Spinal Cord Stimulation For Painful Diabetic Peripheral Neuropathy:

A New Treatment Option to Reduce Pain and Improve Quality of Life

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Faculty Disclosures

- **Dr. Dann:** Advisory Board—Abbott, Medtronic, TerSera; Speaker—Abbott, AIS; Consultant—Medtronic; Speaerks Bureau—Medtronic
- **Dr. Murphy:** Consultant—Medtronic, Relievant; Speaker—Medtronic; Researcher/Research investigator—Celeri Health, Medtronic
- **Dr. Patel:** Consultant—Medtronic
- **Dr. Vogel** disclosed no relevant financial relationship with any ineligible company (commercial interest).

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Medtronic was not involved in the creation or delivery of any program content and does not control whether the materials conform to FDA approved or cleared indications.

Learning Objectives

- Understand the current treatment landscape for DPN and the unmet need
- Identify new treatment approaches for DPN
- Understand the mechanisms and applications for spinal cord stimulation and how to introduce this into your practice
- Work amongst various specialties and referrers to improve quality of life in DPN patients

DPN = diabetic peripheral neuropathy.

Understanding the Current DPN Landscape

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DPN: Prevalence and Impact

- Between 10-26% of patients with diabetes experience painful DPN (P-DPN)
- DPN is prevalent in patients with diabetes
  - 28% in patients with type 1 diabetes mellitus
  - 51% in those with type 2 diabetes mellitus
- Associated with duration of diabetes, comorbid hyperlipidemia, and poor glucose control
- 1/3 of patients experiencing P-DPN require an assistance device such as a cane or wheelchair

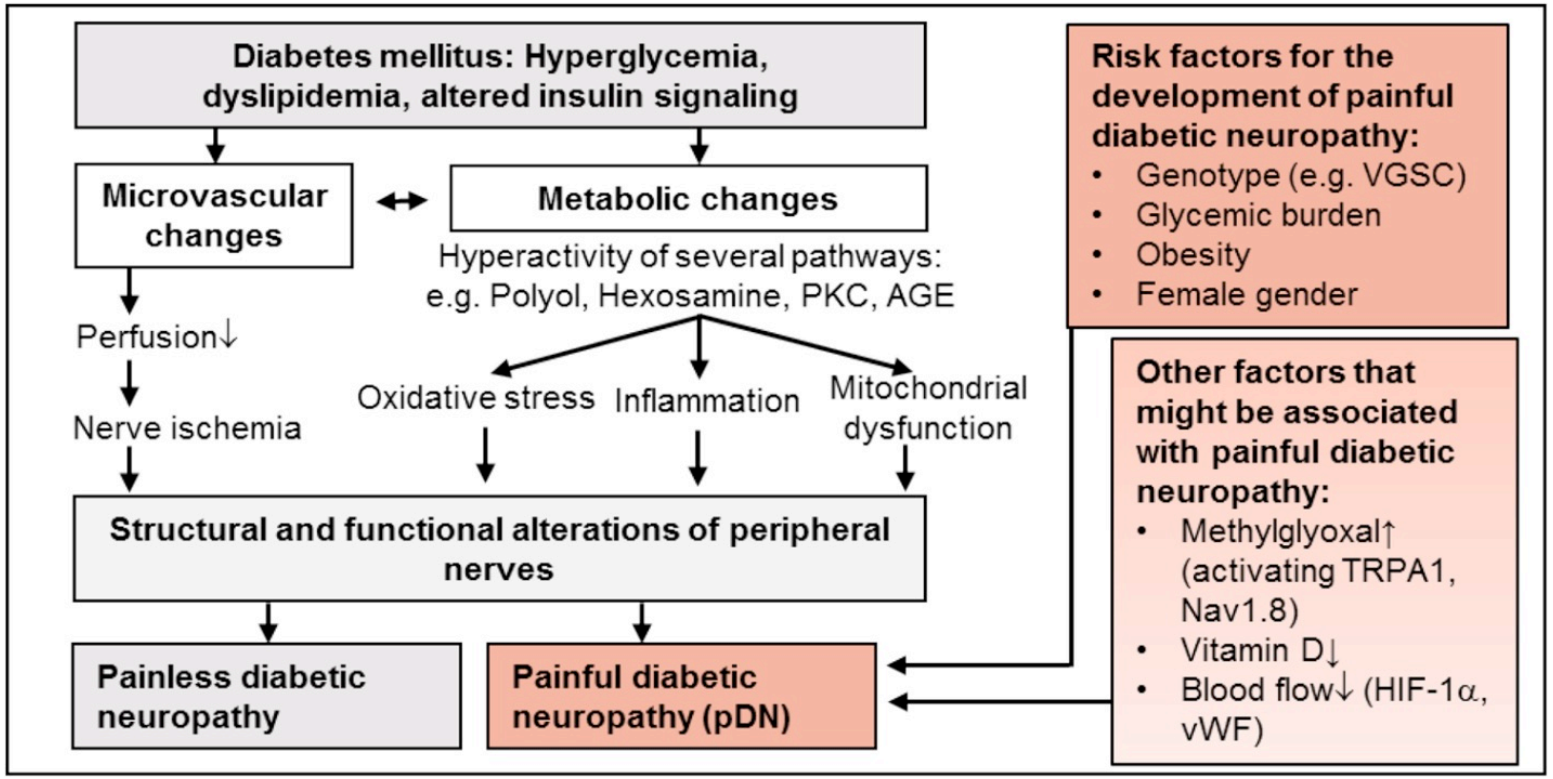
Bondar AC, et al. *Maedica.* 2018;13(3):229-234. Yoo M, et al. *J Diabetes Metab.* 2013;Suppl 10:005.

P-DPN: Presentation

- Patients with DPN present with:
  - Bilateral pain in the feet and lower legs
  - Stabbing/burning pain
- Pain starts in the toes and progresses proximally (length-dependent progression)
- Increased pain during sleep is common
- Increased potential for infection and limb loss due to loss of sensation, impairing awareness of slow to heal wounds

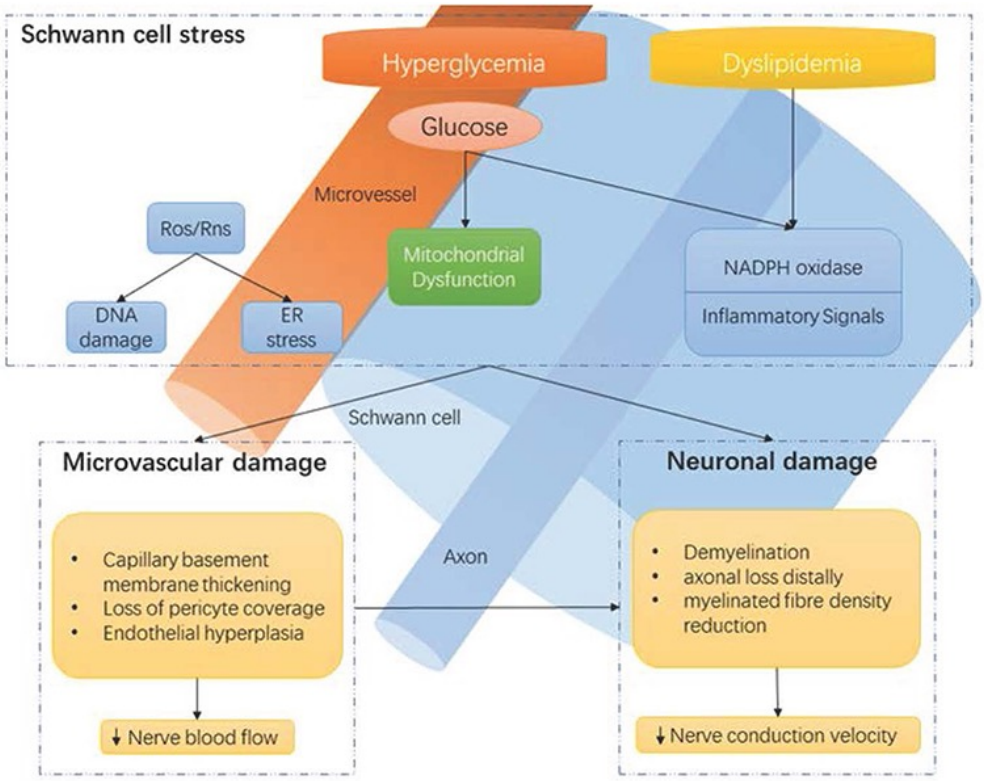
Yoo M, et al. *J Diabetes Metab.* 2013;Suppl 10:005.

Pathophysiology and Potential Risk Factors Related to DPN



Li F, et al. *Diabetes Res Clin Pract*. 2020;166:108289. Yang J, et al. *J Diabetes Investig.* 2021;12(5):828-836. Rosenberger DC, et al. *J Neural Transm (Vienna)*. 2020;127(4):589-624.

Microvascular and Neuronal Damage

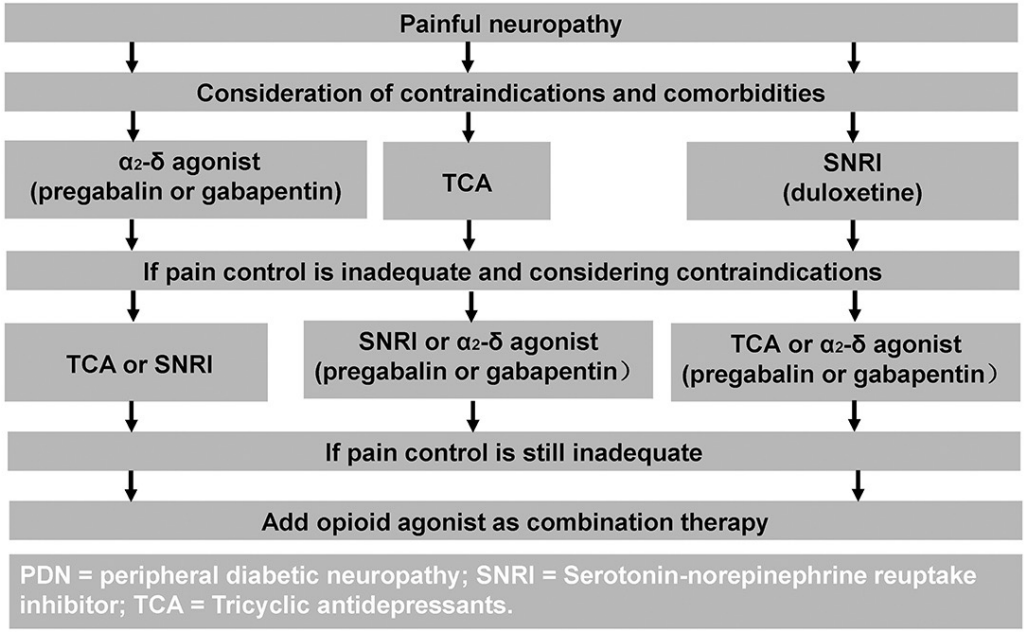


Yang H, et al. *Front Endocrinol*. 2020;10:929.

DPN Treatment Algorithm

Nonpharmacologic Treatment
- Glycemic control via diet and exercise
- Topical agents
- Transcutaneous electrical stimulation, Physical Therapy

Pharmacologic Treatment
- Gabapentin/Pregabalin
- Duloxetine
- Tramadol for refractory or breakthrough pain



Yang H, et al. *Front Endocrinol*. 2020;10:929.

Role of Interventional Pain Physicians in DPN Treatment

- Collaborate between primary care physicians, neurologists, and endocrinologists
- Pain medication management
- Identify, trial, implant, and manage spinal cord stimulator for DPN patients

Spinal Cord Stimulation for DPN

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Department of Neurosurgery and Pain Management
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Houston, Texas

What is Spinal Cord Stimulation?

SCS disrupts the pain signals traveling between the spinal cord and the brain

Patients get a trial first, to evaluate if they are getting pain relief,an increase in their activity and/or decreased use of pain medication

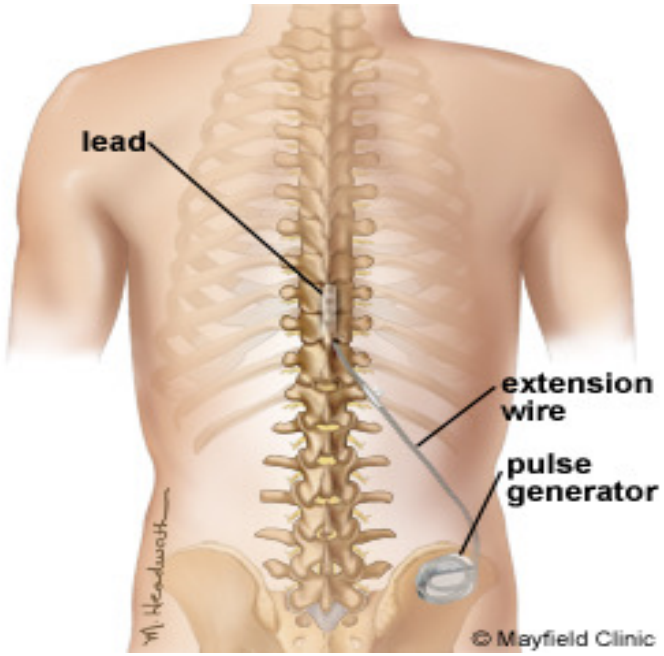
Using a needle, temporary leads (thin flexible wires) are placed in the epidural space

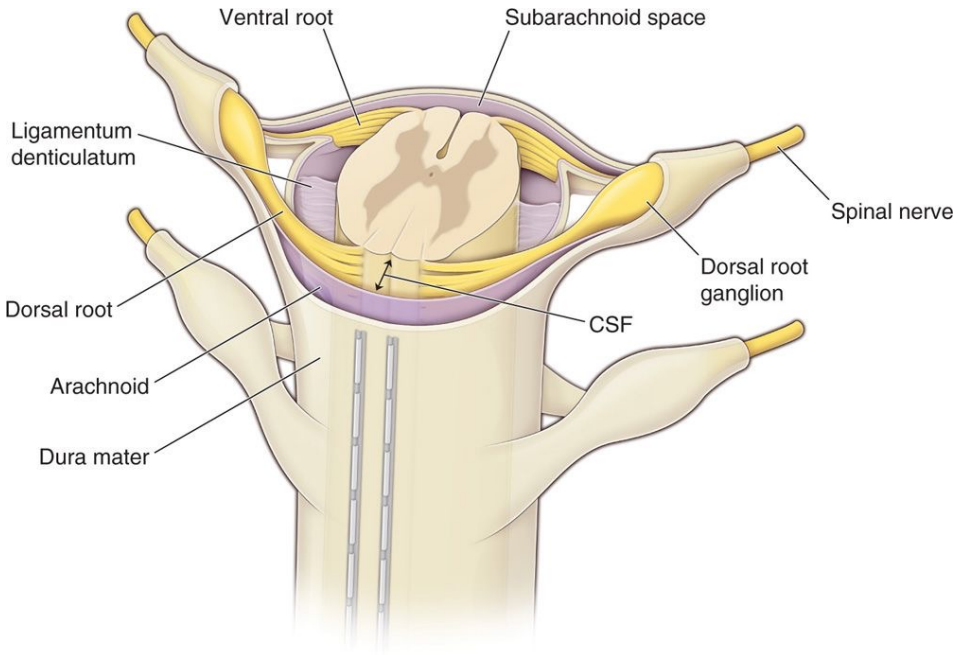
The leads are connected to an external neurostimulator that is secured to the patient's back during the trial, which may last up to a week

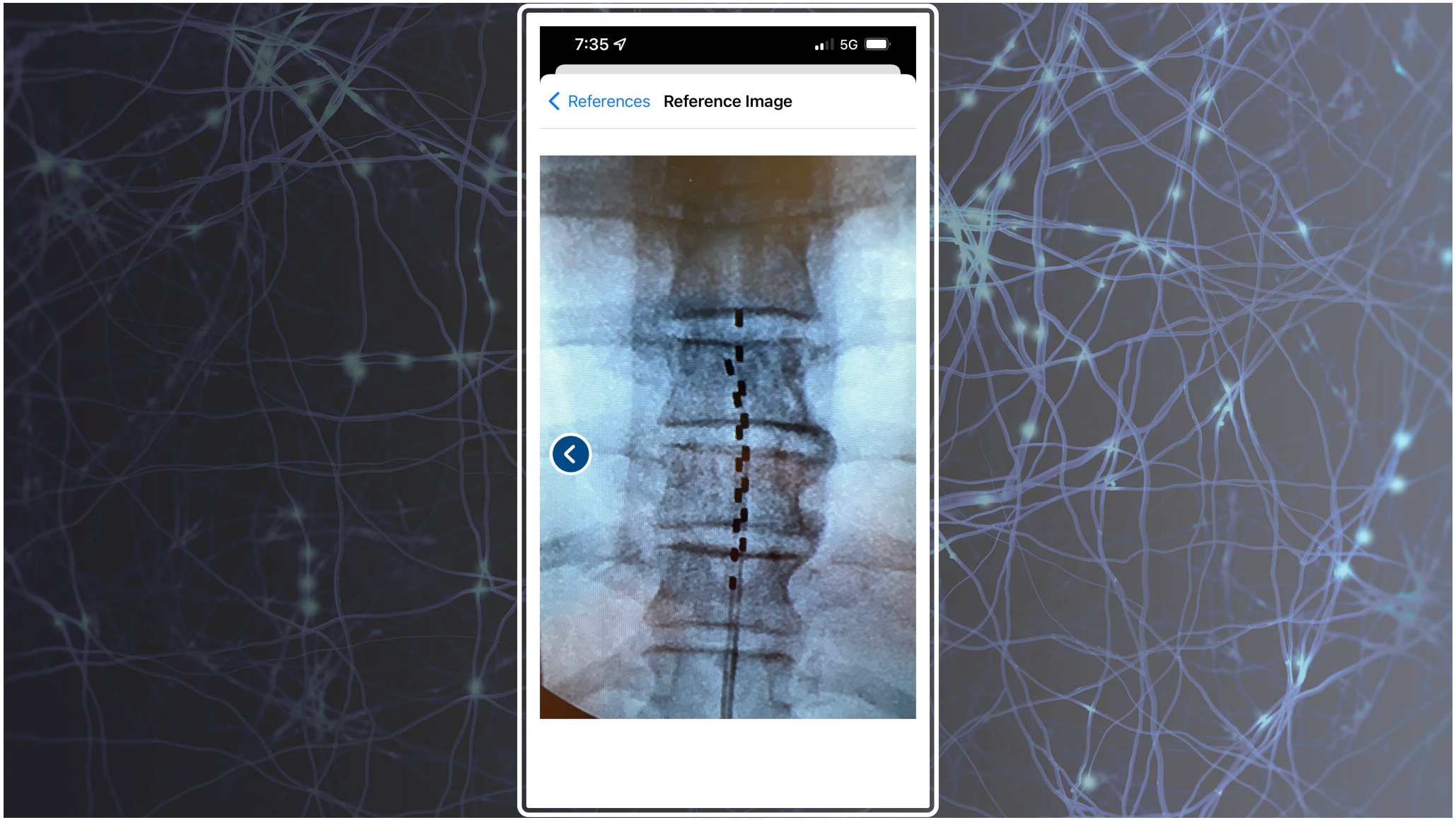
After the trial, the patient and physician decide whether to move forward with permanent implantation

SCS = spinal cord stimulation.

Neurostimulation



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References
Reference Image

Neurostimulation

- Stimulates large, fast conducting sensory fibers in the dorsal columns of spinal cord, thereby inhibiting the slower-conducting A-delta and C nociceptive fibers responsible for pain
- Historically, the most common indication: refractory radicular pain in association w/ failed back surgery syndrome
- Generate an electric impulse near the dorsal surface of spinal cord to alter the perception of pain
- Have been used since 1960s

Indications for Spinal Cord Stimulation

Failed Back Syndrome (FBS) or low back syndrome or failed back or Post-laminectomy syndrome

Radicular pain syndrome or radiculopathies resulting in pain secondary to FBS or herniated disk

Complex Regional Pain Syndrome (CRPS), Reflex Sympathetic Dystrophy (RSD), or causalgia

Diabetic peripheral neuropathy of the lower extremities

Treating DPN: Traditional Spinal Cord Stimulation

Study	Slangen et al. (2014)	de Vos et al. (2014)
Design	RCT	RCT
Population	Refractory DPN	Refractory DPN
Sample Size	36	60
SCS programming	Traditional SCS	Traditional SCS
Primary Endpoint (all randomized, ITT)	≥ 50% pain reduction during daytime or nighttime or a score of ≥ 6 on a 7-point Likert scale of the PGIC scale for pain and sleep	Treatment success at 6 months, ≥ 50% pain reduction
Date	2010-2013	2008-2012
Sponsor	Univ. of Maastricht	Medisch Spectrum Twente
Geography	2 centers in NL	7 centers in NL, BE, DK, DE

RCT = randomized, controlled trial, ITT = intent-to-treat, PGIC = Patient Global Impression of Change.
Slangen, et al. *Diabetes Care.* 2014;37(11):3016-3024. de Vos, et al. *Pain.* 2014;155(11):2426-2431.

Demographics*: Traditional Spinal Cord Stimulation

Measure	SCS (n = 62)	Control (n = 34)
Age (years)	57.7	59.1
Duration of DM (years)	14.8	15.2
Duration of pain (years)	6.6	6.1
Men / Women	65% / 35%	65% / 35%
Type 1 / Type 2	21% / 79%	18% / 82%
Average baseline pain rating	7.2 (6.5-10)	6.6 (5.7-9.6)
Average 6-month pain rating	3.4 (2.2-4.4)	6.6 (5.6-9.5)

***Combined data from both RCTs.**

Slangen, et al. *Diabetes Care.* 2014;37(11):3016-3024. de Vos, et al. *Pain.* 2014;155(11):2426-2431.

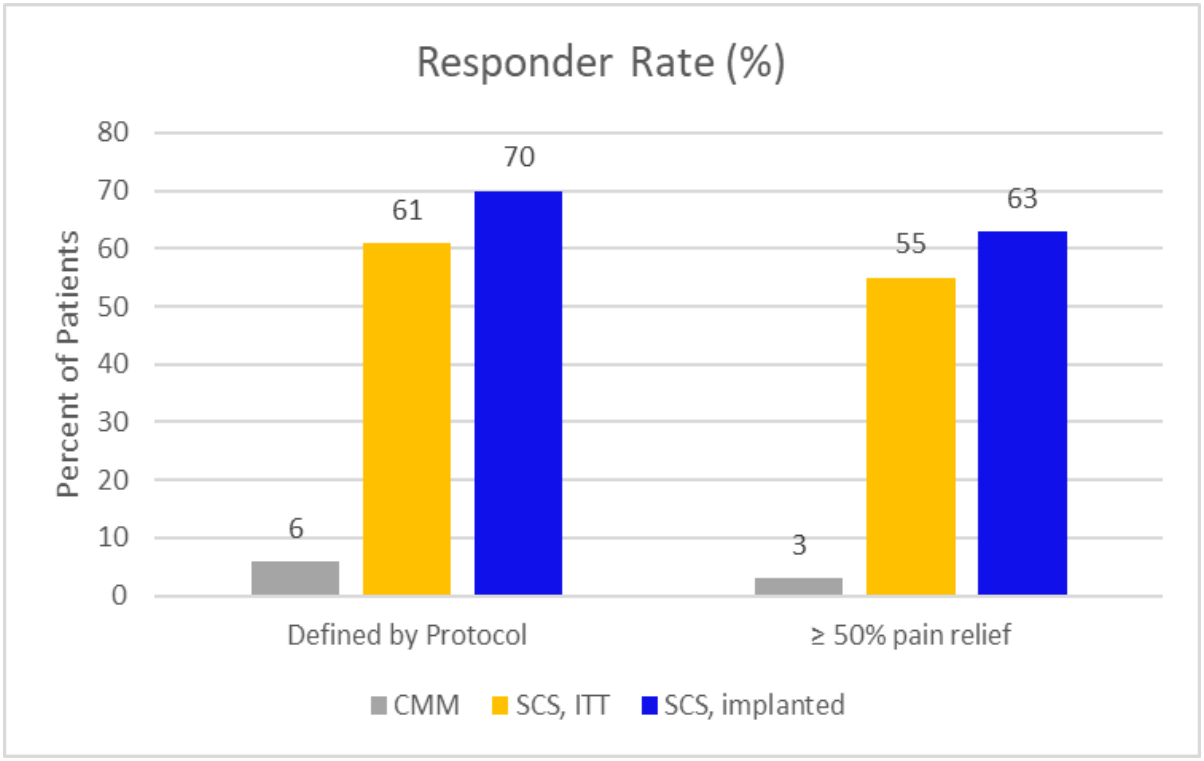
Results*: Traditional Spinal Cord Stimulation

Measure	SCS (n = 62)	Control (n = 34)
Average pain reduction[a]	53%	0%
Responder Rate per protocol[b,c]	61% (48%-73%)	6% (0%-20%)
Responder Rate = 50% reduction in pain[c]	55% (42%-68%)	3% (0%-15%)
Responder Rate per protocol as-treated[d]	70% (56%-82%)	6% (0%-20%)
Responder rate = 50% reduction in pain as-treated[d]	63% (49%-76%)	3% (0%-15%)

[a] Confidence intervals for the percent mean change have not been calculated to avoid bias due to percentage asymmetry
[b] Each study design defined successful pain relief by different measures
[c] Analysis of all randomized subjects in an intent-to-treat approach
[d] Including only subjects who received an SCS system implant

***Combined data from both RCTs.**
Slangen, et al. *Diabetes Care.* 2014;37(11):3016-3024. de Vos, et al. *Pain.* 2014;155(11):2426-2431.

Results*: Traditional Spinal Cord Stimulation



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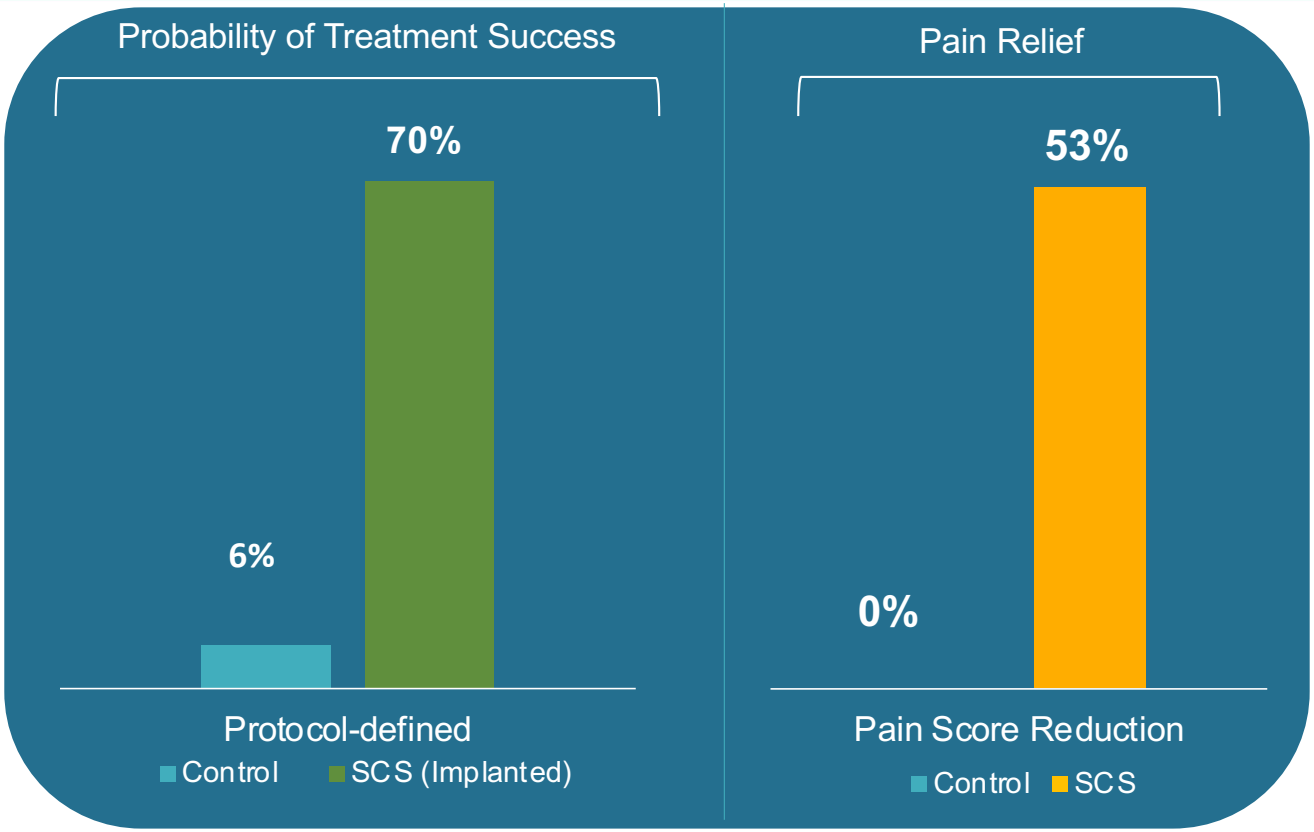
Results*: Traditional Spinal Cord Stimulation



Patients treated with SCS are more likely to achieve ≥ 50% pain relief at 6 months.

The overall odds ratio of 17.4 (95% CI 3.8-79.7; *P*-value <0.001)

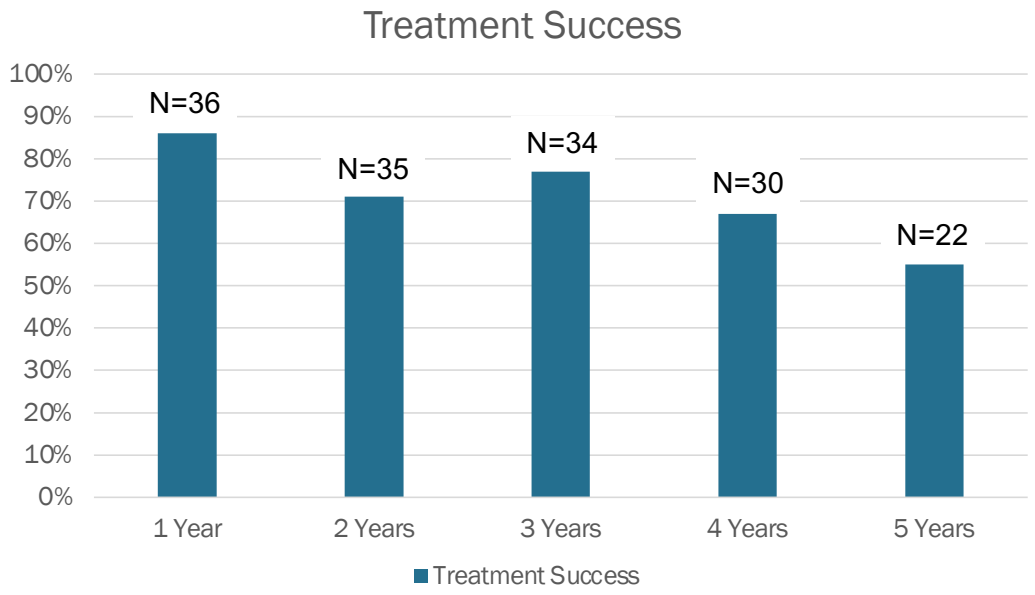
***Combined data from both RCTs.**

Slangen, et al. *Diabetes Care.* 2014;37(11):3016-3024. de Vos, et al. *Pain.* 2014;155(11):2426-2431.

Long-Term Outcomes: Traditional Spinal Cord Stimulation

Long-Term Success

- Combined data from implanted subjects in 1 RCT and a pilot study on low-frequency SCS
- Success ranged from 86% at 1 year to 55% at 5 years



Slangen R, et al. *Diabetes Care*. 2014;37(11):3016-3024. Pluijms WA, et al. *Br J Anaesth*. 2012;109(4):623-629. van Beek M, et al. *Diabetes Care*. 2018;41(1):32-38.

Patient Selection

- Patients may be appropriate candidates for SCS if they:
- Have pain of the **lower limbs** due to **diabetic peripheral neuropathy.**
- Are appropriate candidates for surgery.

Safety Outcomes

Safety Outcomes

Well-tolerated with adverse event profile similar to other SCS studies

Observed Adverse Events in RCTs

- Infection
- Lead migration/lead failure
- Device site pain
- Device site wound issues
- CSF leak
- Uncomfortable stimulation

Exceptions of significance

- 1 death due to subdural hematoma after CSF leak
- Observation of glycemic fluctuation in response to infection

CSF = cerebrospinal fluid.

Slangen R, et al. *Diabetes Care*. 2014;37(11):3016-3024. de Vos CC, et al. *Pain*. 2014;155(11):2426-2431.

Significant Studies for SCS and DPN

- SENZA-PDN (Painful diabetic Neuropathy) randomized clinical trial compared conventional medical management (CMM) with 10-kHz SCS plus CMM
  - Substantial pain relief and improved health-related quality of life sustained over 6 months
  - Study concluded that 10-kHz SCS can safely and effectively treat patients with refractory PDN
- High-frequency 10-kHz SCS improves health-related quality of life (HRQoL) in patients with refractory painful diabetic neuropathy: 12-month results from a randomized controlled trial. This study shows the 10-kHz SCS treatment resulted in substantial pain relief and improvement in overall HRQoL 2.5 to 4.5 fold higher than the minimal clinically important difference. The outcomes were durable over 12 months and support 10-kHz SCS treatment in patients with refractory painful diabetic neuropathy.
- *Neuromodulation in the Treatment of Painful Diabetic Neuropathy: A Review of Evidence for Spinal Cord Stimulation* concludes there is an unmet need for improved PDN therapies and provide data on the safety, effectiveness, and durability of SCS therapy

Petersen EA, et al. *Jama Neurology*. 2021;78(6):687-698. *J Diabetes Sci Technol.* 2022;16(2):332-340. Strand NH, et al. *Mayo Clin Proc Innov Qual Outcomes*. 2022;6(4):347-360.

Conclusions

- SCS is an option for DPN patients who are:
  - Refractory to best efforts in management of their diabetes
  - Refractory to medication management and non-invasive therapies
  - Good candidates for surgery
- When considering a DPN patient for treatment with SCS:
  - Assess their ability to manage their SCS therapy
    - consider ability to recharge and responsiveness to the need for follow-up visits
  - Request a preoperative screening for cardiovascular and kidney disease
  - Adhere to guidelines on perioperative care:
    - ADA
    - NACC
    - Surgical and anesthesia guidelines on perioperative glycemic control

NACC consensus point 28 on antimicrobial envelopes:
"The NACC recommends considering the utilization of antimicrobial envelopes around implantable pulse generators (IPGs) in patients at high risk of infection. Further studies examining efficacy in neuromodulation are warranted."

Diabetes Care. **2016;39:S99–S104. Deer TR, et al. *Neuromodulation*. 2017;20(1):31-50. Sudhakaran S, et al. *Surg Res Pract.* 2015;2015:284063.**

Identifying Appropriate Patients

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Identifying Appropriate Patients That May Benefit from SCS Therapy

Screening of Diabetic Patients

- Physical examination
- Neurofilament testing
- Sensory testing
- Nerve conduction testing
- Electromyography
- Autonomic testing

Identifying Appropriate Patients That May Benefit from SCS Therapy

Screening of Diabetic Patients

A diabetic foot exam checks for infections, injury, bone abnormalities, peripheral vascular disease and neuropathy.

Identifying Appropriate Patients That May Benefit from SCS Therapy

Screening of DPN

Inspection of the Feet:

- Skin color, areas of pigmentation and discoloration, redness, swelling or induration, local tenderness, maceration, ischemia, temperature changes, presence of calluses at pressure points, ulcers, peeling, fissuring between the toes, varicose veins, shiny skin with reduced hair distribution
- Foot deformities like Charcot arthropathy
- Hammer Toes

Painful DPN

Screening of Diabetic Neuropathy

Impaired vibration, and pressure perception.

Neurofilament Testing

Painful DPN

- Numbness or reduced ability to feel pain or temperature changes
- Tingling or burning feeling
- Sharp pains or cramps
- Muscle weakness
- Extreme sensitivity to touch — for some people, even a bedsheet's weight can be painful
- Serious foot problems, such as ulcers, infections, and bone and joint damage

Referral Pathways

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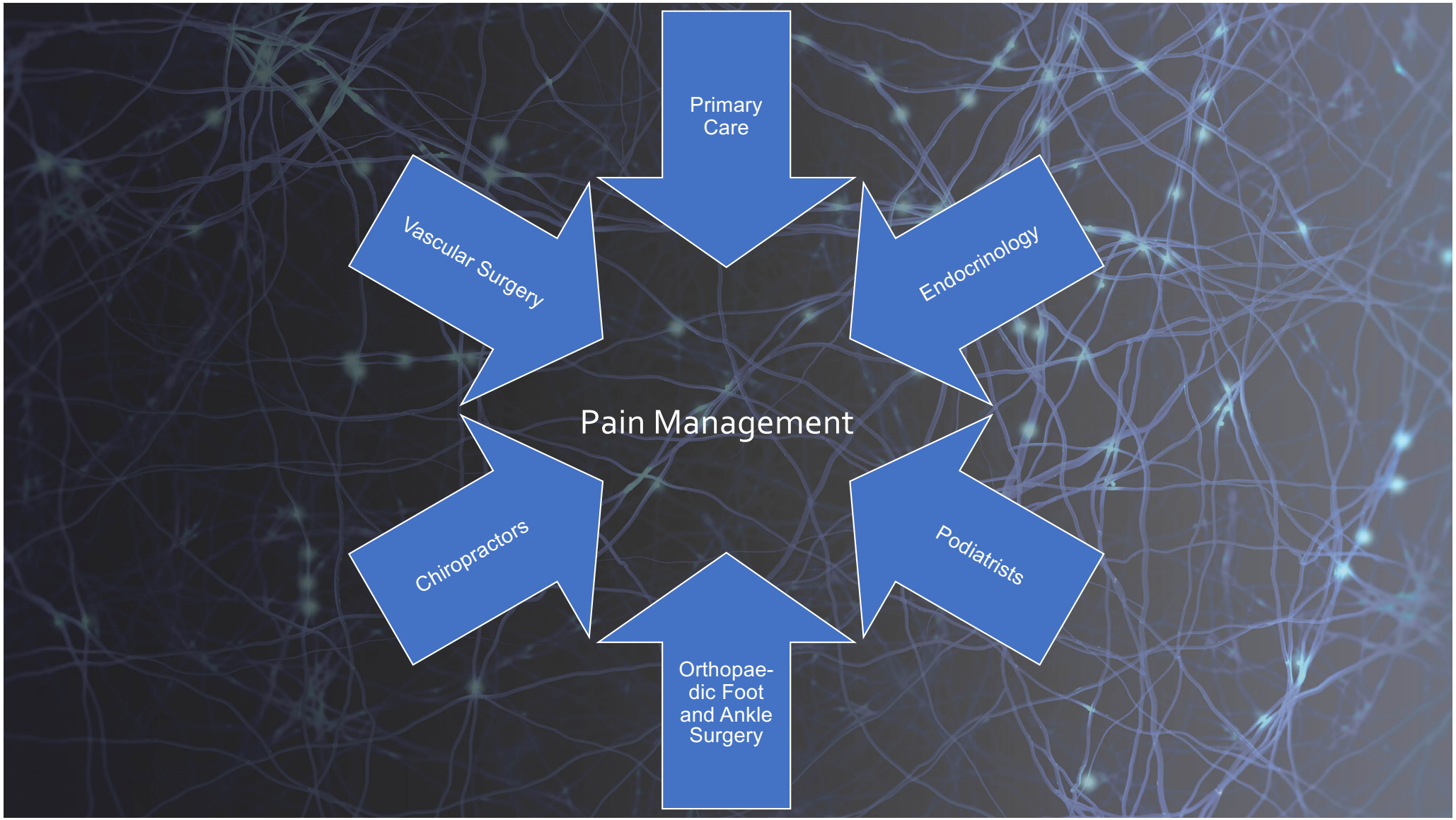
Referral Pathway for Appropriate DPN Patients

- Primary care clinic
- Podiatry clinic
- Orthopedic Clinic
- Wound Clinic
- ER/ Urgent Care/ Walking Clinics

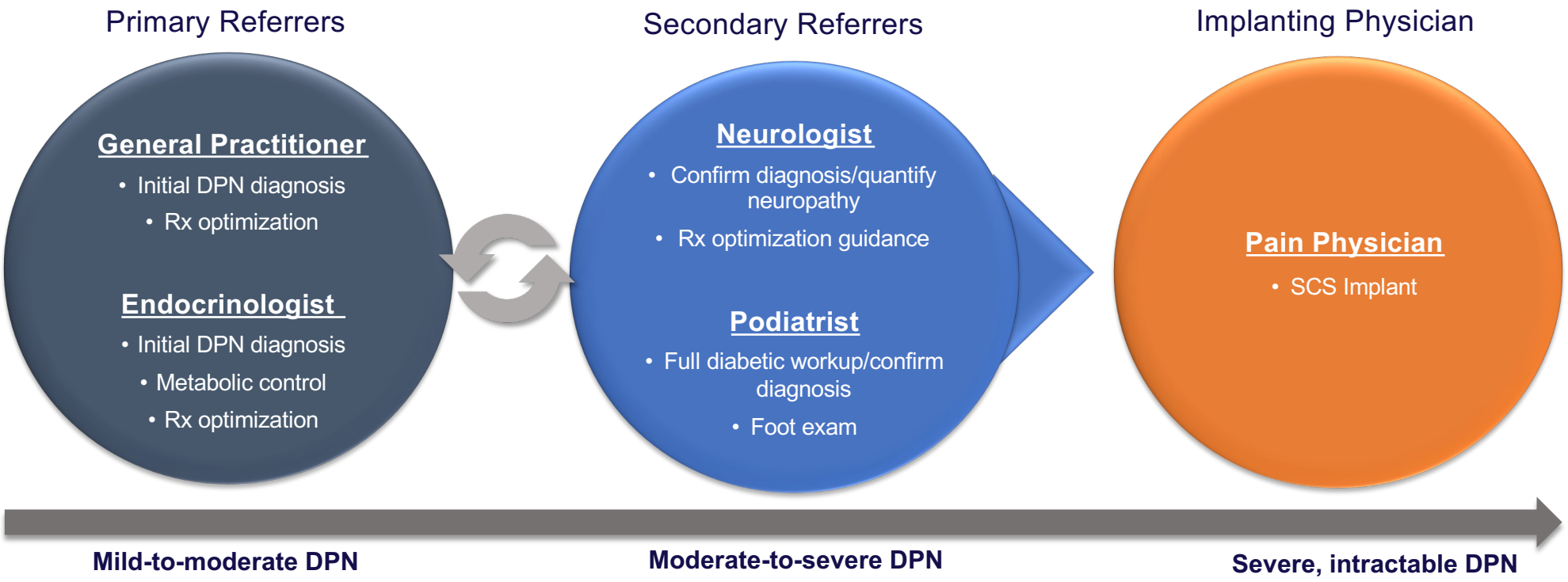
- Neurology Clinic

- Endocrinology/ Diabetologist

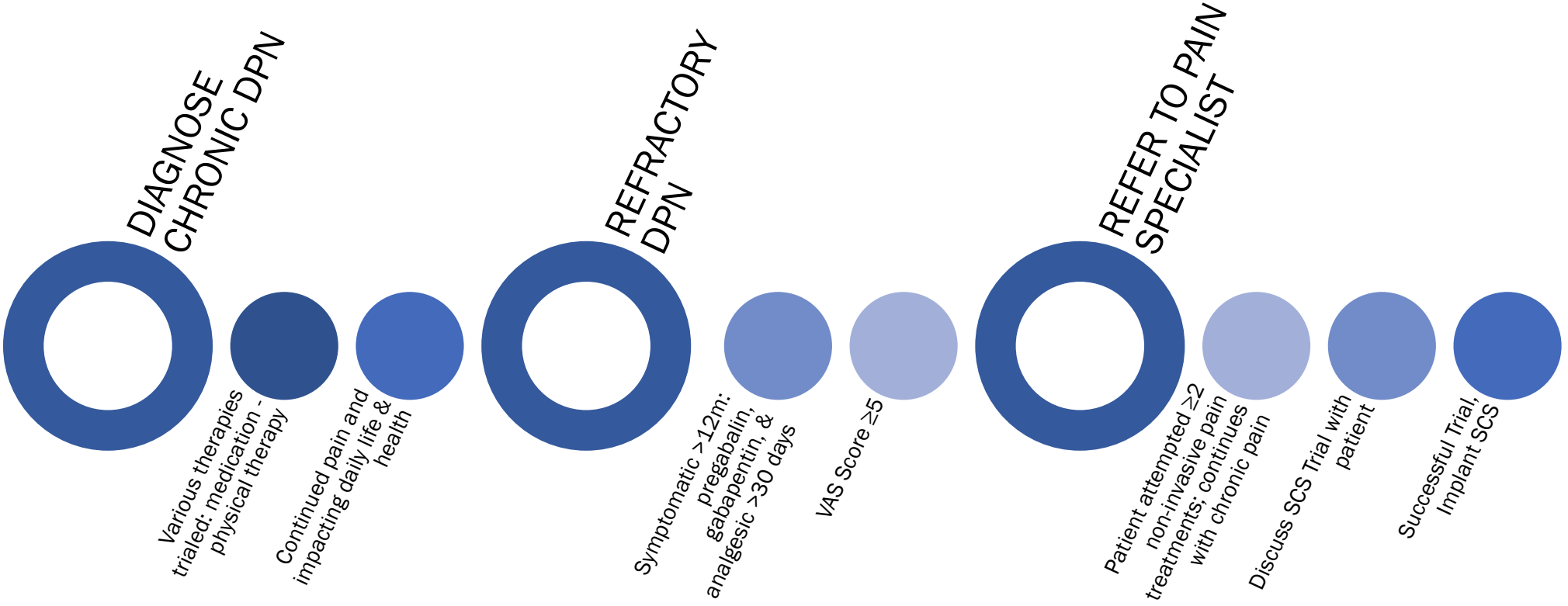
- Pain Management Doctor


Primary Care
Vascular Surgery
Endocrinology
Pain Management
Chiropractors
Podiatrists
Orthopae-dic Foot and Ankle Surgery

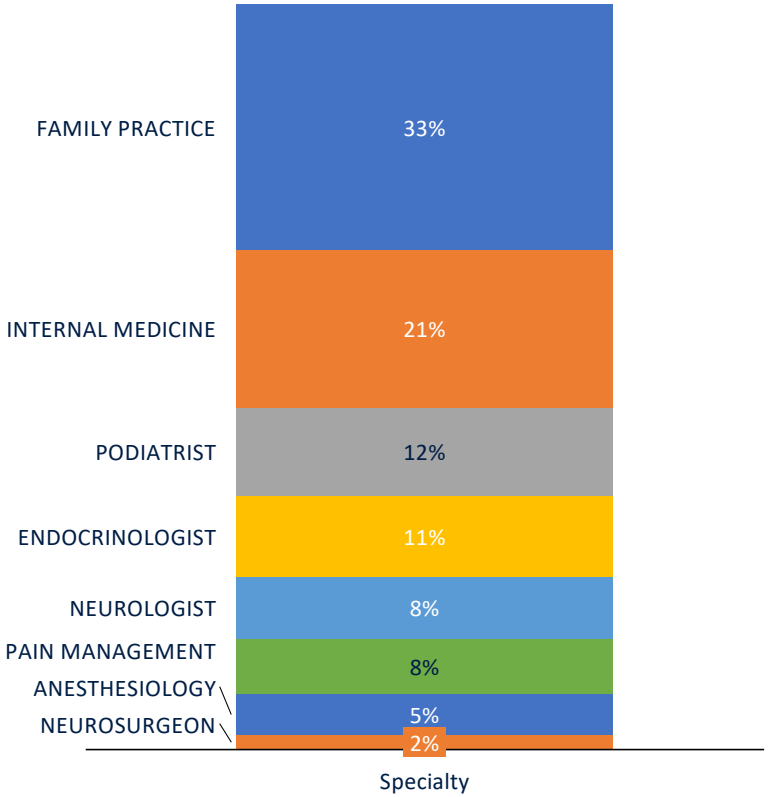
DPN Treatment and Referral Path



Current Patient Pathway from Diagnosis to SCS Treatment



Physician Specialty: All DPN-related Visits in Year Prior to Start of SCS



NOTE: Specialty was missing for 32% of patient visits. The breakdown presented here is only among visits with a specialty listed.
Optum commercial claims data (2008-2019Q2).

Introducing SCS to Patients

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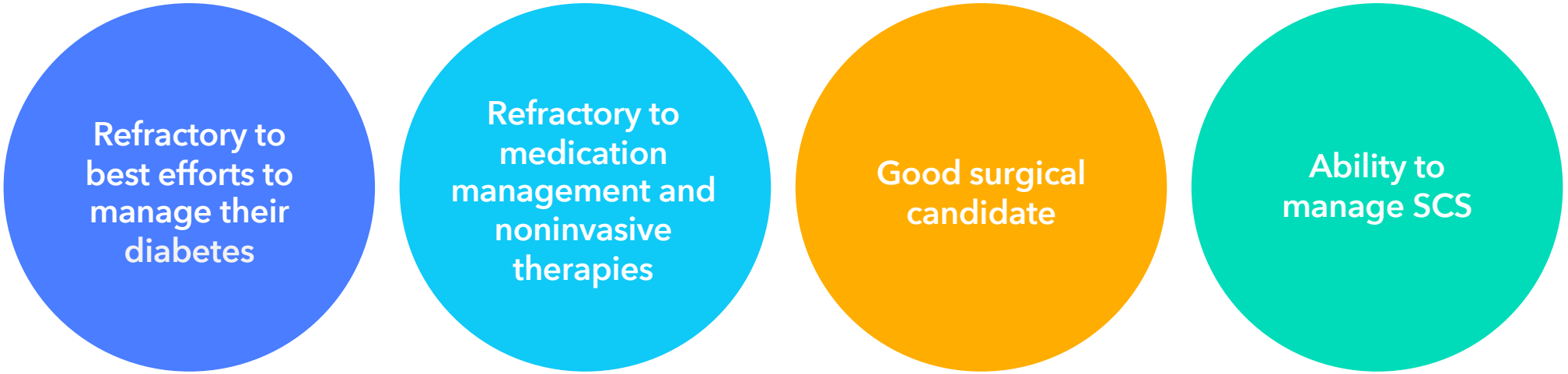
Introducing SCS



Introducing SCS

Preoperative

Request a preoperative health screening for patients with:

- Cardiovascular disease
- Kidney disease
- HbA1C ≥8

NACC Consensus points:

- Optimize HbA1C prior to neuromodulation, if possible
- Careful exam of skin
- Testing for MSSA and MRSA

Intraoperative

Schedule early in day

Maintain blood glucose of <180 mg/dL

NACC Consensus points:

- Recommends considering use of antimicrobial envelopes around INS

Postoperative

Watch for signs of infection, surgical site wound healing, and post-dural puncture headache

Blood glucose may fluctuate in response to any adverse event

Diabetes Care. 2016;39:S99–S104. Deer TR, et al. *Neuromodulation*. 2017;20(1):31-50. Sudhakaran S, et al. *Surg Res Pract.* 2015;2015:284063.

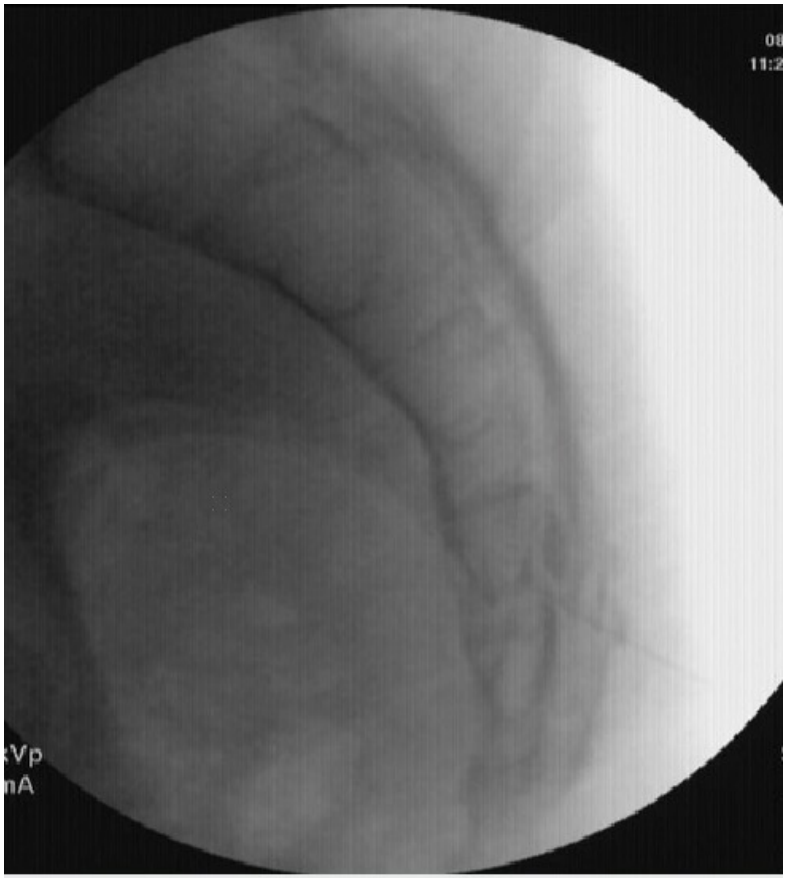
Case Studies

Case Report

- 89-year-old male
  - Referred from orthopedics for bilateral foot pain
  - Current Pain Medications: duloxetine, gabapentin, lidocaine ointment, compound cream
  - Plan: Rotate gabapentin to pregabalin and lidocaine ointment to patches due to inefficacy
    - Lidocaine patch not covered
    - Pregabalin caused sedation

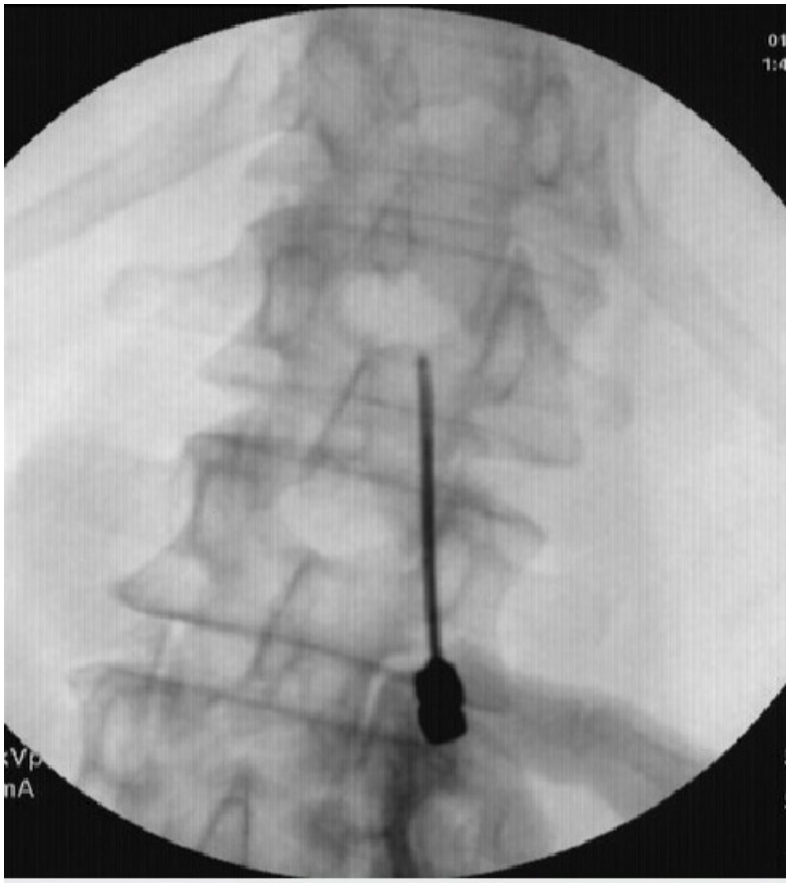
Case Report

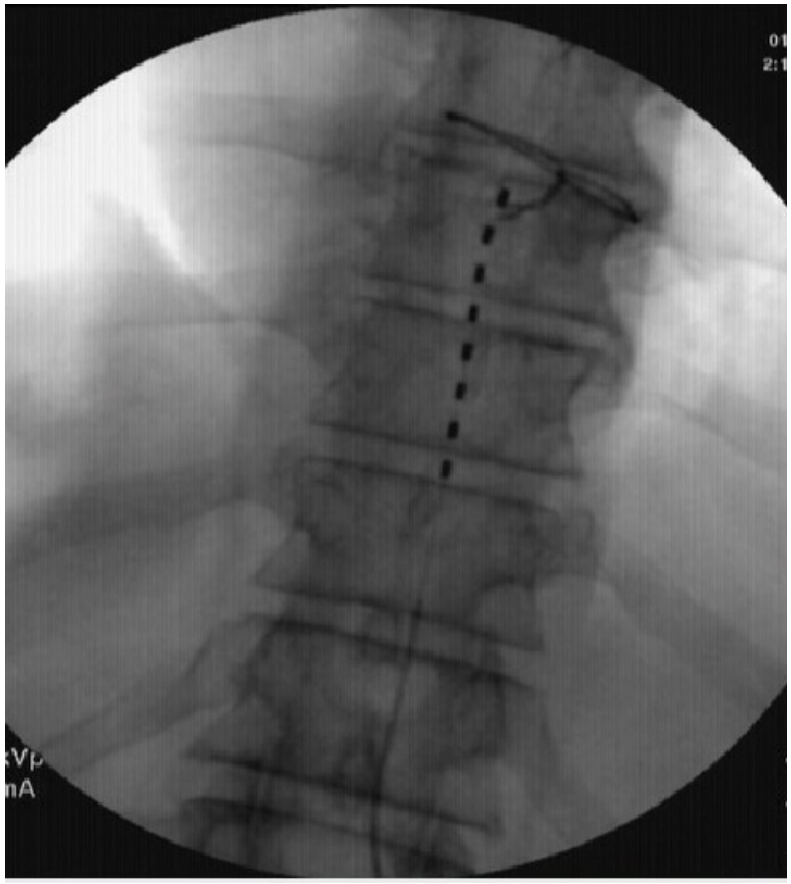
- Plan B
  - Capsaicin patches order - denied
  - Caudal ESI - 80-90% benefit x 24 hours
  - SCS trial ordered



ESI = epidural steroid injection.

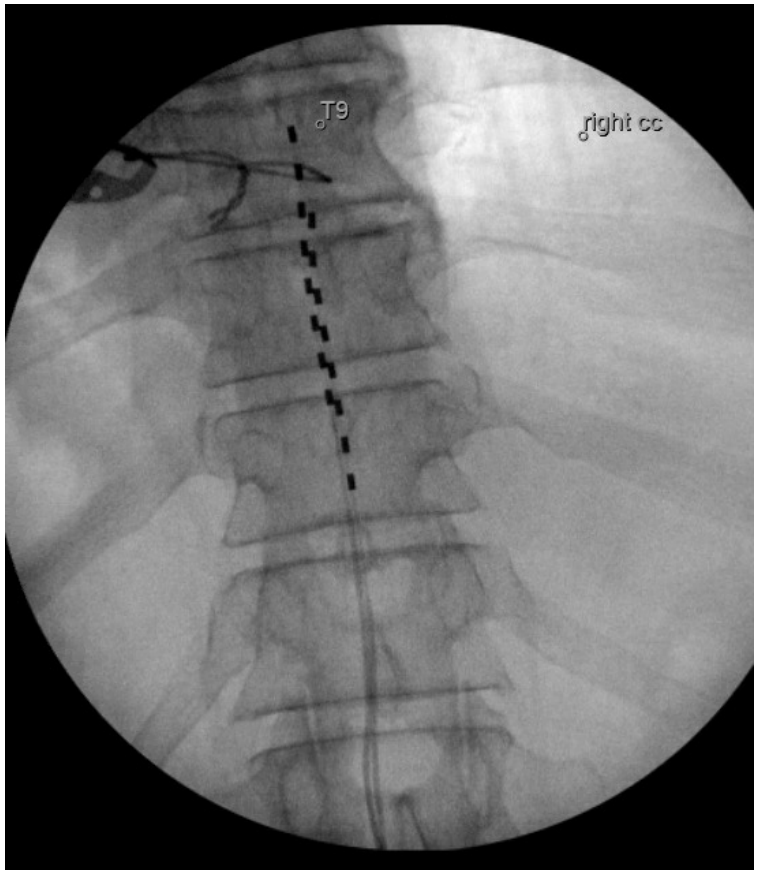
Case Report





Case Report

- Reported 80% benefit after 5-day trial
- Proceeded with implant
- Permanent implant adjusted based on best programming



Case Report

- Permanent SCS with 60%-70% benefit ongoing
- 1-month wound check asked “why am I here”
- Noted in cardiology notes 4 months post-op that “He has recently had surgery for a spinal stimulator and it has helped with his neuropathic pain significantly”
- Has not followed up in clinic since and is still on no oral medications

Case Report

- 60-year-old female
  - Referred from PCP for neck and foot pain
    - Stocking distribution “burning” foot pain, worse at night
  - Existing SCS
    - Generator dead since 2008
    - Doesn’t remember what placed for at this point

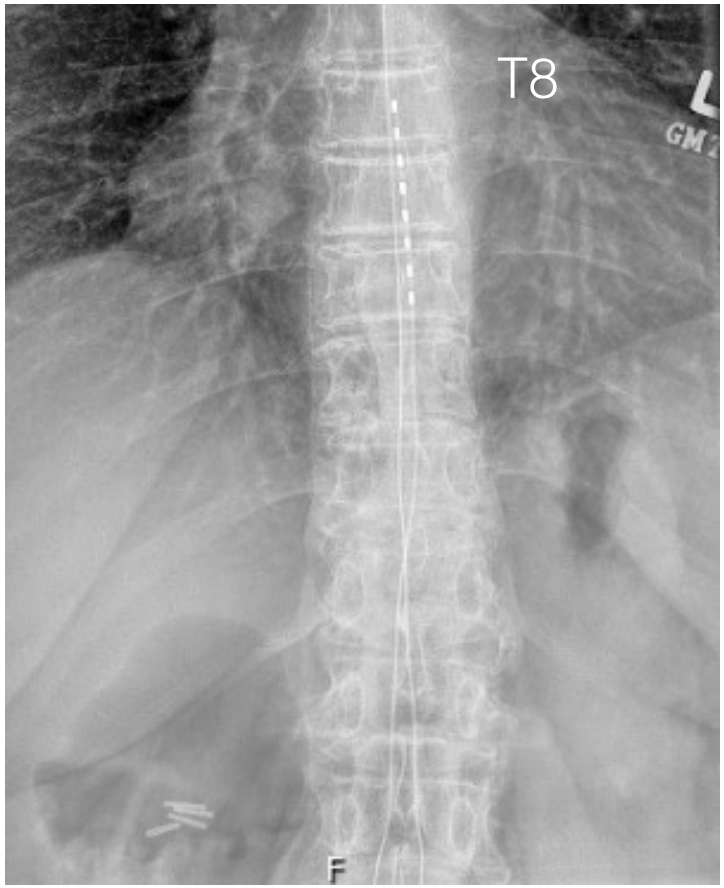
Case Report

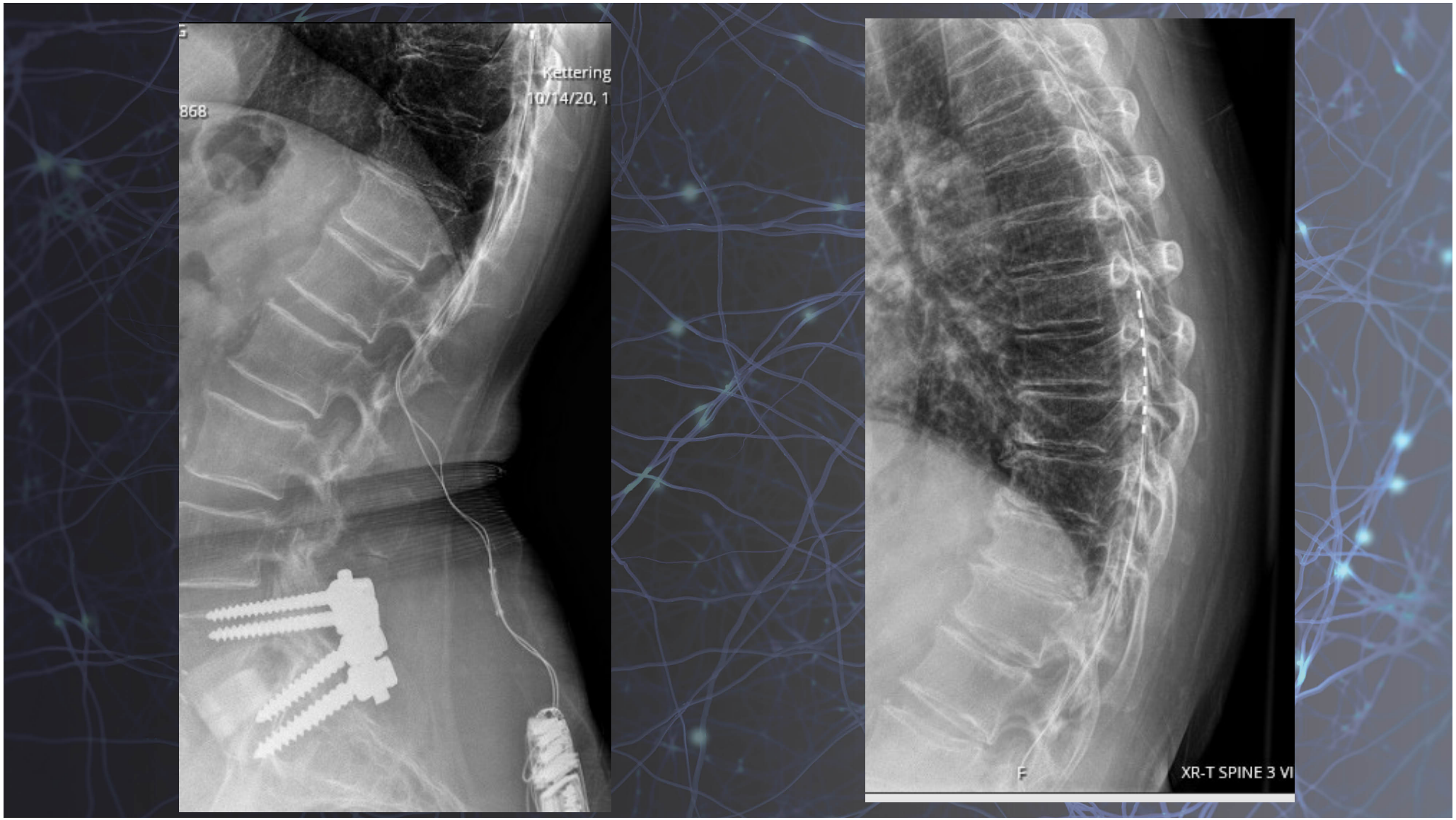
- Previous Treatments
  - Topamax, Pregabalin, Neurontin, Lidocaine ointment/patches, Oxycodone, Tramadol
  - TENS
  - Not a good candidate for steroid injections due to HbA1c 7.6

TENS = transcutaneous electrical nerve stimulation, HbA1c = hemoglobin A1c.

Case Report

- X-rays ordered for evaluation
- Determined could reprogram with new generator
- Replaced 2 months later

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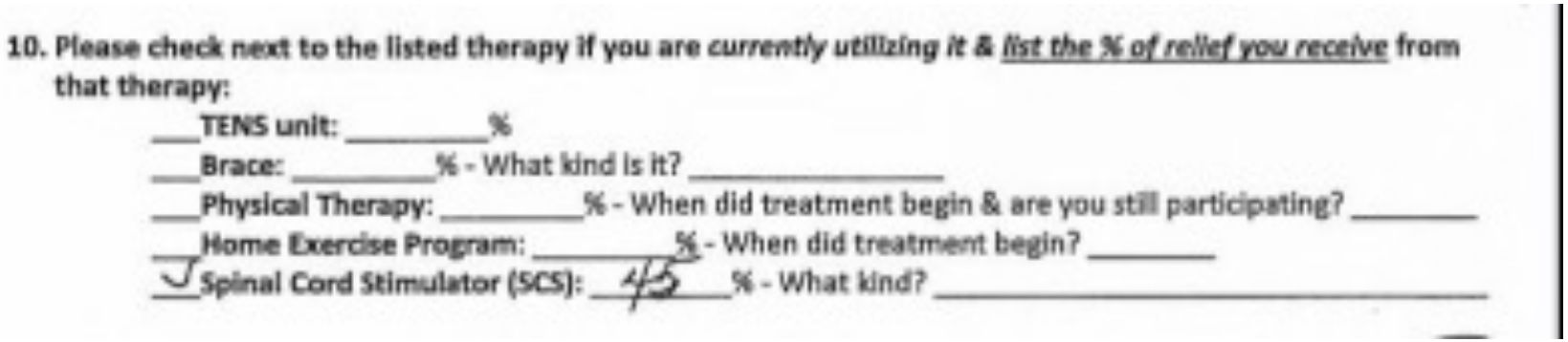
Case Report

- Replacement to rechargeable generator
- Programmed lower lead to cover feet
- 3 years after replacement, reports 45% benefit
- On NO medications for pain



10. Please check next to the listed therapy if you are *currently utilizing it* & *list the % of relief you receive* from that therapy:

___TENS unit: _____%

___Brace: _____% - What kind is it? _____

___Physical Therapy: _____% - When did treatment begin & are you still participating? _____

___Home Exercise Program: _____% - When did treatment begin? _____

J Spinal Cord Stimulator (SCS): 45 % - What kind? _____