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Supplemental nucleus pulposus allograft in patients with lumbar discogenic pain: results of a prospective feasibility study

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Abstract

Background Degeneration of the intervertebral disc is a significant source of chronic axial low back pain. Direct supplementation of degenerated nucleus pulposis (NP) tissue with intradiscally delivered allogeneic NP represents an opportunity to bridge the treatment gap between failed conservative care and spine surgery for patients with lumbar discogenic pain.

Methods Prospective, single-arm clinical study conducted at 6 sites in the US. The primary objective was to determine the magnitude of improvement in back pain severity and back function in patients with chronic lumbar discogenic pain at 12 months after a single intradiscal supplementation procedure using a commercially available NP allograft at up to two vertebral levels identified on magnetic resonance imaging. Back pain severity was evaluated using an 11-point numeric rating scale (NRS) and back function using the Oswestry Disability Index (ODI). Minimal clinically important difference (MCID) and substantial clinical benefit (SCB) were set at ≥ 30% and ≥ 50% over baseline, respectively. The patient acceptable symptom state (PASS) threshold for pain severity was ≤ 3.

Results Twenty-eight participants with a mean age of 44 ± 13 yrs. were enrolled and 22 provided 12-month outcomes. The average overall improvement in back pain severity was 43% through 12 months ($p < 0.001$). Approximately 64% (14 of 22) achieved the MCID in back pain at 12 months, with 55% (12 of 22) realizing SCB. Almost 60% (13 of 22) reported a 12-month back pain severity score of ≤ 3. The corresponding average decrease in ODI values was 50% ($p < 0.001$) with approximately 59% (13 of 22) of study participants achieving the MCID. At baseline approximately 82% (23 of 28) of participants reported severe or crippled back impairment compared to 18% (4 of 22) at 12 months ($p < 0.001$).

Conclusion The results of this study provide additional evidence that supplementation of the degenerated intervertebral disc with intradiscally delivered allogeneic NP is associated with clinically significant pain palliation and functional improvement.

Trial registration This trial was prospectively registered at ClinicalTrials.gov on December 30, 2021 (NCT05201287).

Keywords Nucleus pulposus, Allograft, Discogenic, Back pain, Intradiscal, Degenerative disc disease

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Introduction

The unique morphology, structure and function of the intervertebral disc is the result of the synergistic capacities and influences of an inner gelatinous nucleus pulposus (NP) and a fibrous outer annulus [1–4]. In the healthy disc, there is abundant proteoglycan content in the form of aggrecan which has the dual function of providing substantial load bearing capacity and inhibiting nerve and vascular ingrowth [5–7]. Consequently, the young spine is effectively aneural and avascular to support the most efficient biomechanical function [8, 9].

Unfortunately, the adult human spine remains healthy for a limited duration with disc degeneration commencing as early as the third decade of life [10–14]. With degeneration, the normally highly hydrated intervertebral disc becomes less efficient in its ability to absorb physiological loads [15, 16]. This is due, in large part, to the inability of the nucleus to bind water under compression as collagen fibers become disorganized [17, 18]. Loss of mechanical cushioning resulting from reduced proteoglycan content and diminishing pressure within the NP invariably leads to reduced disc height [19, 20]. Loss of disc integrity precipitates a vicious cycle of advancing degeneration that eventually involves the posterior facet joints which can cause arthrosis, hypertrophy, and possible compression of neural elements [12, 21, 22].

Degeneration of the intervertebral disc is recognized as a significant source of chronic axial low back pain [23–25]. The specific diagnostic characteristics of lumbar discogenic pain associated with degenerative disc disease have been established resulting in the recent issuance of universal diagnostic coding (ICD-10-CM) [26–28]. Consequently, there is a burgeoning pipeline of minimally invasive intradiscal therapies being developed and evaluated for the treatment of lumbar discogenic pain [29–32].

This study was undertaken to determine whether supplementation of degenerated disc tissue with a commercially available allogeneic NP product can ameliorate back pain and functional impairment in patients with lumbar discogenic pain [33]. Herein, we summarize patient reported outcomes at 12 months following treatment with NP allograft.

Patient & methods

Study design and eligibility criteria

This was a prospective, single arm, multicenter clinical study conducted at 6 sites in the US. The primary objective was to determine the magnitude of improvement in back pain severity and back function in patients with chronic lumbar discogenic pain treated with intradiscally delivered allogeneic NP at up to two vertebral levels (L1-S1) and followed for 12 months. This analysis allowed for the evaluation of the durability of single dose treatment and provided the basis for estimations of the sample size necessary for future controlled trials. The number of enrolled participants was based on recommendations of sample size requirements for feasibility studies [34].

Study eligibility criteria included age ≥ 18 years; body mass index (BMI) of < 35 kg/m^2; and chronic lumbar discogenic pain of ≥ 6 months duration unresponsive to conservative management. This included oral pain medication [analgesics, steroids and/or non-steroidal anti-inflammatory drugs (NSAIDs)], structured physical therapy or exercise program prescribed by physical therapist, chiropractor provider or physician specifically for the treatment of low back pain, and epidural steroid injections and/or facet injections/selective nerve blocks.

Discogenic pain was defined using established signs and symptoms at physical exam [26]. Specifically, all patients demonstrated axial midline low back pain in the absence of lower extremity motor/sensory/reflex changes with or without non-radicular/non-sciatic referred leg pain. Additional inclusion criteria included sitting intolerance, pain with forward flexion, and positive pain provocation using the sustained hip flexion maneuver [35]. Study eligibility required a baseline back pain severity score of ≥ 6 on an 11-point (0 to 10) numeric rating scale (NRS) and a back function score of ≥ 40 to ≤ 80 points on the Oswestry Disability Index (ODI). Moderate degeneration of up to two intervertebral discs from L1 to S1 was confirmed by magnetic resonance imaging (MRI) based on a modified Pfirrmann grade 3–7, with or without Modic changes (grades 1 or 2) [36, 37]. Patients with other types/sources of low back pain such as facetogenic, vertebrogenic, neurocompressive, sacroiliac or radicular pain were excluded. Patients with a contained disc protrusion > 5 mm or disc extrusion, or spondylolisthesis > 5 mm were also excluded. Confirmative discography was not required.

Intervention

The target intervertebral disc(s) was injected with a single bolus dose of VIA Disc NP (VIVEX Biologics, Inc., Miami, FL USA). This commercially available product consists of human allogeneic NP processed from donated cadaveric disc tissue, lyophilized, and morselized to particles ≤ 106 µm in size. The morselized NP tissue is then aliquoted into a volume size of 100 mg (± 10%), aseptically sealed, and terminally sterilized via electron-beam irradiation. The tissue is reconstituted at the time of the procedure with 2 ml of sterile saline for delivery into the target intervertebral disc(s). The micronized NP when reconstituted has a high viscosity but remains flowable through a 20G cannula.

The procedure is undertaken with the patient under moderate conscious sedation using a local anesthetic

at the injection site. Fluoroscopic guidance is used to ensure correct needle placement. Briefly, a spinal needle is advanced through Kambin's triangle into the center of the intervertebral disc. A single intradiscal dose of approximately 100 mg of VIA Disc NP mixed with sterile saline (0.9% sodium chloride) is administered to the affected disc(s) according to the product Instructions for Use (IFU). Following the procedure, patients can return home the same day and can resume normal activities the following day.

Post-surgical follow-up to capture patient reported outcomes and evaluate any possible adverse events was compulsory for all patients at 4 weeks post-procedure. Further clinical follow-up was conducted at 3, 6 and 12 months.

Outcome measures and analysis

Patient reported outcomes, NRS and ODI, were analyzed per-protocol and are presented as means (95% CI) at baseline and at each followup interval. The overall improvement in clinical outcomes over baseline was assessed using repeated measures analysis of variance (ANOVA). The difference between baseline values and the 12-month endpoint was confirmed using the paired t-test, 2-tailed. NRS and ODI 12-month responder rates were calculated based on a minimal clinically important difference (MCID) of ≥30% and substantial clinical benefit (SCB) of ≥50% improvement over baseline [38, 39]. Additionally, baseline and 12-month ODI values were categorized by functional impairment severity as minimal (0–20), moderate (21–40), severe (41–60), and crippled (61–80) and compared using the Wilcoxon signed rank test. The 12-month responder rate for NRS patient acceptable symptom state (PASS) score was also computed with a success threshold set at ≤3 [40, 41]. Cross-tabulations were used to explore the association between all patient reported outcomes and baseline Pfirrmann grade (3–7), numbers of levels treated (1 vs. 2) and presence/absence of Modic changes using Fisher's exact test, 2-tailed. All analyses were conducted using SAS 9.4 M8 (Cary, NC, USA). Adverse events were captured at each post procedure followup interval.

Results

Fifty-four patients were prescreened for potential study eligibility based on case history and 28 participants met all inclusion and exclusion criteria and were enrolled as study participants with 22 subjects providing 12-month patient reported outcomes. Table 1 provides background characteristics for all patients. Table 2 provides mean values for back pain and back function at each followup interval.

Table 1 Background characteristics

Characteristic	Patients ($n = 28$)
Female, n (%)	12 (43)
Age, mean (SD) yrs	44 (13)
BMI, mean (SD) kg/m2	27 (4.7)
Number of treated levels, n (%)	
I	12 (43)
II	16 (57)
Levels treated, n (%)	
L4-L5/L5-S1	10 (35.7)
L4-L5	6 (21.4)
L5-S1	5 (17.9)
L2-L3/L5-S1	2 (7.1)
L3-L4/L4-L5	2 (7.1)
L2-L3/L3-L4	1 (3.6)
L3-L4	1 (3.6)
L3-L4/L5-S1	1 (3.6)
Pfirrmann grade, n (%)	
3	9 (32.1)
4	9 (32.1)
5	2 (7.1)
6	4 (14.3)
7	4 (14.3)
Modic changes, n (%)	
0	16 (57.1)
1	1 (3.6)
2	11 (39.3)
Oswestry (ODI), mean (SD)	53.3 (14.5)
Back pain (NRS), mean (SD)	7.1 (1.6)

Study participants experienced an average overall improvement in back pain severity of 43% across all post-procedure followup intervals ($p < 0.001$). Figure 1 provides the mean (95% CI) NRS values at each interval reflecting a statistically significant decrease from baseline (7.1, 95% CI [6.5, 7.7]) to 12 months (3.8, 95% CI [2.5, 5.1]) ($p < 0.001$). Approximately 64% (14 of 22) of participants achieved or exceeded the MCID in back pain at 12 months, with 55% (12 of 22) realizing SCB reflecting a ≥ 50% improvement over pre-injection pain levels. Almost 60% (13 of 22) of participants reported a 12-month back pain severity score of ≤3.

There was corresponding clinical improvement in back function scores across all post-procedure followup intervals with an average decrease in ODI values of 50% ($p < 0.001$) (Fig. 2). ODI values improved from (53, 95% CI [48, 59]) at baseline to (24, 95% CI [15, 33]) at 12 months ($p < 0.001$). By the 12-month followup visit, approximately 59% (13 of 22) of study participants reported a MCID in back function, reflecting an improvement of at least 30% compared

Table 2 Mean (± SD) Back pain and back function values by Followup Interval

Outcome	Baseline ($n = 28$)	Month 1 ($n = 28$)	Month 3 ($n = 27$)	Month 6 ($n = 28$)	Month 12 ($n = 22$)
Back Pain[a], mean (SD)	7.1 (1.6)	3.9 (2.7)	3.3 (2.8)	3.0 (2.9)	3.8 (2.9)
Back Function[a], mean (SD)	53 (15)	28 (20)	24 (19)	23 (20)	24 (20)

[a] Numeric rating scale (11-pt NRS) for back pain; Oswestry Disability Index (ODI) for back function

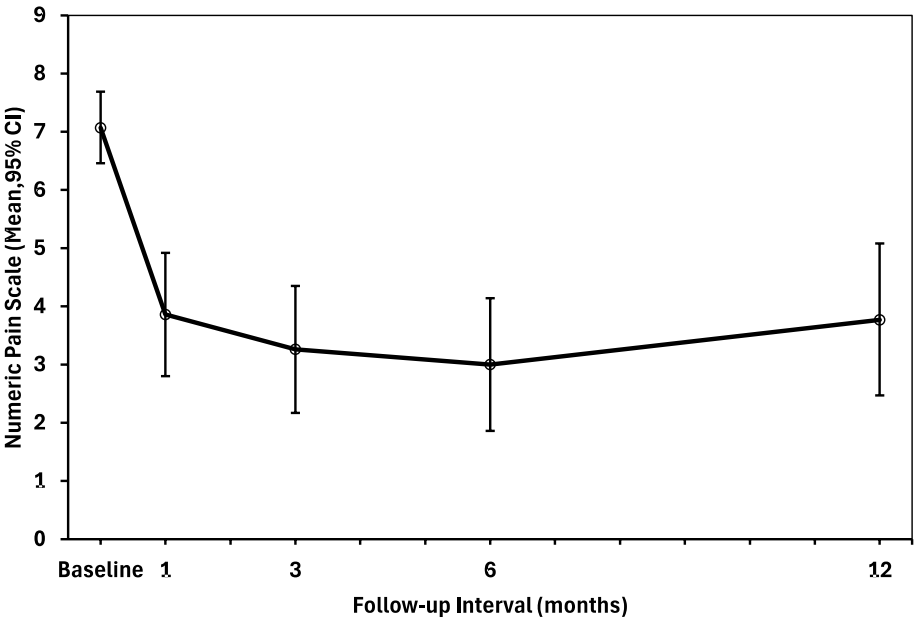

Fig. 1 Line graph showing an average overall longitudinal improvement of 43% in back pain severity scores through 12 months of post-procedure followup ($p < 0.001$). Mean NRS values are 7.1 (baseline, $n = 28$), 3.9 (1 month, $n = 28$), 3.3 (3 months, $n = 27$), 3.0 (6 months, $n = 28$) and 3.8 (12 months, $n = 22$)

to pre-procedural levels. Figure 3 compares the baseline and 12-month distributions in ODI functional impairment severity scores. At baseline approximately 82% (23 of 28) of participants reported that their back impairment was severe or crippled. By 12 months, the percentage of patients reporting severe/crippled impairment was reduced to 18% (4 of 22), and the difference in the distributions was statistically significant ($p < 0.001$).

There was no association between modified Pfirrmann grade, number of levels treated or presence/absence of Modic changes and any of the pain or functional outcomes (range: $p = 0.12$ to 0.43).

There were 3 adverse events categorized as possibly related to the NP product (low back pain, back muscle spasms, thigh pain) and 3 categorized as possibly related to the procedure (low back pain, back muscle spasms, thigh pain). All of these events were considered mild or moderate in severity and have been resolved. There was 1 serious adverse event (injection site inflammation), which was categorized as definitely related to the procedure, and also subsequently resolved. There were no secondary surgical interventions.

Discussion

NP replacement or supplementation has been recognized as a viable approach to the treatment of intervertebral disc degeneration [42]. The NP is largely composed of proteoglycans which have a strong affinity for water. This ability to bind water is responsible for the mechanical cushioning properties of the disc [1, 7]. If these proteoglycans are depleted as occurs with disc degeneration, the disc becomes more rigid, thinner and less compliant [4]. It is likely that there is no better source of replacement proteoglycans than disc material itself which can be obtained and processed with minimal manipulation as an allograft from cadaveric donor sources.

We found that a single intradiscal administration of allogeneic NP provides clinically significant relief of lumbar discogenic pain in approximately two thirds of subjects 12 months after treatment. Importantly, almost 60% of participants in this study reported a 12-month

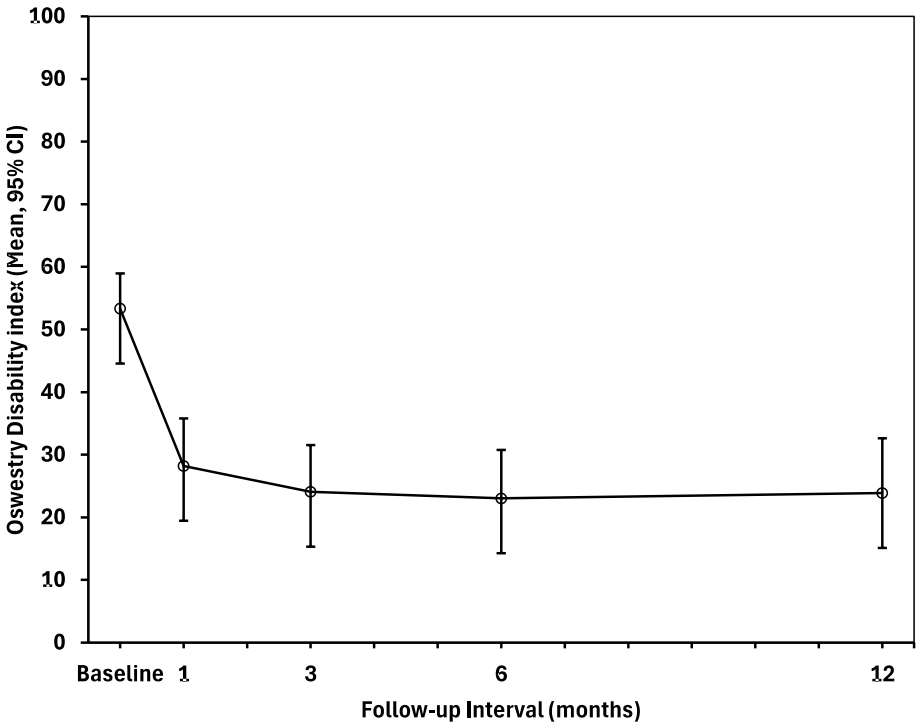

Fig. 2 Line graph showing an average overall longitudinal improvement of 50% in back function scores through 12 months of post-procedure followup ($p < 0.001$). Mean ODI values are 53 (baseline, $n = 28$), 28 (1 month, $n = 28$), 24 (3 months, $n = 27$), 23 (6 months, $n = 28$) and 24 (12 months, $n = 22$)

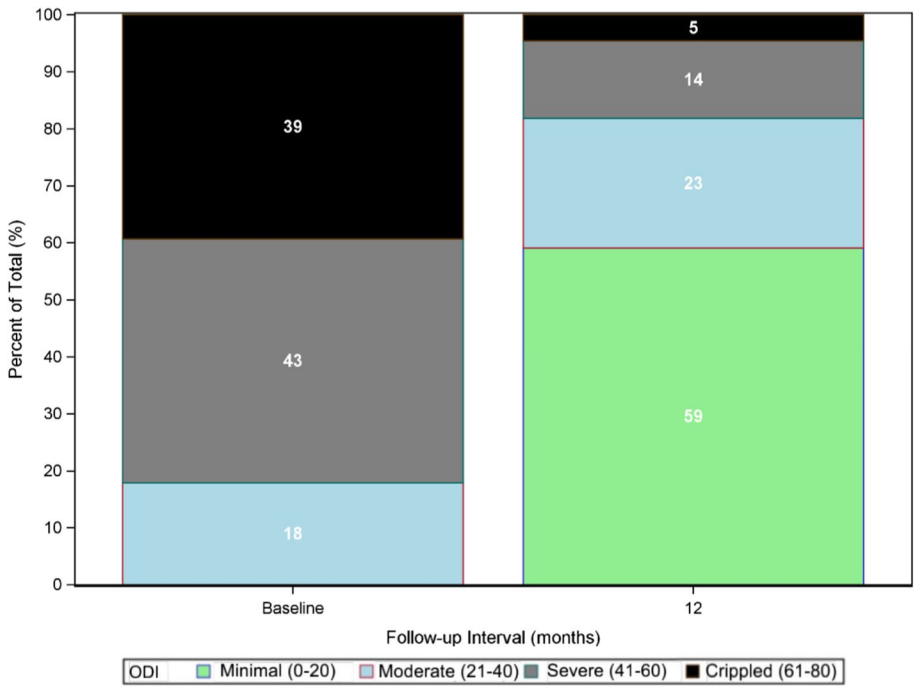

Fig. 3 Comparative distributions of Oswestry Disability Index (ODI) functional impairment categories at baseline and 12 months post-procedure. The difference in these distributions was statistically significant ($P < 0.001$)

post-procedure pain severity score ≤ 3 reflecting substantial symptom amelioration. This threshold, the patient acceptable symptom state or PASS, has been shown to be an important clinical metric for differentiating whether a patient truly feels well as opposed to simply feeling better [41, 43, 44].

The ability to effectively manage chronic lumbar discogenic pain in this patient group for a one-year duration with a single intradiscal NP procedure translated to correspondingly durable improvements in back function. We noted a demonstrable shift in ODI functional impairment categories with almost 60% of participants reporting minimal back impairment at 12 months, up from 0% at study initiation.

These findings confirm and extend our previous 6-month followup report of this study group [33]. We noted no further degradation in treatment efficacy between 6 and 12 months. Lengthening the duration of treatment efficacy has important implications for the potential of intradiscal NP treatment in delaying more invasive surgical options such as disc arthroplasty or instrumented spine fusion. Therefore, it remains essential that this study group continue to be followed longitudinally to assess the extent of treatment efficacy.

There were no noteworthy associations between baseline disc morphology such as Pfirrmann grade or the presence of vertebral bone marrow signal intensity changes at the disc/endplate interface and clinical outcomes. This suggests that the overall 12-month treatment effect of intradiscal NP allograft is similar across all subgroups of patients, including those with or without imaging evidence of Modic changes. We also found that the number of levels treated did not predict outcomes. For example, of the 16 participants who achieved the MCID for back pain severity, 8 were treated at one level and 8 had two treated levels. This finding bodes well for patients where disc degeneration spans multiple lumbar vertebral levels.

The limitations of this study include a small sample size, one serious procedure-related adverse event, lack of a concurrent active or placebo control group, approximately 20% loss to followup at 12 months and absence of followup imaging evidence of potential disc structural changes. These issues limit the generalizability of these findings. Subsequent investigations should address these shortcomings.

Conclusion

There has been renewed interest in the intervertebral disc as a target for minimally invasive intradiscal treatments aimed at ameliorating lumbar discogenic pain [29]. Minimally invasive intradiscal treatments represent an enormous opportunity to improve spine care by delaying or avoiding surgical intervention and enhancing quality of life in patients with discogenic back pain. The results of this study provide additional evidence that supplementation of the degenerated intervertebral disc with intradiscally delivered allogeneic NP is associated with clinically significant pain palliation and functional improvement. This minimally manipulated, off-the-shelf product provides a nonsurgical option that can be delivered through a standard spinal needle under fluoroscopic guidance without altering the normal anatomy of the spine. We encourage further research to ascertain whether clinical adoption of this procedure may help to bridge the current treatment gap for patients experiencing chronic moderate to severe lumbar discogenic pain.

Abbreviations

NP	Nucleus pulposus
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
US	United States
BMI	Body mass index
NRS	Numeric rating scale
ODI	Oswestry disability index
MRI	Magnetic resonance imaging
CI	Confidence interval
ANOVA	Analysis of variance
MCID	Minimal clinically important difference
SCB	Substantial clinical benefit
PASS	Patient acceptable symptom state

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Authors' contributions

D.P.B, T.T.D. and K.A. contributed to study design. D.P.B., T.T.D., K.A., R.K.N., M.J.D., S.C, E.S.Y., and J.W.F. enrolled patients and collected data. D.P.B, T.T.D., K.A., R.K.N., M.J.D., S.C., E.S.Y., J.W.F., J.E.B., and N.M. contributed to data interpretation, manuscript development, and content approval. D.P.B., T.T.D., K.A., R.K.N., M.J.D, J.E.B., and N.M. were publication committee members and made final decision about data submissions.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

All patients provided informed consent. The study was reviewed and approved by an independent institutional review board (IRB), Sterling IRB (Atlanta, GA, USA). The trial was conducted in accordance with the Declaration of Helsinki and prospectively registered at ClinicalTrials.gov on December 30, 2021 (NCT05201287).

Consent for publication

Not applicable.

Competing interests

DPB is a scientific advisor to Vivex Biologics; received grants or contracts from Medtronic, Medical Metrics, Avanos, Relievant, Boston Scientific, Stryker, Sollis Pharmaceuticals, Simplify Medical, Lenoss Medical, Spine BioPharma, Eliem Therapeutics, Smart Soft, Tissue Tech, Vivex, Stratus Medical, Restorative Therapies, Kolon, TissueGene, Companion Spine, DiscGenics; royalties from VIVEX and IZI; consulting fees from Medtronic, Spineology, Merit Medical, Johnson & Johnson, IZI, Techlamed, Peterson Enterprises, Medical Metrics, Avanos, Boston Scientific, Sollis Pharmaceuticals, Simplify Medical, Stryker, Lenoss Medical, Spine BioPharma, Piramal, ReGelTec, Nanofuse, Spinal Simplicity, Pain Theory, Spark Biomedical, Micron Medical Corp, Bronx Medical, Smart Soft, Tissue Tech, RayShield, Stayble, Thermaquil, Vivex, Stratus Medical, Genesys, Abbott, Eliquence, SetBone Medical, Amber Implants, Cerapedics, Neurovasis, Varian Medical Systems, Companion Spine, DiscGenics, Discure, SpinaFX, PainTEQ; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Artio, Sophiris, Eleven Biotherapeutics, Flow Forward, Lenoss Medical, ReGelTech, Spark Biomedical; and support for attending meetings and/or travel from Medtronic, ReGelTec, Nanofuse, Talosix, Spinal Simplicity, Pain Theory, Spark Biomedical, Smart Soft, Tissue Tech, Bronx Medical, Thermaquil, Vivex, Genesys, SetBone Medical, Amber Implants, Cerapedics, SpinaFX. TTD received consulting fees from Abbott, Boston Scientific, Biotronik; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Abbott, Boston Scientific, Biotronik. RKN received consulting fees from Vivex, Boston Scientific, Ferring Pharmaceuticals. MJD is a scientific advisor to Vivex Biologics; received grants or contracts from Spine BioPharma, Restorative, Novartis, SPR, Saol, Paradigm; royalties from Springer; patents from iSpine Ingenuity. SC received grants or contracts from the Cleveland Clinic. ESY received consulting fees from Neurovasis. JWF received support for attending meetings and/or travel from Medtronic, Stryker, Nevro, Seattle Science Foundation, HMP Global, American Society of Neuroradiology, American Society of Spine Radiology; received stock or stock options from BackTable LLC. JEB received support for medical writing from Vivex Biologics; consulting fees from Vivex. NM received consulting fees from Vivex Biologics. The other author, KA, reports no additional conflicts of interest.

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