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P-15 Peptide Enhanced Bone Graft in Transforaminal Lumbar Interbody Fusion

A Randomized, Controlled, Investigational Device Exemption Study Demonstrating Improved Composite Clinical Success

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Study Design. Prospective, multicenter, single-blind, randomized, controlled pivotal study.

Objective. To evaluate whether P-15L (PearlMatrix P-15 Peptide Enhanced Bone Graft) is noninferior in effectiveness to local autograft when applied in single-level instrumented transforaminal lumbar interbody fusion (TLIF).

Summary of Background Data. P-15L, an FDA-designated Breakthrough Drug-Device, is a composite drug-device combination bone graft containing P-15, a 15-amino acid polypeptide,

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The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

The protocol received Institutional Review Board approval in accordance with the Declaration of Helsinki and the International Council for Harmonization Guideline for Good Clinical Practice. All patients provided written informed consent, and HIPAA regulations were followed. The devices/drugs that are the subject of this manuscript have been FDA-approved through a Premarket Approval application in the United States and used as indicated in this study.

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which enhances cell binding, proliferation, and differentiation, resulting in bone formation.

Materials and Methods. Skeletally mature patients, aged 22 to 80 years, with degenerative disc disease (DDD) were randomized 1:1 to P-15L (investigational) or to the local autograft (control) during single-level TLIF with a polyetheretherketone (PEEK) cage and supplemental pedicle screw fixation. The primary outcome was composite clinical success (CCS) at 24 months, defined as: no index level secondary surgical procedures; achievement of fusion; ≥15-point improvement in Oswestry low back pain disability questionnaire (ODI) from baseline; no new or worsening persistent neurological deficit relative to baseline; and no device-related serious adverse events (SAEs).

Results. A total of 290 patients were enrolled at 33 sites: 141 (48.6%) received P-15L, and 149 (51.3%) received local autograft. P-15L was noninferior ($P<0.0001$) and superior ($P=0.002$) to autograft with respect to CCS, with 55.5% of the investigational group achieving composite clinical success compared with 37.5% of the control group. P-15L had a 25.8% higher fusion rate as compared with autograft for the CCS at 24 months (84.3% *vs.* 58.5%, respectively). Device-related SAE rates were similar in both groups.

Conclusion. P-15L was superior to local autograft in achieving clinical success at 24 months. Furthermore, P-15L produced a significantly higher fusion rate as compared with autograft. No meaningful clinical differences were found in the incidence of device-related SAEs. P-15L appears to be a safe and effective option for TLIF.

Level of Evidence. Level I.

Key Words: TLIF, fusion, P-15, peptide, bone graft, autograft, ABM/P-15 matrix, PearlMatrix

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Spinal fusion surgeries are often performed to alleviate pain and enhance function in degenerative spine disease. The aging population, lifestyle factors, and technological advancements have led to a significant increase in spinal fusion surgeries and as a result increased health care costs.[1–6] Clinical success in spinal fusion surgery is influenced by numerous factors, including the patient's overall health; degree of spinal instability; as well as specific comorbidities, including body mass index, diabetes, and nicotine use.[7] These comorbidities have been shown to impair fusion, thereby increasing the risk of pseudarthrosis.[8–12] Long-term stability has been correlated with attaining a solid bony fusion, which is often dependent on the effectiveness of the bone graft.[7]

Transforaminal lumbar interbody fusion (TLIF) is an established treatment for lumbar degenerative conditions unresponsive to nonoperative therapies. Anterior column support through interbody cages plays a primary role in mechanical support and stability, as well as in achieving fusion.[13,14]

Solid incorporation of the cage with bridging fusion is essential to confirm secure mechanical stability.[13,15] Of the bone graft materials available, iliac crest autologous bone grafts are considered the "gold standard" due to their superior integration and bone formation capabilities. However, its harvest results in increased patient morbidity, such as the risk of infection, fracture, and pain, and there is a limited quantity.[16–18] Alternatively, local autograft is used in spinal fusion and has been shown to be effective compared with iliac crest bone grafts.[19–22] The amount of local autograft is limited and can be insufficient to achieve healing, leading surgeons to use alternative biomaterial substitutes, most of which are passive osteoconductive scaffolds.[23,24] Presently, there is a lack of high-level clinical safety evidence for bone grafting material and even less efficacy data on use in humans.[25] Three FDA-approved Class III bioactive drug-device combination bone grafts are available for use in spinal fusion: rhBMP-2 (InFuse; Medtronic Sofamor Danek, Memphis, TN), ABM/P-15 (i-FACTOR; Cerapedics Inc., Westminster, CO), and P-15L (PearlMatrix, Cerapedics Inc.), the investigational treatment evaluated in this study. Both ABM/P-15 and P-15L utilize P-15 peptide technology, but only P-15L is FDA approved for use during transforaminal lumbar interbody fusion (TLIF) procedures.

P-15L, an FDA-designated Breakthrough Device, is a composite bone graft consisting of an anorganic bone mineral (ABM) and P-15, a 15-amino acid polypeptide, simultaneously enhancing the production and remodeling of native bone.[17,26–34] The purpose of this study was to demonstrate that P-15L is a safe and effective alternative to local autologous bone graft when applied in instrumented TLIF in patients with degenerative disc disease (DDD) with up to Grade I spondylolisthesis. The primary hypothesis was that the investigational device (P-15L) is noninferior to local bone autograft control with respect to composite clinical success (CCS) at month 24.

MATERIALS AND METHODS

This study was a prospective, multicenter, single-blind, randomized (1:1), controlled, pivotal study enrolling patients at 33 sites across the United States. Blocked randomization in a 1:1 ratio was performed within the investigational site and stratified by risk group (higher risk *vs.* normal risk). Higher-risk subjects had at least one of the following risk factors: type 2 diabetes, nicotine use, and/or obesity (BMI ≥ 30 kg/m^2).[8–12] The protocol received Institutional Review Board approval in accordance with the Declaration of Helsinki and the International Council for Harmonization Guideline for Good Clinical Practice. All patients provided written informed consent, and HIPAA regulations were followed. The study was registered on www.clinicaltrials.gov (NCT03438747).

Patients included were skeletally mature adults 22 to 80 years old (inclusive) presenting with back and leg pain, Oswestry low back pain disability questionnaire (ODI) score of ≥35, and a planned single-level TLIF (L2-S1) after ≥6 months of failed nonoperative treatment.

Included patients had radiographically determined spinal origin of pain according to ≥ 1 of the following: degenerated/dark disc on MRI; instability (angulation $\geq 5°$ and/or translation ≥ 3 mm on flexion/extension radiographs); osteophyte formation; ligamentous thickening; decreased disc height compared with adjacent levels; and disc herniation. Key exclusion criteria were infection; autoimmune or metabolic disease affecting bone formation (*e.g.* osteoporosis, osteopenia, osteomalacia); use of medication for osteoporosis or other medications that may interfere with fusion (*e.g.* steroids, or has received drugs that interfere with bone metabolism within two weeks of surgery); circulatory, cardiac, or pulmonary disease; active malignancy; previous spinal fusion at the index level; isthmic or grade ≥ 2 spondylolisthesis; pregnant/planning to become pregnant; and a history of substance abuse (recreational drugs, alcohol) within the past two years.

Surgical Procedure

Either open or minimally invasive TLIF procedures were performed using any FDA-cleared PEEK cage and supplemental internal pedicle screw fixation systems cleared by the FDA. In all cases, surgeons performed a laminectomy and neural decompression as indicated based on the patient's symptoms. This was consistent with their routine clinical practice. Specifically, for the TLIF procedure, discectomy was performed with removal of the disc material and preparation of the endplates; if necessary, an osteophytectomy was undertaken. Sizing trial tools were used to determine the appropriate cage. Once the optimal cage size was selected, its central cavity was filled with bone graft, and the PEEK cage was inserted into the prepared disc space. Final positioning of the construct was confirmed radiographically before closure. The interbody space was grafted with either P-15L (investigational) or local autologous bone (control) harvested during the procedure. If the amount of local autologous bone was deemed insufficient, a cancellous allograft chip substitute was allowed as a graft extender. Facet joint decortication was allowed, but no additional graft material could be applied in the posterolateral gutters or the facets. Operative variables recorded include the treatment level, surgical time, estimated blood loss, and anesthesia time.

Outcome Measures

Demographics and preoperative assessments were collected at screening. The primary effectiveness endpoint was Month 24 CCS, a measure comprising five clinical endpoints. A composite endpoint provides a multidimensional assessment of clinical benefit incorporating radiographic, functional, and safety measures, and is consistent with prior study methodologies and FDA guidance. All five of the following endpoints had to be met for a patient to be categorized as achieving CCS: (1) no secondary surgical procedure (SSP) at the index level through month 24, defined as a revision, removal, reoperation, or supplemental fixation. Index-level SSPs included any adjustments to the index level, even for surgeries treating adjacent-level disease. (2) Achievement of fusion by month 24, defined as continuous bridging of mature bone from endplate to endplate with no intervening fractures or discontinuities using high-resolution thin-slice computed tomography (CT) scans (1 mm slices with 1 mm index on axial, sagittal, and coronal reconstructions).[35,36] Continuous bridging bone needed to be visible on at least two contiguous slices or two orthogonal planes to be considered fused. Once fusion was radiographically confirmed, it was assumed that fusion was maintained for all subsequent time points. Lumbar CT fusion status was interpreted by two independent, blinded, board-certified, fellowship-trained, musculoskeletal/neuroradiologists at a centralized imaging lab (Medical Metrics Inc., Houston, TX); disagreements were resolved by a third independent, blinded radiologist. (3) Having ≥ 15-point improvement in ODI from baseline to month 24.[37–40] (4) Having neurological success defined as no new or worsening, persistent sensory or motor deficit from baseline to month 24. The blinded evaluation was performed by a physician experienced in neurological lumbar DDD evaluations. (5) No device-related serious adverse events (SAEs).

Adverse events (AEs), regardless of relatedness to the investigational bone grafts, were fully tracked. AEs were defined as any unfavorable medical occurrence, unintended disease, injury, or clinical signs (including abnormal laboratory findings) in the study participants. SAEs were defined as a more severe type of AE resulting in death; were life-threatening; required inpatient or prolonged hospitalization; caused significant disability or incapacity or required intervention to prevent permanent life-threatening illness or injury or permanent impairment; or led to fetal distress, fetal death, or congenital abnormality/birth defect. The AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 21.0. All safety outcomes were reviewed by a Data and Safety Monitoring Board (DSMB) composed of two independent spine surgeons and a statistician. The DSMB classified adverse events, including secondary surgeries and those related to the bone graft (device-related) or TLIF procedure (procedure-related), as unrelated, possibly related, probably related, or definitely related.

Data Analysis

The primary prespecified study hypothesis was that P-15L is noninferior to local bone autograft with respect to CCS at 24 months. A noninferiority margin of 12.5% was specified. The null hypothesis that the probability of achieving Month 24 CCS was $\geq 12.5\%$ smaller among subjects treated with P-15L compared with control was tested at a one-sided type 1-error rate of 0.05 using a Mantel-Haenszel stratified χ^2 test, stratifying on risk group. If noninferiority was demonstrated, the null hypothesis that the probability of achieving Month 24 CCS was not larger among subjects treated with P-15L compared with controls was tested using a one-sided type 1-error rate of 0.0125. The reduced type 1 error rate was used to control the overall type 1 error to no more than 0.025 when testing superiority in terms of Month 24 CCS and in terms of faster time-to-fusion (the latter results are reported in a companion manuscript).[41] To allow for 80% power to reject the primary null hypothesis and a 15% loss to follow-up, a sample size of 290 patients was targeted for enrollment. The reported analysis is based on the type of bone graft received (Fig. 1).

RESULTS

The analysis included 290 patients; 141 (48.6%) patients received the investigational P-15L and 149 (51.3%) patients received the autograft control; with 119 (85.6%) patients in the investigational group and 128 (86.5%) patients in the control group available for the primary effectiveness endpoint (Month 24 CCS). A total of 65.0% of patients in the investigational group and 81.1% in the control group received >8 mL of the designated bone graft material. Both groups had similar demographics and baseline characteristics (Table 1). The majority of the population (58.9% of the investigational and 60.4% of the control groups) had at least one risk factor [nicotine use, obesity (BMI ≥ 30 kg/m^2) or type 2 diabetes] for pseudoarthrosis at randomization and were considered the higher-risk population. Operative characteristics were similar between treatment groups (Table 2). Both groups had a higher percentage of open procedures and index procedures at L4-L5.

At 24 months, 55.5% (66/119) of the P-15L group and 37.5% (48/128) of the autograft group achieved CCS (difference 18%) (Table 3). P-15L was both noninferior ($P<0.0001$) and superior ($P=0.002$) to autograft with respect to CCS. In addition, 84.3% (107/127) of patients in the P-15L group and 58.5% (76/130) of the autograft group achieved fusion in the CCS measure at 24 months (difference 25.8%). There were no significant differences between treatment groups with respect to ODI improvement, neurological deficits (motor and sensory), and serious device-related AEs.

Eighty patients (56.7%) in the investigational group and 59 patients (39.6%) in the control group had ≥ 1 TLIF procedure-related AE. Compared with the control, the investigational treatment had a significantly higher proportion of patients with TLIF procedure-related AEs (difference = 17.1%) and procedure-related SAEs (difference = 12.8%). In contrast, the differences in percentages

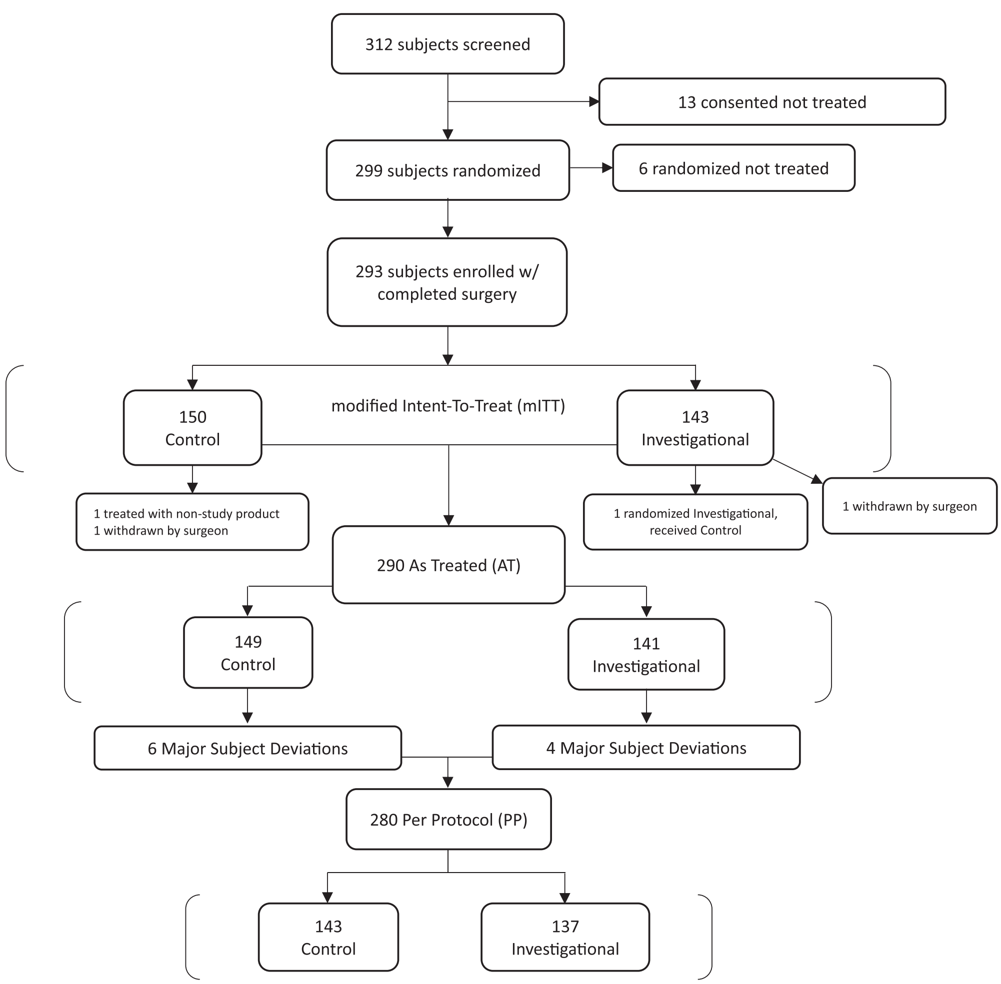

Figure 1. CONSORT flow diagram illustrating participant enrollment, group allocation, and analysis populations for the investigational (P-15L) *versus* control (autograft) groups. Study findings are based on the As Treated (AT) population.

TABLE 1. Patient Demographics

Parameters	P-15L (N = 141), n (%)	Autograft (N = 149), n (%)	*P**
Age at surgery (yr)			0.523
Mean (SD)	58.8 (12.3)	59.6 (10.9)	
Range	26–80	30–79	
Sex			0.548
Male	66 (46.8)	75 (50.3)	
Female	75 (53.2)	74 (49.7)	
Race†			
White (Caucasian)	135 (95.7)	134 (89.9)	0.056
Black or African American	6 (4.3)	13 (8.7)	0.124
Asian	0	1 (0.7)	—
American Indian/ Alaskan Native	0	1 (0.7)	—
BMI (kg/m^2)			0.942
Mean (SD)	31.2 (6.5)	31.2 (5.8)	
Range	16.4–49.7	21.6–47.8	
Higher risk‡			0.790
Yes	83 (58.9)	90 (60.4)	
Diabetes type 2			
Yes	26 (18.4)	29 (19.5)	—
Nicotine use§			
Yes	16 (11.3)	23 (15.4)	—
Obesity (BMI $\geq$ 30 kg/m^2)			
Yes	71 (50.4)	71 (47.7)	—

*Descriptive *P*-values from *t* test for continuous variables and χ^2 test for categorical variables.

†Respondents were asked to check all that apply, and so individual categories are evaluated separately.

‡Defined as having 1 or more of the following risk factors: nicotine use, obesity (BMI $\geq$ 30 kg/m^2), and/or type 2 diabetes at the time of randomization.

§Cigarettes, vaping, patches, and/or chewing tobacco.

BMI indicates body mass index; N, total number of patients with available data; n, number of patients meeting endpoint.

TABLE 2. Surgery and Operative Characteristics

Parameter	P-15L (N = 141), n (%)	Autograft (N = 149), n (%)	*P**
Surgical procedure			0.179
Open	83 (58.9)	76 (51.0)	
Minimally invasive	58 (41.1)	73 (49.0)	
Treatment level, n (%)			0.297
L1-L2	0	1 (0.7)	
L2-L3	6 (4.3)	2 (1.3)	
L3-L4	12 (8.5)	20 (13.4)	
L4-L5	88 (62.4)	88 (59.1)	
L5-S1	35 (24.8)	38 (25.5)	
Facet joint decorticated			0.281
Yes	91 (64.5)	105 (70.5)	
Surgical time (min)			0.413
Mean (SD)	173.1 (51.7)	178.2 (54.6)	
Range	71.0–382.0	79.0–360.0	
Estimated blood loss (mL)			0.538
Mean (SD)	146.2 (144.1)	157.2 (160.9)	
Range	10.0–1100.0	5.0–1000.0	
Anesthesia time (min)			0.515
Mean (SD)	238.6 (60.0)	243.3 (61.1)	
Range	114.0–480.0	160.0–461.0	

*Descriptive *P*-values from a χ^2 test or the Student *t* test for categorical and continuous variables, respectively.

N indicates the total number of patients with available data; n, number of patients meeting endpoint.

of subjects with device-related AEs and device-related SAEs between groups were small and not significant (2.2% and 1%, respectively). Specifically, in the investigational group, 22 patients (15.6%) had $\geq$ 1 device-related AE, and 8 patients had $\geq$ 1 device-related SAE (5.7%). In the control group, 20 patients (13.4%) had $\geq$ 1 device-related AE, and 7 patients (4.7%) had $\geq$ 1 device-related SAE (Table 4). Likewise, there were no significant differences between the investigational or control groups for AEs of special interest (immunologic response, neurological impairment, and excessive bone resorption or formation) or deaths. There were two deaths in the investigational group and one in the control group; none were related to the grafts. Neither the investigational group nor the control group developed heterotopic ossification or osteolysis. Both groups had a low rate of device-related SAEs (Table 5).

The investigational group had 13 SSPs adjudicated as failures by the DSMB (Fig. 2). SSPs adjudicated as failures included modifications to the instrumentation at the index level. Four of the 13 SSPs in the CCS endpoint for P-15L were due to treatment for adjacent-level disease and included modifications to the index level instrumentation (eg, replacement of a screw for the new construct extension) and were not related to the success or failure of the graft material at the index level. Five were procedure-related, seven were procedure- and device-related (six possibly device-related and one probably device-related), and one was neither procedure- nor device-related (adjacent-level disease). None were definitively device-related. The control group had 4 SSPs adjudicated as failures, with all being both procedure- and device-related. One was definitely device-related (pseudoarthrosis). Removing the procedure-related SSPs from the analysis resulted in no significant difference in device-related secondary surgical procedures between P-15L and autograft at 24 months (seven events 5.0% *vs.* four events 2.7%, respectively).

DISCUSSION

The primary hypothesis of this study was that P-15L is a safe and effective alternative to local autologous bone graft for treating patients with up to grade I spondylolisthesis and DDD using TLIF. On the basis of the results of this trial, P-15L has a similar safety profile and higher composite success than autograft. Specifically, at 24 months, P-15L achieved a statistically superior CCS rate of 55.5%, compared with 37.5% in the autograft group. Both groups showed similar improvements in ODI, neurological success, and no meaningful clinical differences in the occurrence of SAEs involving the bone graft devices. P-15L had significantly higher fusion rates over the autograft group at 24 months (84.3% *vs.* 58.5%). These findings, proving the safety and effectiveness of P-15L in the lumbar spine, are also supported by the results of a

TABLE 3. Composite Clinical Success (CCS) at Month 24

	P-15L (N = 141)		Autograft (N = 149)		P-15L–autograft*		
Outcome	**N**	**n (%)**	**N**	**n (%)**	**Diff (%)**	**LB (%)**	**UB (%)**
CCS*	**119**	**66 (55.5)**	**128**	**48 (37.5)**	**18.0**	**7.7**	**28.3**
No SSP at the index level	141	128 (90.8)	149	145 (97.3)	−6.5	−11.9	−1.1
Achievement of fusion by month 24	127	107 (84.3)	130	76 (58.5)	25.8	15.2	36.4
≥ 15-point improvement in ODI from baseline to month 24†	110	86 (78.2)	127	103 (81.1)	−2.9	−13.1	7.4
No new or worsening, persistent neurological deficit†	117	110 (94.0)	127	117 (92.1)	1.8	−4.5	8.1
No motor deficit	118	114 (96.6)	128	124 (96.9)	−0.3	−4.7	4.1
No sensory deficit	119	116 (97.5)	127	121 (95.3)	2.2	−2.4	6.8
No serious device-related adverse event through month 24‡	141	134 (95.0)	149	144 (96.6)	−1.6	−6.2	3.0

*LB of the two-sided 90% CI, or equivalently, the LB of the one-sided 95% noninferiority CI. For noninferiority 90% CI: 18.0 (7.7, 28.3), for superiority 95% CI: 5.7% to 30.2%. The primary study success criterion is LB > −12.5%. Since +7.7% > > −12.5%, the results from this study strongly support noninferiority of P-15L relative to autograft. All other CIs are two-sided 95% CIs. After demonstration of noninferiority in CCS, superiority was tested at a multiplicity control one-sided $\alpha = 0.025/2 = 0.0125$. The one-sided superiority *P*-value is 0.002. Since 0.002 < 0.0125, superiority of P-15L relative to autograft is demonstrated.

†Comparing month 24 to baseline.

‡Relatedness includes possible, probable, and definite relatedness.

CCS indicates composite clinical success; LB, lower bound; N, total number of patients with available data; n, number of patients meeting endpoint; ODI, Oswestry low back pain disability questionnaire; SSP, secondary surgical procedure; UB, upper bound.

cervical randomized controlled trial (RCT) evaluating the only other bone graft incorporating the P-15 peptide (ABM/P-15). That cervical RCT demonstrated high fusion rates and statistical superiority in overall clinical success using ABM/P-15 compared with autograft at one and two years postoperatively in single-level anterior cervical discectomy and fusion.[31,32] These clinical benefits were maintained through six years, with sustained improvements in pain, function, and neurological outcomes, and no meaningful differences in safety or reoperation rates compared with autograft.[33]

In the current RCT, there were no significant differences in baseline demographic characteristics between groups with respect to age, sex, height, BMI, race/ethnicity, and nicotine use status. The study was conducted using a multicenter approach and a population reflective of typical real-world clinical practice. P-15L was used as a standalone alternative to autologous bone, in combination with any FDA-cleared PEEK interbody device and posterior instrumentation. Notably, ~60% of the participants were classified as higher-risk, defined as having one or more of the following risk factors: nicotine use, obesity, or type 2 diabetes. These comorbidities are known to have a significant impact on fusion and clinical success.[8–12,42]

The primary endpoint, CCS, demonstrating P-15L to be superior to autograft in this RCT, is a comprehensive measure integrating five clinically meaningful outcomes. This comprehensive endpoint encompasses fusion, functional gains, SSPs, neurological success, and the absence of SAEs related to the bone graft device over a 24-month follow-up and is typical of endpoints used in FDA spine device studies. Importantly, all five of the composite score endpoints had to be met for a patient to be considered a clinical success.[43,44]

After 24 months, the fusion rate for the investigational group (84.3%) was 25.8% higher than the control group (58.5%). Local autograft is widely used in clinical practice[18] and remains the benchmark control for the evaluation of bone graft alternatives. The autograft fusion rate reported here is consistent with other high-quality RCT studies in single-level TLIF. Nassr *et al.*[45] and Shaffer *et al.*[46] reported local autograft fusion rates of ~56% at 24 months. In order to get accurate fusion assessments, thin-slice CT scans by independent, blinded radiologists were used. Plain lumbar radiography has been shown to accurately assess fusion status in approximately two-thirds of patients.[47] This insensitivity to pseudarthrosis detection leads to higher reported fusion rates with plain radiographs compared with the more accurate thin-slice CT.[36]

This study included a ≥ 15-point improvement in the ODI from baseline to 24 months as self-reported confirmation of improved patient outcome. The reported minimal clinically important difference (MCID) values range from ~9.5 to 15 points in the literature, and therefore, this study chose the upper endpoint. Copay *et al.*[37] calculated an MCID of 12.8 points, while Johnsen *et al.*[38] reported an MCID of 12.88 points with 88% sensitivity and 85% specificity. In addition, a study by Glassman *et al.*[39] suggested that a 15-point improvement in ODI scores, along with maintenance or improvement in SF-36 scores, aligns with good to excellent operative outcomes. Again, the 15-point improvement in the ODI used in this study is at the higher end of what is considered a clinically meaningful change.[37,40]

The CCS considers complications related to secondary surgical procedures, and 90.8% of the investigational group and 97.3% of the control group experienced no SSP. Along with no new or worsening, persistent neurological deficits or serious device-related AEs, this indicates the maintenance of long-term safety. Other high-quality, methodologically similar RCT studies reported a similar absence of SSP rates ranging from 86% to 91.4%.[45,46,48,49] Importantly, there were no meaningful differences between the investigational and control groups concerning graft device-related AEs or SAEs. However, there were a greater number of TLIF procedure-related AEs or SAEs in the investigational group (Table 4). The

TABLE 4. Summary of Adverse Event Rates

Parameter	P-15L (N = 141) Events	n (%)	Autograft (N = 149) Events	n (%)	P-15L–autograft* Diff. (%)	LB	UB
Any AE	607*	122 (86.5)	6171	121 (81.2)	5.3	−3.1	13.8
Any device-related AE†	28	22 (15.6)	22	20 (13.4)	2.2	−5.9	10.3
Any procedure-related AE†	189	80 (56.7)	141	59 (39.6)	17.1	5.8	28.5
Any SAE	68	45 (31.9)	76	44 (29.5)	2.4	−8.2	13.0
Device/procedure-related SAE	45	37 (26.2)	24	20 (13.4)	12.8	3.7	21.9
Device/procedure-related SAE resulting in SSP	17	11 (7.8)	4	4 (2.7)	5.1	0.0	10.3
Device-related SAE	8	8 (5.7)	8	7 (4.7)	1.0	−4.1	6.1
Device-related SAE resulting in SSP	7	7 (5.0)	4	4 (2.7)	2.3	−2.2	6.7
Procedure-related SAE	45	37 (26.2)	24	20 (13.4)	12.8	3.7	21.9
Procedure-related SAE resulting in SSP	17	11 (7.8)	4	4 (2.7)	5.1	0.0	10.3
Any AE of special interest‡	23	18 (12.8)	31	19 (12.8)	0.0	−7.7	7.7
Deaths	2	2 (1.4)	1	1 (0.7)	0.7	−1.6	3.1

*All reported AEs regardless of relatedness.
†Device or procedure relatedness includes possible-, probably-, and definitely related.
‡AEs of special interest are immunologic response, neurological impairment, excessive bone resorption, or formation
AE indicates adverse event; LB, lower bound; N, total number of patients with available data; n, number of patients meeting endpoint; SAE, serious adverse event; SSP, secondary surgical procedure; UB, upper bound.

surgical procedure was technically the same in both groups, suggesting the observed differences in procedure-related event rates are chance occurrences potentially related to randomization. Thus, the more specific comparison of device-related AEs and SAEs rather than procedure-related events provides a more salient evaluation when analyzing the potential for AEs when using P-15L, and there were no significant differences in device-related event rates. Significantly, there were no reports of osteolysis, seroma, or heterotopic ossification using P-15L in this study, which have been previously highlighted as potential risks associated with the use of exogenous growth factors.[50–52]

TABLE 5. Device-Related Serious Adverse Events

Device-related serious adverse event	P-15L (N = 141) Events	n (%)	Autograft (N = 149) Events	n (%)
Dural tear	0	0	0	0
Graft complication	0	0	0	0
Lumbar vertebral fracture	0	0	1	1 (0.7)
Pain in extremity	0	0	0	0
Pseudarthrosis*	2	2 (1.4)	4	4 (2.7)
Cerebrospinal fluid leakage	0	0	0	0
Back pain	1	1 (0.7)	1	1 (0.7)
Radiculopathy†	1	1 (0.7)	0	0
Sciatica	0	0	0	0
Spinal claudication	0	0	1	1 (0.7)
Device dislocation	0	0	0	0
Implant subsidence	0	0	0	0
Wound infection‡	1	1 (0.7)	0	0
Heterotopic ossification	0	0	0	0
Osteolysis	0	0	0	0
Seroma	0	0	0	0
Others§	3	3 (2.1)	1	1 (0.7)

*Pseudarthrosis includes events reported under the MedDRA terms pseudarthrosis and incomplete spinal fusion.
†Radiculopathy includes events reported under the MedDRA terms lumbar radiculopathy, radiculopathy, and radicular pain.
‡Wound infection includes events reported under the MedDRA terms postoperative wound infection and wound infection.
§Others include musculoskeletal and connective tissue disorders.
N indicates the total number of patients with available data; n, number of patients meeting endpoint.

This study has some limitations. The results are specific to single-level instrumented TLIF procedures in patients with DDD with up to grade I spondylolisthesis; however, there is inherent variability in surgical technique. Further, TLIF is a technically demanding procedure with known restrictions that can create a challenging fusion environment. These include limited disc access; difficulty with endplate preparation, cage and graft placement; and the use of smaller interbody cages, which result in reduced graft volume and surface area for fusion compared with anterior or lateral approaches.[5,53,54] Moreover, a surgeon's specialty may add variability; however, research suggests that differences in training do not translate to differences in patient outcomes. A large matched-cohort analysis by Shukla *et al.*[55] and a systematic review by Wang *et al.*[56] found no significant differences in complication, reoperation, or readmission rates between specialties after adjusting for relevant factors. These findings support the generalizability of our results and reflect real-world practice.

PEEK cages were also used, which are known to have less optimal osteointegration properties. In addition, posterolateral fusion (PLF), which is often combined with interbody fusion (circumferential approach) to enhance spinal stability, was excluded from this study. Some studies have reported that, compared with a combined circumferential approach, standalone interbody or PLF techniques may be associated with lower fusion rates, less effective pain relief, and higher rates of postoperative complications, including reoperations.[57–59] Nevertheless, the existing literature presents heterogeneous findings, underscoring the need for high-quality, comparative studies to establish the most effective surgical approach.[60]

Despite the high number of bone graft substitutes available, there is a paucity of high-quality clinical data to support evidence-based decision-making for the majority

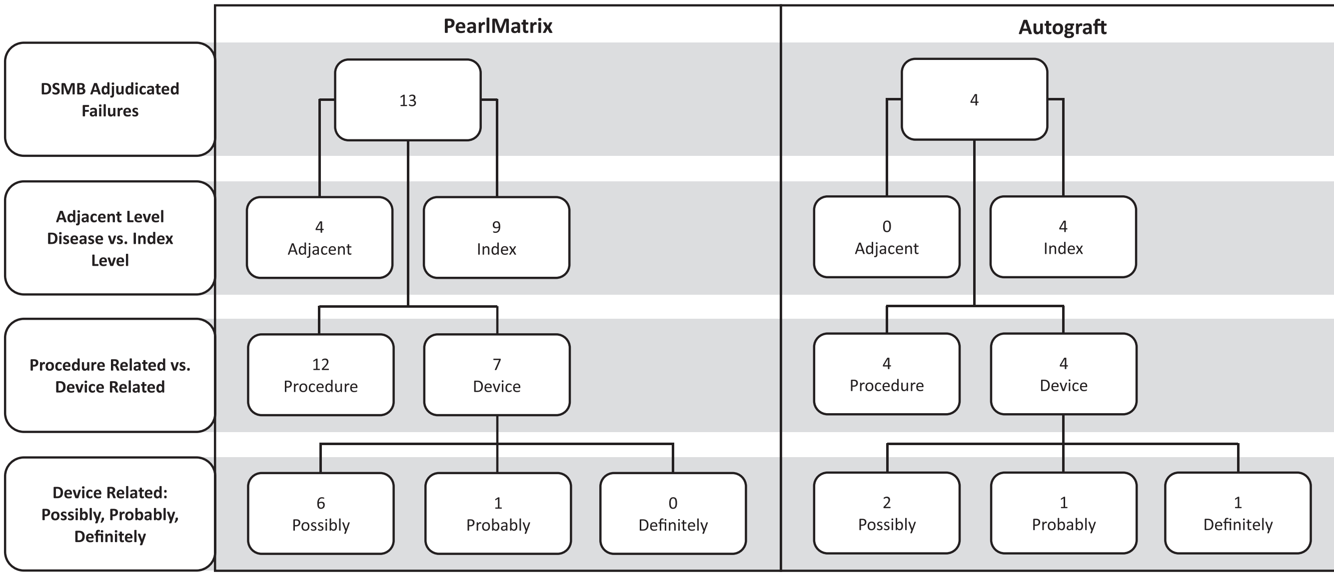

Figure 2. Flow diagram illustrating the breakdown in secondary surgical procedures (SSPs) between the investigational (P-15L) and control (autograft) groups, by adjacent-level disease and procedure- *versus* device-related. Device-related is further categorized by degree of relatedness (possibly, probably, and definitely). DSMB indicates Data and Safety Monitoring Board.

of these products.[25] The results from this study demonstrate that P-15L not only equals but surpasses the clinical effectiveness of local autologous bone. P-15L is currently the only biological regulated as a drug-device combination approved for use as a bone graft substitute in TLIF procedures in conjunction with an interbody device.

CONCLUSION

Instrumented TLIF with P-15L yielded superior composite clinical success and a significantly higher fusion rate when compared with instrumented TLIF with local autograft at 24 months. P-15L has a similar safety profile to local autograft.

➢ Key Points

- ❑ P-15L demonstrated superior clinical success compared with the local autograft control in transforaminal lumbar interbody fusion (TLIF) at 24 months.
- ❑ P-15L fusion, assessed using thin-slice CT and independent reviewers, showed a higher fusion rate than the local autograft control in TLIF with instrumentation at 24 months.
- ❑ P-15L showed no apparent safety concerns when compared with autograft.

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References

1. Bono CM, Lee CK. Critical analysis of trends in fusion for degenerative disc disease over the past 20 years: influence of technique on fusion rate and clinical outcome. *Spine*. 2004;29: 455–463.
2. Deyo RA, Gray DT, Kreuter W, et al. United States trends in lumbar fusion surgery for degenerative conditions. *Spine*. 2005;30: 1441–1445.
3. Mannion AF, Pittet V, Steiger F, et al. Development of appropriateness criteria for the surgical treatment of symptomatic lumbar degenerative spondylolisthesis (LDS). *Eur Spine J*. 2014;23: 1903–1917.
4. Martin BI, Mirza SK, Spina N, et al. Trends in lumbar fusion procedure rates and associated hospital costs for degenerative spinal diseases in the United States, 2004 to 2015. *Spine*. 2019;44:369–376.
5. Mobbs RJ, Phan K, Malham G, et al. Lumbar interbody fusion: techniques, indications and comparison of interbody fusion options including PLIF, TLIF, MI-TLIF, OLIF/ATP, LLIF and ALIF. *J Spine Surg*. 2015;1:2–18.
6. Rathbone J, Rackham M, Nielsen D, et al. A systematic review of anterior lumbar interbody fusion (ALIF) versus posterior lumbar

interbody fusion (PLIF), transforaminal lumbar interbody fusion (TLIF), posterolateral lumbar fusion (PLF). *Eur Spine J*. 2023;32: 1911–1926.
7. Cruz A, Ropper AE, Xu DS, et al. Failure in lumbar spinal fusion and current management modalities. *Semin Plast Surg*. 2021;35: 54–62.
8. Phan K, Fadhil M, Chang N, et al. Effect of smoking status on successful arthrodesis, clinical outcome, and complications after anterior lumbar interbody fusion (ALIF). *World Neurosurg*. 2018; 110:e998–e1003.
9. Thever Y, Han Lincoln LM, Gatot C, et al. Do diabetic patients have poorer clinical and radiological outcomes following minimally invasive transforaminal lumbar interbody fusion? *Int J Spine Surg*. 2023;17:708–714.
10. Steinmetz MP, O'Toole JE, Harrop JS, et al. Adverse impact of diabetes on spine fusion and patient-reported outcomes: a systematic review and meta-analysis. *Spine*. 2025;50:E347–E360.
11. O'Toole JE, Sasso RC, Harrop JS, et al. Adverse impact of obesity on lumbar spine fusion, patient-reported outcomes and costs: a systematic review and meta-analysis. *Spine*. 2025;50:1208–1218.
12. Khalooeifard R, Oraee-Yazdani S, Vahdat Shariatpanahi Z. Obesity and posterior spine fusion surgery: a prospective observational study. *Int J Orthop Trauma Nurs*. 2022;45:100920.
13. Thaler M, Lechner R, Gstottner M, et al. The use of beta-tricalcium phosphate and bone marrow aspirate as a bone graft substitute in posterior lumbar interbody fusion. *Eur Spine J*. 2013;22:1173–1182.
14. Zhang K, Sun W, Zhao CQ, et al. Unilateral versus bilateral instrumented transforaminal lumbar interbody fusion in two-level degenerative lumbar disorders: a prospective randomised study. *Int Orthop*. 2014;38:111–116.
15. Bono CM, Khandha A, Vadapalli S, et al. Residual sagittal motion after lumbar fusion: a finite element analysis with implications on radiographic flexion-extension criteria. *Spine*. 2007;32:417–422.
16. D'Souza M, Macdonald NA, Gendreau JL, et al. Graft materials and biologics for spinal interbody fusion. *Biomedicines*. 2019;7:75.
17. Cheng CT, Vyas PS, McClain EJt, et al. The osteogenic peptide P-15 for bone regeneration: a narrative review of the evidence for a mechanism of action. *Bioengineering*. 2024;11:599.
18. Campana V, Milano G, Pagano E, et al. Bone substitutes in orthopaedic surgery: from basic science to clinical practice. *J Mater Sci Mater Med*. 2014;25:2445–2461.
19. Tuchman A, Brodke DS, Youssef JA, et al. Iliac crest bone graft versus local autograft or allograft for lumbar spinal fusion: a systematic review. *Global Spine J*. 2016;6:592–606.
20. Park JB, Yang JH, Chang DG, et al. Comparison of union rates between autogenous iliac crest bone graft and local bone graft as fusion materials in lumbar fusion surgery: an evaluation of up to 3-level fusion. *World Neurosurg*. 2020;139:e286–e292.
21. Ito Z, Matsuyama Y, Sakai Y, et al. Bone union rate with autologous iliac bone versus local bone graft in posterior lumbar interbody fusion. *Spine*. 2010;35:E1101–E1105.
22. Ito Z, Imagama S, Kanemura T, et al. Bone union rate with autologous iliac bone versus local bone graft in posterior lumbar interbody fusion (PLIF): a multicenter study. *Eur Spine J*. 2013;22: 1158–1163.
23. Abjornson C, Brecevich A, Callanan T, et al. ISASS recommendations and coverage criteria for bone graft substitutes used in spinal surgery. *Int J Spine Surg*. 2018;12:757–771.
24. Gillman CE, Jayasuriya AC. FDA-approved bone grafts and bone graft substitute devices in bone regeneration. *Mater Sci Eng C Mater Biol Appl*. 2021;130:112466.
25. Wang JC, Yoon ST, Brodke DS, et al. Development of AOSpine BOnE (bone osteobiologics and evidence) classification. *Global Spine J*. 2020;10:871–874.
26. Bhatnagar RS, Qian JJ, Wedrychowska A, et al. Design of biomimetic habitats for tissue engineering with P-15, a synthetic peptide analogue of collagen. *Tissue Eng*. 1999;5:53–65.
27. Bhatnagar RS, Qian JJ, Gough CA. The role in cell binding of a beta-bend within the triple helical region in collagen alpha 1 (I) chain: structural and biological evidence for conformational tautomerism on fiber surface. *J Biomol Struct Dyn*. 1997;14:547–560.
28. Qian JJ, Bhatnagar RS. Enhanced cell attachment to anorganic bone mineral in the presence of a synthetic peptide related to collagen. *J Biomed Mater Res*. 1996;31:545–554.
29. Yang XB, Bhatnagar RS, Li S, et al. Biomimetic collagen scaffolds for human bone cell growth and differentiation. *Tissue Eng*. 2004;10: 1148–1159.
30. Hanks T, Atkinson BL. Comparison of cell viability on anorganic bone matrix with or without P-15 cell binding peptide. *Biomaterials*. 2004;25:4831–4836.
31. Arnold PM, Sasso RC, Janssen ME, et al. i-Factor bone graft vs autograft in anterior cervical discectomy and fusion: 2-Year follow-up of the randomized single-blinded Food and Drug Administration investigational device exemption study. *Neurosurgery*. 2018;83: 377–384.
32. Arnold PM, Sasso RC, Janssen ME, et al. Efficacy of i-Factor Bone Graft versus autograft in anterior cervical discectomy and fusion: results of the prospective, randomized, single-blinded Food and Drug Administration investigational device exemption study. *Spine*. 2016; 41:1075–1083.
33. Arnold PM, Vaccaro AR, Sasso RC, et al. Six-year follow-up of a randomized controlled trial of i-FACTOR Peptide-Enhanced Bone Graft versus local autograft in single-level anterior cervical discectomy and fusion. *Neurosurgery*. 2023;92:725–733.
34. Loenen ACY, Connor J, Johnson S, et al. Peptide enhanced bone graft substitute presents improved short-term increase in bone volume and construct stiffness compared to iliac crest autologous bone in an ovine lumbar interbody fusion model. *Global Spine J*. 2022;12:1330–1337.
35. Shah RR, Mohammed S, Saifuddin A, et al. Comparison of plain radiographs with CT scan to evaluate interbody fusion following the use of titanium interbody cages and transpedicular instrumentation. *Eur Spine J*. 2003;12:378–385.
36. Santos ER, Goss DG, Morcom RK, et al. Radiologic assessment of interbody fusion using carbon fiber cages. *Spine (Phila Pa 1976)*. 2003;28:997–1001.
37. Copay AG, Glassman SD, Subach BR, et al. Minimum clinically important difference in lumbar spine surgery patients: a choice of methods using the Oswestry Disability Index, Medical Outcomes Study questionnaire Short Form 36, and pain scales. *Spine J*. 2008;8: 968–974.
38. Johnsen LG, Hellum C, Nygaard OP, et al. Comparison of the SF6D, the EQ. 5D, and the oswestry disability index in patients with chronic low back pain and degenerative disc disease. *BMC Musculoskelet Disord*. 2013;14:148.
39. Glassman S, Gornet MF, Branch C, et al. MOS short form 36 and Oswestry Disability Index outcomes in lumbar fusion: a multicenter experience. *Spine J*. 2006;6:21–26.
40. Hung M, Saltzman CL, Kendall R, et al. What are the MCIDs for PROMIS, NDI, and ODI instruments among patients with spinal conditions? *Clin Orthop Relat Res*. 2018;476:2027–2036.
41. Harrop J, O'Toole JE, Chaput CD, et al. P-15 peptide enhanced bone graft improves time to fusion in transforaminal lumbar interbody fusion: a randomized, controlled, investigational device exemption study. *Spine*. 2025. doi:10.1097/BRS.0000000000005580.
42. Takahashi S, Suzuki A, Toyoda H, et al. Characteristics of diabetes associated with poor improvements in clinical outcomes after lumbar spine surgery. *Spine*. 2013;38:516–522.
43. Vaccaro AR, Whang PG, Patel T, et al. The safety and efficacy of OP-1 (rhBMP-7) as a replacement for iliac crest autograft for posterolateral lumbar arthrodesis: minimum 4-year follow-up of a pilot study. *Spine J*. 2008;8:457–465.
44. Soriano Sanchez JA, Soriano Solis S, Soto Garcia ME, et al. Radiological diagnostic accuracy study comparing Lenke, Bridwell, BSF, and CT-HU fusion grading scales for minimally invasive lumbar interbody fusion spine surgery and its correlation to clinical outcome. *Medicine*. 2020;99:e19979.
45. Nassr A, Coric D, Pinter ZW, et al. Lumbar facet arthroplasty versus fusion for Grade-I degenerative spondylolisthesis with stenosis: a prospective randomized controlled trial. *J Bone Joint Surg Am*. 2024; 106:1041–1053.
46. Shaffer A, Yu AK, Yu A, et al. One- and 2-year outcomes of lumbar

facet arthroplasty versus spinal fusion in young (< 65 years) and old (≥ 65 years) patients for the treatment of degenerative spondylolisthesis and stenosis. *N Am Spine Soc J*. 2024;19:100329.
47. Choudhri TF, Mummaneni PV, Dhall SS, et al. Guideline update for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 4: radiographic assessment of fusion status. *J Neurosurg Spine*. 2014;21:23–30.
48. Vaccaro AR, Lawrence JP, Patel T, et al. The safety and efficacy of OP-1 (rhBMP-7) as a replacement for iliac crest autograft in posterolateral lumbar arthrodesis: a long-term (> 4 years) pivotal study. *Spine*. 2008;33:2850–2862.
49. Blumenthal S, McAfee PC, Guyer RD, et al. A prospective, randomized, multicenter Food and Drug Administration investigational device exemptions study of lumbar total disc replacement with the CHARITE artificial disc versus lumbar fusion: part I: evaluation of clinical outcomes. *Spine*. 2005;30:1565–1575.
50. Carragee EJ, Hurwitz EL, Weiner BK. A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: emerging safety concerns and lessons learned. *Spine J*. 2011; 11:471–491.
51. Fu R, Selph S, McDonagh M, et al. Effectiveness and harms of recombinant human bone morphogenetic protein-2 in spine fusion: a systematic review and meta-analysis. *Ann Intern Med*. 2013;158: 890–902.
52. Hustedt JW, Blizzard DJ. The controversy surrounding bone morphogenetic proteins in the spine: a review of current research. *Yale J Biol Med*. 2014;87:549–561.
53. Saela S, Pompliano M, Varghese J, et al. Minimally invasive transforaminal lumbar interbody fusion (MI-TLIF): a video technique guide. *JBJS Essent Surg Tech*. 2023;13:e21.00065.
54. Yoo JS, Min SH, Yoon SH. Fusion rate according to mixture ratio and volumes of bone graft in minimally invasive transforaminal lumbar interbody fusion: minimum 2-year follow-up. *Eur J Orthop Surg Traumatol*. 2015;25(suppl 1):S183–S189.
55. Shukla GG, Matur AV, Childress K, et al. Surgeon experience matters: an exact matched analysis of tlif outcomes demonstrates no difference in surgical outcomes between experienced neurosurgeons and orthopedic surgeons. *Spine*. 2024;49:772–779.
56. Wang Y, Zhang R, Huang Q, et al. Comparative assessment of surgical outcomes and cost-efficiency between orthopedic surgeons and neurosurgeons in degenerative lumbar spine surgery: a systematic review with pairwise and proportional meta-analysis. *Neurosurg Rev*. 2025;48:308.
57. Shim JH, Kim WS, Kim JH, et al. Comparison of instrumented posterolateral fusion versus percutaneous pedicle screw fixation combined with anterior lumbar interbody fusion in elderly patients with L5-S1 isthmic spondylolisthesis and foraminal stenosis. *J Neurosurg Spine*. 2011;15:311–319.
58. Macki M, Bydon M, Weingart R, et al. Posterolateral fusion with interbody for lumbar spondylolisthesis is associated with less repeat surgery than posterolateral fusion alone. *Clin Neurol Neurosurg*. 2015;138:117–123.
59. Zhu Z, Xuan A, Xu C, et al. Comparison of clinical efficacy in the treatment of lumbar degenerative disease: posterior lumbar interbody fusion, posterior lumbar fusion, and hybrid surgery. *Int J Spine Surg*. 2024;18:756–768.
60. Liu XY, Qiu GX, Weng XS, et al. What is the optimum fusion technique for adult spondylolisthesis-PLIF or PLF or PLIF plus PLF? A meta-analysis from 17 comparative studies. *Spine*. 2014;39: 1887–1898.

