An Evidence-Based Approach to Neurogenic Claudication

mild® Treatment Algorithm

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INTRODUCTION

mild is a minimally invasive lumbar decompression procedure used to treat lumbar spinal stenosis (LSS) patients who are suffering from the symptoms of neurogenic claudication (NC). The *mild* Procedure received FDA clearance in 2006. To date, over 30,000 patients have been treated with *mild* in the United States. This broad usage is supported by two Level 1 randomized controlled trials (RCTs), 5 controlled prospective studies, and 17 other retrospective studies, case series, meta-analyses, health economics analyses and reviews published in peer-reviewed journals (see APPENDIX). Published long term results at both 1-year and 2-year follow-up have shown clinically meaningful and statistically significant improvements in function and pain levels. Comparison of *mild* to treatment with epidural steroid injections (ESIs) in two RCTs has shown statistical superiority of *mild* over ESIs for both pain reduction and improved function.

The purpose of this report is to provide a detailed algorithm for the integration of *mild* as first-line therapy and standard of care, in treating symptoms of NC after failure of conservative management.

NEUROGENIC CLAUDICATION (NC)

NC is a source of debilitating pain causing significant functional disability.[1] These symptoms are caused by mechanical compression of neural elements which limits blood supply leading to painful ischemia. The pain and discomfort of NC occurs when standing or walking and is relieved by sitting. Upon patient presentation, NC must be differentiated from radicular pain, which is a different cause of low back and leg pain. Specifically, radicular pain is related to inflammation of a nerve root and requires a different course of treatment with a focus on reducing inflammation.[2,3]

NC symptoms are caused by mechanical compression of neural elements

DIAGNOSIS OF NC

NC patients almost always present with degenerative soft tissue and bony pathology related to a combination of disc protraction, hypertrophic ligamentum flavum (HLF), facet joint hypertrophy, and osteophytes.[1,4,5] These patients generally suffer from multiple spinal comorbidities that contribute to restricted space in the spinal canal.[6,7] HLF specifically has been reported to play a dominant role in the load-induced narrowing of the lumbar spinal canal, contributing between 50% and 85% of central canal narrowing.[5] Most patients with NC also present with stenosis at multiple levels.[4,8]

Patient presentation with NC is initially confirmed through symptomatic diagnosis, and verified with imaging studies, such as MRI. Sandella et al. described the following diagnostic screening criteria to confirm symptoms of NC in LSS patients[9]:

NC patients generally suffer from multiple spinal comorbidities

NC SYMPTOMATIC DIAGNOSIS

- ✓ Pain/discomfort in leg, buttocks, or lower back while walking or standing
- ✓ Bending forward, sitting down, or rest provides relief
- ✓ Flexes forward while walking
- ✓ Difficulty standing unaided without bending at the waist for more than 15 minutes
- ✓ Difficulty walking unaided without bending at the waist for more than one quarter mile

AFTER NC DIAGNOSIS— NEXT STEPS

Once diagnosed with NC using both symptom evaluation and imaging, patients generally begin a regimen of conservative care, which may include back braces, physical therapy, pain medications, and home exercise programs. These conservative measures may provide temporary relief for some patients.

Following failure of non-invasive conservative care, LSS patients suffering from NC often undergo a series of ESIs. Unfortunately, while ESIs may alleviate inflammation related to radicular pain, the success of ESIs in the treatment of NC pain resulting from compression or ischemia of neural structures, is generally limited and short-term.[8] A double-blind RCT of 400 patients reported by Friedly et al. in the *New England Journal of Medicine* found that epidural injection of glucocorticoids plus lidocaine offered minimal or no short-term benefit as compared with epidural injection of lidocaine alone.[10] These results are supported by Fukusaki et al. in a report concluding that ESIs have no beneficial effect on NC associated with spinal canal stenosis as compared with epidural block with a local anesthetic alone.[11]

An additional consideration that is important regarding the use of ESIs, is the immunosuppressive properties of steroids. Patients receiving steroids have an increased susceptibility to many types of opportunistic infections, and it is recommended that patients with existing risk factors should consider avoiding or limiting steroid therapy.[12,13] Also, the relative risk of lower respiratory tract infection was reported to be very high during the first weeks of glucocorticoid exposure, and the risk of infection increases with age.[14]

Eliminate use of steroids altogether or move to *mild* after failure of the first ESI

Given these considerations, many physicians have updated their standard of care for LSS patients with NC to either eliminate the use of steroids altogether, or move on after failure of the first ESI. Patients who are potential candidates for the *mild* Procedure should be evaluated early for this treatment option. The *mild* Procedure offers statistically superior efficacy to ESIs, has been proven to be as safe as an ESI, and is a steroid-free procedure, thereby limiting immunosuppression risk.

THE *mild* PROCEDURE

mild is an efficient, low risk, minimally invasive lumbar decompression procedure that removes a root cause of stenosis in order to significantly improve mobility and reduce pain. *mild* uses a dorsal approach to decompress the spinal canal by selectively removing small portions of lamina and HLF. This outpatient procedure is performed through a small 5.1-mm port using fluoroscopic guidance for visualization. The tiny access port limits trauma to surrounding structures, thereby preserving spinal stability. *mild* can be performed unilaterally or bilaterally, and at multiple levels. The procedure is generally performed with monitored anesthesia care and local anesthetic supplementation. Recovery times are rapid, and *mild* patients typically resume normal activity within 24 hours with no restrictions. Importantly, the *mild* Procedure leaves no implants behind and does not limit the use of subsequent procedures that are more invasive.

mild removes a root cause of stenosis and leaves no implants behind

SAFETY AND EFFICACY

The excellent safety profile, as well as clinically meaningful and statistically significant efficacy of the *mild* Procedure, is supported by a robust base of published scientific evidence, including two Level 1 RCTs, five Level 2 prospective controlled studies, 3 retrospective studies and 3 case series. In addition, 3 meta-analyses, 2 health economics reports, and 6 literature reviews have been published in the peer-reviewed literature. This broad foundation of scientific evidence includes both industry-sponsored and independent reports. Results of all published studies and analyses are presented in the APPENDIX.

Overwhelming evidence from 13 clinical studies & >20 published papers

In the Level 1 ENCORE RCT involving over 300 patients randomized to *mild* or ESIs as the control, *mild* was shown to be statistically and significantly superior to ESIs in the treatment of patients suffering from painful NC and central stenosis due to HLF. All ENCORE patients presented with HLF; however only 5% had central canal stenosis alone. Importantly, the frequent presence of comorbid foraminal stenosis, facet hypertrophy, or bulging disc was a positive predictor of success with *mild* in the ENCORE study. There were no serious device- or procedure-related adverse events (AE), and a low 1.3% of patients experienced a device- or procedure-related AE. ENCORE showed no difference in safety between *mild* and ESIs, thereby providing Level 1 evidence that *mild* is as safe as an ESI.[7, 15-17]

mild is as safe as an ESI, with superior efficacy

Mekhail and colleagues from Cleveland Clinic reported statistically significant improvement in both standing time and walking distance for patients treated with *mild* from baseline to 1-year follow-up. At 1 year post-*mild* Procedure, patients were able to stand 7 times longer with an increased mean standing time of 8 minutes to 56 minutes. Over the same period, these *mild* patients could walk 16 times farther with an increased mean walking distance of 246 feet to nearly 4,000 feet. In this study, pain levels also improved significantly at 1-year follow-up. This important study demonstrated that *mild* helps patients to stand longer and walk further with less pain (FIGURE 1).[8]

Patients were able to stand longer and walk further with less pain

Cleveland Clinic Study, 1-Year Outcomes[8]

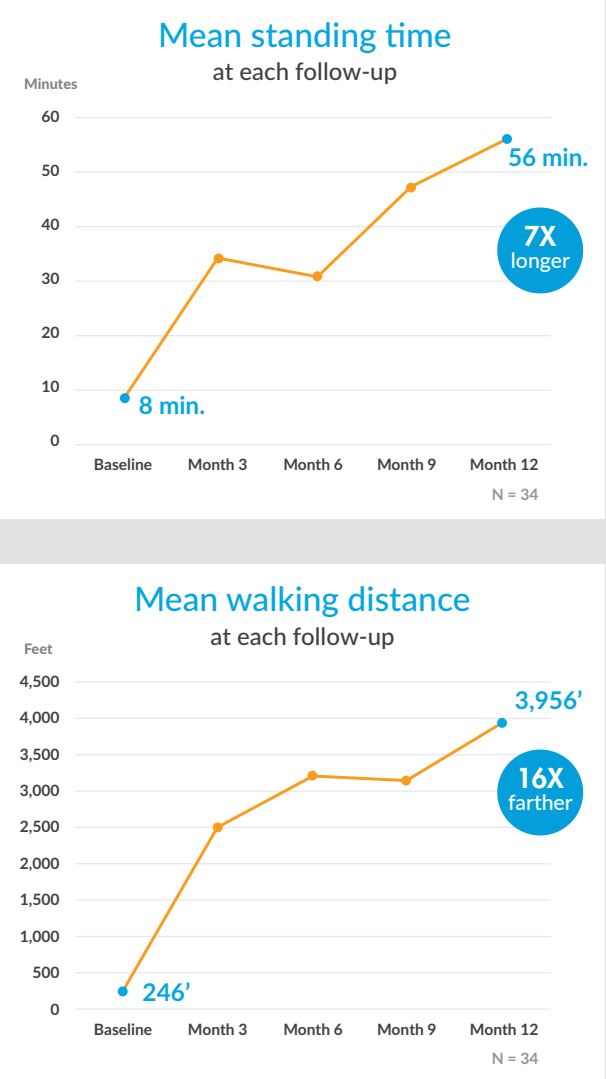

FIGURE 1:

Statistically significant improvement in standing time and walking distance at 1-year follow-up after *mild*.

DURABILITY

Follow-up of patients enrolled in the ENCORE Study included a 2-year assessment of function, pain and safety for patients in the *mild* arm only. As reported by the ENCORE Investigators, all outcome measures demonstrated clinically meaningful and statistically significant improvement from baseline through 6-month, 1-year and 2-year follow-ups. The authors concluded that *mild* showed excellent long-term durability, and there was no evidence of spinal instability through 2 years.[7] Also, at 2 years, Oswestry Disability Index (ODI) responders improved by 32 points, and Numeric Pain Rating Scale (NPRS) responders improved by 5 points[16] (FIGURE 2).

Clinically meaningful and statistically significant improvement in function and pain through 2 years

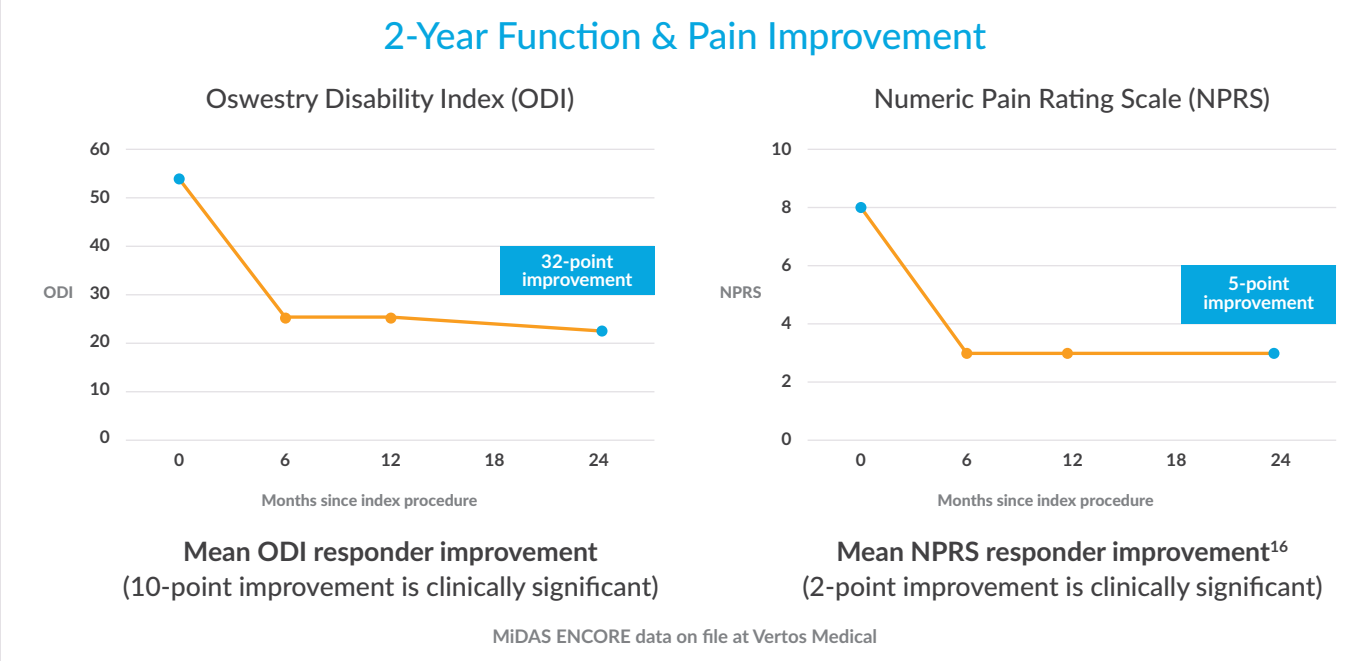

FIGURE 2: Function and pain improvement at 2-year follow-up after *mild*.

HYPERTROPHIC LIGAMENTUM FLAVUM (HLF) AND OTHER SPINAL COMORBIDITIES

mild is specifically intended for NC patients with central stenosis due to HLF; however, presentation with multiple spinal comorbidities is common for these patients. While HLF contributes to up to 85% of central canal narrowing, other comorbidities such as bulging discs, osteophyte complexes, foraminal narrowing, and facet hypertrophy are also potential factors in spinal canal narrowing and compression that result in NC.

HLF contributes up to 85% of central canal narrowing

It has been postulated that treating one source of spinal canal narrowing may provide overall decompressive relief due to the severely confined and interconnected architectures of the lumbar spine. Specifically, removal of small amounts of lamina and hypertrophic ligament with the *mild* Procedure provides enough space to limit NC symptoms caused by HLF as well as other spinal comorbidities. This concept is supported by results from the ENCORE Study where a majority of patients had comorbid foraminal stenosis, facet hypertrophy, and bulging disc, which were all a positive predictor of success with *mild*. Therefore, these comorbid findings are not a contraindication to the use of *mild*.[7,17]

Comorbid foraminal stenosis, facet hypertrophy and bulging disc were positive predictors of success

mild VS OTHER SPINE INTERVENTIONS

A comprehensive safety comparison of *mild* versus other lumbar spine interventions was conducted by the MiDAS ENCORE Investigators and published in their 2-year ENCORE paper.[7] This comparison presented in TABLE 1 shows that reoperation and spinal fracture rates are lower. It also shows that safety is better for *mild*, versus spacers, surgical decompression, and spinal fusion. Given the durability of outcomes, the minimally invasive nature of the procedure, and its robust success rate, the authors conclude that *mild* is an excellent choice for first-line therapy for LSS patients suffering from NC symptoms and HLF.

TABLE 1: Safety Comparison Through 2-Year Follow-up for Lumbar Spine Procedures.

2-YEAR OUTCOMES	*mild*[7]	Interspinous Process Distraction[18,19]		Surgical Decompression[19,20]	Fusion[21-25]
		Superion®	X-STOP®		
Reoperation	5.6%	20%	14.4-26%	6-7.8%	12.5-16.9%
Device- and Procedure-Related AEs	1.3%	Device-related		Intra-operative 9.9% Postoperative 12.3%	23.3% 18% early/6% late
		11.6%	7.5%		
		Procedure-related			
		14.2%	15.9%		
Device- and Procedure-Related Serious AEs	0%	8.4%	9.5%		
Lumbar Spine Fractures	0%	16.3%	8.5%	-	4.2%
Removal of Hardware	No implants	16.3%	12.4%	No implants	4.3%

***mild* is an excellent choice for first-line therapy for LSS patients suffering from NC symptoms and HLF**

mild COST-EFFECTIVENESS

An analysis by Udeh et al. compared the 2-year cost-effectiveness of three options to treat lumbar spinal stenosis patients: ESIs, laminectomy, and *mild*. This analysis accounted for costs associated with the initial procedure, complications, and repeat/revision or alternate procedures after failure of the index procedure. In this analysis, *mild* was determined to be the most cost-effective alternative, followed by ESIs and then laminectomy. The authors concluded that for LSS patients with moderate to severe NC symptoms, *mild* offers a cost-effective alternative to continuing with repeated serial ESIs or proceeding to laminectomy.[26]

PATIENT SELECTION

mild candidates must have a confirmed clinical diagnosis of NC based on symptomology. Once conservative measures have failed, NC patients may be considered for *mild* treatment and must meet the following criteria:

mild CANDIDATES

- ✓ HLF ≥ 2.5 mm, confirmed by imaging
- ✓ Spinal stability ≤ Grade II
- ✓ Central canal stenosis, including those with comorbid conditions such as foraminal stenosis, lateral stenosis, facet hypertrophy, or disc bulge

Once conservative measures have failed, NC patients may be considered for *mild* treatment

Additional patient selection considerations include the increasing prevalence of osteoporosis, which is important given the reported 16.3% and 4.2% rates of lumbar spine fractures for interspinous spacers and spinal fusion, respectively (TABLE 1). Unlike these techniques, the patient's bone integrity/ osteoporosis is not an exclusion for the *mild* Procedure and will not negatively affect outcomes of *mild*.[27] Also, since interspinous spacers cannot be deployed at L5-S1, *mild* may provide the only option for treatment of L5-S1 stenosis secondary to HLF for patients who are not surgical candidates. Finally, if the patient has NC symptoms with severe neurological compromise, open decompression/stabilization should be considered.

PRE-*mild* PROCEDURE CONSIDERATIONS

While the amount of radiation exposure is low during a *mild* Procedure, certain steps can be taken to ensure that these levels are minimized. Pulse and low dose fluoroscopy are recommended, as well as the use of circular collimation and appropriate shielding. A study conducted by Drs. Lam, Kim, and Sayed from Kansas University Medical Center demonstrated a substantial reduction in radiation exposure utilizing pulse fluoroscopy under low dose exposure and circular collimation.[28] In addition, potential for allergic reaction to contrast media must be considered. Fortunately, the incidence of serious adverse reactions to contrast agents used in spinal procedures is extremely low at an estimated 0.04%.[29] This rate of 4 in 10,000 is consistent with the rates estimated by the American College of Radiology.[30]

THE NEXT STEP IS *mild*

Once conservative measures are shown to provide limited or no relief for NC patients, a physician can move straight to *mild*. Recently, the excellent safety profile and superior efficacy of *mild* has led some practitioners to eliminate the use of ESIs for treating NC altogether. If an ESI is preferred as a first-step diagnostic, a single ESI can be administered with contrast medium to define patient anatomy and access for subsequent *mild* treatment.

ESI failure is typically defined as less than 50% relief at the 2-week follow-up. Once an ESI has failed to help with NC symptoms, the low-risk and least invasive *mild* Procedure is the next step. *mild* is proven to be as safe as an ESI with durable effect, patients typically resume normal activity within 24 hours with no restrictions, and it does not involve implants or limit subsequent treatment options.

The *mild* treatment algorithm presented here spans patient care from initial NC diagnosis through follow-up at 3-6 months post-*mild*. (FIGURE 3.) Patients diagnosed with NC traditionally undergo a regimen of conservative care. Based on the evidence, there is a case to be made for moving straight to *mild* after identification of NC symptoms and confirmation of HLF ≥ 2.5 mm. If an initial ESI is done, and provides < 50% relief at 2 weeks, the patient should be assessed for *mild* candidacy. Patients confirmed to be *mild* candidates are then treated with the *mild* Procedure and continue with post-*mild* recommended care over the next 3-6 months.

Based on evidence, *mild* is the next step after failure of conservative care

mild POST-PROCEDURE CARE CONSIDERATIONS

While each patient faces different circumstances, the following are general *mild* post-procedure care considerations:

1. Following treatment with *mild*, patients typically resume normal activity within 24 hours with no restrictions; at-home conditioning and a progressive walking program can be initiated immediately, as tolerated.
2. Standard follow-up generally includes a post-op visit at 2 weeks. If the patient can benefit from continued functional conditioning, a 4 to 6 week formal physical therapy regimen specifically for LSS with NC may be prescribed.
3. Assessment of patient outcomes and success should be focused on standing time, walking distance, and patient satisfaction, and may include other functional assessments.
4. A follow-up with the physician is typically conducted at 4 to 6 weeks post-*mild* Procedure, and then monthly for the next 2 months.
5. In the event the patient is continuing to experience discomfort from other pain generators, it is recommended to wait 10 to 12 weeks before proceeding with additional treatment.

Patients typically resume normal activity within 24 hours with no restrictions

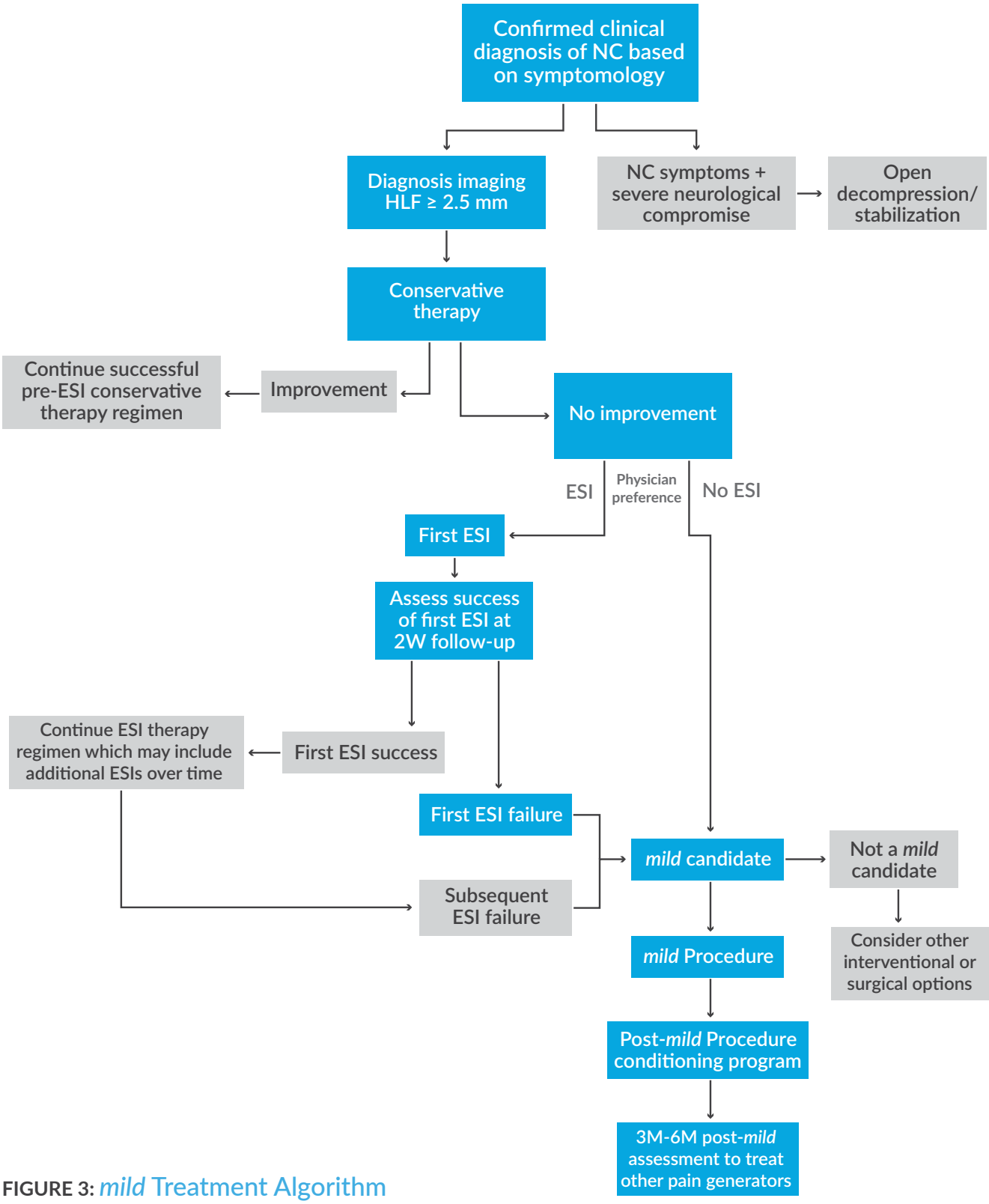

FIGURE 3: *mild* Treatment Algorithm

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APPENDIX: *mild* PUBLICATIONS AND EVIDENCE

Article Title	Populations	Outcomes
Staats PS, Chafin TB, Golovac S, et al., for the MiDAS ENCORE investigators. Long-term safety and efficacy of minimally invasive lumbar decompression procedure for the treatment of lumbar spinal stenosis with neurogenic claudication: 2-Year results of MiDAS ENCORE. (2018) (7)	**PROSPECTIVE, MULTICENTER RANDOMIZED CONTROLLED TRIAL:** 302 Patients, 26 sites Medicare beneficiaries who are lumbar spinal stenosis (LSS) patients with neurogenic claudication (NC) and verified hypertrophic ligamentum flavum (HLF) Comparator: Epidural steroid injections (ESIs)	*mild* showed excellent long-term durability, and no evidence of spinal instability through 2-year follow-up. Reoperation and spinal fracture rates are lower, and safety is higher for *mild* versus other lumbar spine interventions. All outcome measures demonstrated clinically meaningful and statistically significant improvement from baseline through 6-month, 1-year and 2-year follow-ups. Given the minimally invasive nature of this procedure, its robust success rate, and durability of outcomes, *mild* is an excellent choice for first-line therapy for select patients. **Mobility / Disability:** ODI ≥ 10-point improvement is clinically meaningful ZCQ Symptom severity / Physical function ≥ 0.5-point improvement is clinically meaningful ZCQ Patient satisfaction ≤ 2.5 indicates that the patient is satisfied with the procedure Mean improvement / 6-month / 1-year / 2-year ODI / 20.4 / 19.5 / 22.7 ZCQ Symptom severity / 0.8 / 0.9 / 1.0 ZCQ Physical function / 0.7 / 0.6 / 0.8 ZCQ Patient satisfaction* / 2.1 / 2.1 / 2.0 **Pain reduction:** NPRS ≥ 2-point improvement is clinically meaningful Mean improvement / 6-month / 1-year / 2-year NPRS / 3.1 / 3.3 / 3.6 Safety: • No serious device- or procedure-related adverse events (AE) • 1.3% device- or procedure-related AE Low surgical reoperation rate: 5.6% at 2-year

Article Title	Populations	Outcomes
Benyamin RM, Staats PS, for the MiDAS ENCORE investigators. *mild* Is an Effective Treatment for Lumbar Spinal Stenosis with Neurogenic Claudication: MiDAS ENCORE Randomized Controlled Trial. (2016) (15)	**PROSPECTIVE, MULTICENTER RANDOMIZED CONTROLLED TRIAL:** 302 Patients, 26 sites Medicare beneficiaries who are LSS patients with NC and verified HLF Comparator: ESIs	1-year results of the ENCORE randomized controlled trial demonstrated that *mild* is statistically superior to ESIs in the treatment of LSS patients with NC. Primary and secondary efficacy outcome measures achieved statistical superiority in the *mild* group compared to ESIs. The within-group change from baseline to 1-year follow-up was statistically significant for all efficacy endpoints. Further, there were no significant differences in safety profile between *mild* and ESIs.
Staats PS, Benyamin RM, for the MiDAS ENCORE Investigators. MiDAS ENCORE: Randomized Controlled Clinical Trial Report of 6-Month Results. (2016) (31)	**PROSPECTIVE, MULTICENTER RANDOMIZED CONTROLLED TRIAL:** 302 Patients, 26 sites Medicare beneficiaries who are LSS patients with NC and verified HLF Comparator: ESIs	6-month follow-up data from the ENCORE randomized controlled trial demonstrated that the *mild* Procedure is statistically superior to ESIs. The results of all primary and secondary efficacy outcome measures achieved statistically superior outcomes in the *mild* group versus ESIs. Further, there were no statistically significant differences in the safety profile between *mild* and ESIs. This study provides strong evidence of the effectiveness of *mild* versus ESIs in the ENCORE patient population.
Brown LL. A double-blind, randomized, prospective study of epidural steroid injection vs. the *mild* Procedure in patients with symptomatic lumbar spinal stenosis. (2012) (32)	**PROSPECTIVE, SINGLE CENTER, DOUBLE-BLIND, RANDOMIZED CONTROLLED TRIAL:** 38 Patients Symptomatic LSS patients with painful lower limb NC and HLF as a contributing factor. Comparator: ESIs	*mild* provides statistically significantly better pain reduction and improved functional mobility vs. treatment with ESI. In the *mild* group, change from baseline to both 6-week and 12-week follow-ups were statistically significant for all efficacy endpoints. **Mobility / Disability:** • ODI (*mild*): 11.1-point improvement at 6-week • ODI (ESI): 5.7-point improvement at 6-week • ZCQ Patient satisfaction (*mild*): 2.2 points at 6-week* • ZCQ Patient satisfaction (ESI): 2.8 points at 6-week* • ODI (*mild*): 18.6-point improvement at 12-week • ZCQ Patient satisfaction (*mild*): 1.8 points at 12-week* **Pain Reduction:** • VAS (*mild*): 2.5-point improvement at 6-week • VAS (ESI): 0.1-point improvement at 6-week • VAS (*mild*): 2.9-point improvement at 12-week **Safety:** No major device- or procedure-related complications

Article Title	Populations	Outcomes
Chopko BW. Long-term results of percutaneous lumbar decompression for LSS: 2-year outcomes. (2013) (33)	**PROSPECTIVE, MULTICENTER:** 45 Patients, 11 sites	At 2-year follow-up, patients experienced statistically significant improvement in pain levels and functional mobility with no major device- or procedure-related AE. **Mobility/Disability:** ODI: Statistically significant 8.6-point improvement at 2-year. 11.6-point improvement within responders ZCQ: All ZCQ domains showed statistically significant improvement at 2-year. • Symptom severity: 0.9-point improvement • Pain subdomain: 1.1-point improvement • Neuro-ischemic subdomain: 0.7-point improvement • Physical function: 0.4-point improvement • Patient satisfaction 2.2 points* **Pain Reduction:** • VAS: Statistically significant 2.4-point improvement at 2-year 71% responder rate defined as VAS score improvement of ≥1. Responders demonstrated 3.8-point improvement at 2-year (50% reduction) **Safety:** No major device or intraprocedural AE
Mekhail N, Vallejo R, Coleman MH, Benyamin RM. Long-term results of percutaneous lumbar decompression *mild* for spinal stenosis. (2012) (34)	**PROSPECTIVE, MULTICENTER:** 58 Patients, 11 sites NC defined as low back, buttock, or leg pain associated with prolonged standing and walking and that eased with flexion, sitting, or lying down. Evidence of HLF >2.5mm as a contributing factor was required.	*mild* demonstrated efficacy by significantly improving mobility and reducing pain associated with LSS at 1-year post-procedure. The reduction of pain and improvement in physical function and mobility were sustained at 1-year, and were statistically and clinically significant. **Mobility/Disability:** • ODI: 11.9-point improvement at 1-year • ZCQ Pain subdomain: 1.2-point improvement at 1-year • ZCQ Neuro-ischemic subdomain: 0.8-point improvement at 1-year • ZCQ Physical function: 0.6-point improvement at 1-year • ZCQ Patient satisfaction: 2.2 points at 1-year* **Pain Reduction:** • VAS: 2.9-point improvement at 1-year **Safety:** No major *mild* device- or procedure-related AE

Article Title	Populations	Outcomes
Deer TR, Kim CK, Bowman RG, Ranson MT, Yee BS. (2012), Study of percutaneous lumbar decompression and treatment algorithm for patients suffering from neurogenic claudication. (2012) (35)	**PROSPECTIVE, SINGLE CENTER:** 46 Patients LSS patients suffering from NC primarily caused by HLF.	*mild* Procedure was shown to be safe, with properly diagnosed patients experiencing significant improvement in mobility and significant reduction of pain at 1 year after the procedure. Change from baseline to 1-year follow-up was statistically significant for all efficacy endpoints. **Mobility/Disability:** • ODI: 17.4-point improvement at 1-year • ZCQ Symptom severity: 1.2-point improvement at 1-year • ZCQ Pain subdomain: 1.2-point improvement at 1-year • ZCQ Neuro-ischemic subdomain: 1.1-point improvement at 1-year • ZCQ Physical function: 0.8-point improvement at 1-year • ZCQ Patient satisfaction: 1.9 points at 1-year* **Pain Reduction:** VAS: 2.9-point improvement at 1-year **Safety:** No reports of major device- or procedure-related adverse events
Mekhail N, Costandi S, Abraham B, Samuel SW. Functional and patient-reported outcomes in symptomatic lumbar spinal stenosis following percutaneous decompression. (2012) (8)	**PROSPECTIVE, SINGLE CENTER:** 40 Patients NC and radiographic T2-weighted MRI-confirmed HLF ≥ 4.0 mm. Failure of conservative treatment was also required with lumbar decompression medically indicated in all cases.	*mild* Procedure demonstrated statistically significant improvement in both function and pain at 1-year follow-up. **Mobility/Disability:** • Roland-Morris disability index (RMQ): 7.7-point improvement at 1-year • Standing time: Seven-fold improvement from 8 minutes to 56 minutes at 1-year • Walking distance: Sixteen-fold improvement from 246 feet to 3,956 feet at 1-year • **Pain Reduction:** • Pain Disability Index (PDI): 22.6-point improvement at 1-year • VAS: 3.5-point improvement at 1-year **Safety:** No reports of major device- or procedure-related AE

Article Title	Populations	Outcomes
Chopko B, Caraway DL. MiDAS I (*mild* decompression alternative to open surgery): a preliminary report of a prospective, multi-center clinical study. (2010) (36)	**PROSPECTIVE, MULTICENTER:** 78 Patients, 14 sites Symptomatic LSS primarily caused by dorsal element hypertrophy, prior failure of conservative therapy, radiologic evidence of LSS, HLF ≥ 2.5 mm, central canal sectional area ≤ 100 square mm, anterior listhesis ≤ 5.0 mm, and ability to walk at least 10 feet unaided before being limited by pain.	*mild* Procedure demonstrated efficacy in improving mobility and reducing pain associated with lumbar spinal canal stenosis. Change from baseline to 6-week follow-up was statistically significant for all efficacy endpoints. **Mobility/Disability:** • ODI: 17.9-point improvement at 6-week • ZCQ Symptom severity: 1.3-point improvement at 6-week • ZCQ Pain subdomain: 1.5-point improvement at 6-week • ZCQ Neuro-ischemic subdomain: 1.1-point improvement at 6-week • ZCQ Physical function: 0.7-point improvement at 6-week • ZCQ Patient satisfaction: 2.0 points at 6-week* **Pain Reduction:** • VAS: 3.6-point improvement at 6-week **Safety:** No major device- or procedure-related complications
Durkin B, Romeiser J, Shroyer AL, et al. Report from a quality assurance program on patients undergoing the *mild* Procedure. (2013) (37)	**RETROSPECTIVE, SINGLE CENTER:** 50 Patients Observational cohort study	This analysis showed significant pain reduction and significantly improved function at 1-month, 3-month and 6-month follow-ups based on patient reported outcome measures (ODI, ZCQ, NRS and NIH PROMIS Pain Interference Scores). There were no major complications such as bleeding, dural punctures, or nerve injuries secondary to the application of *mild* during the procedure.
Deer TR, Kapural L. New image-guided ultra-minimally invasive lumbar decompression method: the *mild* Procedure. (2010) (38)	**RETROSPECTIVE, MULTICENTER:** 90 patients, 12 sites	This safety survey found no major AE or complications related to the *mild* devices or procedure. No incidents of dural puncture or tear, blood transfusion, nerve injury, epidural bleeding, or hematoma were observed.

Article Title	Populations	Outcomes
Lingreen R, Grider JS. Retrospective review of patient self-reported improvement and post-procedure findings for *mild* (minimally invasive lumbar decompression). (2010) (39)	**RETROSPECTIVE, SINGLE CENTER:** 42 Patients Spinal stenosis and HLF as the primary feature.	*mild* Procedure appears to offer a safe and effective alternative for patients suffering from LSS. **Mobility/Disability:** • 73% reported improved activities of daily living at 30-days • 57% reported improved ability to walk > 15 min at 30-days • 59% reported improved ability to stand > 15 min at 30-days **Pain Reduction:** • VAS: 3.8-point improvement at 30-days **Safety:** No device- or procedure-related major AE **Patient Satisfaction:** • 86% would recommend *mild*
Basu S. *mild* Procedure: single-site experience prospective IRB study. (2012) (40)	**CASE SERIES:** 27 Patients Failed conservative therapy; NC, with radiographic confirmation of HLF > 2.5 mm	*mild* has shown to be safe, effective, and cost-effective treatment for LSS patient with NC. At 6-month, all improvements in pain, function, and mobility were statistically and clinically significant. **Mobility/Disability:** • ODI: 24-point improvement at 6-month • ZCQ Pain subdomain: 1.71-point improvement at 6-month • ZCQ Neuro-ischemic subdomain: 2.08-point improvement at 6-month • ZCQ Physical function: 1.17-point improvement at 6-month • ZCQ Patient satisfaction: 1.86 points at 6-month* **Pain Reduction:** • VAS: 5.2-point improvement at 6-month **Safety:** No device- or procedure-related serious complications
Wong WH. *mild* interlaminar decompression for the treatment of lumbar spinal stenosis: procedure description and case series with 1-year follow-up. (2012) (41)	**CASE SERIES:** 17 Patients	*mild* Procedure provided significant pain relief at 1-year post-treatment and increased mobility for patients with symptomatic LSS. **Mobility/Disability:** • ODI: 26.6-point improvement at 1-year **Pain Reduction:** • VAS: 5.4-point improvement at 1-year **Safety:** No reports of major device- or procedure-related AE

Article Title	Populations	Outcomes
Chopko BW. A novel method for treatment of lumbar spinal stenosis in high-risk surgical candidates: pilot study experience with percutaneous remodeling of ligamentum flavum and lamina. (2011) (42)	**CASE SERIES:** 14 Patient study of high-risk surgical patients Many of the patients had physiologically limiting coexistent issues, such as oxygen-dependent pulmonary fibrosis, prior stroke, and systemic malignancies.	*mild* Procedure achieved statistically significant improvement in pain reduction. **Mobility/Disability:** • ODI: 6.1-point improvement at 23.5-weeks **Pain Reduction:** • VAS: 4.0-point improvement at 23.5-weeks **Safety:** No dural tears, CSF leaks, or wound healing complications were observed
Mekhail NA, Costandi SJ, Armanyous S, et al. The Impact of Age on the Outcomes of Minimally Invasive Lumbar Decompression for Lumbar Spinal Stenosis. (2020) (43)	**META-ANALYSIS:** Comparison of outcomes between Adults (< 65) and Older Adults (≥ 65) Four studies, 49 Adults vs 160 Older Adults	Analysis of 4 studies indicated that symptom improvements for Adults and Older Adults were significant from baseline, and no statistically significant difference was observed between the two age groups. These results illustrate that *mild* can be an effective treatment regardless of adult patient age.
Levy RM, Deer TR. Systematic safety review and meta-analysis of procedural experience using percutaneous access to treat symptomatic lumbar spinal stenosis. (2012) (44)	**META-ANALYSIS:** Systematic review of 373 patients, 32 sites All patients had failed conservative management and had symptomatic LSS with NC with HLF ≥ 2.5 mm as a predominant factor	1-year efficacy data showed statistically significant improvement in pain and mobility with excellent safety profile. **Mobility/Disability:** • ODI: 16.0-point improvement at 1-year **Pain Reduction:** • VAS: 3.9-point improvement at 1-year **Safety:** No reports of major device- or procedure-related AE
Schomer DF, Solsberg D, Wong W, Chopko BW. *mild* lumbar decompression for the treatment of lumbar spinal stenosis. (2011) (45)	**META-ANALYSIS:** 107 patients, 17 sites	Patients treated with *mild* Procedure demonstrated statistically significant symptomatic improvement over baseline. When compared to open surgery, *mild* efficacy is favorable and complication rates are much lower. **Mobility/Disability:** • ODI: 17.1-point improvement at 3-month **Pain Reduction:** • VAS: 3.9-point improvement at 3-month **Safety:** No device- or procedure-related serious complications

Article Title	Populations	Outcomes
Udeh BL, Costandi S, Dalton JE, Ghosh R, Yousef H, Mekhail N. The 2-year cost-effectiveness of 3 options to treat lumbar spinal stenosis patients. (2015) (26)	**HEALTH ECONOMICS:** Cost-utility Decision-analytic Model Medicare payer perspective using 2013 fee schedule was adopted to insure fair reliable comparison of the cost to render such treatment.	QALY (quality-adjusted life years) This study used a cost-utility decision-analytic model. Expected incremental costs and health benefits were compared with the standard of care. 1. *mild* strategy appears to be the most cost-effective ($43,760/QALY) 2. ESIs are the next best alternative ($81,518/QALY) 3. Laminectomy surgery was the least cost-effective ($125,985/QALY)
Wang JJ, Bowden K, Pang G, Cipta A. Decrease in health care resource utilization with *mild*. (2013) (46)	**HEALTH ECONOMICS:** Health Resource Utilization 22 patients Comparison of health care resource utilization before and after minimally invasive lumbar decompression (*mild*) procedure. Case series from Veteran's Administration health care system.	After *mild*, there was close to 45% reduction in time spent in specialty care and an almost fourfold decrease in number of interventional pain procedures performed on patients with LSS. Over half of the patients no longer required chronic pain management to treat their LSS symptoms. Not only is *mild* a reliable method to treat LSS, *mild* also appears to reduce the consumption of limited health care resources.
Jain S, Deer T, Sayed D, et al. Minimally invasive lumbar decompression: a review of indications, techniques, efficacy and safety. (2020) (16)	**REVIEW:** In-depth description of the *mild* Procedure and comprehensive examination of safety and efficacy.	*mild* has demonstrated excellent efficacy and safety in two randomized controlled trials, together with 11 other controlled clinical studies. With an established safety profile equivalent to ESIs, and efficacy superior to ESIs, *mild* can reasonably be positioned early in the treatment algorithm. Based on extensive review of the literature, robust safety and efficacy through 2 years, and in line with the minimally invasive spine treatment guidelines, *mild* should be considered as the first intervention after failure of conservative measures for LSS patients with LFH ≥2.5 mm showing signs/symptoms of neurogenic claudication.
Merkow J, Varhabhatla N, Manchikanti L, Kaye AD, Urman RD, Yong RJ. Minimally Invasive Lumbar Decompression and Interspinous Process Device for the Management of Symptomatic Lumbar Spinal Stenosis: A Literature Review. (2020) (47)	**REVIEW:** Review of 13 studies	Based on the available evidence, *mild* and Superion® are safe and modestly effective minimally invasive procedures for patients with symptomatic LSS. It is the authors' recommendation that these procedures may be incorporated as part of the continuum of treatment options for patients meeting clinical criteria.

Article Title	Populations	Outcomes
Lawrence MM, Hayek SM. Minimally invasive lumbar decompression: a treatment for lumbar spinal stenosis. (2013) (48)	**REVIEW:** Review of current literature regarding efficacy, safety, and cost effectiveness.	The recent literature shows that percutaneous lumbar decompression is a minimally invasive treatment option that affords a high level of safety, improved function, decreased pain scores, and is cost-effective.
Chen H, Kelling J. *mild* Procedure for Lumbar Decompression: A Review. (2012) (49)	**REVIEW:** Review of current literature regarding efficacy, safety, and cost-effectiveness.	Demonstrated a similar level of symptom relief and a significantly better safety profile with *mild* than with surgical treatments. Patients who undergo the procedure will have a faster recovery with significant improvement of their NC and pain-related issues with significantly lower rates of AE with more cost-effectiveness as compared to open surgical decompression with or without fusion.
Deer TR. Minimally invasive lumbar decompression for the treatment of spinal stenosis of the lumbar spine. (2012) (50)	**REVIEW:** Review of the technique and current literature regarding efficacy and safety.	Studies reviewed have been published in peer-reviewed articles; all showed positive correlated outcomes across all measures (ODI, VAS, ZCQ, SF-12v2, walking distance, and standing time), with durability thus far, mea¬sured to 1-year. In addition, studies have shown excellent safety results with no serious AE including blood loss requiring transfusion, infection, dural tear, or nerve injury.
Deer TR, Mekhail N, Lopez G, Amirdelfan K. Minimally invasive lumbar decompression for spinal stenosis. (2011) (51)	**REVIEW:** Review of the current literature regarding efficacy, safety, and cost-effectiveness.	*mild* Procedure can safely and effectively reduce pain, improve functionality, and minimally change spinal biomechanics and stability in LSS patients who have failed conservative treatment and who are not yet in need of, or who do not desire more invasive open surgical decompression procedures.

*ZCQ Patient satisfaction ≤ 2.5 indicates that the patient is satisfied with the procedure.
NPRS: Numeric Pain Rating Scale
ODI: Oswestry Disability Index
SF-12v2: SF-12® Health Survey
VAS: Visual Analog Scale
ZCQ: Zurich Claudication Questionnaire