

# Bone or Soft Tissue Healing and Fusion Enhancement Products

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[➔ Instructions for Use](#)

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## Related Commercial Policies

- [Ablative Treatment for Spinal Pain](#)
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- [Prolotherapy and Platelet Rich Plasma Therapies](#)
- [Surgical Treatment for Spine Pain](#)

## Community Plan Policy

- [Bone or Soft Tissue Healing and Fusion Enhancement Products](#)

## Coverage Rationale

[➔ See Benefit Considerations](#)

The following are proven and medically necessary for the enhancement of fusion and/or bone healing:

- Autografts
- Demineralized bone matrix (DBM)
- Allograft-based products
- Recombinant human bone morphogenetic protein-2 (e.g., rhBMP-2, InFUSE) 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 L4-S1, with or without spondylolisthesis of no more than grade 1 (25% displacement) at the involved level
  - The fusion is single level
  - Failure of at least 6 months of non-operative medical treatment
- The InFUSE/MASTERGRAFT™ Posterolateral Revision Device system when used according to U.S. Food and Drug Administration (FDA) indications in individuals who meet all 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)
  - Treatment of 2 or more levels of the lumbar spine
  - 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 fusion and/or bone healing due to insufficient evidence of efficacy:

- Cell-based (e.g., mesenchymal stem cells (MSC))
- Ceramic-based products (e.g., beta tricalcium phosphate (b-TCP), calcium phosphate, calcium sulfate and bioactive glass) used alone or in combination with other grafts including bone marrow aspirate
- Human amniotic membrane bone graft substitute materials, including amniotic fluid stem cell substitutes for the treatment of spine disease or in spine surgery
- Recombinant human bone morphogenetic protein-7 (rhBMP-7) including but not limited to, Osteogenic Protein-1 (OP-1® Implant & Putty) with or without use of other devices
- Recombinant human bone morphogenetic protein-2 (e.g., rhBMP-2, InFUSE) and InFUSE/MASTERGRAFT™ Posterolateral Revision Device for all other indications not included [above](#)
- The OptiMesh® deployable grafting 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
<b>Bone or Soft Tissue Healing and Fusion Enhancement Products</b>	
22558 22585 22899	<p>Medical notes documenting all of the following:</p> <ul style="list-style-type: none"> <li>● Condition requiring procedure</li> <li>● History and co-morbid medical condition(s)</li> <li>● Member’s symptoms, pain, location, and severity including functional impairment that is interfering with activities of daily living (meals, walking, getting dressed, driving)</li> <li>● Physical exam, including neurologic exam</li> <li>● History and duration of previous therapy, when applicable including: <ul style="list-style-type: none"> <li>○ Physical therapy</li> <li>○ Medications (injections)</li> <li>○ Previous surgery</li> <li>○ Bracing</li> <li>○ Other attempted treatments</li> </ul> </li> <li>● Whether the surgery will be performed with direct visualization or only with endoscopic visualization</li> <li>● Complete report(s) of diagnostic tests and imaging</li> <li>● 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.]</li> <li>● Specify the allograft product [including brand name(s)] to be used: <ul style="list-style-type: none"> <li>○ Autograft</li> <li>○ Demineralized bone matrix (DBM) allograft</li> <li>○ Allograft (cadaver, etc.)</li> <li>○ Bone morphogenetic protein-2 (BMP-2) (e.g., Infuse® Bone Graft or Infuse/MASTERGRAFT™ or Posterolateral Revision Device system)</li> <li>○ Bone morphogenetic protein-7 (BMP-7)</li> <li>○ Amniotic tissue membrane</li> <li>○ Ceramic-based products (e.g., beta tricalcium phosphate (b-TCP), etc.)</li> <li>○ Cell-based products (e.g., mesenchymal stem cells)</li> <li>○ OptiMesh</li> </ul> </li> </ul>

\*For code descriptions, see the [Applicable Codes](#) section.

# Definitions

**Allograft:** An allograft is obtained from a person other than the surgical candidate. Harvested through a minimally invasive procedure, this allograft provides a population of osteoprogenitor cells and critical growth factors that help cell differentiation, leading to bone healing. It can include cadaveric bone and/or tissue from a bone bank. It may be used alone or in combination with another material. Even when used alone, allograft must be processed to decrease the likelihood of disease transmission and immunogenic response.

More recently, processing methods used for preparation of some allografts have been refined and products are now available that manufacturers claim retain higher concentrations of naturally occurring growth factors and/or stem cells. Human growth factors such as fibroblast growth factor, insulin-like growth factor, transforming growth factor-beta, and microglobulin-B, are examples of osteogenic growth factors that are naturally found within the matrix of bone.

**Anorganic Bone Graft Materials:** Anorganic bone graft materials are a type of xenograft bone graft substitute made from other than human material, such as cow (i.e., bovine) or coral, and is typically used in combination with other types of bone graft materials, for example with collagen or a calcified matrix. The animal bone is processed to remove any organic components (i.e., anorganic bone material) reducing concerns of disease transmission or immunogenic reactions. Some of the anorganic type xenograft materials may be used as stand-alone graft material to enhance healing.

**Autograft:** An autograft is taken directly from the patient undergoing surgery. The usual site for an autograft harvest is the posterior iliac crest. When autograft material is of an insufficient volume, of poor quality, or cannot be used for any other reason, another type of material must be used for the bone graft.

**Bone Morphogenetic Proteins (BMP) and Recombinant Human Bone Morphogenetic Proteins (rhBMP):** RhBMP is a unique subgroup of graft substitutes. Bone morphogenetic proteins are naturally occurring proteins found in human bone and play an active role in bone formation. Recombinant human bone morphogenetic proteins act as an adjunct to autogenous bone grafts and are used commonly with spinal instrumentation devices (i.e., cages) during lumbar fusion and for fracture repair.

**Carrier Systems:** Function to maintain the concentration of the rhBMP at the treatment site, provide temporary scaffolding for osteogenesis and prevent extraneous bone formation. Carrier systems have included inorganic material, synthetic polymer, natural polymers and bone allograft. The rhBMP and carrier may be inserted via a delivery system, which may also function to provide mechanical support. The carrier and delivery system are important variables in the clinical use of rhBMPs.

**Cell-Based Products:** Bone graft substitutes that are cell-based use cells to generate new tissue either alone, with other biomaterials, or seeded onto a support matrix (e.g., in combination with allograft material). One material proposed for use in combination with allograft is mesenchymal stem cells (MSC), obtained from bone marrow aspirate. Potential uses of MSCs for orthopedic applications include treatment of damaged bone, cartilage, ligaments, tendons, and intervertebral discs.

**Ceramic-Based Products:** Ceramic-based bone graft substitutes include materials such as calcium phosphate, calcium sulfate and bioactive glass, used alone or in combination with other grafts. Some ceramic-based products (e.g., calcium phosphate-collagen composites, beta-tricalcium phosphate) are combined with collagen to augment healing; collagen composites may include bovine material similar to that used with cell-based products. Several types of calcium phosphates, including tricalcium phosphate, synthetic hydroxyapatite, and coralline hydroxyapatite are available in pastes, putties, solid matrices, and granules.

**Combination Bone Graft Substitutes:** A newer practice in the use of bone graft substitutes is to combine different materials, with the theory that each different property working together will work in synergy with another in the healing and grafting process.

**Concentrated Bone Marrow Aspirate (CBMA):** CBMA is produced from native BMA, usually obtained from the iliac crest or local vertebrae. The bone marrow aspirate contains stem cells that have been proposed to help with the healing of some bone and joint conditions.

**Demineralized Bone Matrix (DBM):** DBM is a type of allograft; it is produced by acid extraction of allograft bone (known as decalcification). Based on manufacturing techniques, DBM may be a freeze-dried powder, granules, gel, putty, or strips. After processing, the material contains 90% type I collagen and 10% noncollagen protein containing a variety of bone growth

stimulators such as bone morphogenetic protein (BMPs). The bone growth stimulators induce osteoblast formation (osteinduction) from the patient's osteogenic stem cells. Added materials provide a three-dimensional substance into which capillaries, osteogenic cells, and other tissue can migrate and produce new bone (osteoconduction). DBM is commonly used as a bone graft extender for posterolateral spinal fusion surgery.

**Human Amniotic Tissue Membrane:** The innermost layer of the amniotic fetal membrane is considered a source of collagen that acts as a scaffold for the attachment of cells. Recently, amniotic membrane allografts have been investigated for various uses including use as bone void fillers during spinal and other orthopedic surgeries to enhance bone healing.

**InFUSE Bone Graft:** InFUSE Bone Graft is the premium product for autograft replacement due to its high osteoinductivity. Infuse bone graft is recombinant human bone morphogenetic protein-2 (rhBMP-2) applied to an absorbable collagen sponge carrier (ACS). One of the functions of the protein is to stimulate natural bone formation.

**OptiMesh Grafting System:** OptiMesh is a conformable, porous, polymeric containment device that is inserted into the evacuated disc space and filled with a mixture of cortico-cancellous allograft with demineralized bone matrix, autograft, and bone marrow aspirate to aid traumatic fracture repair and interbody fusion.

**Orthobiologics:** Are designed to substitute for real bone, but they can also enhance bone-fracture healing or bone fusion by providing substances that are either osteoconductive or osteoinductive (described in further detail below). Some products may have both properties. Orthobiologics require an invasive surgical procedure to place the material in the bone void site or at the site of bone fusion.

- **Osteoconductive Matrix Materials:** Osteoconductive materials provide a three-dimensional substance into which capillaries, osteogenic cells, and other tissue can migrate and produce new bone. This material acts only as a scaffold into which the new bone cells grow.
- **Osteoinductive Bone Graft Substitutes:** Osteoinduction means that the product induces osteoblast formation from the patient's own osteogenic stem cells that are already present at the fusion site. The osteoinductive properties of bone tissue are attributed to bone morphogenetic proteins (BMPs).

Bone graft substitutes have overlapping properties and are made of a variety of materials such as polymers (degradable and nondegradable), ceramics and composites (calcium phosphate, calcium sulfate, and bioactive glass), factor-based techniques (recombinant growth factors) and cell-based techniques (mesenchymal stem cells).

**RhBMP-7/Osteogenic Protein-1 (OP-1® Implant & Putty):** A second type of human bone morphogenetic protein is rhBMP-7, marketed in the United States as OP-1® Implant for use in healing fractures of the long bones, and OP-1™ Putty for use in spinal fusion. OP-1™ Putty is a recombinant human bone morphogenetic protein-7 (rhBMP-7) and type 1 bovine bone collagen matrix combined with the putty additive carboxymethylcellulose sodium. It is intended to aid in treating lumbar spine pseudoarthrosis.

## 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)
20932	Allograft, includes templating, cutting, placement and internal fixation, when performed; osteoarticular, including articular surface and contiguous bone (List separately in addition to code for primary procedure)

CPT Code	Description
20933	Allograft, includes templating, cutting, placement and internal fixation, when performed; hemicortical intercalary, partial (i.e., hemicylindrical) (List separately in addition to code for primary procedure)
20934	Allograft, includes templating, cutting, placement and internal fixation, when performed; intercalary, complete (i.e., cylindrical) (List separately in addition to code for primary procedure)
22558	Arthrodesis, anterior interbody technique, including minimal discectomy to prepare interspace (other than for decompression); lumbar
22585	Arthrodesis, anterior interbody technique, including minimal discectomy to prepare interspace (other than for decompression); each additional interspace (List separately in addition to code for primary procedure)
22899	Unlisted procedure, spine

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## Description of Services

The composition of allograft and synthetic bone graft substitutes and their mechanism of action can vary widely. Bone graft materials are often combined to extend graft availability and enhance healing. Used alone or in combination, bone graft substitutes may be utilized for many orthopaedic applications including spinal fusion. The carrier and delivery system are important variables in the clinical use of rhBMPs, and different clinical applications, such as long bone nonunion, or interbody or intertransverse fusion, may require different dosages of rhBMP along with different carriers and delivery systems.

## 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

### Bone Morphogenetic Protein (rhBMP or BMP)

As a result of reported complications and the recent concern regarding safety and efficacy, use of rhBMP-2 products should be limited to the FDA-approved labeling indications. Evidence in the peer-reviewed scientific literature is insufficient and does not provide strong support to safety and efficacy to enhance bone healing.

Hayes (2018) the literature search identified a large body of moderate-quality evidence suggests that, compared with an autograft, use of rhBMP-2 for lumbar spinal fusion provides more rapid fusion and/or a somewhat greater likelihood of achieving fusion. Use of rhBMP-2 also appears reasonably safe for lumbar fusion over the short term. 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.

ECRI (2017) performed literature review specific to use of demineralized bone matrix for orthopedic and spine procedures. ECRI reported that DBM is a safe and effective bone graft substitute for use in orthopedic and spine procedures.

ECRI (2017) reviewed the evidence of five clinical studies of anterior interbody lumbar fusion. The authors reported a consensus statement for ALIF and use of Infuse increased the fusion rate compared with iliac crest bone graft (ICBG) but suggested that patients be informed of potential complications associated with Infuse. Based upon the published literature, we conclude that rhBMP-2 is likely associated with an increased rate of radiographic arthrodesis when compared with ICBG [iliac crest bone graft]. However, this does not necessarily translate to an improvement in clinical outcomes. Although rhBMP-2 limits the morbidity associated with harvesting ICBG, which may explain the shorter operative times and less blood loss, patients should be counseled regarding the potential complications that are specific to rhBMP-2 utilization including osteolysis and

retrograde ejaculation. rhBMP-2 may also be associated with lumbar plexopathy when utilized in the transposas lumbar fusion cases.

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.

The U.S. Food and Drug Administration reported a higher incidence of cancer in patients who had spinal arthrodesis and were exposed to a high dose of recombinant human bone morphogenetic protein-2 (rhBMP-2). The purpose of this study was to determine the risk of cancer after spinal arthrodesis with BMP. Kelly et al. (2014) performed a retrospective analysis of the incidence of cancer in 467,916 Medicare patients undergoing spinal arthrodesis from 2005 to 2010. Patients with a preexisting diagnosis of cancer were excluded. The main outcome measure was the relative risk of developing new malignant lesions after spinal arthrodesis with or without exposure to BMP. The relative risk of developing cancer after BMP exposure was 0.938. In the BMP group, 5.9% of the patients developed an invasive cancer compared with 6.5% of the patients in the control group. The relative risk of developing cancer after BMP exposure was 0.98 in males and 0.93 in females. The control group showed a higher incidence of each type of cancer except pancreatic cancer. The authors concluded that recent clinical use of BMP was not associated with a detectable increase in the risk of cancer within a mean 2.9-year time window.

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.

In a systematic review and meta-analysis of randomized, controlled trials and cohort studies by Fu et al. (2013), the clinical effectiveness of BMP-2 in spine fusion was assessed. This review found that in spinal fusion, rhBMP-2 has no proven clinical advantage over bone graft and may be associated with important harms, making it difficult to identify clear indications for rhBMP-2. Earlier disclosure of all relevant data would have better informed clinicians and the public than the initial published trial reports did.

Chrastil and others (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 and colleagues describes a retrospective case review of 1037 subjects who underwent posterolateral spine fusion using rhBMP-2, with a focus on complication rates (2011). 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."

### ***Agency for Healthcare Research and Quality (AHRQ)***

The AHRQ in 2010 concluded that the evidence supports the use of rhBMP-2 for fusion of the lumbo-sacral spine. However, there is insufficient evidence to make conclusions regarding the use of BMP-7 to aid fusion in the lumbar spine. There is moderate evidence that the use of rhBMP-2 in cervical spine fusion increases cervical swelling and related complications. The strength of the evidence on clinical outcomes is moderate for on-label use of rhBMP-2 to enhance bony fusion in acute open shaft tibial fractures if the device is applied within 14 days of the initial fracture. BMP-7 may be used as an alternative to autograft in recalcitrant long-bone non-unions where use of an autograft is not feasible and alternative treatments have failed. The strength of the evidence is moderate that rhBMP-2 does not provide an advantage in prosthesis implantation and functional loading compared to autograft plus allograft bone for sinus augmentation.

A retrospective review by Yaremchuk et al. (2010) compared the incidence and severity of complications in patients undergoing cervical spinal procedures. A total of 775 patients were included. BMP was utilized in 260 of these patients. The authors found that patients in the BMP group had a higher incidence of acute airway obstruction. This was due to an extensive soft-tissue inflammatory reaction that is most likely to occur 2 to 7 days after surgery.

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.

Although early evidence supports safety and efficacy when used according to FDA indications, adverse events have been reported which include ectopic bone formation, bone resorption or remodeling at the graft site, hematoma, neck swelling, and painful seroma (Dural tears, bowel/bladder and sexual dysfunction, failure to fuse and paralysis have also been reported as well

as carcinogenicity and teratogenic effects. Recently there has been concern more specifically safety and efficacy of rhBMP-2 used in spinal fusion surgeries (Benglis et al. 2008).

## ***Professional Societies***

### **American Association of Neurological Surgeons and Congress of Neurological Surgeons**

(2014) 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.
- 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.

### **American Academy of Orthopaedic Surgeons (AAOS)**

Although the American Academy of Orthopaedic Surgeons does not have a formal position statement, the Orthopaedic Device Forum initially published a document addressing the use of bone graft substitutes in 2001 (Greenwald, et al., 2001). The forum noted at that time, and again in 2006 and 2008, that the currently marketed products vary in their composition and their claimed mechanisms of action—not all substitutes perform the same. Selection should be based on reasoned burdens of proof which include the examination of the product claims and whether or not they are supported by preclinical and human studies in site specific locations, where they are to be utilized in surgery. The AAOS noted it is imperative to appreciate the level of evidence claimed in the latter studies.

### **North American Spine Society (NASS)**

NASS (2014) has coverage recommendations for the recombinant human bone morphogenetic protein-2 (rhBMP-2). The Society notes that coverage recommendations do not represent a 'Standard of Care' nor are they intended as a fixed treatment protocol.

## **Ceramic-Based Products**

There is insufficient reliable evidence in the form of high-quality peer-reviewed medical literature to establish the efficacy or effects on health care outcomes.

ECRI (2018) conducted a literature review of synthetic bone graft substitutes versus autograft or allograft for treating lumbar spinal degenerative diseases. The review concluded that calcium phosphate and principal bone salt as well as Beta tricalcium phosphate ( $\beta$ -TCP) were effective in terms of fusion, functional outcomes, and complications for lumbar spinal degenerative disease. This review found the overall quality of the evidence was low with high potential for bias (few RCTs), small sample sizes, and high risk of bias in many studies because of variability in patient characteristics and lack of standardization and variability in reporting of outcomes; also, many studies lacked data on some important outcomes, such as infection. Thus, definitive conclusions or recommendations regarding the use of these synthetic materials should be made cautiously and within the context of the limitations of the evidence. (Buser et al. 2016)

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, we 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 from these data.



## Cell-Based Products

The use of cell-based bone graft substitutes has been and continues to be investigated for various procedures, including spinal fusion and for intervertebral disc regeneration. The lack of adequate controls, randomization and blinding and the small sample sizes precludes definitive conclusions regarding the net health benefit of cell-based therapy.

Hayes (2018) conducted concentrated bone marrow aspirate (CBMA) for spinal surgery literature review. Overall, a low-quality body of evidence is available to evaluate the use of CBMA for spinal surgeries. The limited evidence suggests that the balance of benefits and harms of concentrated BMA are at least comparable with those of alternative available graft materials. There is a paucity of long-term safety data from the randomized controlled trials. The overall quality of the evidence was assessed taking into consideration the quality of individual studies; the precision, directness, and consistency of data; and the applicability of the data to general practice.

Several preclinical studies have been conducted to evaluate the effectiveness of Mesenchymal stem cells (MSCs) in tissue regeneration. Caudwell and colleagues (2014) conducted a systematic review of preclinical studies using MSC and scaffolds in the treatment of knee ligament regeneration. The authors concluded, based on their investigation of 21 articles, that preclinical evidence of ligamentous regeneration with MSC and scaffold use was established, but limited clinical evidence exists to support recently developed scaffolds.

Kerr et al. (2011) conducted a retrospective review to analyze the clinical effectiveness of mesenchymal stem cells allograft (OsteoCel<sup>®</sup>) 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. Followup 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 Membrane

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 that amniotic tissue membrane improves health outcomes when used in lumbar spine fusion. Long term safety and efficacy have not been established. The function, structure, and characteristics of human amnion have been widely studied; however, there are very little research data to support the benefits of these tissues for orthopedic problems.

No professional guidelines offered recommendations regarding the use of amniotic-derived tissues for the treatment of orthopedic conditions.

## 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.

Products used for bone growth and bone grafts products are extensive. See 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 April 15, 2020)

## Centers for Medicare and Medicaid Services (CMS)

Medicare does not have a National Coverage Determinations (NCDs) specifically for the use of bone or soft tissue healing and fusion enhancement products. Local Coverage Determinations (LCDs) exist for HCPCS codes Q4186 and Q4187. See the LCDs for [Application of Bioengineered Skin Substitutes to Lower Extremity Chronic Non-Healing Wounds](#) and [Wound Application of Cellular and/or Tissue Based Products \(CTPs\), Lower Extremities](#).

Medicare does not have NCDs or LCDs for use of the following products:

- Cell-based (e.g., mesenchymal stem cells [MSC]) products
- Ceramic-based products (e.g., beta tricalcium phosphate (b-TCP), calcium phosphate, calcium sulfate and bioactive glass) used alone or in combination with other grafts including bone marrow aspirate
- Human amniotic membrane bone graft substitute materials, including amniotic fluid stem cell substitutes for the treatment of spine disease or in spine surgery
- Recombinant human bone morphogenetic protein-7 (rhBMP-7) including but not limited to, OP-1® Implant & Putty with or without use of other devices
- InFUSE/MASTERGRAFT™ Posterolateral Revision Device
- The OptiMesh® deployable grafting system
- Recombinant human bone morphogenetic protein-2 (e.g., rhBMP-2, InFUSE)

(Accessed April 23, 2020)

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## Policy History/Revision Information

Date	Summary of Changes
08/01/2020	<p><b>Template Update</b></p> <ul style="list-style-type: none"> <li>Reformatted policy; transferred content to new template</li> </ul> <p><b>Coverage Rationale</b></p> <ul style="list-style-type: none"> <li>Revised list of proven and medically necessary products for the enhancement of fusion and/or bone healing; replaced: <ul style="list-style-type: none"> <li>“Demineralized bone matrix (DBM) <i>allograft</i>” with “demineralized bone matrix (DBM)”</li> <li>“Allografts” with “allograft-based products”</li> <li>“Bone Morphogenetic Protein-2 (rhBMP-2) and Infuse® <i>Bone Graft</i>” with “<i>recombinant human bone morphogenetic protein-2 (e.g., rhBMP-2, InFUSE)</i>”</li> </ul> </li> <li>Revised coverage criteria for: <p><b><i>Recombinant Human Bone Morphogenetic Protein-2 (e.g., rhBMP-2, InFUSE) of the Lumbar Spine</i></b></p> <ul style="list-style-type: none"> <li>Added criterion requiring “the fusion is single-level”</li> <li>Replaced criterion requiring: <ul style="list-style-type: none"> <li>“<i>Implanted via an anterior or oblique approach and used in conjunction with an Infuse Bone Graft fusion device</i>” with “<i>the approach is anterior or oblique and used in conjunction with an FDA-approved interbody fusion device</i>”</li> <li>“<i>At one level from L4-S1 [with] no more than grade I spondylolisthesis at the involved level</i>” with “<i>the fusion involves vertebral bodies L4-S1, with or without spondylolisthesis of no more than grade 1 (25% displacement) at the involved level</i>”</li> <li>“<i>Failure of at least 6 months of non-operative treatment</i>” with “<i>failure of at least 6 months of non-operative medical treatment</i>”</li> </ul> </li> </ul> <p><b><i>InFUSE/MASTERGRAFT™ Posterolateral Revision Device System</i></b></p> <ul style="list-style-type: none"> <li>Replaced criterion requiring “<i>autologous bone and/or bone marrow harvest is not feasible or is not expected to promote fusion; these individuals are diabetics and smokers</i>” with “<i>autologous bone and/or bone marrow harvest is not feasible or is not expected to promote fusion</i>”</li> </ul> </li> <li>Revised list of unproven and not medically necessary products for the enhancement of fusion and/or bone healing; replaced: <ul style="list-style-type: none"> <li>“<i>Amniotic membrane products in the treatment of spine disease or in spine surgery</i>” with “<i>human amniotic membrane bone graft substitute materials, including amniotic fluid stem cell substitutes for the treatment of spine disease or in spine surgery</i>”</li> <li>“<i>Bone Morphogenetic Protein-7 (BMP-7), OP-1 Implant and OP-1 Putty with or without use of other devices (including the PEEK device)</i>” with “<i>recombinant human bone morphogenetic</i>”</li> </ul> </li> </ul>

Date	Summary of Changes
	<p>protein-7 (rhBMP-7) <i>including but not limited to, Osteogenic Protein-1 (OP-1® Implant &amp; Putty) with or without use of other devices</i></p> <ul style="list-style-type: none"> <li>○ “<i>Infuse® Bone Graft and The InFUSE/MASTERGRAFT™ Posterolateral Revision Device</i> for all other indications not included [as proven and medically necessary in the policy]” with “<i>recombinant human bone morphogenetic protein-2 (e.g., rhBMP-2, InFUSE) and The InFUSE/MASTERGRAFT™ Posterolateral Revision Device</i> for all other indications not included [as proven and medically necessary in the policy]”</li> </ul> <p><b>Definitions</b></p> <ul style="list-style-type: none"> <li>● Updated definition of: <ul style="list-style-type: none"> <li>○ Human Amniotic Tissue Membrane</li> <li>○ RhBMP-7/Osteogenic Protein-1 (OP-1® Implant &amp; Putty)</li> </ul> </li> </ul> <p><b>Applicable Codes</b></p> <ul style="list-style-type: none"> <li>● Removed HCPCS codes Q4100, Q4149, Q4186, and Q4187</li> </ul> <p><b>Benefit Considerations</b></p> <ul style="list-style-type: none"> <li>● Revised language to indicate 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</li> </ul> <p><b>Supporting Information</b></p> <ul style="list-style-type: none"> <li>● Updated <i>Clinical Evidence, CMS, and References</i> sections to reflect the most current information</li> <li>● Archived previous policy version 2020T0410X</li> </ul>

## 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 MCG™ Care Guidelines, 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.