Spinal Fusion and Bone Healing Enhancement Products

Policy Number: 2023T0410EE
Effective Date: October 1, 2023

Instructions for Use

Table of Contents **Page**

Related Commercial/Individual Exchange Policies

- Discogenic Pain Treatment
- Minimally Invasive Spine Surgery Procedures
- Prolotherapy and Platelet Rich Plasma Therapies
- Skin and Soft Tissue Substitutes

Community Plan Policy

- Spinal Fusion and Bone Healing Enhancement Products

Application

UnitedHealthcare Commercial

This Medical Policy applies to all UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange

This Medical Policy applies to Individual Exchange benefit plans in all states except for Colorado.

Coverage Rationale

See Benefit Considerations

The following are proven and medically necessary for the enhancement of spinal fusion:

- Autografts (including Bone Marrow Aspirate used for bone grafting)
- Demineralized Bone Matrix (DBM) without added products listed below as unproven and not medically necessary
- Allograft-based products not listed below as unproven and not medically necessary
- InFUSE® Bone Graft (Recombinant human bone morphogenetic protein-2 (rhBMP-2) of the lumbar spine when the following criteria are met:
  - The approach is anterior or oblique and used in conjunction with an FDA-approved interbody fusion device
  - Skeletally mature individual (18 years of age or older or radiographic evidence of epiphyseal closure) with degenerative disc disease (DDD)
  - The fusion involves vertebral bodies L2-S1, without or with spondylolisthesis of no more than grade 1 (25% displacement) at the involved level
  - The fusion is single level

- The InFUSE/MASTERGRAFT™ Posterolateral Revision Device System (or InFUSE BMP used with MASTERGRAFT) when used according to U.S. Food and Drug Administration (FDA) indications, **contraindications, warnings, and precautions** in individuals who meet all of the following criteria:
  - Implanted via a posterolateral approach
  - Presence of symptomatic posterolateral lumbar spine pseudoarthrosis
  - Skeletally mature patient (older than 21 years of age or radiographic evidence of epiphyseal closure)
  - Autologous bone and/or bone marrow harvest is not feasible or is not expected to promote fusion

The following are unproven and not medically necessary for the enhancement of spinal fusion and bone healing due to insufficient evidence of efficacy and/or safety:

- Allograft based products:
  - Cell-based (e.g., mesenchymal stem cells (MSC)
  - Human amniotic tissue materials, including amniotic fluid stem cell substitutes
  - Recombinant human bone morphogenetic protein-2 (e.g., rhBMP-2, InFUSE) and InFUSE/MASTERGRAFT™ (or InFUSE BMP used with Mastergraft or Mastergraft alone) Posterolateral Revision Device for **all** other indications not included above
- Ceramic-Based Products (e.g., beta tricalcium phosphate (b-TCP), calcium phosphate, calcium sulfate) used alone or in combination with other grafts including Bone Marrow Aspirate
- Bioactive Glass used alone or in combination with other grafts including Bone Marrow Aspirate
- Expandable Interbody Fusion System

Documentation Requirements

Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The documentation requirements outlined below are used to assess whether the member meets the clinical criteria for coverage but do not guarantee coverage of the service requested.

CPT Codes*	Required Clinical Information
Fusion Enhancement Products	

20930
20931
20939
22899
	Medical notes documenting the following, when applicable:
	• Condition requiring procedure
	• History and co-morbid medical condition(s)
	• Member's symptoms, pain, location, and severity including functional impairment that is interfering with activities of daily living (meals, walking, getting dressed, driving)
	• Physical exam, including neurologic exam
	• History and duration of previous therapy, when applicable including:
	  ○ Physical therapy
	  ○ Medications (injections)
	  ○ Previous surgery
	  ○ Bracing
	  ○ Other attempted treatments
	• Whether the surgery will be performed with direct visualization or only with endoscopic visualization
	• Complete report(s) of diagnostic tests and imaging
	• Describe the surgical technique(s) planned [e.g., AxialLIF®, XLIF, ILIF, OLIF, LALIF, image-guided minimally invasive lumbar decompression (MILD®), percutaneous endoscopic discectomy with or without laser, etc.]
	• Specify the Allograft product [including brand name(s)] to be used

*For code descriptions, refer to the Applicable Codes section.

Definitions

Allograft: The transplant of an organ or tissue from one individual to another of the same species with a different genotype (MedicineNet).

Autograft: Tissue transplanted from one part of the body to another in the same individual (MedicineNet).

Bioactive Glass: Silicate glass-based materials with osteoconductive and osteoinductive properties (Gomez).

Bone Marrow Aspirate: Liquid bone marrow aspirated through a needle (MedicineNet).

Bone Morphogenetic Proteins (BMP) and Recombinant Human Bone Morphogenetic Proteins (rhBMP): Naturally occurring osteoinductive proteins that initiate a cascade resulting in the differentiation of local host MSCs into osteoblasts. Recombinant DNA technology allows the production of large and highly purified quantities of BMP (Pinter 2022).

Ceramic-Based Products: Mineral salts produced at high temperatures to create various structures with osteoconductive properties. Ceramic-based bone graft substitutes include hydroxyapatite, calcium phosphate, tricalcium phosphate, calcium sulfate and Bioactive Glass (ECRI, 2022).

Demineralized Bone Matrix (DBM): DBM is a type of Allograft; it is produced by dissolving the mineralized portion of bone and leaving behind only the collagen matrix and growth factors. The collagen matrix provides weak osteoconductive capacity, while the retained growth factors are osteoinductive. DBM must be combined with a carrier that serves as a more potent osteoconductive scaffold (Pinter 2022).

Duo™ Ti Expandable Interbody Fusion System: An implant that is designed to provide mechanical support of the intradiscal space as an adjunct to fusion. The implant is designed with a porous central cavity for graft containment, a rounded nose to aid in implant insertion, and rigid teeth to resist migration (FDA).

Human Amniotic Tissue Membrane: A multilayer tissue forming the innermost layer of the amniotic sac that surrounds the developing fetus. It is comprised of 5 layers, from the inside out: a single layer of epithelial cells, a thick basement membrane, a compact layer, a fibroblast layer, and a spongy layer that abuts the surrounding chorion (Heckman).

InFUSE™ Bone Graft: A bone graft that helps stimulate natural bone formation and remodeling and avoids the need for harvesting bone from other parts of a patient's body. Infuse contains recombinant human Bone Morphogenetic Protein-2 (rhBMP-2) and is approved for use in certain spine, dental, and trauma indications (Medtronic).

OptiMesh® Expandable Interbody Fusion System: A device that is intended to maintain the relative position of bone graft material within a vertebral body defect (FDA). The implant expands in three dimensions when filled to create an anatomy-conforming interbody fusion implant (Spineology).

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
20930	Allograft, morselized, or placement of osteopromotive material, for spine surgery only (List separately in addition to code for primary procedure)
20931	Allograft, structural, for spine surgery only (List separately in addition to code for primary procedure)
20939	Bone marrow aspiration for bone grafting, spine surgery only, through separate skin or fascial incision (List separately in addition to code for primary procedure)
22899	Unlisted procedure, spine

Description of Services

Autologous iliac bone grafting has long been the gold standard for bone grafting in spinal fusion due to its osteoconductive, osteoinductive, and osteogenic abilities, however it is associated with donor site morbidity. .Biological products such as Bone Marrow Aspirate, recombinant human bone morphogenetic protein-2 (rhBMP-2), and Demineralized Bone Matrix may improve spinal fusion success rates and enhance bone healing. Some biological products such as human amniotic membrane derivatives, and cell-based products, as well as synthetics such as Ceramic-Based Products and Bioactive Glass, are being investigated for their ability to improve outcomes.

Benefit Considerations

Certain benefit plans allow exceptions to cover experimental, investigational, or unproven services for life-threatening illnesses when specific conditions are met. The member-specific benefit plan document must be reviewed to make coverage decisions for such services.

Clinical Evidence

Recombinant Bone Morphogenetic Protein (rhBMP or BMP)

Im et al. (2022) conducted a prospective, single-institution, therapeutic investigative clinical study to explore the effectiveness and feasibility of injectable Escherichia coli-derived recombinant human bone morphogenetic protein-2 (injectable E-rhBMP-2, a combination of E. coli-derived recombinant human bone morphogenic protein-2 and a hydrogel type beta-tricalcium phosphate carrier) as a bone substitute for anterior lumbar interbody fusion (ALIF) of the lumbosacral junction in adult spinal deformity (ASD) patients. Twenty patients (average age: 69.1 years; 19 female and one male; average fusion level: 7.95) diagnosed with ASD with sagittal imbalance who underwent surgical treatment including ALIF at the lumbosacral junction from December 2017 to January 2019 were evaluated. Injectable E-rhBMP-2 was prepared by dissolving 3 mg of E. coli-derived recombinant human bone morphogenetic protein-2 in 1.5 ml H2O and mixing in situ with 9 g hydrogel type beta-tricalcium phosphate. This bone graft substitute was loaded onto a metal ALIF cage and L5–S1 ALIF was performed in routine manner. Then posterior column osteotomy with multilevel oblique lumbar interbody fusion or pedicle subtraction osteotomy with accessory rod technique was performed to restore sagittal balance. Patients were followed up for 12 months. CT-based fusion rates were examined at 6 and 12 months after surgery. Also, clinical outcomes (Oswestry Disability Index [ODI], Visual Analog Scale [VAS] score of the back and leg) were evaluated at 6 and 12 months after surgery. All postoperative adverse events were evaluated for the association with injectable E.BMP-2. Of the 20 patients, loss to follow-up occurred with one patient at 6 months after surgery and one patient at 12 months after surgery, resulting in a total of 18 patients who were available for follow-up. Six months after surgery, 68.4% patients achieved solid fusion. Twelve months after surgery, 100% fusion rate was achieved. Compared to baseline values, ODI scores improved to 45.8% and 63.7%, VAS (back) improved to 69.2% and 72.8%, and VAS (leg) improved to 49.2% and 64.8%, respectively, at 6 and 12 months after surgery ($p < 0.001$ for all). Ten cases of adverse events occurred; however, no adverse events were associated with injectable E-rhBMP-2. The authors concluded injectable E-rhBMP-2 will be an effective bone graft substitute when achieving solid interbody fusion in the lumbosacral junction. Limitations include a small sample size making it difficult to decide whether these conclusions can be generalized to a larger population. In addition, the short terms follow-up did not allow for assessment of intermediate and long-term outcomes. Further research with randomized controlled trials is needed to validate these findings.

Meng et al. (2022) conducted a retrospective study evaluating the clinical and radiographic effect of recombinant human bone morphogenetic protein-2 (rhBMP-2) in pars repair of lumbar spondylolysis. Direct pars repair and pedicle screw fixation was performed, which were added with 1 mg of rhBMP-2 and iliac crest bone graft in the study group (rhBMP-2 group, n = 32) and iliac crest bone graft alone in the autograft group (n = 36). Patients completed the visual analog scale and the Oswestry Disability Index pre-operation, 3, 6, and 12 months after the operation. Computed tomography scans with axial and sagittal reconstructions were performed at 6, 9, 12, 18, and 24 months postoperatively. Baseline demographic data showed no difference between 2 groups. There were differences for the Oswestry Disability Index score at 3- and 6-months post-operatively, which were higher in the autograft group. There was no difference between the groups with respect to the overall union status. As for union speed, the trabecular bone appeared earlier and union rates were higher in rhBMP-2 group than in the autograft group at 9, and 12 months post-operatively. No complications were identified in either group. One case in the rhBMP-2 group and 2 cases in the autograft group underwent revision surgery. The authors concluded when compared with

iliac crest bone graft alone, the use of rhBMP-2 can accelerate fusion in pars repair for young patients with spondylolysis. The union rates were different at 9 and 12 months after surgery. This study showed no clinical difference when adding rhBMP-2 compared with iliac crest bone graft alone. The limitations of this study include bias because of retrospective, single-center and nonrandomized study, as well as the small sample size, which may weaken the study's ability to detect differences between study subgroups and determine the significance of these differences. Further research with randomized controlled trials is needed to validate these findings.

A Hayes (2021; updated 2022) comparative effectiveness review identified a large body of moderate-quality evidence that suggests that compared with an autograft, the use of rhBMP-2 for lumbar spinal fusion provides more rapid fusion and/or a somewhat greater likelihood of achieving fusion, but this did not consistently result in reduced pain or disability or better QOL. Use of rhBMP-2 also appears reasonably safe for lumbar fusion over the short term. Similar results were seen in studies related to cervical fusion, however the small number and quality of studies as well as varied treatment protocols limit's reliability of the findings. There is a lack of studies regarding the use of rhBMP-2 for thoracic fusion and the efficacy and safety cannot be determined. Furthermore, due to the limited duration of follow-up in almost all of the reviewed studies, it has not been possible to determine the clinical significance of more complete fusion with rhBMP-2, and it has not been possible to rule out certain serious long-term risks of rhBMP-2, including a low potential risk of cancer. Additional long-term studies are needed to determine whether the benefits outweigh the potential risks.

Liu et al. (2020) conducted a systematic review and meta- analysis regarding the comparative clinical effectiveness and safety of rhBMP versus autologous iliac crest bone graft (ICBG) in lumbar fusion. Twenty randomized controlled trials identified through May 2019, with a total of 2,185 patients met the inclusion criteria of age 18 to 80 years, suffering from lumbar degenerative diseases requiring lumbar fusion, and the RCT compared rhBMP with ICBG (patients with spinal deformities, fractures, tumors or infections, cases demonstrated spondylolisthesis classified higher than Meyerding Grade II, follow-up was < 12 months, and there were incomplete follow-up data were excluded). The primary outcomes assessed included fusion success, improvement on the Oswestry disability index (ODI), improvement on short form 36 (SF-36), improvement on the Numeric Rating Scale (NRS) for back pain and leg pain, adverse events, and reoperation. Secondary outcomes included operation time, intraoperative blood loss, and duration of hospital stay. The overall results showed improvement across all primary outcomes. The fusion success rate for rhBMP-2 was approximately 5.5 times higher than that observed in ICBG, with reoperation rates about 60% of ICBG. Adverse events and complications showed no significant differences. The authors acknowledged that the quality of evidence in this meta-analysis is limited by the low quality of the original studies. Most evaluated studies did not report their randomization or allocation methods. Nearly all studies failed to use independent blinding. The authors concluded that evidence is still lacking to support rhBMP superiority to ICBG, and future research should address using more rigorous methods including accurate reporting of pre- and post-operative scores and follow up of long-term complications.

In 2017, James et al. presented a review article regarding the side effects of rhBMP-2. Since its FDA approval in 2002, increased use has resulted in a growing and well- documented body of side effects that include postoperative inflammation (and associated adverse effects), ectopic bone formation, osteoclast-mediated bone resorption, and inappropriate adipogenesis. Additionally, several large-scale studies have confirmed the relative frequency of adverse events associated when used for cervical spine fusions, and in 2008, the FDA issued a public health notification regarding the life-threatening complications associated with recombinant human bone morphogenetic protein for this use. The authors stress that the use of rhBMP-2 in appropriately selected patients with impaired fusion capacity can result in better overall long-term outcomes, however there are risks when the product is used off label or for inappropriate indications, and dosing.

Faundez et al. (2016) conducted an extensive review of randomized controlled trials (RCTs) and controlled series. Review confirmed that the use of rhBMP-2 following FDA-approved recommendations (i.e., one-level ALIF surgery with an LT-cage) is safe. The rate of complications is low, and the AEs had been identified by the FDA during the pre-marketing clinical trials. The clinical efficiency of rhBMP-2 is equal or superior to that of allogenic or autologous bone graft in respect to fusion rate, low back pain disability, patient satisfaction and rate of re-operations. For all other off-label use, the safety and effectiveness of rhBMP-2 have not been established, and further RCTs with high level of evidence are required.

Rodgers et al. (2013) investigated published results of industry funded trials of recombinant human bone morphogenetic protein 2 (rhBMP-2) in spinal fusion matching underlying trial data by comparing three different data sources: individual participant data, internal industry reports, and publicly available journal publications and conference abstracts. Outcomes from 11 of the 17 manufacturer-sponsored studies were reported in 32 publications. The authors concluded that the published

literature only partially represents the total data known to have been collected on the effects of rhBMP-2. This did not lead to substantially different results for meta-analysis of effectiveness outcomes. In contrast, reporting of adverse event data in trial publications was inadequate and inconsistent to the extent that any systematic review based solely on the publicly available data would not be able to properly evaluate the safety of rhBMP-2. Analysis of individual participant data enabled the most complete, detailed, and in-depth analysis and was not more resource intensive than extracting, collating, and analyzing aggregate data from multiple trial publications and conference abstracts. Confidential internal reports presented considerably more adverse event data than publications, and in the absence of individual participant data access to these reports would support more accurate and reliable investigation, with less time and effort than relying on incomplete published data.

Chrastil et al. (2013) published a systematic review of the spectrum of complications reported in the literature after posterior interbody fusions of the lumbar spine augmented with BMP. Seventeen articles were identified and reviewed that addressed the use and complications of BMP use during PLIF and TLIF procedures. The studies ranged from level I prospective randomized trial to case reports of complications. The authors reported appreciable rates of BMP-specific complications, including heterotopic ossification within the epidural space or neuroforamina, postoperative radiculitis, and endplate osteolysis with interbody device subsidence. They conclude by stating, “High-quality clinical trials should be initiated to develop appropriate paradigms to maximize the safety and efficacy of BMP for posterior interbody fusions.”

In a prospective, longitudinal cohort study of 688 patients from 3 studies, Burkus et al. (2011) analyzed antibody formation to BMP-2, bovine collagen, and human collagen after three prospective clinical studies investigating rhBMP. Neutralizing antibodies were assessed using a cell bioassay. The incidence of antibodies to bovine and human collagen was determined. Radiographic and clinical outcome data were assessed to determine whether antibodies were correlated to patient outcomes. The authors concluded that formation of anti-BMP-2 antibodies was low and transient. No neutralizing antibodies were observed. Formation of antibodies did not affect fusion success or appear to have clinical sequelae.

A report by Glassman et al. (2011) describes a retrospective case review of 1037 subjects who underwent posterolateral spine fusion using rhBMP-2, with a focus on complication rates. They reported that medical and surgical complications were observed in 190 of 1037 subjects, with 81 major complications and 110 minor complications. New or more severe postoperative radicular symptoms were noted in 7 subjects. Complications directly related to rhBMP-2 were observed in at least 1 and in a worst-case analysis, in as many as 6 subjects. The authors concluded that, "There were extremely few complications directly attributed to rhBMP-2/ACS, and the overall complication rates were consistent with established norms.”

A systematic review by Agarwal et al. (2009) compared the efficacy and safety of osteoinductive bone graft substitutes using autografts and allografts in lumbar fusion. Of 732 potential studies, 17 studies met the inclusion criteria (nine examined rhBMP-2, three examined rhBMP-7, three examined demineralized bone matrix, and two examined autologous growth factor). Primary outcome measures were nonunion as defined by failure to fuse as demonstrated on CT scans or plain x-rays. Secondary outcome measures were failure to demonstrate improvement on the Oswestry Low-Back Pain Disability Questionnaire (or Oswestry Disability Index [ODI]). When compared with autologous iliac crest bone graft (AIBG), recombinant human BMP-2 significantly increased union as evidenced by radiographic imaging, while rhBMP-7 showed no difference in radiographic nonunion. Neither rhBMP-2 nor rhBMP-7 demonstrated a significant improvement on the Oswestry Disability Index when compared with (AIBG). The controlled trials of demineralized bone matrix or autologous growth factor in comparison with AIBG showed no significant differences in radiographic nonunion. The authors concluded that rhBMP-2 may be an effective alternative to facilitate lumbar fusion in single-level lumbar DJD compared to AIBG. However, the data is limited for rhBMP-7, demineralized bone matrix, and autologous growth factor. The authors note the following limitations: English only published studies were reviewed; there were no double blinded studies; analyses of the efficacy of bone graft substitutes other than rhBMP-2 was limited by the study size and number; and there is a potential for bias because device manufacturers sponsored several studies and more than 1 author reported conflicts of interest.

Dimar et al. (2009) conducted a multicenter, prospective, randomized study of 463 patients at 29 sites. Patients had symptomatic single-level lumbosacral degenerative disease with no greater than grade-1 spondylolisthesis treated with single-level instrumented posterolateral arthrodesis through an open midline approach. Patients were randomly assigned to receive either the recombinant human bone morphogenetic protein-2 matrix group (239 patients) or the autogenous iliac crest bone-graft group (224 patients). Outcomes were evaluated with the Oswestry Disability Index, Short Form-36, and back and leg pain scores preoperatively and at 1.5, 3, 6, 12, and 24 months postoperatively. Radiographs and computed tomography scans were made at 6, 12, and 24 months postoperatively to evaluate for fusion. Of the 463 patients who had surgery, 410 (194 iliac crest bone graft group and 216 rhBMP-2 matrix group) were available for assessment at 2 years after surgery. Both groups showed

similar improvements in clinical outcomes and reduced pain. Radiographic and computed tomography scans showed a greater incidence of fusion in the rhBMP-2 group. Patients requiring a second surgery was higher in the iliac crest bone graft group (36 patients vs. 20) than the rhBMP-2 group. The authors concluded that the use of recombinant human bone morphogenetic protein-2 in instrumented posterolateral lumbar arthrodesis produces earlier and higher fusion rates than does iliac crest bone graft.

Ceramic-Based Products

Ceramic products include a variety of biologically inert compounds (including tricalcium phosphate, calcium sulfate, and hydroxyapatite) that can be constructed as a scaffold to simulate the mineral phase of bone. They are osteoconductive, but are generally not osteoinductive, and greater success rates have been achieved when used with a source of cells such as autograft or BMA. They vary widely based on differences in composition, manufacturing, porosity, and structure which may ultimately affect their efficacy. There is insufficient high-quality evidence to come to determine the efficacy and safety of these products on health care outcomes, and how they compare with established bone grafting procedures.

A 2022 ECRI clinical evidence assessment entitled Bicera Bone Graft Substitute (Wiltrom Corp. Ltd.) for Filling Bone Defects reported on the safety and effectiveness of Bicera compared to bone grafts and other natural or synthetic bone substitutes. Bicera is a biocompatible ceramic composed of hydroxyapatite and beta-tricalcium. Evidence from one nonrandomized comparison study and two small case series is too limited in quantity and quality to determine how well Bicera works compared with autografts, allografts, or other bone graft materials bone fillers. Large well-designed studies are needed.

A 2022 ECRI clinical evidence assessment entitled Ceramic Bone Graft Substitutes for Spinal Fusion and Long Bone Voids reported on the effectiveness and safety of ceramic bone graft substitutes for spinal fusion and long bone void filling compared to ICBG and other alternative materials. Based on the results for spinal fusion, one SR reported that cages filled with nanocrystalline HA or homologous bone had similar fusion rates and function outcomes after anterior lumbar interbody fusion. For cervical fusion, one RCT reported ceramic-based synthetics used alone had the lowest fusion rate compared with other bone graft material, and when combined with allograft the fusion rates were slightly higher. Another RCT reported polyetheretherketone cages filled with allograft produced significantly better fusion rates than cages filled with tricalcium phosphate, and another reported polyetheretherketone cages with or without tricalcium phosphate filler produced better than 97% fusion at 24 months. It was concluded ceramic bone graft substitutes are safe and may aid cervical and lumbar fusion and long bone void repair, but due to the mixed results of the studies, the superiority to ICBG or other bone graft materials cannot be determined, and large well-designed and conducted RCTs comparing specific ceramic and ceramic/bone graft material combinations with ICBG, and other bone graft materials are needed.

Griffoni et al. (2022) conducted a prospective pilot clinical study to evaluate the degree of fusion and new bone formation achieved by the use of moldable ceramic paste bone graft substitute, SINTLife, an Mg-doped hydroxyapatite (HA) product. From February 2017 to September 2019, a total of 16 individuals who had indications of single- or multiple-level postero-lateral spinal fusion due to degenerative lumbar spine diseases were included in this study and followed up for 18 months. Three individuals dropped out due to adverse events post-surgery. Results showed a successful degree of fusion of about 62% at the 12-month follow-up and an improvement of quality of life and health status following surgery, as evaluated by clinical scores (ODI, VAS, and EQ-5L). No adverse events related to the material were reported. Considering all the patients, the VAS score at baseline was 7.2 ±1.8, and it decreased to 4.7 ±1.69 at 6-month follow-up, while it remained stable at 12–18-month follow-up (4.8 ±2.4), with a statistically significant difference between baseline and follow-up scores, starting from 6 months after surgery ($p < 0.0004$). The Oswestry Disability Index at baseline was 48.3 ±14.5, and it decreased to 31.6 ±14.7 at 6-month follow-up and remained stable at 12–18-month follow-up (33.3 ±18.3), with a statistically significant difference between baseline and follow-up scores, starting from 6 months after surgery ($p < 0.0006$) (Figure 5). The EQ-5L score at baseline was 45 ±15, and it increased to 62 ±13 at 6-month follow-up, and it was 64.5 ±22 at 12–18-month follow-up, with a statistically significant difference between baseline and follow-up scores, starting from 6 months after surgery ($p < 0.0003$). Differences between ODI, VAS, and EQ-5D scores at 12–18-month follow-up, as compared to 6-month FU values, were not statistically significant, and a sensitive analysis performed by considering only those patients who underwent all three follow-up visits (n = 13) confirmed the trend. Three adverse events (i.e., inflammatory reactions) were recorded in the follow-up period, with one requiring surgical debridement and the remaining treated with anti-inflammatory agents The authors concluded that this pilot study shows the effectiveness and the safety profile of an Mg-doped HA bone graft substitute used to achieve postero-lateral fusion in the treatment of degenerative spine diseases, laying down the basis for further larger clinical investigations.

In a 2020 systematic review and meta-analysis, Cottrill et al. (included in ECRI ceramic based bone graft substitutes clinical evidence assessment above) reported on the results in the published literature regarding silicate-substituted calcium phosphate (SiCaP) bone grafts and improved spinal fusion rates. Ten studies that included 694 patients were included. The primary endpoint was radiographic fusion rate and patient reported outcomes (PROs) in VAS and ODI at last follow up. The results showed that Across all studies, the mean fusion rate for patients treated with SiCaP bone grafts was 93%. There was no significant difference in fusion rates reported by case series and RCTs, or between single-center and multicenter studies. Fusion was achieved at 100% is adolescent idiopathic scoliosis (AIS) patients. Fusion rates were similar across interbody fusion, posterior/posterolateral fusion, and circumferential cervical fusion procedures, and between patients treated with SiCaP alone and SiCaP used in conjunction with bone marrow aspirate (BMA) and/or autograft. In studies that examined interbody fusion, titanium interbody devices had higher fusion rates than PEEK devices, and rates of fusion did not significantly differ between single or multi-level, or cervical or thoracic columbar procedures. Among the three RCTs included, there was no difference in fusion rates among patients that received SiCaP vs those that received grafts supplemented with rhBMP-2. PROs showed patients that received SiCaP reported significant improvement in VAS back and leg pain, and ODI. The authors concluded that SiCaP achieved successful fusion in 93% of patients treated. The SR is limited by the high heterogeneity of the included studies, as well as comparison to other graft materials. Further high-quality research is needed to validate these findings.

A 2018 ECRI clinical evidence assessment, updated in 2021 entitled i-Factor Bone Graft (Cerapedics, Inc.) for Lumbar Fusion Procedures, reported on the efficacy of the i-Factor bone graft and how it compares to autograft and allograft bone. i- Factor is a biologic bone graft made of a small peptide (P-15 Osteogenic Cell Binding Peptide), bound to an anorganic bone mineral. Limited evidence suggests that i-Factor is safe and effective, however too few patients have been included to determine its superiority to autografts, allografts, or other bone graft materials. Two ongoing randomized controlled trials expected to be completed in 2027 are likely to address this gap.

Nickoli et al. (2014) performed a systematic view of thirty studies with 1,332 patients. The overall fusion rate for all ceramic products as a bone graft extender in the lumbar spine was 86.4%. Age, gender, method of evaluation (plain radiographs, computed tomography, or combination), or specific ceramic product did not significantly affect fusion rate. Ceramics used in combination with local autograft resulted in significantly higher fusion rates compared with all other adjuncts, and bone marrow aspirate and platelet concentrates resulted in significantly lower fusion rates. The authors concluded that ceramic-based bone grafts represent a promising bone graft extender in lumbar spine fusion when an osteoinductive stimulus, such as local bone graft is available. Although all studies included patients with a degenerative lumbar pathology, critical exclusion criteria were not standardized. As a result, important patient variability could have influenced fusion rates including cigarette smoking, immunosuppression, and medical comorbidities. Also, given the lack of standardization and variability in reporting, the authors were unable to obtain information on other important complications such as infection. In addition, radiographic reporting methods varied among studies, which could certainly affect outcomes. Finally, because volume and technique of ceramic use was so inconsistently reported, recommendations could not be drawn.

Bioactive Glass

Bioactive glasses are a class of synthetic silica-based bioactive materials that have unique bone forming properties, and have been introduced as bone graft substitutes. Typically composed of 4 different oxide materials: SiO2, CaO, Na2O, and P2O5, they have unique properties when compared to other synthetic bioresorbable bioactive ceramics (i.e. calcium phosphates, hydroxyapatite (HA), and tricalcium phosphate (TCP). They are claimed to exhibit faster rates of hydroxyl carbonated apatite (HCA) and bone bonding formation, and higher osteoconductivity. There is insufficient high-quality evidence to come to conclusions on the efficacy and safety of these products on health care outcomes, and how they compare with established procedures.

A 2022 ECRI clinical evidence assessment entitled Bioactive Glass Bone Graft Substitutes for Spinal Fusion and Long Bone Voids reported on the effectiveness and safety of bioactive glasses (BGs) for spinal fusion and long bone void filling compared to ICBG and other alternative materials. Due to insufficient, very low-quality evidence whether BG is as effective as ICBG or other bone graft materials cannot be determined, and RCTs comparing specific BGs and BG/graft combinations to the current gold standard ICBG are needed.

Gomez and Westerland (2021, included in the ECRI clinical evidence assessment) conducted a retrospective case series review of 39 patients who underwent primary multilevel instrumented fusions for degenerative cervical disc disease treated with a porous PEEK interbody spacer and a third-generation bioactive glass synthetic bone graft substitute (BioSphere® Putty, Synergy

Biomedical, Wayne, PA, USA). Patients were assessed using accepted standard outcome measurements including VAS and neck disability index, immediately following surgery, and at 3-, 6-, 12-, and 24-months post operatively. The mean follow up period was 16 months. Lateral radiographs were used to assess sagittal alignment, disc space height, arthrodesis status, osseous integration, and implant migration. Sagittal plane angulation was measured by Cobb's criteria. Seventeen patients (43%) underwent a two-level fusion; 12 (31%) underwent a three-level fusion; 9 (23%) underwent a four-level fusion; and 1 (3%) underwent a five-level fusion. The results showed significant improvements in VAS and neck disability index, and these were maintained up to one year follow up. All patients improved or maintained neurological status up to one year. Radiographic outcomes showed that all patients demonstrated osseous integration of the interbody spacers to the vertebral endplates and trabeculated new bone formation across the fused interspace. No radiographic lucencies developed, and dynamic flexion/extension radiographs showed was no motion, migration of the implants, broken screws, or plates. There was a significant improvement in the fusion segment lordosis, C2–C7 lordosis angle, as well as T1 slope and disc height remained unchanged. Statistically significant improvement was not shown for sagittal vertical axis or proximal and distal adjacent segment lordosis. No adverse events were reported. The authors concluded that third generation bioactive glass is a promising and effective method to enhance spinal fusion. This study is limited by a small number of participants and larger, well-designed studies are needed to validate these findings.

Lee et al. (2020) conducted a prospective, stratified randomized, multicenter, follow-up study aimed to evaluate the long-term clinical efficacy and safety of CaO-SiO2-P2O5-B2O3 glass ceramics (BGS-7) spacers in 1-level posterior lumbar interbody fusion (PLIF) at a 4-year follow-up. According to 1-year follow-up results, BGS-7 spacer showed similar fusion rates and clinical outcomes compared with titanium cage. A long-term follow-up study beyond 2 years is necessary to investigate the status of intervertebral bone graft volumes. Moreover, longer follow-up is necessary to evaluate the safety and efficacy of BGS-7 spacers as they remain in the intervertebral space for a long time. Evaluation of 62 of the 74 patients who underwent 1-level PLIF was performed. During 1-level PLIF, titanium cages filled with autologous local bone were inserted into the control group patients and BGS-7 spacers were inserted to the experimental group patients. Bone fusion was evaluated by plain radiography and thin section computed tomography. Visual Analog Scale (VAS), the Oswestry Disability Index (ODI), Short Form-36 Health Survey (SF-36), and evaluation of safety were conducted after 48 months. Computed tomography scan showed a bone fusion rate of 90.6% in the BGS-7 spacer group and 93.3% in the control group, with no differences between groups. The BGS-7 spacer group showed a larger area directly fused to the endplate than the control group ($p < 0.001$). The BGS-7 spacer group showed an increase in the fused area compared with the titanium group at 1- and 4-year follow-up. The ODI, SF-36, back pain, and lower limb pain in both groups showed improvement after surgery, and no differences were observed between the groups. Both groups showed no additional adverse events. The authors concluded that the 4-year follow-up study showed similar fusion rates and clinical outcomes in both the BGS-7 spacer and autologous bone with a titanium cage in 1-level PLIF. However, the BGS-7 spacer implants showed a larger area of fusion with the endplates than that of autologous bone with a titanium cage. Therefore, the results demonstrated that the BGS-7 spacer can be considered as a novel intervertebral spacer to achieve successful spinal fusion without safety concerns for long-term use. A limitation to this study focused on the safety of the BGS-7 should be analyzed beyond 4 years, because BGS7 spacers would remain in the intervertebral spaces for a long period of time. Further research is needed to determine the clinical relevance of these findings.

Westerland and Borden (2020) conducted a retrospective clinical case series to evaluate the use of a novel, spherical bioactive glass bone graft (BioSphere® Putty) as a graft material for cervical and lumbar interbody fusion. Data was gathered for a combined 248 patients who underwent 115 anterior cervical decompression and fusion (ACDF), 103 transforaminal lumbar interbody fusion (TLIF), and 30 anterior lumbar interbody fusion (ALIF) procedures by a single surgeon. BioSphere Putty was used in combination with cancellous allograft (ACDF and ALIF) or in combination with autograft (TLIF). Successful clinical outcomes were determined by a combination of the presence of complete radiographic fusion and a decrease in VAS at 1-year and 1- and 2-year follow-up. Only 43 of the 248 patients were followed for 2 years. At follow up, radiographically all patients demonstrated fusion, and there were no clinically adverse events. One-year VAS scores demonstrated significant decreases in pre-operative pain for both ACDF patients (78% decrease) and lumbar patients (66% decrease TLIF/ALIF). By 2 years, VAS scores continued to drop with significant decreases for the ACDF patients (96%), TLIF patients (82%), and ALIF patients (80%). Combined with the 100% radiographic fusion rates, patients, this resulted in a clinical success rate of 93% for the ACDF patients and 89% for the TLIF/ALIF patients. The authors concluded that Biosphere Putty demonstrates successful outcomes in cervical and lumbar interbody fusion surgeries. This study is limited by the retrospective design, high risk of bias, and small number of participants evaluated at 2 years. Further well designed high quality research is warranted.

Cell-Based Products

Cell-based products contain native bone cells such as mesenchymal stem cells, osteoblasts, or pre-osteoblasts, and are often combined with cancellous allograft chips and/or DBM. The use of cell-based bone graft substitutes continues to be investigated for various procedures, including spinal fusion and for intervertebral disc regeneration. There is a lack of high quality evidence demonstrating definitive conclusions regarding the net health benefit of cell-based products.

A 2022 ECRI clinical evidence assessment entitled OsteoAMP Bone Graft (Bioventus, LLC.) for Cervical Spinal Surgery, reported on the safety and effectiveness of OsteoAMP and how it compares with other bone graft substitutes for cervical spine surgery. OsteoAMP is an allogeneic bone graft substitute processed from human cadaver bone, and undergoes proprietary processing techniques to preserve BMPs and other growth factors. Two case series totaling 259 patients, had a high risk of bias due to retrospective design and lack of controls and randomization. Neither reported on patient-oriented outcomes, and only one reported on adverse events (AEs). No comparative data was available to assess how well OsteoAMP works compared with other bone graft substitute options. Large prospective studies comparing OsteoAMP with bone autograft and with autograft alternatives are needed.

A 2016 ECRI clinical evidence assessment entitled OsteoAMP Bone Graft (Bioventus, LLC.) for Lumbar Spine Surgery was updated in 2022, and reported on the safety and effectiveness of OsteoAMP, and how it compares with other bone graft substitutes for lumbar spine surgery. Four studies were identified that provided data, but none compared OsteoAMP to bone autograft, or other substitutes other than one that compared it to the Infuse® Bone Graft. It was concluded that the evidence is too limited in quality and quantity to determine if OsteAMP works as well as, or better than other bone graft substitutes, and large prospective studies are needed.

Hsieh et al. (2019- included in ECRI clinical evidence assessment below) conducted a systematic comparative review of the evidence regarding the use of allogenic stem cell products for spine fusion when compared with other bone graft materials in patients with degenerative disease of the cervical or thoracolumbar spine. Eleven studies met the inclusion criteria, the majority were retrospective case series and only 2 retrospective cohort studies were identified, one on lumbar fusion and one on cervical fusion. Both were considered a moderately high risk of bias. No evidence on the impact of patient or intervention characteristics on effectiveness or safety was available for any of the studies included. Across case series, allogenic stem cell products appeared to be associated with improved pain and function, however in the absence of methodologically sound comparative studies, conclusions regarding effectiveness or safety cannot be drawn. While the use is promising, there is a lack of high-quality studies and further research is needed.

A 2019 ECRI clinical evidence assessment, updated in 2022, entitled Osteocel Cellular Allograft (NuVasive, Inc.) for Spinal Fusion Procedures concluded that the available evidence is at too high a risk of bias to determine whether the presence of living cells (Osteocel is made of cancellous bone processed to preserve bone-forming cells) results in better healing following lumbar or cervical spine surgery compared to other bone graft substitutes. Well designed, high quality studies are needed.

A 2019 ECRI clinical evidence assessment, updated in 2022, entitled Bio4 Viable Bone Matrix (Osiris Therapeutics, Inc.) for Lumbar Fusion Procedures identified no published studies that examined the safety and efficacy of Bio4, or how it compares to similar products. Bio4 is derived from donated human bone and is minimally processed to preserve bone-forming cells.

A 2019 ECRI clinical evidence assessment, updated in 2022, entitled PrimaGen Advanced Allograft (Zimmer Biomet) for Lumbar Fusion Procedures identified no published studies that examined the safety and efficacy of the PrimaGen Advanced Allograft, or how it compares to similar products. PrimaGen is derived from donated human bone and is minimally processed to preserve bone-forming cells. Hayes (2020, updated in 2022) conducted a health technology assessment on the use of concentrated bone marrow aspirate (CBMA) for spinal surgery Ten studies addressed lumbar spinal fusion, and two addressed cervical spinal fusion. Overall, a low-quality body of evidence is available to evaluate the use of CBMA for spinal surgeries, and substantial uncertainty exists regarding the benefits of CBMA as an adjunct for spinal fusion. There is a lack of consensus on the optimal enrichment technique, delivery method and the CBMA preparations, and additional well-designed studies are needed to establish whether use of CBMA is associated with inferior fusion success compared with other approaches for lumbar spinal fusion.

Kerr et al. (2011) conducted a retrospective review to analyze the clinical effectiveness of mesenchymal stem cells allograft (Osteocel, NuVasive, Inc.) to achieve radiological arthrodesis in adult patients undergoing lumbar interbody fusion surgery for

different indications. Fifty-two consecutive patients received lumbar interbody fusion at one (69%) or two contiguous (31%) levels of lumbar spine for various indications. Procedures performed were circumferential fusion (67%), ALIF (17%) and TLIF (16%). Follow-up radiographic data was analyzed to establish arthrodesis versus failure (pseudarthrosis), number of months until achievement of fusion, and possible factors affecting the fusion rate. Follow up ranged from 8 to 27 (median, 14) months. Solid arthrodesis was achieved in 92.3% of patients at median follow up time of 5 months (95% CI; range, 3 to 11 months). Kaplan-Meier survival curves and Mantle-Cox test were conducted to assess the effect of various factors on the rate of fusion. Statistics showed that increasing age (older than 50 years) and habitual smoking delayed the fusion time and increased the risk of pseudarthrosis. The use of Osteocel allograft is safe and effective in adult patients undergoing lumbar interbody spinal fusion procedure. Increased age and habitual smoking delays fusion but gender, previous surgery at the index level, type of procedure and number of levels do not affect the fusion rates. The study is limited by retrospective study design. Additional studies, preferably long-term randomized controlled trials, are needed to further validate these results.

Human Amniotic Tissue

A search of the peer-reviewed medical literature databases of amniotic tissues in orthopedic applications show a need for future research. There is limited evidence in human models that amniotic tissue membrane improves health outcomes when used in lumbar spine fusion. Long term safety and efficacy have not been established.

Expandable Interbody Fusion Systems

There is insufficient evidence in the form of high-quality peer-reviewed medical literature to establish the efficacy of the Expandable Interbody Fusion System on spine fusion outcomes.

Kucharzyk et al. (2023) conducted a retrospective study to review and analyze collected perioperative, radiographic, and clinical outcome data following treatment with either a static or minimally invasive expandable transforaminal lumbar interbody fusion (TLIF) device for the treatment of spondylolisthesis, degenerative disc disease, spinal stenosis, disc herniation, or degenerative scoliosis. Patients treated with either static or expandable transforaminal lumbar interbody fusion devices (ProLift® Expandable Spacer System) for the treatment of spondylolisthesis, degenerative disc disease, spinal stenosis, disc herniation, or degenerative scoliosis at L4-L5 or L5-S1 were chosen from retrospective data. Outcomes included radiographic and spinopelvic changes, patient-reported outcomes, and incidence of nonunion and revision surgery. One hundred patients were included (Static: 50; Expandable: 50). Demographics between groups were similar, with some differences in comorbidities and spinal disease diagnosis. Radiographically, changes in disc height, foraminal height, and lordosis were improved in the Expandable group up to 2 years ($p < 0.001$). Improvements in patient reported outcomes were more favorable in the Expandable group. The authors concluded patients who underwent transforaminal lumbar spinal fusion via minimally invasive surgery, the Expandable device group, demonstrated improved radiographic, and patient reported outcomes compared to a static cage over 2 years. Prospective randomized controlled trials, with larger sample sizes and long-term patient follow-up are needed to validate these findings.

Kucharzyk and Miller (2020) conducted a retrospective, single-center study to evaluate the two-year clinical safety and effectiveness outcomes of a multi-expandable interbody fusion device (Luna 3D Interbody Fusion System) in patients undergoing posterior or transforaminal lumbar interbody fusion. Key patient-reported outcomes included back pain severity, leg pain severity, and the Oswestry Disability Index (ODI). Radiographic assessments included disc height (anterior, posterior, and average), foraminal height, segmental lordosis, subsidence, implant migration, and pseudarthrosis. A total of 50 consecutive patients were treated with transforaminal lumbar interbody fusion (TLIF) using the multidimensional expandable implant and followed at regular intervals over two years post-procedure. Procedural blood loss was minimal (median 200 ml), and the mean hospital stay was 2.1 days. Perioperative complications were reported in three patients and included a dural tear, postoperative ileus, and end-plate violation. All complications were successfully managed conservatively. There were no nerve root injuries or perioperative infections. Over the two-year follow-up period, one case of subsidence and one case of implant migration were noted on radiographic imaging but required no treatment. Comparing the values reported at baseline and two years, the mean ODI score decreased by 61%, back pain severity decreased by 67%, and leg pain severity decreased by 80% (all $p < 0.001$). One case of non-union was observed and the corresponding two-year fusion rate was 98%. The authors concluded that the utilization of a minimally invasive, multidimensional, expandable interbody implant was safe and effective over two years of clinical follow-up. The implant allows the surgeon to re-establish sagittal balance and to provide a larger surface area for fusion as compared to traditional minimally invasive interbody devices. This study is limited by its retrospective observations, single-center patient population, and lack of a controlled comparator group. The findings of this study need to be validated by well-designed studies.

Clinical Practice Guidelines

American Academy of Neurological Surgeons (AANS)

In a 2014 guideline update for the performance of fusion procedures for degenerative disease of the lumbar spine, the AANS makes the following recommendations:

- The use of demineralized bone matrix (DBM) as a bone graft extender is an option for 1- and 2-level instrumented posterolateral fusions.
- The use of b-tricalcium phosphate (b-TCP)/local autograft as a substitute for autologous iliac crest bone (AICB) is an option for single-level instrumented posterolateral fusion due to comparable fusion rates and clinical outcomes.

Hydroxyapatite/Calcium Extenders

- The use of hydroxyapatite (HA) with local autograft/bone marrow aspirate (BMA) as a substitute for AICB in an option for instrumented posterolateral fusion due to comparable fusion rates and clinical outcomes.
- The use of HA can be considered an option as a graft extender when mixed with AICB for instrumented posterolateral fusions.
- There is insufficient evidence to recommend for or against the use of a HA-glass/BMA composite as an autograft substitute for posterolateral fusion.
- The use of calcium sulfate preparations mixed with local autograft, as a substitute for autologous iliac crest bone, (AICB), is an option for instrumented posterolateral fusions. (Kaiser 2014)

rhBMP-2

The use of rhBMP-2 as a graft option has been associated with unique complications that the surgeon should be aware of when considering its use.

Interbody Fusion

- As a substitute for AICB for anterior lumbar interbody fusion (ALIF) with threaded interbody cages is an option due to similar fusion rates and clinical outcomes.
- As a substitute for AICB for single-level posterior lumbar interbody fusion (PLIF) is an option due to similar fusion rates and clinical outcomes; however, formation of heterotopic bone has been observed.
- As a bone graft extender can be considered as an option when performing a transforaminal lumbar interbody fusion (TLIF) procedure with a structural interbody graft.
- There is insufficient evidence to make a recommendation regarding the use of rhBMP-2 as a supplement for stand-alone ALIF procedures using femoral ring allograft or with a resorbable spacer when performing TLIF procedures.

Posterolateral Fusion

- Supplemented with 15% HA/85% b-TCP matrix as a substitute for AICB is an option in single-level posterolateral instrumented fusions given the consistent observation of comparable fusion rate and clinical outcomes.
- Supplemented with graft extenders as an alternative to AICB is an option for single-level, instrumented posterolateral fusions in patients older than 60 years.
- As a graft extender with either AICB or local bone is an option in patients undergoing either instrumented or non-instrumented posterolateral fusions.

There is insufficient evidence to formulate a recommendation regarding the use of rhBMP-2/local bone as a substitute for AICB when performing revision posterolateral fusions or the use of rh- BMP-2/calcium-based extenders for single level posterolateral fusions in patients who smoke and elect to undergo surgery for lumbar spondylosis.

North American Spine Society (NASS)

In a 2017 evidence-based coverage policy recommendation for allograft and demineralized bone matrix for spinal fusion, the NASS identified the following scope and clinical indications:

Structural Allograft

Structural cortical or corticocancellous allograft bone (fresh-frozen or freeze-dried), with or without additional autograft, is indicated for use in anterior cervical spinal reconstruction in the following clinical scenarios:

- Anterior Cervical Discectomy and Fusion
  - Uninstrumented single level
  - Instrumented single-level
  - Instrumented multilevel
- One or more level cervical corpectomy

Posterior Cervical Fusion

Structural allograft is indicated for posterior upper cervical and occipitocervical instrumented fusion:

- Nonstructural allograft bone
- Demineralized Bone Matrix (DBM) may be indicated for anterior cervical spinal reconstruction and fusion for cervical radiculopathy and/or myelopathy in the following clinical scenarios:
  - Anterior Cervical Discectomy and Fusion
  - Cervical Corpectomy
  - Posterior Cervical Fusion
  - Thoracolumbar Spine Fusion
    - Structural cortical and corticocancellous allograft bone (with or without additional autograft)
      - Interbody Fusion (including transforaminal (TLIF), posterior (PLIF) and anterior (ALIF) lumbar interbody fusion)
      - Anterior Corpectomy and Fusion
    - Nonstructural Allograft (with or without additional autograft)
      - Posterior Instrumentation and Fusion
      - In combination with structural allograft or synthetic cages for thoracolumbar interbody fusion

DBM combined with autograft is indicated for use in posterior instrumented fusion. There is no significant evidence at this time for use as a stand-alone product in non-instrumented posterior fusion or anterior fusions.

Iliac crest bone autograft (ICBG) remains the “gold standard” material for structural and nonstructural bone graft in cervical and thoracolumbar spine fusion, though the morbidity associated with its harvest, including fracture, infection, neurologic injury, and chronic pain at the harvest site, have led to allograft becoming a more frequently used non-autogenous bone graft material in spine surgery.

In a 2014 evidence- based coverage policy recommendation for recombinant human bone morphogenic protein (rhBMP-2), the NASS states rhBMP-2 may be considered as an adjunct to spinal fusion for the following diagnoses:

- Stand-Alone Anterior Lumbar Interbody Fusion (ALIF) in all patient groups except males with a strong reproductive priority.
- Posterolateral Lumbar Fusion in patients at high risk for nonunion with autogenous bone graft or in those with inadequate or poor-quality autogenous bone available.
- Posterior Lumbar Interbody Fusion (PLIF and TLIF) in patients at high risk for nonunion with autogenous bone graft or in those with inadequate or poor-quality autogenous bone available.
- Posterior Cervical or Thoracic Fusions
  - In pediatric patients at very high risk for fusion failure (e.g., neuromuscular scoliosis, occipitocervical pathology.
  - In adult patients at high risk for nonunion, for example, revision surgery.
- Anterior cervical fusion in patients at high risk for nonunion.

The society also states that rhBMP-2 should not be used for the following:

- Routine anterior and posterior cervical fusion procedures.
- Single level posterior/posterolateral fusions in healthy adults.
- Routine pediatric spine fusion procedures (e.g., adolescent idiopathic scoliosis).

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Allografts are considered tissues for transplantation. FDA: “Minimally manipulated human bone for transplantation: Human cells or tissue intended for implantation, transplantation, infusion, or transfer into a human recipient is regulated as a human cell, tissue, and cellular and tissue-based product or HCT/P.” If combined with other materials, the resulting product is considered a

device and regulated by the FDA as a medical device. Refer to the following website for more information: https://www.fda.gov/vaccines-blood-biologics/tissue-tissue-products. (Accessed May 11, 2023)

Products used for bone growth and bone grafts products are extensive. Refer to the following website for more information and search by product name in device name section: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed May 11, 2023)

In 2018, the FDA granted 501K premarket approval for the Bicera® Resorbable Bone Substitute. Refer to the following website for more information: https://www.accessdata.fda.gov/cdrh_docs/pdf17/K172237.pdf. (Accessed May 11, 2023)

In July 2002, the FDA granted 510K premarket approval for the InFUSE™ Bone Graft/LT-CAGE™. It has several supplements. Refer to the following website for more information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P000058. (Accessed May 11, 2023)

In November 2015, the FDA granted 510 (k) premarket approval for the i-FACTOR® peptide enhanced bone graft. Refer to the following website for more information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm. (Accessed May 11, 2023)

In October 2008, the FDA granted the InFUSE/MASTERGRAFT Humanitarian Device Exemption. Refer to the following website for more information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfHDE/hde.cfm?id=375525. (Accessed May 11, 2023)

In November 2003 the FDA granted 510(k) premarket approval for the OptiMesh® Expandable Interbody Fusion System for maintaining the relative position of bone graft material within a vertebral body defect that does not impact the stability of the vertebral body and does not include the vertebral endplates. Refer to the following website for more information: https://www.accessdata.fda.gov/cdrh_docs/pdf/K014200.pdf. (Accessed May 11, 2023)

In September 2020, the OptiMesh® Expandable Interbody Fusion System was granted De Novo classification for expanded indications allowing the use with bone graft and supplemental posterior fixation in lumbar interbody fusion. Refer to the following website for more information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/denovo.cfm?id=DEN200010. (Accessed May 11, 2023)

In February 2021, the FDA granted 510(k) premarket approval for the Duo™ Expandable Interbody Fusion System for intervertebral body fusion at one level, or two contiguous levels in the lumbar spine from L2 to L5 in patients with degenerative disc disease with up to Grade I spondylolisthesis at the involved level. Refer to the following website for more information: https://www.accessdata.fda.gov/cdrh_docs/pdf21/K210155.pdf. (Accessed May 11, 2023)

References

Agarwal, R, Williams, K, Umscheid, CA, et al. Osteoinductive bone graft substitutes for lumbar fusion: a systematic review. J Neurosurg Spine. 2009;11(6):729-740.

Chrastil J, Low JB, Whang PG,. Complications associated with the use of the recombinant human bone morphogenetic proteins for posterior interbody fusions of the lumbar spine. Spine (Phila Pa 1976). 2013; 38(16):E1020-1027.

Cottrill E, Premananthan C, Pennington Z, et al. Radiographic and clinical outcomes of silicate-substituted calcium phosphate (SiCaP) bone grafts in spinal fusion: Systematic review and meta-analysis. J Clin Neurosci. 2020 Nov;81:353-366.

Dimar JR 2nd, Glassman SD, Burkus JK, et al. Clinical and radiographic analysis of an optimized rhBMP-2 formulation as an autograft replacement in posterolateral lumbar spine arthrodesis. J Bone Joint Surg Am. 2009 Jun; 91(6):1377-86.

ECRI Institute. Bicera Bone Graft Substitute (Wiltrom Corp. Ltd.) for Filling Bone Defects. April 2022.

ECRI Institute. Bio4 Viable Bone Matrix (Osiris Therapeutics, Inc.) for Lumbar Fusion Procedures. September 2019; Updated February 2022.

ECRI Institute. Clinical Evidence Assessment. Bioactive Glass Bone Graft Substitutes for Spinal Fusion and Long Bone Voids. April 2022.

ECRI Institute. Clinical Evidence Assessment. Ceramic Bone Graft Substitutes for Spinal Fusion and Long Bone Voids. January 2022.

ECRI. Clinical Evidence Assessment. OsteoAMP Bone Graft (Bioventus, LLC.) for Cervical Spinal Surgery. April 2022.

ECRI. Clinical Evidence Assessment. OsteoAMP Bone Graft (Bioventus, LLC.) for Lumbar Spine Surgery. June 2016; Updated April 2022.

ECRI Institute. Osteocel Cellular Allograft (NuVasive, Inc.) for Spinal Fusion Procedures. February 2019; Updated February 2022.

ECRI Institute. PrimaGen Advanced Allograft (Zimmer Biomet) for Lumbar Fusion Procedures. February 2019; Updated February 2022.Glassman SD, Gum JL, Crawford CH 3rd, et al. Complications with recombinant human bone morphogenetic protein-2 in posterolateral spine fusion associated with a dural tear. Spine J. 2011; 11(6):522-526.

Gomez G, Westerlund LE. Clinical and radiographic outcomes using third-generation bioactive glass as a bone graft substitute for multi-level anterior cervical discectomy and fusion-a retrospective case series study. J Spine Surg. 2021 Jun;7(2):124-131.

Griffoni C, Tedesco G, Canella V, et al. Ceramic bone graft substitute (Mg-HA) in spinal fusion: a prospective pilot study. Front Bioeng Biotechnol. 2022 Nov 17;10:1050495.

Guzman JZ, Merrill RK, Kim JS, et al. Bone morphogenetic protein use in spine surgery in the United States: how have we responded to the warnings? Spine J. 2017 Sep;17(9):1247-1254.

Hayes Inc. Health Technology Assessment. Concentrated bone marrow aspirate for spinal surgery. Lansdale, PA: May 2020; Updated May 2022.

Hayes Inc. Medical Technology Directory. Comparative effectiveness review of recombinant human bone morphogenetic protein (rhBMP) for use in spinal fusion. Lansdale, PA: January 2021.

Heckmann N, Auran R, Mirzayan R. Application of amniotic tissue in orthopedic surgery. Am J Orthop (Belle Mead NJ). 2016 Nov/Dec;45(7):E421-E425.

Hsieh PC, Buser Z, Skelly AC, et al. Allogenic Stem Cells in Spinal Fusion: A Systematic Review. Global Spine J. 2019 May;9(1 Suppl):22S-38S.

Im SK, Lee JH, Lee KY, et al. Effectiveness and feasibility of injectable Escherichia coli-derived recombinant human bone morphogenetic protein-2 for anterior lumbar interbody fusion at the lumbosacral junction in adult spinal deformity surgery: a clinical pilot study. Orthop Surg. 2022 Jul;14(7):1350-1358.

James AW, LaChaud G, Shen J, et al. A Review of the Clinical Side Effects of Bone Morphogenetic Protein-2. Tissue Eng Part B Rev. 2016 Aug;22(4):284-97.

Kaiser MG, Groff MW, Watters WC 3rd, et al. Guideline update for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 16: bone graft extenders and substitutes as an adjunct for lumbar fusion. J Neurosurg Spine. 2014 Jul;21(1):106-32.

Kelly MP, Savage JW, Bentzen SM, et al. Cancer risk from bone morphogenetic protein exposure in spinal arthrodesis. J Bone Joint Surg Am. 2014 Sep 3;96(17):1417-22.

Kerr et al. The use of osteo-conductive stem-cells allograft in lumbar interbody fusion procedures: an alternative to recombinant human bone morphogenetic protein. J Surg Orthop Adv. 2011 Fall;20(3):193-7.Liu S, Wang Y, Liang Z, et al. Comparative clinical effectiveness, and safety of bone morphogenetic protein versus autologous iliac crest bone graft in lumbar fusion: A meta-analysis and systematic review. Spine (Phila Pa 1976). 2020 Jun 15;45(12):E729-E741.

Kucharzyk DW, Miller LE. Two-year clinical and radiographic results with a multidimensional, expandable interbody implant in minimally invasive lumbar spine surgery. Cureus. 2020 Feb 21;12(2):e7070.

Kucharzyk DW, Budimir D, Waldorff EI, et al. The effect of expandable versus static lordotic interbody implants in minimally invasive spine surgery: patient reported outcomes, sagittal alignment, and restoration of disc height and foraminal height. J Spine Surg. 2023 Mar 30;9(1):39-53.

Lee JH, Kim SK, Kang SS, et al. A long-term follow-up, multicenter, comparative study of the radiologic, and clinical results between a CaO-SiO2-P2O5-B2O3 bioactive glass ceramics (BGS-7) intervertebral spacer and titanium cage in 1-level posterior lumbar interbody fusion. Clin Spine Surg. 2020 Aug;33(7):E322-E329.

MedicineNet. Medical Definitions. 2022.

Medtronic, Inc. https://global.medtronic.com/xg-en/e/response/infuse-bone-graft.html. Accessed May 11, 2023.

Meng H, Gao Y, Zhao G, et al. Use of recombinant human bone morphogenetic protein-2 with iliac crest bone graft instead of iliac crest bone graft alone in lumbar spondylolysis. Clin Spine Surg. 2022 Mar 1;35(2):E314-E319.

Mummaneni PV, Dhall SS, Eck JC, et al. Guideline update for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 11: interbody techniques for lumbar fusion. J Neurosurg Spine. 2014 Jul;21(1):67-74.

Nickoli MS, Hsu WK. Ceramic-based bone grafts as a bone grafts extender for lumbar spine arthrodesis: a systematic review. Global Spine J. 2014 Aug;4(3):211-6.

North American Spine Society (NASS) Coverage Policy Recommendations for Spinal Fusion: Allograft and Demineralized Bone Matrix. 2017.

North American Spine Society (NASS) Coverage Policy Recommendations: Recombinant Human Bone Morphogenetic Protein (rhBMP-2). 2014. Spineology®, Inc. https://www.spineology.com/united-states/our-products/OptiMesh. Accessed May 11, 2023.

Zhang Y, Jiang Y, Zou D, et al. Therapeutics for enhancement of spinal fusion: A mini review. J Orthop Translat. 2021 Dec 6;31:73-79.

Policy History/Revision Information

Date	Summary of Changes
10/01/2023	**Application** ***Individual Exchange Plans*** • Removed language indicating this Medical Policy does not apply to Individual Exchange benefit plans in the states of Massachusetts, Nevada, and New York **Supporting Information** • Archived previous policy version 2023T0410DD

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.