Prior Authorization Review Panel
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
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Plan: AmeriHealth Caritas Pennsylvania	**Submission Date**: 6/1/2024
Policy Number: ccp.1232	**Effective Date:** 7/2016 **Revision Date:** May 1, 2024
Policy Name: Bone graft substitutes	

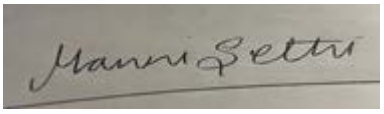
Type of Submission – Check all that apply:

New Policy
X Revised Policy*
Annual Review – No Revisions
Statewide PDL

***All revisions to the policy must be highlighted using track changes throughout the document.**

Please provide any clarifying information for the policy below:

See tracked changes below.

Name of Authorized Individual (Please type or print):	**Signature of Authorized Individual:**
Manni Sethi, MD, MBA, CHCQM	

Bone graft substitutes

Clinical Policy ID: CCP.1232

Recent review date: 5/2024

Next review date: 9/2025

Policy contains: Bone graft substitutes; recombinant human bone morphogenetic protein-2.

AmeriHealth Caritas has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas' clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by AmeriHealth Caritas, on a case by case basis, when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas' clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas' clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas will update its clinical policies as necessary. AmeriHealth Caritas' clinical policies are not guarantees of payment.

Coverage policy

The following bone graft substitutes are clinically proven and, therefore, may be medically necessary for enhancement of bone healing (Fischer, 2013; Laurencin, 2006; McNamara, 2015; Papageorgiou, 2016):

- Autograft based, used alone.
- Allograft-based, allograft bone used alone or in combination with other materials, including demineralized bone matrix.
- Ceramic or polymer-based synthetic bone graft substitutes, used alone or in combination with other materials.
- Bone graft substitutes containing an organic bone material (e.g., bovine or coral) when used alone or combined with another medically necessary bone graft substitute.

Recombinant human bone morphogenetic protein-2 is clinically proven and, therefore, may be medically necessary when used in accordance with U.S. Food and Drug Administration approved indications and labelling instructions:

- INFUSE® Bone Graft (Medtronic Inc., Minneapolis, Minnesota) for:
    - Primary treatment for skeletally mature members with acute, open tibial shaft fractures stabilized with intramedullary nail fixation after appropriate wound management, if applied within 14 days after the initial fracture (U.S. Food and Drug Administration, 2004).
    - Dental localized alveolar ridge augmentation for defects associated with extraction sockets and sinus augmentation (U.S. Food and Drug Administration, 2007).
- INFUSE® Bone Graft LT-CAGE (Medtronic, Inc., Minneapolis, Minnesota) when used only with the INFUSE Bone Graft for single-level lumbar spinal fusion and all of the following criteria (U.S. Food and Drug Administration, 2002):
    - When autologous iliac crest bone graft is not feasible.

- Skeletally mature patients (older than 18 years of age or no radiographic evidence of epiphyseal closure) with degenerative disc disease from L4 to S1; grade I spondylolisthesis at the involved level may be present.
- At least six months of non-operative treatment.
- Using an anterior open or laparoscopic approach.

Limitations

All other uses of bone graft substitutes are investigational/not clinically proven and, therefore, not medically necessary.

Mesenchymal stem cell therapy is investigational/not clinically proven and, therefore, not medically necessary for all orthopedic applications, including, but not limited to, use in repair or regeneration of musculoskeletal tissue (Killington, 2018).

Allograft bone products containing viable stem cells are investigational/not clinically proven and, therefore, not medically necessary for all orthopedic applications, including, but not limited to, demineralized bone matrix with stem cells.

All other uses of recombinant human bone morphogenetic protein-2 are not medically necessary.

Contraindications to the INFUSE Bone Graft include, but are not limited to:

- Known hypersensitivity to the components of the formulation or the titanium cage.
- Near the vicinity of a resected or extant tumor, any active malignancy, or a malignancy undergoing treatment.
- Active infection at the operative site.
- Inadequate neurovascular status.
- Compartment syndrome of the affected limb.
- Pregnancy.

Alternative covered services

No alternative covered services were identified during the writing of this policy.

Background

Bone grafting is a surgical procedure that replaces missing bone with material from patient's own body, or an artificial, synthetic, or natural substitute. Bone grafting exploits the bone tissue's ability to regenerate completely if provided the space into which to grow. As natural bone grows, it generally replaces the graft material completely, resulting in a fully integrated region of new bone.

Autologous cancellous bone graft remains the gold standard, because it provides the three elements required for bone regeneration: osteoconduction, osteoinduction, and osteogenic cells (Grabowski, 2013). The complications and morbidity from harvesting autologous bone have driven the search for reliable and safe bone graft substitutes (Giannoudis, 2005).

Bone graft substitutes include cancellous and cortical allograft bone, ceramics, demineralized bone matrix, bone marrow, and composite grafts. Currently, no single alternative graft material provides all three elements for bone regeneration. Synthetic bone substitutes or xenografts can be used as an alternative to autologous graft to overcome problems of additional surgeries or limited graft availability, but synthetic grafts, often made of hydroxyapatite or other naturally occurring and biocompatible substances, lack osteoinductive or osteogenic properties. Composite grafts combine scaffolding properties with biological elements, such as demineralized

bone matrix or bone derivatives, to stimulate cell proliferation and differentiation and, eventually, osteogenesis. Xenografts, such as a bovine species, are used as a calcified matrix (Grabowski, 2013).

Classification of bone grafts is based on material, grouped as follows (Laurencin, 2006):

- Autograft-based — used alone. Properties of action are osteoconductive, osteoinductive, and osteogenic.
- Allograft-based — allograft bone used alone or in combination with other materials. Properties of action are osteoconductive and osteoinductive.
- Natural and recombinant growth factor-based — used alone or in combination with other materials. Properties of action are osteoinductive and both osteoconductive and osteoinductive with carrier materials.
- Cell-based — used to generate new tissue alone or seeded onto a support matrix. Properties of action are osteogenic and both osteogenic and osteoconductive with carrier materials.
- Ceramic-based — calcium phosphate, calcium sulfate, and bioactive glass used alone or in combination. Properties of action are osteoconductive and limited osteoinductive when mixed with bone marrow.
- Polymer-based — degradable and nondegradable polymers used alone and in combination with other materials. Properties of action are osteoconductive and bioresorbable in degradable polymer.
- Miscellaneous — uses coral hydrogel-hydroxyapatite granules, blocks, and composite. Properties of action are osteoconductive and bioresorbable.

Findings

The clinical applications for each type of material are dictated by its particular structural and biochemical properties (Laurencin, 2006). The most common use of bone grafting is restoring the edentulous area of a missing tooth in application of dental implants. In general, bone grafts are either used in block (such as from chin or ascending ramus area of lower jaw) or are particulated to adapt better to a defect. The grafted, vascularized fibulas have been used to restore skeletal integrity to long bones of limbs in which congenital bone defects exist and to replace segments of bone after trauma or malignant tumor invasion. Other uses include fusing joints to prevent movement, repairing broken bones that have bone loss, and repairing broken bones that have not yet healed.

The ideal bone-graft substitute is biocompatible, bioresorbable, osteoconductive, osteoinductive, structurally similar to bone, easy to use, and cost-effective. Currently marketed products are variable in their composition and claimed mechanisms of action. It is reasonable that not all bone graft substitute products will perform the same.

Future biosynthetic bone implants may obviate the need for autologous bone grafts. There is increasing interest in combining an osteoconductive protein in an osteoconductive carrier medium to facilitate timed-release delivery and/or to provide a material scaffold for bone formation (Laurencin, 2006). Further, advances in tissue engineering, with “the integration of the biological, physical, and engineering sciences,” will generate new carrier constructs that repair, regenerate, and restore tissue to its functional state. These constructs are likely to encompass additional families of growth factors, evolving biological scaffolds, and incorporation of mesenchymal stem cells. Ultimately, the development of ex vivo bioreactors capable of bone manufacture with the appropriate biomechanical cues will provide tissue-engineered constructs for direct use in the skeletal system. Finally, as researchers continue to find new materials and biologic approaches to bone repair, the future of bone graft substitutes continues to be an expanding topic of interest.

The North American Spine Society found that the evidence was insufficient to recommend the use of one's own bone graft or bone substitutes in posterolateral fusion for degenerative lumbar spondylolisthesis. Four randomized controlled studies (n = 577) patients were reviewed. The largest trial (n = 335) found no differences

in outcomes between recombinant human bone morphogenetic protein-7 putty and harvest from the pelvis bone, though bridging bone formed less with the putty. The putty had shorter surgery times and less bleeding. Smaller trials found comparable fusion rates, function, and safety between calcium sulfate with local bone versus harvest, and between coral hydroxyapatite versus harvest, though one suggested better fusion with harvest. The limited evidence suggests similar effectiveness but substitutes may reduce pelvis bone harvest issues for fusion in this population (North American Spine Society, 2014).The major concerns associated with allografts are antigenicity and risk of disease transmission from donor to recipient (Campana, 2014). To minimize this risk, the production of an allograft worthy of distribution and implantation requires strict attention to detail through a comprehensive process. With an increasing clinical requirement for bone grafting procedures, there is a commensurate increase in patients' demands for assurance that bank bone will not be infected with pathogens. The U.S. Food and Drug Administration (2024) requires that manufacturers of human allograft products, including bone, be registered.

A narrative review (Zhang, 2017) assessed the need for natural bone substitutes with specific mention of nacre, or mother-of-pearl, as an organic matrix-calcium carbonate coupled shell structure. Nacre is produced by mollusks. In vivo and in vitro studies have revealed that nacre is osteoinductive, osteoconductive, biocompatible, and biodegradable. The authors concluded that there is great potential clinically for nacre as a bone graft substitute.

In 2018, we added three systematic reviews (Fischer, 2013; McNamara, 2015; Papageorgiou; 2016) to this policy, and we received a specific request to evaluate the medical necessity of recombinant human bone morphogenetic protein as an alternative or adjunct to autologous bone grafts for osteoinduction and bone healing. Two products have been approved that use recombinant human bone morphogenetic protein -2 (also known as dibotermin alfa) as the main ingredient (U.S. Food and Drug Administration, 2002, 2004, 2007):

- INFUSE bone graft for tibial shaft fractures, dental sinus augmentation, and alveolar ridge augmentation.
- INFUSE titanium LT-CAGE when used with the INFUSE bone graft for single level spinal fusion procedures from L4 to S1.

INFUSE offers at least comparable osteoinductive advantages to those of autologous grafts, particularly when autologous grafts are not feasible, but a range of adverse events and several off-label uses have been reported (Krishnakumar, 2017; Poorman, 2017; Zadegan, 2017). Inconsistent and often inadequate reporting of adverse events makes assessment of the relative benefits and harms associated with recombinant human bone morphogenetic protein -2 and other surgical alternatives difficult to determine. The evidence is sufficient to support INFUSE for the approved indications that have a more predictable safety profile when used in accordance with labelling requirements, and, particularly, when autologous bone grafting alone is not feasible (Fu, 2013; Kelly, 2016; Lin, 2016; Simmonds, 2013).

In 2019, we added two systematic reviews (Cicciu, 2018; Killington, 2018) with no changes to the policy coverage.

In 2020, we added eight systematic reviews and meta-analyses to the policy: five addressed bone augmentation in oral surgery (Al-Moraissi, 2020; Avila-Ortiz, 2019; Dragonas, 2019; Liu, 2019; Stumbras, 2019); one addressed bony defects caused by giant cell tumor (Vaishya, 2019); and two addressed application of bone morphogenetic protein-2 to the spine (Mariscal, 2020; Stark, 2019). The new information is consistent with the current policy, and no policy changes are warranted.

In 2021, we added three systematic reviews and meta-analyses to the policy. Cottrill (2020) analyzed three randomized controlled trials and seven case series of the radiographic and clinical outcomes of a newer-generation synthetic ceramic called silicate-substituted calcium phosphate bone grafts, which is designed to maximize osteoinduction and osteoconduction in spinal fusion (Cottrill, 2020). From the case series (n = 694 patients treated with the intervention), 93% of patients successfully achieved arthrodesis, along with significant

improvements in back pain (visual analog score -3.3 points), leg pain (visual analog score -4.8 points), and Oswestry Disability Index (-31.6 points) by last follow-up that ranged from six months to 36 months ($P < .001$ for each). Fusion rates were similar regardless of surgical approach, spine levels involved, or other procedures used. In the randomized controlled trials, fusion rates were similar between patients treated with silicate-substituted calcium phosphate bone grafts and those treated with recombinant human bone morphogenetic protein-2 supplemented grafts (odds ratio 1.11, $P = .83$). However, the heterogeneity of the data and lack of comparative data to other graft materials limits the generalizability of these results.

Two systematic reviews and meta-analyses confirm the relative safety and effectiveness of recombinant human bone morphogenetic protein and autologous bone graft in lumbar fusion (Liu, 2020) and in cleft lip and palate augmentation (Xiao, 2020). The new information requires no policy changes.

In 2022, we added several meta-analyses, that determined

- The most effective grafting material for maxillary sinus augmentation was bovine xenograft and bone marrow concentrate (81%), while autologous bone graft was least effective (57%) (Trimmel, 2021).
- For maxillary sinus floor augmentation, decellularized xenograft-derived cancellous bone scaffolds are effective alternatives to autologous bone graft (Amini, 2021).
- Morphogenetic protein-2 outcomes are superior to autologous iliac crest bone graft after lumbar spine fusion (Wu, 2021).

In 2023, we removed the citation and reference for a Local Coverage Determination issued by the Centers for Medicare and Medicaid Services. We added two systematic reviews/meta-analyses by the same team on long bone non-union after recombinant human bone morphogenetic proteins versus autologous bone graft. One review of 14 studies (n = 1,782) found significantly higher healing rate and significantly shorter healing time in moderate-quality studies after recombinant human bone morphogenetic proteins (Xie, 2023a), while the other, a review of five studies (n = 394) found no basis for adding the procedure to autologous bone graft (Xie, 2023b).

In 2024, we added North American Spine Society's 2014 decision to not recommend bone graft substitutes. We also found a systematic review that included 22 studies with a total of 613 biopsy samples (n = 477 patients). A meta-analysis found that adding growth factors to particulate bone grafts in maxillary sinus floor augmentation procedures did not significantly increase new bone formation compared to controls. However, sub-group analyses found that using platelet-rich plasma or platelet-rich fibrin resulted in 49% more new bone formation than controls alone ($P = .004$), with moderate heterogeneity between studies. Regarding other outcomes, areas treated with growth factors presented 57% fewer residual graft particles after healing than controls ($P < .0001$). A significant 1.85-fold increase in connective tissue formation was noted in areas treated with recombinant human bone morphogenetic protein-2 (rhBMP-2) after healing ($P = .03$). These findings provide quantitative evidence that selective growth factors like platelet concentrate and rhBMP-2 can enhance aspects of bone regeneration in maxillary sinus floor augmentation (Mendes, 2023).

References

On April 9, 2024, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were "Bone Transplantation" (MeSH), "Bone Substitutes," (MeSH), "allograft," "autograft," "bone reconstruction," "bone repair," "calcium sulphate," "ceramic," "hydroxyapatite," "implant," and "polymer." We included the best available evidence according to established

evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

5/2016: .initial review date and clinical policy effective date: 7/2016

7/2017: Policy references updated.

7/2018: Policy references updated. Coverage expanded to include recombinant human bone morphogenetic protein -2 (INFUSE) products.

5/2019: Policy references updated.

5/2020: Policy references updated.

5/2021: Policy references updated.

5/2022: Policy references updated.

5/2023: Policy references updated.

5/2024. Policy references updated.