Medical Coverage Policy

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Bone Graft Substitutes

Table of Contents

Related Coverage Resources

Autologous Platelet-Derived Growth Factors (Platelet-Rich Plasma [PRP])
Bone Growth Stimulators: Electrical (Invasive, Noninvasive), Ultrasound
eviCore Spine Surgery Guidelines
Miscellaneous Musculoskeletal Procedures
Stem Cell Therapy for Orthopedic Applications
Tissue-Engineered Skin Substitutes

INSTRUCTIONS FOR USE

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will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This Coverage Policy addresses bone graft substitutes. For the intent of this policy, many bone graft substitutes that are resorbed into the body, (e.g., allograft materials, bone void fillers with or without antibiotics, synthetic materials, recombinant bone morphogenetic proteins), do not meet the definition of an implant; they are considered surgical supplies. Implants are devices or materials which are placed into a surgically or naturally formed cavity of the human body to continuously assist, restore, or replace the function of an organ system or structure of the human body throughout its useful life. Implants generally include but are not limited to: stents, artificial joints, shunts, plates, screws, anchors and radioactive seeds, in addition to non-soluble, or solid plastic materials used to augment tissues or to fill in areas traumatically or surgically removed. Furthermore, materials defined by the United States Food and Drug Administration (FDA) as being "resorbable" materials (e.g., resorbable calcium salt bone void filler) are not considered to be implants. Over time, these materials are dissolved completely and replaced by bone tissue.

Coverage Policy

See EviCore Spine Surgery Guidelines for spine-related bone graft use.

See Medical Coverage Policy Stem Cell Therapy for Orthopedic Applications (CP 0552) for stem cell therapy (regenerative therapy) for orthopedic and/or musculoskeletal conditions.

See Medical Coverage Policy Autologous Platelet-Derived Growth Factors (Platelet-Rich Plasma [PRP]) (CP 0507) for uses of autologous platelet-derived growth factors (APDGF), for multiple conditions and indications.

Bone Graft Materials/Substitutes
The following bone graft materials and/or substitutes, used alone or in combination, are each considered medically necessary for enhancement of bone healing:

- autografts
- allograft-based, including demineralized bone matrix (DBM)
- ceramic or polymer-based synthetic bone graft substitutes
- bone graft substitutes containing inorganic bone material (e.g., bovine, coral) when used alone or combined with another covered bone graft substitute
- orthopedic/device/drug matrix/absorbable bone void filler, antimicrobial-eluting

The following bone graft materials and/or substitutes are each considered experimental, investigational, or unproven for the enhancement of bone healing:

- human amniotic membrane bone graft substitute materials, including amniotic fluid stem cell substitutes
- cell-based substitutes (e.g., mesenchymal stem cells used alone, added to other biomaterials for grafting, or seeded onto scaffolds, including allograft materials that undergo enhanced processing to retain and condense inherent cells/growth factors)

- human growth factor substitutes (e.g., fibroblast growth factor, insulin-like growth factor)
- bone marrow aspirate processed to concentrate growth factors, stem cells or mesenchymal cells, (e.g., concentrated bone marrow aspirate, centrifuged bone marrow aspirate), used alone or in combination with other bone graft materials (e.g., allograft)
- bone graft substitutes containing inorganic bone material (e.g., bovine, coral) when combined with any non-covered bone graft substitute
- bone graft substitutes used to reduce donor site morbidity (e.g., iliac crest donor site reconstruction)

Recombinant Bone Morphogenetic Protein (rhBMP)
rhBMP-2 (i.e., INFUSE® Bone Graft) is considered medically necessary in surgical repair of an acute, open tibial shaft fractures when BOTH of the following criteria are met:

- fracture is stabilized with intramedullary (IM) nail fixation
- rhBMP–2 is applied within 14 days of the fracture

rhBMP–2 is not covered or reimbursable for ALL other indications, including the following:

- rhBMP–2 (i.e., INFUSE® Bone Graft) as an alternative or adjunct treatment for sinus augmentation and/or localized alveolar ridge augmentation

rhBMP-7 (i.e., OP–1™) is considered experimental, investigational, or unproven for ALL indications.

Dental implants are specifically excluded under many benefit plans. When coverage for dental implants is excluded, the use of bone graft materials in conjunction with a dental implant, including sinus and/or alveolar ridge augmentation, is similarly not covered.

Health Equity Considerations

Health equity is the highest level of health for all people; health inequity is the avoidable difference in health status or distribution of health resources due to the social conditions in which people are born, grow, live, work, and age.

Social determinants of health are the conditions in the environment that affect a wide range of health, functioning, and quality of life outcomes and risks. Examples include safe housing, transportation, and neighborhoods; racism, discrimination and violence; education, job opportunities and income; access to nutritious foods and physical activity opportunities; access to clean air and water; and language and literacy skills.

General Background

Bone grafts can be harvested from the patient (autograft), a cadaver (allograft), or they can be synthetic. 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 orthopedic applications including fracture healing, filling cavities and defects, bridging joints, establishing the continuity of long bone and providing bone blocks. For most of the indications noted above, there is sufficient evidence to support safety and effectiveness, although for some

indications clinical studies are limited, for others there is no evidence, and for some types of materials, clinical studies are not required.

U.S Food and Drug Administration (FDA)
FDA classifies a product as a drug, device, biological product, or combination product.6 A combination product is composed of any combination of a drug and device; a biological product and device; a drug and biological product; or a drug, device, and biological product.

FDA has published guidance documents related to bone grafts. Bone grafts intended to fill bony voids or gaps caused by trauma or surgery that are not intrinsic to the bony structure's stability, or those aiming to fill, augment, or reconstruct periodontal or bony defects of the oral and maxillofacial region are considered Class II devices. Bone grafts containing drugs are considered a therapeutic biologic and are regulated as Class III devices, requiring a PMA. Cultured cells combined with other materials (i.e., bone grafts) are considered combination products and may be regulated as devices or biological products.

Nonstructural allograft and cellular allograft materials are considered human cells, tissues and cellular tissue-based products and as such do not require preclinical or clinical data by the FDA. Synthetic bone grafts and demineralized bone matrices (DBM) are considered Class II materials and fall under the FDA 510(k) regulatory. Other materials, such as those that are considered drug-device combinations require premarket approval (PMA).

Autografts
Autografts are considered the established standard graft material and are typically retrieved from the patient's tibia, fibula, ileum or iliac crest, by way of a surgical procedure and are then placed at the surgical site. The advantage of autograft is the high probability of success—autograft possesses all of the necessary characteristics such as osteoconductivity, osteogenicity, and osteoinductivity. The disadvantages associated with autografts are that the amount of autogenous bone available for grafting is limited; autografts are associated with increased morbidity; increased anesthesia time and blood loss; and post-operative donor site complications.

The iliac crest is the most common site for autograft harvesting. Once the actual bone graft is obtained the site is allowed to heal independently without backfilling. However, there is often post-operative harvest site pain associated with this procedure. The use of various bone graft substitutes are being investigated for backfilling of iliac crest harvest sites, as a method of reducing pain and for improving cosmesis. Despite this proposed use there is insufficient data in the peer-reviewed published scientific literature supporting the effectiveness of iliac reconstruction with any type of graft material. Most of the published studies involve small sample populations with inconsistent clinical outcomes for reducing donor site morbidity. The use of bone graft substitutes for this indication is not recommended at this time due to lack of data supporting safety, efficacy and improved clinical outcomes.

Autologous bone marrow aspirate obtained from the iliac crest is also commonly used during orthopedic procedures as an adjunct to other graft materials to enhance bone healing. Freshly harvested bone marrow aspirate contains osteogenic precursor cells (mesenchymal stem cells, growth factors) and once aspirated may be injected directly into defects or mixed with other grafting materials. In theory, combining bone marrow aspirate with an osteoconductive and osteoinductive bone graft material will avoid associated disadvantages of iliac crest graft harvest and improve healing. Although injecting aspirate directly into defects or mixing with other allograft materials is commonly performed, it is considered integral to the surgical procedure.

Another proposed use of bone marrow is aspirate involves various cell retention and processing methods which are now being utilized to increase cell concentration. It has been suggested that

stem cell concentration is directly related to overall effectiveness and as a result, in order to increase the concentration of osteoprogenitor cells various cell retention processing methods (e.g., centrifugation) may be employed. Although the amount of aspirate required and proposed indications vary, the process has also been referred to as bone marrow nucleated cell concentrate (BMAC) or autologous bone marrow mononuclear cells (BMMC). The techniques for concentrating bone marrow aspirate vary, as well as the resulting cell concentration and cell viability. Comparative data in the medical literature is insufficient to support clinical effectiveness of concentrated bone marrow aspirate and strong evidence-based conclusions cannot be made at this time.

Allografts
One alternative to autograft is the use of allografts. Allograft offers the advantage of avoiding additional surgery and potential complications associated with harvesting host bone during the primary procedure. Allograft materials are frequently used during various orthopedic procedures and may also be used alone or in combination with other materials. Cancellous allograft is used primarily to pack and fill bony voids, while cortical allograft is used primarily to fill large osseous defects. Allografts are readily available from bone banks and provide osteoconductive (e.g., structural support) properties, however they lack osteogenic properties. Allografts may give less consistent clinical results, and there may be an increased risk of disease transmission and immunogenic response. When allografts are intensively processed to decrease these risks, the osteoinductive potential is lessened, and the processing removes osteogenic cells and reduces mechanical strength. AlloGro® Demineralized Bone Matrix (Wright Medical, Arlington, TN); Dynagraft-D™ (Citagenix, Laval, Quebec, Canada); Opteform® (Exactech, Inc., Gainesville, FL); Grafton® (Osteotech, Eatontown, NJ); OrthoBlast (IsoTis Orthobiologics, Irvine, CA); TruFuse® (minSURG™ Corp., Clearwater, FL); and NuFix™ (Nutech Medical, Birmingham, AL) are examples of allograft-based bone graft substitutes.

Allografts can be processed to retain higher concentrations of inherent growth factors and/or stem cells. With improved processing methods some allograft 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, platelet-derived growth factor, transforming growth factor-beta, and microglobulin-B, are examples of osteogenic growth factors that are naturally found within the matrix of bone. Despite availability and current use, clinical superiority has not been demonstrated in the medical literature supporting the use of these materials. How these allograft bone graft materials, processed to retain higher concentrations of inherent growth factors and/or stem cells, improve the rate and quality of bone formation compared to other available allograft bone graft substitutes, has not yet been firmly established.

Demineralized bone matrix (DBM) is a type of allograft. It is produced through a process that involves the decalcification of cortical bone (produced by acid extraction of allograft bone); substantially decreasing the structural strength. However, it is more osteoinductive than ordinary allograft. Although the reason for this is not completely understood, it has been speculated that the osteoinductive growth factors contained in the extracellular bone matrix are more easily accessed once the mineral phase of the bone has been removed. Allograft DBM preparations available for use include Osteotech's Grafton®, Regeneration Technology's Osteofil® and Medtronic's Magnifuse to name a few. These preparations differ in shape and size of DBM particles, the amount of inherent growth factors, the amount of residual minerals, and the type of carrier materials. DBM is available in various forms such as freeze-dried powder, granules, gel, putty or strips.

Inorganic Bone Graft Materials

Inorganic bone graft material is 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., inorganic bone material) reducing concerns of disease transmission or immunogenic reactions. Some of the inorganic type xenograft materials (e.g., Bio-Oss) may be used as stand-alone graft material to enhance healing, such as when used for dental implants. When used according to U.S. Food and Drug Administration (FDA) approved indications, either alone or combined with other bone graft materials proven effective, inorganic bone graft materials are considered safe and effective for promoting bone formation.

Bone Graft Substitutes
Due to the limitations of autogenous bone and allograft material, and the number of surgeries that require grafting, investigators have developed grafting alternatives, some of which are available for current use and others which are still in developmental stages. Bone graft substitutes have overlapping properties and are often made of a variety of materials such as polymers (degradable and nondegradable), ceramics and composites (calcium phosphate, calcium sulfate, and bioactive glass), factor-based materials (recombinant growth factors) and cell-based materials (mesenchymal stem cells). Some authors classify bone graft substitutes according to these materials. However, these substitutes can also be classified based on their characteristics, such as

- osteoconduction (e.g., calcium sulfate, ceramics, calcium phosphate, cements, collagen), osteoinduction (e.g., DMB, rhBMPs, growth factors),
- osteogenesis (e.g., bone marrow aspirate), or
- combined (composites).

Nonetheless, the ideal bone graft substitute must provide scaffolding for osteoconduction, growth factors for osteoinduction and progenitor cells for osteogenesis. In addition, the bone graft substitute must be able to integrate with the host.

The role of bone graft substitutes is to provide a medium for osteoconduction rather than osteoinduction and can provide variable levels of structural support. These materials appear to be safe when used according to FDA indications; however, each type of product is under varying degrees of regulation and in some cases safety and efficacy of these products remain unproven through human trials. For the intent of this coverage policy, bone graft substitutes are described as those that are cell-based, ceramic-based, polymer-based and factor-based. Synthetic substitutes generally consist of ceramic and polymer based materials.

Cell-based: Bone graft substitutes that are cell-based use cells to generate new tissue either alone, with other biomaterials (osteoconductive carriers, for example cancellous bone chips or DBM), or seeded onto a support matrix (e.g., in combination with allograft material). Support matrix materials may include xenograft (i.e., bovine) or human type I collagen.

The use of mesenchymal and other cell-based bone graft substitutes has been and continues to be investigated for various procedures. Although currently under investigation, data published in the medical literature supporting safety and efficacy for these indications are lacking.

Ceramic-based: 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 considered bone graft extenders and are combined with collagen to augment healing; collagen composites may include bovine material similar to that used with cell-based products. Because these materials lack osteogenic and osteoinductive properties, they cannot be used as stand-alone bone graft. Several types of calcium phosphates, including tricalcium phosphate, synthetic hydroxyapatite, and coralline hydroxyapatite are available in pastes, putties, solid matrices, and granules.

When used, calcium sulfate is less desirable for weight bearing applications due to loss of mechanical properties during degradation. When implanted into living tissue, bioactive glass forms a bond with pre-existing bone, however there are only a few products commercially available and use is primarily in dental applications. Synthetic hydroxyapatite (e.g., ProOsteon® Implant 500 [Interpore Cross, Int., Irvine, CA]) is brittle, has little tensile strength and is typically used for bone defects with internal fixation. A pure beta-tricalcium phosphate scaffold, Vitoss® Synthetic Cancellous Bone Filler (Orthovita, Inc., Malvern, PA) is intended for use in small defects in the extremities, pelvis, and spine. Other ceramic-based materials include but are not limited to:

- Osteograf® (Ceramed, Lakewood, CO)
- Norian SRS (Skeletal Repair System) (Synthes, Inc., West Chester, PA)
- Osteoset® (Wright Medical, Arlington, TN)
- Actifuse™ (ApaTech Limited, Elstree, Hertfordshire, UK)
- Integra MOZAIK™ Osteoconductive Scaffold (Integra LifeSciences, Plainsboro, NJ)
- PRO-DENSE® Bone Graft Substitute paste (Wright Medical Technology, Inc., Arlington, TN)

Subchondral injection of calcium phosphate bone substitute, into the area of subchondral bone edema, as part of treatment for osteochondritis dissecans of the knee, and other joints has been reported in the literature (Levy, Cousins, 2020; Bonadio, et al., 2017; Cohen, Sharkey, 2016; Abrams, et al., 2013). Conservative treatment of osteoarthritis-related bone marrow lesions generally includes pain control, reduction in weight bearing, activity modification, and appropriate nutrition including additional calcium and vitamin D during treatment if appropriate. One procedure aimed at treating such defects, the Subchondroplasty® (SCP®) procedure (Zimmer Holdings, Inc.; Warsaw, IN), is a minimally invasive surgery designed to access and treat bone defects associated with chronic bone marrow lesions by filling them with a biomimetic bone substitute material. This material theoretically acts as a scaffold around which new bone growth may occur.

Nairn et al. (2020) published the results of a systematic review evaluating safety and early results of Subchondroplasty® for the treatment of bone marrow lesions. The authors review included 17 studies, all studies were graded as level 4 evidence except one which was graded level 3. The review included 756 subjects in total, 13 studies investigated use for the knee and four evaluated use for foot and ankle joint pain related to a bone marrow lesion. Mean pain scores using VAS improved postoperatively (7.8 +/- 0.6 to 3.4 +/- 0.7), functional scores improved when reported (IKDC 31.7 ± 1.9-54.0 ± 4.2 and KOOS 38.1 ± 0.6-70.0 ± 4.1) and there were high levels of patient satisfaction postoperatively. Complications occurred in seven cases, most seriously osteomyelitis and avascular necrosis. In addition, the authors reported that the rate at which subjects converted to arthroplasty ranged from 12.5 to 30% with followup ranging from 10 months to seven years. In the author's opinion, low quality studies supported a reduction of pain, improved function, high patient satisfaction and a subsequent delay in more invasive procedures. However additional high quality studies with long term followup are required to determine any impact to clinical practice recommendations.

Evidence in the peer reviewed scientific literature evaluating injection of a calcium phosphate bone substitute into the area of subchondral bone edema, or of the Subchondroplasty® procedure, in the treatment of chronic bone marrow lesions / bone marrow edema is lacking. As a result, evidence-based conclusions regarding safety, efficacy, and impact on health outcomes cannot be firmly established.

Polymer-based: Polymer-based substitutes are polymers that are either degradable or nondegradable and may be used alone or in combination with other materials. Degradable

polymers are resorbed by the body allowing it to heal itself without foreign bodies remaining. Types of polymer-based substitutes include but are not limited to:

- Cortoss® (Orthovita, Inc., Malvern, PA [Stryker])
- OPLA (TMH Biomedical, Inc., Duluth, MN)
- Immix (OsteoBiologics, Smith and Nephew, Memphis, TN).

Factor-based: Factor-based bone graft substitutes consist of human growth factors and recombinant growth factors used alone or in combination with other materials. Factor-based osteogenic bone graft substitutes include but are not limited to:

- human growth factors (e.g., fibroblast growth factor, insulin-like growth factor, transforming growth factor-beta), used alone or in combination with other materials
- recombinant bone morphogenetic proteins (rhBMP), used as an adjunct to autografts

Antimicrobial-eluting: New 2024 HCPCS code C1602 Orthopedic/device/drug matrix/absorbable bone void filler, antimicrobial-eluting (implantable): Allografts and bone graft substitutes can be impregnanted with antibiotics. A local antibiotic delivery system with biodegradable drug carrier can be considered a therapeutically efficient platform for the treatment of osteomyelitis. Using appropriate carriers, specific amount of the antimicrobial agents and controlling the released rate of the drug can help in the infection control and limit the recurrence rate. Additionally, if the delivery system made osteogenic in nature, they can exert dual function of eradicating the pathogens and assisting the bone regeneration after surgical debridement (Shi et al., 2022; Wassif, et al., 2021; Peeters, et al., 2019; van Vugt, et al., 2016).

An allograft example is OSTEOmycin® Orthopaedic. This product is cancellous bone chips impregnated with tobramycin or vancomycin. Another example is Cerament G. This device-drug combination product is a resorbable, gentamicin-eluting ceramic bone void filler intended for use as a bone void filler in skeletally mature patients as an adjunct to systemic antibiotic therapy and surgical debridement (standard treatment approach to a bone infection) as part of the surgical treatment of osteomyelitis in defects in the extremities.

Human growth factors: Fibroblast growth factor (FGF), insulin-like growth factor (ILGF), transforming growth factor-beta (TGF-beta) and bone morphogenetic protein (BMP) are human growth factors found in the matrix of bone. Some of these factors have been isolated in research settings for use alone or in combination with other materials; however, evidence in the published, peer-reviewed scientific literature is insufficient to support safety and efficacy at this time.

Recombinant Bone Morphogenetic Proteins (rhBMP)
RhBMP is a unique subgroup of graft substitutes. The function of BMP is to promote differentiation of mesenchymal cells into chondrocytes and osteoblasts, to promote differentiation of osteoprogenitors into osteoblasts, and to influence skeletal pattern formation. Recombinant human bone morphogenetic proteins act as an adjunct to autogenous bone grafts.

RhBMP–2
In 2004, INFUSE® Bone Graft was approved for open tibial fractures with an intermedullary (IM) nail fixation. In March 2007, INFUSE Bone Graft was approved as an alternative to autogenous bone grafts for sinus augmentations, and for localized alveolar ridge augmentations for defects associated with extraction sockets.
The use of RhBMP–2 product should be limited to the FDA-approved labeling indications.

Fracture Repair: In 2004, INFUSE® Bone Graft was approved for open tibial fractures with an intermedullary (IM) nail fixation. The use of RhBMP–2 product should be limited to the FDA-approved labeling indications.

is for the treatment of patients with acute, open tibial shaft fractures when all the following criteria are met:

- The fracture must be stabilized with intramedullary (IM) nail fixation after appropriate wound management.
- The rhBMP–2 must be applied within 14 days after the initial fracture.
- The prospective patient should be skeletally mature.

The FDA notes the following contraindications to use of the product:

- possible or confirmed pregnancy
- sensitivity to titanium, titanium alloy, cow (bovine) Type I collagen, or rhBMP–2
- infection near the area of the surgical incision
- previous or current tumor at the site of use
- high risk of amputation of the affected leg
- compartment syndrome of the affected leg

Published clinical studies evaluating the use of rhBMP–2 in patients with tibial fractures support safety and efficacy (Swiontkowski, et al., 2006; Jones, et al., 2006; Govender, yet al., 2002).

Sinus Augmentation/Alveolar Ridge Augmentation: In March 2007 the INFUSE® Bone Graft (Medtronic Sofamor Danek, Memphis, TN) was approved as an alternative to autogenous bone grafts for sinus augmentations, and for localized alveolar ridge augmentations for defects associated with extraction sockets. The use of RhBMP–2 product should be limited to the FDA-approved labeling indications.
According to the FDA, INFUSE Bone Graft is used to fill space where bone is needed in order to place endosseous dental implants. Dental implants should be placed if there is sufficient bone to stabilize them. When the sinus wall is thin, there is not enough bone to place dental implants. In a procedure known as sinus augmentation, a sinus graft is inserted into the floor of the sinus (i.e., the roof of the upper jaw). Dental implants can then be inserted and stabilized in the new sinus bone. The alveolar ridge of the jaw is the bone that surrounds the roots of the teeth. When a tooth is extracted, a socket remains which later heals; however, typically, previous height and width are not restored. Alveolar ridge augmentation is a procedure performed to increase bone volume, making treatment with dental implants possible.

The FDA notes the following contraindications to use for oral surgical procedures:

- in patients with an active infection at the operative site
- in patients who are pregnant
- in patients who are hypersensitive to rhBMP–2 or bovine type I collagen
- in an area where there was a tumor

Evidence in the published scientific literature evaluating rhBMP–2 for oral maxillofacial surgery consists of few published clinical trials (Esposito, et al., 2007; Boyne, et al., 2005; Fiorellini, et al., 2005; Jung, et l., 2003). Although the study results suggest that this technique may be a promising treatment option, the evidence in the published, peer-reviewed, scientific literature is insufficient to allow strong conclusions regarding the long-term effectiveness of rhBMP–2 for sinus augmentation and alveolar ridge augmentation. Published studies have been small in sample size, and data on long-term outcomes are lacking. Patient selection criteria are not well-defined. Some studies have indicated that rhBMP–2 is safe and enhances bone maturation. However, additional well-designed clinical trials assessing long-term health outcomes are needed to validate these results.

RhBMP–7/ OP–1™ Implant
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. The FDA approved the OP–1 Implant for use in specifically-defined patients under a humanitarian device exemption (HDE) (H010002).

A HUD is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the United States per year. An HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose.

Fracture Repair: The FDA gave HDE approval for the use of rhBMP–7 to treat nonunion of long bones. It is a powder that is mixed with normal saline to form a paste which is applied during surgery. The substance is marketed in the U.S. as OP–1™ Implant (Stryker Biotech, Hopkinton, MA).

The FDA approval indicates that the substance is appropriate for use in the surgical repair of long bone nonunion when both of the following patient selection criteria are met:

- autograft is not feasible
- alternative treatments have failed

The use of the product is contraindicated in patients with the following conditions:

- allergy to OP–1 or collagen
- existing tumor or tumor removed at or near the fracture or history of malignancy
- previous history of cancer
- skeletal immaturity
- pregnancy

Studies evaluating the use of rhBMP–7 for nonunion of long bones are limited by small sample size and short term follow-up. Although there is some evidence of successful clinical outcomes resulting from the use of rhBMP-7 for the treatment of nonunion in the published scientific literature (Ronga, et al., 2006; Maniscalco, et al., 2002; Friedlaender, et al., 2001; Geesink, et al., 1999) evidence is insufficient to draw strong conclusions regarding safety and efficacy.

Professional Societies/Organizations

American Association of Orthopaedic Surgeons (AAOS): The AAOS 2022 Evidence-Based Clinical Practice Guideline on Management of Anterior Cruciate Ligament (ACL) Injuries states:

> <u>Autograft vs. Allograft</u>
> When performing an ACL reconstruction, surgeons should consider autograft over allograft to improve patient outcomes and decrease ACL graft failure rate, particularly in young and/or active patients. Quality of Evidence: High; Strength of Recommendation: Strong (Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention.)
>
> <u>Autograft Source</u>
> When performing an ACL reconstruction with autograft for skeletally mature patients, surgeons may favor BTB to reduce the risk of graft failure or infection, or hamstring to reduce the risk of anterior or kneeling pain. Quality of Evidence: High; Strength of

Recommendation: Moderate (Evidence from two or more "High" quality studies with consistent findings for recommending for or against the intervention) (AAOS, 2022).

American Orthopaedic Foot & Ankle Society (AOFAS): The AOFAS 2022 Position Statement on The Use of Osteochondral Transplantation for the Treatment of Osteochondral Lesions of the Talus states:

> The American Orthopaedic Foot & Ankle Society (AOFAS) endorses the use of osteochondral autograft and allograft transplantation for the treatment of osteochondral lesion of the talus, especially large diameter lesions, cystic lesions, and those that have failed previous surgical treatment. AOFAS does not consider these procedures to be experimental in a patient population that has failed nonoperative management.

American Academy of Periodontology (AAP): An AAP 2022 published a Best Evidence systematic review (Suarez-Lopez, et al., 2022) on the efficacy of biologics for alveolar ridge preservation/reconstruction and implant site development. Clinical recommendations regarding rhBMP-2 included:

Alveolar ridge augmentation (ARA)

1. Level of certainty: Low for rhBMP-2
2. Net benefit rating (benefit-harm estimation): Modest or uncertain additional clinical benefits outweigh potential harms or benefits balanced with potential harms.
3. Adverse events and complications: No relevant adverse events and/or complications related to the use of rhBMP-2 were reported in the selected studies. Patient reported outcome measures (PROMS) were assessed in one study reporting slight superiority for the test group using rhBMP-2.
4. Strength of clinical recommendation: Expert opinion supports the use of rhBMP-2 for alveolar ridge augmentation (ARA). Evidence is lacking; the level of certainty is low and, consequently, expert opinion guides the recommendation of this intervention.

Maxillary sinus floor augmentation (MSFA)

1. Level of certainty: Low for rhBMP-2.
2. Net benefit rating (benefit-harm estimation): Modest or uncertain additional clinical benefits outweigh potential harms or benefits balanced with potential harms.
3. Adverse events and complications: No relevant adverse events and/or complications related to the use of rhBMP-2 were reported in the selected studies.
4. Strength of clinical recommendation: Expert opinion supports the use of rhBMP-2 for MSFA. Evidence is lacking; the level of certainty is low and, consequently, expert opinion guides the recommendation of this intervention (Suarez-Lopez, et al., 2022)

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD	National	No Determination found	
LCD		No Determination found	

Note: Please review the current Medicare Policy for the most up-to-date information.
(NCD = National Coverage Determination; LCD = Local Coverage Determination)

Coding Information

Notes:

1. This list of codes may not be all-inclusive since the American Medical Association (AMA) and Centers for Medicare & Medicaid Services (CMS) code updates may occur more frequently than policy updates.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Most bone graft substitutes used to enhance bone healing do not have a specific CPT or HCPCS code to represent the material. However, there are specific CPT codes to differentiate by type of graft. For all other procedures, coverage will be considered based on the clinical indication and type of material for the procedure requested.

Autograft, Allograft (non rhBMP-2), Synthetic (Ceramic/Polymer), Bone Void Fillers

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	Description
20900	Bone graft, any donor area; minor or small (eg, dowel or button)
20902	Bone graft, any donor area; major or large
20999	Unlisted procedure, musculoskeletal system, general
27899	Unlisted procedure, leg or ankle

HCPCS Codes	Description
C1602††	Orthopedic/device/drug matrix/absorbable bone void filler, antimicrobial-eluting (implantable)
C1734††	Orthopedic/device/drug matrix for opposing bone-to-bone or soft tissue-to bone (implantable)
C9359††	Porous purified collagen matrix bone void filler (Integra Mozaik Osteoconductive Scaffold Putty, Integra OS Osteoconductive Scaffold Putty), per 0.5 cc
C9362††	Porous purified collagen matrix bone void filler (Integra Mozaik Osteoconductive Scaffold Strip), per 0.5 cc
L8699††	Prosthetic implant, not otherwise specified

††**Note: May not be separately reimbursed to the facility.**

Factor-based (rhBMP-2)

Considered Medically Necessary when criteria in the applicable policy statements listed above are met and when used to report rhBMP–2 for surgical repair of acute, open tibial fracture:

CPT®* Codes	Description
20999	Unlisted procedure, musculoskeletal system, general
27899	Unlisted procedure, leg or ankle

HCPCS Codes	Description

C1734†	Orthopedic/device/drug matrix for opposing bone-to-bone or soft tissue-to bone (implantable)
L8699†	Prosthetic implant, not otherwise specified

†**Note: May not be separately reimbursed to the facility**

Not covered or reimbursable when used to report rhBMP–2 for ALL other indications including adjunct treatment for sinus augmentation and/or localized alveolar ridge augmentation.

CPT®* Codes	**Description**
21208	Osteoplasty, facial bones; augmentation (autograft, allograft, or prosthetic implant)
21210	Graft, bone; nasal, maxillary or malar areas (includes obtaining graft)
21499	Unlisted musculoskeletal procedure, head
31299	Unlisted procedure, accessory sinuses

HCPCS Codes	**Description**
L8699†	Prosthetic implant, not otherwise specified

†**Note: May not be separately reimbursed to the facility**

Considered Experimental/Investigational/Unproven when used to report rhBMP–7 (i.e., OP–1™) for ALL indications:

CPT®* Codes	**Description**
20930	Allograft, morselized, or placement of osteopromotive material, for spine surgery only (List separately in addition to code for primary procedure)
20999	Unlisted procedure, musculoskeletal system, general
23929	Unlisted procedure, shoulder
24999	Unlisted procedure, humerus or elbow
25999	Unlisted procedure, forearm or wrist
27599	Unlisted procedure, femur or knee
27899	Unlisted procedure, leg or ankle

HCPCS Codes	**Description**
C1734†	Orthopedic/device/drug matrix for opposing bone-to-bone or soft tissue-to bone (implantable)
L8699†	Prosthetic implant, not otherwise specified

†**Note: May not be separately reimbursed to the facility**

Considered Experimental/Investigational/Unproven when used to report human amniotic membrane bone graft substitute, cell-based/mesenchymal stem cell used as

bone graft substitute, factor-based, synthetic or allograft substitute following autograft harvest for iliac crest reconstruction (i.e., back fill grafting of an iliac crest donor site):

CPT®* Codes	Description
20999	Unlisted procedure, musculoskeletal system, general
27299	Unlisted procedure, pelvis or hip joint
27599	Unlisted procedure, femur or knee
29999	Unlisted procedure, arthroscopy

HCPCS Codes	Description
C1762†	Connective tissue, human (includes fascia lata)
C1889†	Implantable/insertable device, not otherwise classified
L8699†	Prosthetic implant, not otherwise specified

†**Note: May not be separately reimbursed to the facility**

Considered Experimental/Investigational/Unproven when used to report bone marrow aspirate or bone marrow fluid concentrated or centrifuged for growth factors, stem cell, or mesenchymal cell application:

CPT®* Codes	Description
38232	Bone marrow harvesting for transplantation; autologous
38241	Hematopoietic progenitor cell (HPC); autologous transplantation

References

1. Abrams GD, Alentorn-Geli E, Harris JD, Cole BJ. Treatment of a lateral tibial plateau osteochondritis dissecans lesion with subchondral injection of calcium phosphate. Arthrosc Tech. 2013 Jul 19;2(3):e271-4.

2. American Academy of Orthopaedic Surgeons. Management of Anterior Cruciate Ligament Injuries Evidence-Based Clinical Practice Guideline. August 22, 2022. Accessed Sept 2024. Available at URL address: https://www.aaos.org/quality/quality-programs/clinical-practice-guidelines/

3. American Academy of Orthopaedic Surgeons. The Diagnosis and Treatment of Osteochondritis Dissecans. Evidence-Based Clinical Practice Guideline. Dec 2023. Accessed Sept 2024. Available at URL address: https://www.aaos.org/quality/quality-programs/clinical-practice-guidelines/

4. American College of Rheumatology. Clinical Practice Guidelines. Accessed Sept 2024. Available at URL address: https://rheumatology.org/clinical-practice-guidelines

5. American Orthopaedic Foot & Ankle Society (AOFAS). Position Statement. The Use of Osteochondral Transplantation for the Treatment of Osteochondral Lesions of the Talus.

July 29, 2022. Accessed Sept 2024. Available at URL address: https://www.aofas.org/research-policy/position-statements-clinical-guidelines

6. Bohner M. Design of ceramic-based cements and putties for bone graft substitution. Eur Cell Mater. 2010 Jul 1;20:1-12.

7. Bonadio MB, Giglio PN, Helito CP, Pécora JR, Camanho GL, Demange MK. Subchondroplasty for treating bone marrow lesions in the knee - initial experience. Rev Bras Ortop. 2017 Apr 28;52(3):325-330.

8. Bornes TD, Adesida AB, Jomha NM. Mesenchymal stem cells in the treatment of traumatic articular cartilage defects: a comprehensive review. Arthritis Res Ther. 2014;16(5):432.

9. Calcei JG, Rodeo SA. Orthobiologics for Bone Healing. in Sports Med. 2019 Jan;38(1):79-95.

10. Christensen BB, Olesen ML, Hede KTC, Bergholt NL, Foldager CB, Lind M. Particulated Cartilage for Chondral and Osteochondral Repair: A Review. Cartilage. 2020 Feb 13:1947603520904757.

11. Cohen SB, Sharkey PF. Subchondroplasty for Treating Bone Marrow Lesions. J Knee Surg. 2016 Oct;29(7):555-563.

12. Dziadosz M, Basch RS, Young BK. Human amniotic fluid: a source of stem cells for possible therapeutic use. Am J Obstet Gynecol. 2016 Jan 6.

13. Esposito M; Grusovin MG; Coulthard P; Worthington HV. Interventions for replacing missing teeth: bone augmentation techniques for dental implant treatment. The Cochrane Database of Systematic Reviews 2007 Issue 4, Copyright © 2007 The Cochrane Collaboration.

14. Fiorellini JP, Howell TH, Cochran D, Malmquist J, Lilly LC, Spagnoli D, Toljanic J, Jones A, Nevins M. Randomized study evaluating recombinant human bone morphogenetic protein-2 for extraction socket augmentation. J Periodontol. 2005 Apr;76(4):605-13.

15. Friedlaender GE, Perry CR, Cole JD, Cook SD, Cierny G, Muschler GF, et al. Osteogenic protein-1 (bone morphogenetic protein-7) in the treatment of tibial nonunions: a prospective, randomized clinical trial comparing rhOP-1 with fresh bone autograft. J Bone Joint Surg Am. 2001;83-A(Suppl 1 Pt 2):S151-8.

16. Geesink RG, Hoefnagels NH, Bulstra SK. Osteogenic activity of OP-1 bone morphogenetic protein (BMP-7) in a human fibular defect. J Bone Joint Surg Br. 1999;81-B(4):710-8.

17. Gillman CE, Jayasuriya AC. FDA-approved bone grafts and bone graft substitute devices in bone regeneration. Mater Sci Eng C Mater Biol Appl. 2021 Nov;130:112466.

18. Govender S, Csimma C, Genant HK, Valentin-Opran A, Amit Y, Arbel R, et al; BMP-2 Evaluation in Surgery for Tibial Trauma (BESTT) Study Group. Recombinant human bone morphogenetic protein-2 for treatment of open tibial fractures: a prospective, controlled, randomized study of four hundred and fifty patients. J Bone Joint Surg Am. 2002;84-A(12):2123-34.

19. Hofmann A, Gorbulev S, Guehring T, Schulz AP, Schupfner R, Raschke M, Huber-Wagner S, Rommens PM; CERTiFy Study Group. Autologous Iliac Bone Graft Compared with Biphasic

Hydroxyapatite and Calcium Sulfate Cement for the Treatment of Bone Defects in Tibial Plateau Fractures: A Prospective, Randomized, Open-Label, Multicenter Study. J Bone Joint Surg Am. 2020 Feb 5;102(3):179-193.

20. Jacob CC, Daw JH, Santiago-Torres J. The efficacy of antibiotic-impregnated calcium sulfate (AICS) in the treatment of infected non-union and fracture-related infection: a systematic review. J Bone Jt Infect. 2023 Mar 22;8(2):91-97.

21. Jones AL, Bucholz RW, Bosse MJ, Mirza SK, Lyon TR, Webb LX, Pollak AN, Golden JD, Valentin-Opran A; BMP-2 Evaluation in Surgery for Tibial Trauma-Allograft (BESTT-ALL) Study Group. Recombinant human BMP-2 and allograft compared with autogenous bone graft for reconstruction of diaphyseal tibial fractures with cortical defects. A randomized, controlled trial. J Bone Joint Surg Am. 2006 Jul;88(7):1431-41.

22. Jung RE, Glauser R, Schärer P, Hämmerle CH, Sailer HF, Weber FE. Effect of rhBMP-2 on guided bone regeneration in humans. Clin Oral Implants Res. 2003 Oct;14(5):556-68.

23. Kapil N, Samuel LT, Kamath AF. Management of Bone Marrow Lesions of the Hip With Subchondral Calcium Phosphate Injection: Surgical Technique and Tips. Arthrosc Tech. 2020 Jun 13;9(7):e863-e875.

24. Khokhar K, Conaghan PG. Bone in osteoarthritis: imaging and interventions. Curr Opin Rheumatol. 2022 Jan 1;34(1):73-78.

25. Maniscalco P, Gambera D, Bertone C, Rivera F, Crainz E, Urgelli S. Healing of fresh tibial fractures with OP-1. A preliminary report. Acta Biomed Ateneo Parmense. 2002;73(1-2):27-33.

26. Marmotti A, de Girolamo L, Bonasia DE, Bruzzone M, Mattia S, Rossi R, Montaruli A, Dettoni F, Castoldi F, Peretti G. Bone marrow derived stem cells in joint and bone diseases: a concise review. Int Orthop. 2014 Sep;38(9):1787-801.

27. NuVasive, Inc. Osteocel Plus. Accessed Sept 2024. Available at URL address: https://www.nuvasive.com/search/osteocel+plus/

28. Sage K, Levin LS. Basic principles of bone grafts and bone substitutes. In: UpToDate, Colwell, AS (Ed). UpToDate. Waltham, MA. Literature review current through Aug 2024. Topic last updated: Mar 18, 2024.

29. OSTEOmycin® Orthopaedic. Product Information. Accessed Oct 2024. Available at URL address: https://www.allogenrx.com/osteomycin-orthopaedic

30. Peeters A, Putzeys G, Thorrez L. Current Insights in the Application of Bone Grafts for Local Antibiotic Delivery in Bone Reconstruction Surgery. J Bone Jt Infect. 2019 Oct 15;4(5):245-253.

31. Ronga M, Baldo F, Zappala G, Cherubino P; BMP-7 Italian Observational Study (BIOS) Group. Recombinant human bone morphogenetic protein-7 for treatment of long bone non-union: An observational, retrospective, non-randomized study of 105 patients. Injury. 2006 Sep;37(9 Suppl):S51-6.

32. Shi X, Wu Y, Ni H, Li M, Zhang C, Qi B, Wei M, Wang T, Xu Y. Antibiotic-loaded calcium sulfate in clinical treatment of chronic osteomyelitis: a systematic review and meta-analysis. J Orthop Surg Res. 2022 Feb 19;17(1):104.

33. Suarez-Lopez Del Amo F, Monje A. Efficacy of biologics for alveolar ridge preservation/reconstruction and implant site development: An American Academy of Periodontology best evidence systematic review. J Periodontol. 2022 Dec;93(12):1827-1847. Accessed Sept 2024. Available at URL address: https://aap.onlinelibrary.wiley.com/doi/toc/10.1002/19433670.aap-clin-sci-papers https://www.perio.org/research-science/best-evidence-consensus-bec/ https://aap.onlinelibrary.wiley.com/doi/toc/10.1002/(ISSN)1943-3670.Best-Evidence-Consensus-Meeting

34. Swiontkowski MF, Aro HT, Donell S, Esterhai JL, Goulet J, Jones A, et al. Recombinant human bone morphogenetic protein-2 in open tibial fractures. A subgroup analysis of data combined from two prospective randomized studies. Bone Joint Surg Am. 2006 Jun;88(6):1258-65.

35. U.S. Food and Drug Administration. Premarket Approval (PMA). INFUSE BONE GRAFT. Decision Date: 04/30/2004. Accessed Sept 2024. Available at URL address: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P000054 https://www.accessdata.fda.gov/cdrh_docs/pdf/p000054c.pdf https://www.accessdata.fda.gov/cdrh_docs/pdf/P000054b.pdf (ACUTE, OPEN TIBIAL SHAFT FRACTURES)

36. U.S. Food and Drug Administration. Humanitarian Device Exemption (HDE). OP-1 IMPLANT. HDE Number: H010002. Decision Date: 10/17/2001. Accessed Dec 2023. Available at URL address: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfhde/hde.cfm?id=H010002 (rhBMP–7)

37. U.S. Food and Drug Administration. Osteofil Allograft Paste. 510(k) Summary K043420. Accessed Sept 2024. Available at URL address: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K043420 https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K043421 (skeletal system [e.g., the extremities, spine and pelvis])

38. U.S. Food and Drug Administration. CERAMENT G. De novo (DEN210044, May 17, 2022) Accessed Oct 2024. Available at URL address: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/denovo.cfm?id=DEN210044 (gentamicin-eluting ceramic bone void filler) https://www.accessdata.fda.gov/cdrh_docs/pdf21/DEN210044.pdf https://www.fda.gov/news-events/press-announcements/fda-roundup-may-20-2022

39. van Vugt TA, Geurts J, Arts JJ. Clinical Application of Antimicrobial Bone Graft Substitute in Osteomyelitis Treatment: A Systematic Review of Different Bone Graft Substitutes Available in Clinical Treatment of Osteomyelitis. Biomed Res Int. 2016;2016:6984656.

40. Veillette CJ, McKee MD. Growth factors--BMPs, DBMs, and buffy coat products: are there any proven differences amongst them? Injury. 2007 Mar;38 Suppl 1:S38-48.

41. Vulcano E, Murena L, Falvo DA, Baj A, Toniolo A, Cherubino P. Bone marrow aspirate and bone allograft to treat acetabular bone defects in revision total hip arthroplasty: preliminary report. Eur Rev Med Pharmacol Sci. 2013 Aug;17(16):2240-9.

42. Wassif RK, Elkayal M, Shamma RN, Elkheshen SA. Recent advances in the local antibiotics delivery systems for management of osteomyelitis. Drug Deliv. 2021 Dec;28(1):2392-2414.

Revision Details

Type of Revision	Summary of Changes	Date
Focused Review	• Removed policy statements for spine-related content, which is delegated to EviCore as of 11/01/2024.	11/01/2024
Annual Review	• Revised policy statement for bone graft materials and/or substitutes	2/15/2024