

Predictors of Response	VAS Change	95% CI	*P* value
Gender (Male)	0.82	0.13, 1.51	0.022*
Pain Detect Total Score	-0.056	-0.11, -0.003	0.039*
Change in VAS at end of trial	0.57	0.31, 0.83	<0.0001*

Table 2B. *Predictors of patient's response, defined as binary outcome of VAS responder or non-responder.*

Predictors of Response	Odds Ratio	95% CI	*P* value
Gender (1: Male, 0: Female)	0.336	0.121, 0874	0.029*
Pain Detect Score	1.084	1.006, 1.172	0.037*

Predicting ODI Responders

As described above, an ODI responder was defined as a patient who had a reduction in ODI score of at least 10 points or who had an ODI score of fewer than 20 points at 24 months (minimally disabled). To investigate variables that may predict ODI response, univariate logistic regression was performed on the baseline characteristics. This analysis resulted in only age (P = 0.006) and PAINDetect score (P = 0.049) as statistically significant predictors. In the final regression model ac-

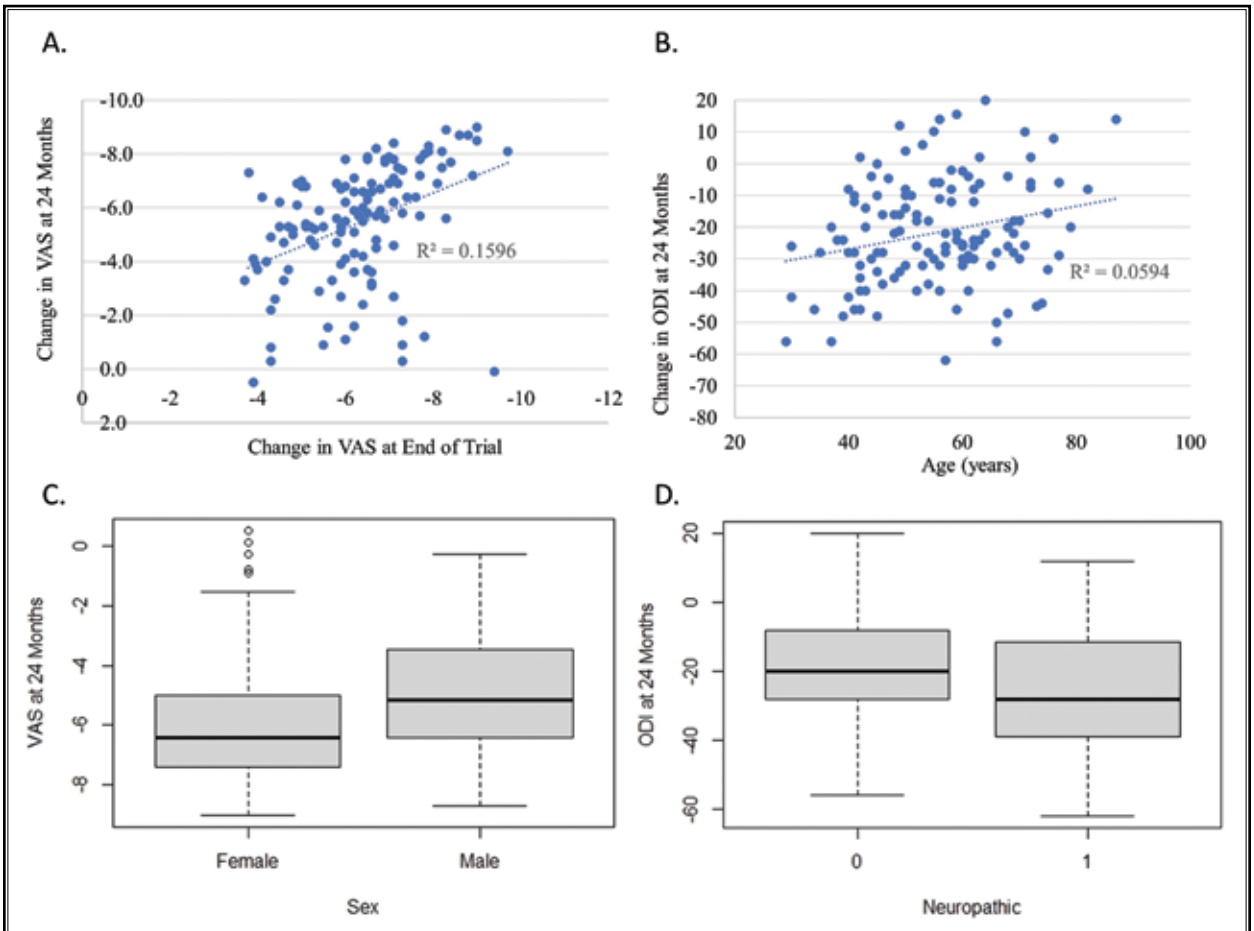

Fig. 2. *(A) Change in VAS from baseline at end of trial and 24 months. (B) Change in ODI by age at 25 months. (C) Mean VAS by gender. (D) Mean change in ODI at 24 months by presence of neuropathic pain.*
ODI: Owestry Disability Index; VAS: visual analog scale.

cording to AIC stepwise variable selection, age, PHQ-9 value, and baseline ODI score were retained (Table 3B). In this model, the odds of an ODI response decreased by a multiplicative factor of 0.536 with each decade of age. The odds of an ODI response decreased by a multiplicative factor of 0.892 with each additional point of baseline PHQ-9 and increased by a multiplicative factor of 1.063 with each additional point of baseline ODI.

Finally, a CART was also fit to the data, but no significant predictors remained after pruning the tree (34).

Table 3A. *Predictors of response defined as point change in ODI.*

Predictors of Response	ODI Change	95% CI	*P* value
Age	0.36	0.13, 0.57	0.002*
PHQ-9	0.71	0.18, 1.23	0.009*
Radiculopathy	5.73	0.36, 11.11	0.039*
Neuropathic (PainDETECT ≥ 19)	-7.57	-13.2, -1.94	0.01*
Baseline ODI	-0.51	-0.80, -0.22	0.009*
Baseline VAS	4.49	0.61, 8.37	0.025*
Change in VAS at end of trial	3.51	0.50, 6.53	0.024*

Table 3B. *Predictors of response defined as binary outcome of ODI responder or non-responder.*

Predictors of Response	Odds Ratio	95% CI	*P* value
Age	0.940	0.901, 0.976	0.002*
PHQ-9	0.892	0.813, 0.973	0.012*
Baseline ODI	1.063	1.014, 1.117	0.013*

Discussion

This analysis contributes to the growing body of literature exploring pain predictors and functional outcomes of 10 kHz SCS therapy for chronic pain. It is also the first analysis of its kind studying the population of patients with nonsurgical back pain. Here, we found that patients presenting with neuropathic pain (as measured by PainDETECT ≥ 19) and female gender had improved odds of being pain responders to 10 kHz SCS therapy. Independently, higher age and the presence of depression (as measured by PHQ-9 score) both reduced the odds that a patient would be an ODI responder. While chronic pain is recognized to impact patients' function and quality of life (35), this analysis provides evidence that there are different predictors for the pain and functional responses to SCS therapy, reinforcing that both dimensions of patient state should be considered when evaluating therapies for chronic pain (36-38).

Knowing the heterogeneous underlying pathophysiology of NSRBP, we examined demographic and clinical characteristics at the baseline for their association with long-term pain outcomes at 24 months after implantation. SCS has historically been positioned as a treatment for neuropathic pain (39). Therefore, we sought to explore the predictive capacity of baseline neuropathic pain for long-term outcomes. The present study required predominant neuropathic pain as assessed by the investigator but did not use the patient-reported PainDETECT score as an inclusion criterion. As such, this study was able to demonstrate the predictive capacity of the PainDETECT tool. Other investigators have used PainDETECT to identify neuropathic pain for additional diagnostic evaluation (40), yet there is no generally accepted objective metric for determining if axial back pain is nociceptive, neuropathic, or mixed. A previous feasibility study of 10 kHz SCS for nonsurgical back pain utilized PainDETECT as a screening tool and criterion for inclusion in the study (41). Our analysis shows PainDETECT to be statistically associated with long-term pain outcomes following 10 kHz SCS therapy. But the clinical significance is not clear, since a higher PainDETECT score increases the odds of treatment response only slightly (odds ratio = 1.08) per the multivariate regression model.

In terms of pain etiology, 46% of the NSRBP patients in the current analysis presented with radiculopathy, and there was an association between radiculopathy and reduced ODI response. But there were no other significant associations between pain etiology and the classification of a patient as a pain or function responder.

We found that mental health and older age may negatively affect functional outcomes, since both were associated with less improvement in ODI score. This finding is consistent with other studies that found age to be predictive of reduced ODI response to therapy (42,43). Further studies may be helpful in advancing physicians' understanding of how to provide additional psychosocial support for patients and thereby improve disability/functional outcomes in patients with mental health challenges. Other studies have noted the impact of self-efficacy, disability, pain, and sociodemographic characteristics on chronic low back pain (44). Moreover, this study showed that being female was a predictor of therapy response at 24 months, which is in contrast to reports of female patients having poorer pain self-efficacy (44) and an increased probability of explantation (45).

Previous work looking at predictive measures for conventional SCS has generally focused on short-term outcomes. Psychological measures were found to be useful in predicting patients' overall treatment satisfaction in the early postoperative stages (26,46). Like the current analysis, previous studies have found underlying pain etiology not to be predictive of pain relief (47). The number of years since diagnosis, the reason the patient was deemed unsuitable for spine surgery, and the underlying cause of pain were not predictive of pain or functional outcomes up to 24 months in this analysis. This finding suggests 10 kHz SCS has broad utility in pain relief and the improvement of functional outcomes across a diverse patient group, as in NSRBP.

Previous predictive studies have also examined the utility of pre-implant trials. In a study exploring outcome predictors following conventional SCS therapy, a machine-learning algorithm was demonstrated to be superior to percutaneous pre-implant screening trials at predicting therapy success, potentially calling into question the utility of pre-implant trials (48). However, in this analysis, the magnitude of pre-implant trial pain relief was investigated as a predictor of therapy success in patients who had all met the pre-implant trial success criteria. This design was inherently unable to determine whether an unsuccessful trial could also result in success with a permanent implantation. But the pain relief obtained in pre-implant trials, somewhere between 50 and 100 percent, was predictive of permanent implantation response, suggesting that current definitions of trial success may be insufficient.

Generally, the existing research focusing on predictive analyses aims to identify the best patients to receive SCS therapy, which has broader implications for health care utilization. Patient selection is critical to optimizing the cost-effectiveness of therapy, especially because the incidence of chronic back pain is increasing, as is health care utilization for the condition, including interventional therapy and SCS (49,50). A claims database analysis focusing on the NRSBP population has shown that 10 kHz SCS treatment leads to a median $9,926.00 in HCU cost savings 6 months after implantation, and factoring in the cost of device acquisition, 10 kHZ SCS therapy becomes cost-effective in 2.25 years (35). This conclusion is similar to that of the analysis showing the cost-effectiveness of 10 kHz SCS at 2.1 years based on HCU data from the NSRBP RCT (20).

Limitations

Our understanding of the contribution of factors that predict SCS's ability to yield clinically important improvements in pain and functional outcomes would benefit from future studies and/or meta-analyses of appropriately comparable studies that are powered to assess predictive capabilities. Studies with higher sample sizes would provide more power to analyze dichotomous outcomes like responder rates.

Stepwise selection of variables in regression has been criticized for overfitting the data, particularly when a large set of predictor variables is investigated. The present analysis attempted to address this issue with the use of a CART tree model that was pruned with cross-validation to avoid overfitting the data, but this method may not detect some relationships. The results regarding predictor variables presented in this paper should be considered exploratory and replicated in the future.

Because the current study was pragmatic, we did not limit the study based on pain etiology. There was an average of 2.5 pain etiologies listed for each patient, and in these etiologies, the predominant cause of the patients' pain is not clear. Although other studies have also not identified an association with underlying etiology (47), this analysis is difficult when multiple etiologies are present in most patients. Another limitation impacting interpretation of this analysis was that there might have been important baseline characteristics that were not collected. Furthermore, patients' self-assessment might have been affected by mental health, so objective measures of function, such as wearables, may provide different insights into this relationship.

Because this study is a sub-analysis of an RCT, the application of our findings to real-world patients is also unknown. It may be valuable to design a study that does not require positive trial response for permanent implantation to further explore the value of successful trials in predicting long-term therapy success.

Conclusion

This analysis identifies predictors of long-term pain relief and functional improvement with 10 kHz SCS and investigates the utility of the PainDETECT tool in predicting therapy outcomes. In a diverse group of patients with NSRBP who met pre-implant trial criteria for permanent implantation, we showed that the presence of neuropathic pain at the baseline and female gender improved the odds of being a pain responder, while higher age and the presence of depression led to reduced odds of being a functional improvement responder. In addition to the predictive measures, we

gathered additional evidence supporting the ongoing role of pre-implant trials in the patient selection process. While the results of this analysis do not provide a clear solution for improving patient selection for SCS in clinical practice, they point at further areas of research utilizing the characteristics tested here as well as other potential predictive baseline metrics.

Acknowledgments

The authors would like to thank Dr. Cat Panwar BSc Biotechnology (Hons.), PhD, from Panwar Health for assisting with the preparation of this manuscript.

Author Contributions

Conception and design: JP, CW, RA. Acquisition of data: LK, CW, AC, JP, MB, EP, DS, NP. Analysis and interpretation of data: LK, CW, CK, RA. Critically revising the article: LK, CW, RA. Approved final version of the manuscript: LK, CW, AC, JP, MB, EP, DS, CK, RA, NP.

Conflicts of Interest

An independent statistician, Dr. Colleen Kelly, performed all data analysis and contributed to the critical revision of the manuscript. Investigators and Nevro authors contributed to manuscript writing and critical revision. Dr. Kapural: scientific advisory board for Avanos, Gimer, Neuralace, Nevro, PainTeQ and Presidio; consultant for Avanos, FUS Mobile, Neuralace, Nevro, Nalu, and Xalud; and research contracts with Nevro, Neuros, Avanos, Medtronic, NeuraLace, and Gimmer Medical. Dr. Calodney: consultant for Nevro, Medtronic, Stryker, and Saluda; research support from PainTeq. Dr. Pilitsis: grant support from Medtronic, Boston Scientific, Abbott, NIH 2R01CA166379, NIH R01EB030324, NIH Blueprint 3U54EB015408, and NIH U44NS115111; medical advisor for Aim Medical Robotics; and stock equity in Aim Medical Robotics. Dr. Petersen: research support from Medtronic, Neuros Medical, Nevro, ReNeuron, SPR, and Saluda; consultant for Abbott Neuromodulation, Medtronic Modulation, Neuros Medial, Nevro, Saluda, Biotronik, and Vertos; and stock options from SynerFuse and neuro42. Dr. Sayed: consultant for clinical and research support for the study described from Nevro. Dr. Wu: consultant for Nevro, Boston Scientific, Medtronic, Abbott, and NeuroOne. Ms. Azalde: employee of Nevro Corp. All other authors certify that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

References

1. Wu A, March L, Zheng X, et al. Global low back pain prevalence and years lived with disability from 1990 to 2017: Estimates from the Global Burden of Disease Study 2017. *Ann Transl Med* 2020; 8:299.
2. Froud R, Patterson S, Eldridge S, et al. A systematic review and meta-synthesis of the impact of low back pain on people's lives. *BMC Musculoskelet Disord* 2014; 15:50.
3. Knezevic NN, Candido KD, Vlaeyen JWS, et al. Low back pain. *Lancet* 2021; 398:78-92.
4. Goudman L, Rigoard P, Billot M, Duarte RV, Eldabe S, Moens M. Patient selection for spinal cord stimulation in treatment of pain: Sequential decision-making model - a narrative review. *J Pain Res* 2022; 15:1163-1171.
5. Chou R, Qaseem A, Snow V, et al. Diagnosis and treatment of low back pain: A joint clinical practice guideline from the American College of Physicians and the American Pain Society. *Ann Intern Med* 2007; 147:478-491.
6. Manchikanti L, Boswell MV, Singh V, et al. Comprehensive evidence-based guidelines for interventional techniques in the management of chronic spinal pain. *Pain Physician* 2009; 12:699-802.
7. Manchikanti L, Kaye AD, Soin A, et al. Comprehensive evidence-based guidelines for facet joint interventions in the management of chronic spinal pain: American Society of Interventional Pain Physicians (ASIPP) guidelines facet joint interventions 2020 guidelines. *Pain Physician* 2020; 23:S1-S127.
8. Manchikanti L, Knezevic NN, Navani A, et al. Epidural interventions in the management of chronic spinal pain: American Society of Interventional Pain Physicians (ASIPP) comprehensive evidence-based guidelines. *Pain Physician* 2021; 24:S27-S208.
9. Bernstein IA, Malik Q, Carville S, Ward S. Low back pain and sciatica: Summary of NICE guidance. *BMJ* 2017; 356:i6748.
10. Rosenblum A, Marsch LA, Joseph H, Portenoy RK. Opioids and the treatment of chronic pain: Controversies, current status, and future directions. *Exp Clin Psychopharmacol* 2008; 16:405-416.
11. Eckermann JM, Pilitsis JG, Vannaboutathong C, Wagner BJ, Province-Azalde R, Bendel MA. Systematic literature review of spinal cord stimulation in patients with chronic back pain without prior spine surgery. *Neuromodulation* 2021; 25:648-656.
12. Tieppo Francio V, Polston KF, Murphy MT, Hagedom JM, Sayed D. Management of chronic and neuropathic pain with 10 kHz spinal cord stimulation technology: Summary of findings from preclinical and clinical studies. *Biomedicines* 2021; 9:644.
13. Karri J, Orhurhu V, Wahezi S, Tuan T, Deer T, Abd-Elsayed A. Comparison of spinal cord stimulation waveforms for treating chronic low back pain: Systematic review and meta-analysis. *Pain Physician* 2020; 23:451-460.
14. Christelis N, Simpson B, Russo M, et al. Persistent spinal pain syndrome: A proposal for failed back surgery syndrome and ICD-11. *Pain Med* 2021;

22:807-818.

15. Fontaine D. Spinal cord stimulation for neuropathic pain. *Rev Neurol (Paris)* 2021; 177:838-842.
16. Oliveira CB, Maher CG, Pinto RZ, et al. Clinical practice guidelines for the management of non-specific low back pain in primary care: An updated overview. *Eur Spine J* 2018; 27:2791-2803.
17. Patel N, Calodney A, Kapural L, et al. High-frequency spinal cord stimulation at 10 kHz for the treatment of nonsurgical refractory back pain: Design of a pragmatic, multicenter, randomized controlled trial. *Pain Pract* 2021; 21:171-183.
18. Kapural L, Jameson J, Johnson C, et al. Treatment of nonsurgical refractory back pain with high-frequency spinal cord stimulation at 10 kHz: 12-month results of a pragmatic, multicenter, randomized controlled trial. *J Neurosurg Spine* 2022; 11:1-12.
19. Patel N, et al. Two-year outcomes from a multicenter randomized controlled trial investigating the effects of 10kHz spinal cord stimulation on nonsurgical refractory back pain. Paper presented at: American Association of Neurological Surgeons Annual Meeting, April 23, 2023; Los Angeles, California.
20. Patel NP, Wu C, Lad SP, et al. Cost-effectiveness of 10-kHz spinal cord stimulation therapy compared with conventional medical management over the first 12 months of therapy for patients with nonsurgical back pain: Randomized controlled trial. *J Neurosurg Spine* 2022; 38:249-257.
21. Kapural L, Calodney A. Retrospective efficacy and cost-containment assessment of 10 kHz spinal cord stimulation (SCS) in non-surgical refractory back pain patients. *J Pain Res* 2022; 16:3589-3595.
22. Rajkumar S, Yang LZ, Venkatraman V, et al. Health care resource utilization of high-frequency spinal cord stimulation for treatment of chronic refractory low back pain. *Neuromodulation* 2023; 26:115-123.
23. Eldabe S, Buchser E, Duarte RV. Complications of spinal cord stimulation and peripheral nerve stimulation techniques: A review of the literature. *Pain Med* 2016; 17:325-336.
24. Kumar K, Bishop S. Financial impact of spinal cord stimulation on the healthcare budget: A comparative analysis of costs in Canada and the United States. *J Neurosurg Spine* 2009; 10:564-573.
25. Eldabe S, Duarte RV, Gulve A, et al. Does a screening trial for spinal cord stimulation in patients with chronic pain of neuropathic origin have clinical utility and cost-effectiveness (TRIAL-STIM)? A randomised controlled trial. *Pain* 2020; 161:2820-2829.
26. Prabhala T, Kumar V, Gruenthal E, et al. Use of a psychological evaluation tool as a predictor of spinal cord stimulation outcomes. *Neuromodulation* 2019; 22:194-199.
27. Sparkes E, Duarte RV, Mann S, Lawrence TR, Raphel JH. Analysis of psychological characteristics impacting spinal cord stimulation treatment outcomes: A prospective assessment. *Pain Physician* 2015; 18:E369-377.
28. Campos WK, Linhares MN, Sarda J, et al. Determinants for meaningful clinical improvement of pain and health-related quality of life after spinal cord stimulation for chronic intractable pain. *Neuromodulation* 2019; 22:280-289.
29. Eldabe S, Obara I, Panwar C, Caraway D. Biomarkers for chronic pain: Significance and summary of recent advances. *Pain Res Manag* 2022; 2022:1940906.
30. Hagg O, Fritzell P, Nordwall A; Swedish Lumbar Spine Study Group. The clinical importance of changes in outcome scores after treatment for chronic low back pain. *Eur Spine J* 2003; 12:12-20.
31. Ostelo RW, de Vet HC. Clinically important outcomes in low back pain. *Best Pract Res Clin Rheumatol* 2005; 19:593-607.
32. Freynhagen R, Baron R, Gockel U, Tölle T. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin* 2006; 22:1911-1920.
33. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: Validity of a brief depression severity measure. *J Gen Intern Med* 2001; 16:606-613.
34. Krzywinski M, Altman N. Classification and regression trees. *Nature Methods* 2017; 14:757-758.
35. Raja SN, Carr DB, Cohen M, et al. The revised International Association for the Study of Pain definition of pain: Concepts, challenges, and compromises. *Pain* 2020; 161:1976-1982.
36. Chapman JR, Norvell DC, Hermsmeyer JT, et al. Evaluating common outcomes for measuring treatment success for chronic low back pain. *Spine (Phila Pa 1976)* 2011; 36:S54-68.
37. DeVine J, Norvell DC, Ecker E, et al. Evaluating the correlation and responsiveness of patient-reported pain with function and quality-of-life outcomes after spine surgery. *Spine (Phila Pa 1976)* 2011; 36:S69-74.
38. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain* 2008; 9:105-121.
39. Wolter T. Spinal cord stimulation for neuropathic pain: Current perspectives. *J Pain Res* 2014; 7:651-663.
40. Konig SL, Prusak M, Pramhas S, Windpassinger M. Correlation between the neuropathic PainDETECT screening questionnaire and pain intensity in chronic pain patients. *Medicina (Kaunas)* 2021; 57:353.
41. Al-Kaisy A, Palmisani S, Smith TE, et al. 10 kHz high-frequency spinal cord stimulation for chronic axial low back pain in patients with no history of spinal surgery: A preliminary, prospective, open label and proof-of-concept study. *Neuromodulation* 2017; 20:63-70.
42. Hunter CW, Guyer R, Froimson M, DePalma MJ. Effect of age on outcomes after allogeneic disc tissue supplementation in patients with chronic discogenic low back pain in the VAST trial. *Pain Manag* 2022; 12:301-311.
43. Iversen T, Solberg TK, Wilsgaard T, Waterloo K, Brox JI, Ingebrigtsen T. Outcome prediction in chronic unilateral lumbar radiculopathy: Prospective cohort study. *BMC Musculoskelet Disord* 2015; 16:17.
44. Ferrari S, Vanti C, Pellizzer M, Dozza L, Monticone M, Pillastrini P. Is there a relationship between self-efficacy, disability, pain and sociodemographic characteristics in chronic low back pain? A multicenter retrospective analysis. *Arch Physiother* 2019; 9:9.
45. Slyer J, Scott S, Sheldon B, Hancu M, Bridger C, Pilitsis JG. Less pain relief, more depression, and female sex correlate with spinal cord stimulation explants. *Neuromodulation* 2020; 23:673-679.
46. Poulsen DM, Sorensen JCH, Blichfeldt-Eckhardt MR, et al. Pain catastrophizing does not predict spinal cord stimulation outcomes: A cohort study of 259 patients with long-term follow-up. *Neuromodulation* 2021; 24:76-85.
47. Krames ES, Oakley JC, Foster AM, et al. Spinal cord stimulation has comparable

efficacy in common pain etiologies. *Neuromodulation* 2008; 11:171-181.

48. Ounajim A, Billot M, Goudman L, et al. Machine learning algorithms provide greater prediction of response to SCS than lead screening trial: A predictive AI-based multicenter study. *J Clin Med* 2021; 10:4764.
49. Manchikanti L, Pampati V, Vangala BP, et al. Spinal cord stimulation trends of utilization and expenditures in fee-for-service (FFS) Medicare population from 2009 to 2018. *Pain Physician* 2021; 24:293-308.
50. Manchikanti L, Pampati V, Soin A, et al. Trends of expenditures and utilization of facet joint interventions in fee-for-service (FFS) Medicare population from 2009-2018. *Pain Physician* 2020; 23:S129-S147.