Prior Authorization Review Panel
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
Policies submitted without this form will not be considered for review.

Plan: AmeriHealth Caritas Pennsylvania & Keystone First	Submission Date: 6/1/2025
Policy Number: CCP.1232	Effective Date: 7/1/2016 Revision Date: 5/2025
Policy Name: Bone graft substitutes	

Type of Submission:

☐ New Policy	☒ Prior Authorization Policy
☒ Revised Policy*	☐ Base Policy
☐ Annual Review- no revisions	☐ Experimental/Investigational Policy
	☐ Statewide PDL
	☐ Other:

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

Please provide any clarifying information for the policy below:

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

Bone graft substitutes

Clinical Policy ID: CCP.1232

Recent review date: 5/2025

Next review date: 9/2026

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

Keystone First- CHIP has developed clinical policies to assist with making coverage determinations. Keystone First- CHIP's 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 Keystone First- CHIP, 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. Keystone First- CHIP's 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. Keystone First- CHIP's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First- CHIP will update its clinical policies as necessary. Keystone First- CHIP's 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

Clinical Guidelines

For spinal fusion, the North American Spine Society (2014) evaluated four randomized controlled trials (n = 577) and found insufficient evidence to recommend either autologous bone grafts or substitutes for posterolateral fusion in degenerative lumbar spondylolisthesis. The largest trial (n = 335) reported no significant differences in clinical outcomes between recombinant human bone morphogenetic protein-7 putty and iliac crest harvest, though the putty led to less bridging bone formation but reduced operative time and blood loss. Smaller trials showed comparable fusion rates, function, and safety for calcium sulfate with local bone or coral hydroxyapatite versus iliac crest harvest, with one suggesting marginally better fusion with harvest. These findings suggest that bone graft substitutes may reduce complications associated with pelvic bone harvest while achieving similar effectiveness in this context.

In pediatric congenital pseudarthrosis of the tibia (CPT), the CPAM-LRC consensus panel (Song, 2025) recommends operative management for patients over 2 years old, involving complete excision of the pseudarthrosis site, sufficient autogenous bone grafting, and fixation using combined external and intramedullary methods (e.g., Ilizarov with intramedullary rods). Based on a systematic review of 74 studies (n = 1513 patients, 1525 tibias), this approach achieved a primary union rate of 84% and a final union rate of 93.3%, with a refracture rate of 22.3%. Vascularized fibular grafts and cross-union techniques were identified as viable alternatives to corticocancellous autografts, though no consensus was reached on adjuvants like recombinant human bone morphogenetic proteins due to inconclusive benefits. These recommendations underscore autogenous grafts as the standard while supporting substitutes in complex cases where traditional grafting may be challenging.

For foot and ankle conditions, the American Orthopaedic Foot & Ankle Society (2022) endorses osteochondral autograft and allograft transplantation as non-experimental options for treating osteochondral lesions of the talus,

particularly in cases with large defects, cysts, or prior surgical failures. This guideline supports the use of both autogenous and allogeneic grafts to restore cartilage and bone integrity, highlighting their established role in addressing significant talar defects. Similarly, the American Academy of Orthopaedic Surgeons (2023) guideline on Osteochondritis Dissecans (OCD) recommends surgical options, including grafting, for symptomatic patients with unstable or displaced lesions, regardless of skeletal maturity. Based on limited evidence, this guideline supports grafting to stabilize lesions and promote healing, though specific graft types are not prioritized, indicating flexibility in choosing autografts or allografts based on clinical context.

In knee reconstruction, the American Academy of Orthopaedic Surgeons (2022) provides robust guidance for Anterior Cruciate Ligament (ACL) reconstruction, issuing a strong recommendation based on high-quality evidence to prefer autografts over allografts in young or active patients due to lower graft failure rates and potentially better outcomes (Brophy, 2023). For skeletally mature patients, a moderate recommendation suggests selecting between bone-patellar tendon-bone (BTB) or hamstring autografts by balancing lower risks of graft failure and infection with BTB against reduced anterior or kneeling pain with hamstring grafts. The guideline also strongly advocates reconstruction over repair for ACL tears requiring surgery, citing lower revision risks. These recommendations emphasize the superiority of autografts in ACL reconstruction while acknowledging allografts as viable in less active or older patients, guiding graft selection to optimize functional outcomes.

The use of orthobiologics, particularly cell-based therapies, is approached with significant caution. A consensus conference convened by the American Academy of Orthopaedic Surgeons and National Institutes of Health (Chu, 2019) raised concerns about the widespread use of unproven biologic treatments, particularly minimally manipulated cell products marketed as "stem cells." These products do not meet scientific criteria for stem cells and should be termed "cell therapy," with clear patient communication about their unproven status. The consensus recommends adopting minimum standards for characterizing biologics (e.g., MIBO checklists), establishing high-quality patient registries, and conducting rigorous clinical trials to evaluate safety and efficacy before broad adoption. Consequently, mesenchymal stem cell therapies and allograft products containing viable stem cells are considered investigational for most orthopedic applications, highlighting the need for robust evidence to support their use over established grafting techniques.

Regulatory oversight ensures the safety of allograft substitutes. To address risks of antigenicity and disease transmission, the U.S. Food and Drug Administration (2024) mandates that manufacturers of human allograft products, including bone, adhere to strict registration and processing standards (Campana, 2014). This framework supports the safe integration of allografts as alternatives to autografts in various orthopedic applications, reinforcing their role in clinical practice while ensuring patient safety.

Systematic Reviews

Systematic reviews synthesize evidence on the safety and efficacy of bone graft substitutes across spinal, foot and ankle, dental, maxillofacial, and other orthopedic applications, providing insights into their clinical utility and limitations. In spinal fusion, Fitzgerald (2025) reviewed 21 studies (n = 3,321 participants), including three randomized controlled trials, one cohort study, and four case series on Infuse™ (recombinant human bone morphogenetic protein-2) and 10 studies on other grafts for lumbar interbody fusion in degenerative disc disease. The review found comparable fusion rates between Infuse™ (90.9–100%) and iliac crest bone graft (66.7–95.8%, p=0.102–0.903, n = 266 across two randomized controlled trials), with Infuse™ reducing operative time (1.4–1.9 hours vs. 2.0–3.3 hours, p<0.001–0.006, n = 282) and blood loss (95–109.8 ml vs. 153.1–167 ml, p=0.017–0.400, n = 282), though high risk of bias and limited comparative data for non-Infuse™ grafts were noted. Biddau (2024) evaluated 27 studies (n = 66,027 participants) on anterior lumbar interbody fusion, with 18 studies focusing on recombinant human bone morphogenetic protein-2, reporting high fusion rates (88.5–100%) but increased complications like retrograde ejaculation (6.3% vs. 1.2%, P=0.001) and pseudoarthrosis (odds

ratio 1.44, 95% CI: 1.16–1.76). Allografts (84.2–96%), synthetics (77.78–100%), and peptide-based grafts (93.6%) showed promise but lacked robust data. Mariscal (2020) affirmed the efficacy of synthetic ceramics and morphogenetic proteins in spinal fusion, though specific quantitative data were not reported. Cicciu (2018) and Killington (2018) confirmed the safety and effectiveness of recombinant human bone morphogenetic protein-2 in spinal applications, aligning with current policies, without detailing participant numbers.

In foot and ankle surgery, Hoveidaei (2024) conducted a systematic review and meta-analysis of eight studies (n = 894 patients, n = 497 synthetic grafts, n = 397 autologous grafts), finding no significant differences in CT fusion rates (odds ratio 0.95, 95% CI: 0.69–1.31, I^2 = 0%), AOFAS functional scores (standardized mean difference 0.03, 95% CI: -0.13–0.18, I^2 = 27%), or surgical complications (odds ratio 1.03, 95% CI: 0.59–1.78, I^2 = 60%) between synthetic and autologous grafts. Hartman (2025) reviewed 13 non-randomized studies (n = 363 patients, n = 397 procedures) on demineralized bone matrix, reporting osseous union rates of 85.6% (n = 238/278) in fusion cohorts and 100% in fifth metatarsal and calcaneal fracture cohorts, with complication rates of 27.2% (n = 99) and failure rates of 10.8% (n = 43). Non-union rates were comparable between demineralized bone matrix (12.9%, n = 4/31) and non-demineralized bone matrix cohorts (14.8%, P = 0.83), though low evidence quality and study heterogeneity were limitations.

In dental and maxillofacial applications, Al-Moraissi (2020), Avila-Ortiz (2019), Dragonas (2019), Liu (2019), and Stumbras (2019) supported the effectiveness of xenografts and recombinant protein-enhanced grafts for maxillary sinus and alveolar ridge augmentation, though participant numbers were not specified. Deandra (2024) reviewed seven studies (n = 83 participants) on regenerative periodontal surgery, finding comparable clinical attachment level outcomes between early (4 weeks) and later (6 months) orthodontic treatment initiation, with autografts, allografts, xenografts (e.g., deproteinized bovine bone mineral), and alloplasts (e.g., β-tricalcium phosphate) all demonstrating success. Mohanasatheesh (2024) examined biphasic calcium phosphate for dental extraction socket preservation in two randomized controlled trials (n = 74 participants, n = 26 from Mardas, n = 48 from Uzeda), reporting significantly increased bone density ($p<0.05$) with a 60% hydroxyapatite and 40% β-tricalcium phosphate ratio after 6 months, though limited trial numbers prevented meta-analysis.

Across general orthopedic applications, Fischer (2013), McNamara (2015), and Papageorgiou (2016) supported bone graft substitutes in alveolar ridge augmentation, sinus lift procedures, and long-bone defect repair, without reporting specific participant counts. Vaishya (2019) endorsed substitutes for bony defects caused by giant cell tumors, also without quantitative details. Limitations across reviews include high risk of bias, inconsistent fusion definitions, reliance on retrospective or industry-funded studies, and small sample sizes, underscoring the need for standardized reporting and well-designed trials to strengthen evidence for bone graft substitutes.

Meta-Analyses

Meta-analyses provide quantitative evidence on the efficacy and safety of bone graft substitutes across spinal, maxillofacial, and orthopedic applications. Cottrill (2020) analyzed three randomized controlled trials and seven case series (n = 694 patients) on silicate-substituted calcium phosphate grafts in spinal fusion, reporting a 93% arthrodesis rate and 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 six to 36 months (P < .001 for each). Fusion rates were comparable to recombinant human bone morphogenetic protein-2 (odds ratio 1.11, P = .83). Lee (2024) evaluated five studies (n = 598 patients) on recombinant human bone morphogenetic protein-2 in posterior cervical fusion, finding a significantly lower risk of pseudarthrosis (odds ratio 0.44; 95% CI, 0.21–0.92; P = 0.03) compared to autografts or allografts, with no significant increase in neurologic (odds ratio 1.86; P = 0.08) or immediate medical complications (odds ratio 0.77; P = 0.28). However, high-dose recombinant human bone morphogenetic protein-2 (>2.1 mg/level) increased wound infection risk (P = 0.03). Wu (2021) reported superior spinal fusion outcomes with morphogenetic protein-2 compared to iliac crest autografts. Liu (2020) and Xiao (2020) confirmed equivalent outcomes for recombinant human bone morphogenetic protein versus

autologous grafts in lumbar fusion and cleft lip/palate reconstruction. Alawami (2025) analyzed eight studies (n = 154 patients) on recombinant human bone morphogenetic protein-2 for alveolar cleft reconstruction in children, finding no significant difference in bone filling (mean difference -1.24; 95% CI, -4.14 to 1.67) between recombinant human bone morphogenetic protein-2 (61.11% ± 24.6%) and iliac crest grafts (59.12% ± 18.59%), though iliac crest grafts achieved higher bone height (78.65% ± 14.38% vs. 67.5% ± 5.45%). Trimmel (2021) found bovine xenograft with bone marrow concentrate (81%) outperformed autologous grafts (57%) in maxillary sinus augmentation. Amini (2021) supported decellularized xenograft scaffolds as effective alternatives. Mendes (2023) analyzed 22 studies (n = 477 patients), finding that growth factors like platelet-rich plasma increased new bone formation by 49% (P = .004) in maxillary sinus augmentation, with recombinant human bone morphogenetic protein-2 increasing connective tissue formation 1.85-fold (P = .03). Xie (2023a) reviewed 14 studies (n = 1,782) on long bone non-union, finding recombinant human bone morphogenetic proteins had higher healing rates and shorter healing times than autologous grafts in moderate-quality studies. Xie (2023b), reviewing five studies (n = 394), found no benefit in combining recombinant proteins with autologous grafts.

Other Evidence

Other evidence, including narrative reviews and cohort studies, highlights emerging bone graft substitute options. Laurencin (2006) described the ideal substitute as biocompatible, bioresorbable, osteoconductive, osteoinductive, and structurally similar to bone, noting future biosynthetic implants may reduce reliance on autologous grafts. Zhang (2017) reviewed nacre (mother-of-pearl) as a biocompatible, osteoinductive, and biodegradable substitute with potential clinical applications. Fu (2013), Kelly (2016), Lin (2016), and Simmonds (2013) supported the use of INFUSE (recombinant human bone morphogenetic protein-2) for approved indications like tibial fractures and spinal fusion when autologous grafting is not feasible, despite reported adverse events (Krishnakumar, 2017; Poorman, 2017; Zadegan, 2017). Campana (2014) noted concerns with allografts, including antigenicity and disease transmission risks, emphasizing strict regulatory oversight by the U.S. Food and Drug Administration (2024).

In 2025, we revised the findings section and incorporated five clinical guidelines and consensus statements (American Academy of Orthopaedic Surgeons, 2022; American Academy of Orthopaedic Surgeons, 2023; American Orthopaedic Foot & Ankle Society, 2022; Brophy & Lowry, 2023; Chu et al., 2019). In addition, we added nine articles, including four systematic reviews with meta-analyses (Alawami, 2025; Hoveidaei, 2024; Johnson, 2024; Lee, 2024) and five systematic reviews (Biddau, 2024; Deandra, 2024; Fitzgerald, 2025; Hartman, 2025; Mohanasatheesh, 2024) to the policy, incorporating their findings on bone graft substitutes in spinal fusion, foot and ankle surgery, dental applications, and pediatric alveolar cleft treatment (Lee, 2024; Fitzgerald, 2025; Johnson, 2024; Biddau, 2024; Hoveidaei, 2024; Hartman, 2025; Deandra, 2024; Mohanasatheesh, 2024; Alawami, 2025)

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On April 9, 2025, 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.

5/2025: Policy references updated.