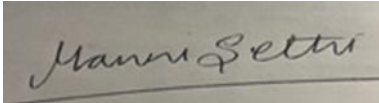


Prior Authorization Review Panel  
MCO Policy Submission

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: 6/1/2026                                                            |  |
| Policy Number: CCP.1232                                                                                                                                                            |                                                                | Effective Date: 7/1/2016<br>Revision Date: 5/1/2026                                  |  |
| Policy Name: Bone graft substitutes                                                                                                                                                |                                                                |                                                                                      |  |
| Type of Submission:                                                                                                                                                                |                                                                | Type of Policy:                                                                      |  |
| <input type="checkbox"/> New Policy                                                                                                                                                | <input checked="" type="checkbox"/> Prior Authorization Policy |                                                                                      |  |
| <input checked="" type="checkbox"/> Revised Policy*                                                                                                                                | <input type="checkbox"/> Base Policy                           |                                                                                      |  |
| <input type="checkbox"/> Annual Review- no revisions                                                                                                                               | <input type="checkbox"/> Experimental/Investigational Policy   |                                                                                      |  |
|                                                                                                                                                                                    | <input type="checkbox"/> Statewide PDL                         |                                                                                      |  |
|                                                                                                                                                                                    | <input type="checkbox"/> Other:                                |                                                                                      |  |
| <p>*All revisions to the policy <u>must</u> be highlighted using track changes throughout the document.</p> <p>Please provide any clarifying information for the policy below:</p> |                                                                |                                                                                      |  |
| 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: 5/2026

Next review date: 9/2027

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

*Keystone First has developed clinical policies to assist with making coverage determinations. Keystone First'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, 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'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's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First will update its clinical policies as necessary. Keystone First'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 materials, 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 U.S. Food and Drug Administration-approved indications and labeling 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 members (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 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 the patient's own body (autograft), or with 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). Harvesting autologous bone has caused complications and morbidity, which led to 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 — materials such as coral hydrogel-hydroxyapatite granules, blocks, and composite.

## 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, it 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.

Regulatory status varies by product type. Some bone graft substitutes are cleared through the U.S. Food and Drug Administration 510(k) pathway as Class II devices, such as resorbable calcium salt bone void fillers and synthetic dental bone grafting materials, while recombinant human bone morphogenetic protein-2 products are regulated through premarket approval pathways. A 510(k) clearance indicates substantial equivalence to a legally marketed predicate device and should not be interpreted as evidence of clinical superiority over other graft materials.

As of April 2026, FDA premarket approval records for INFUSE™ Bone Graft identify two clinically relevant labeling expansions during the preceding five years. In 2023, FDA approved expanded use of INFUSE® Bone Graft with additional Medtronic interbody fusion devices, including specified Anteralign LS and TL devices. In 2026, FDA approved INFUSE™ Bone Graft for transforaminal lumbar interbody fusion at one or two adjacent levels from L2 to S1 for symptomatic degenerative disc disease confirmed by history and radiographic studies, after at least six months of nonoperative treatment, when used with an FDA-cleared intervertebral body fusion device and metallic screw-and-rod system.

In pediatric congenital pseudarthrosis of the tibia, the consensus panel (Song, 2025) recommends operative management for individuals 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 participants, 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 recommends surgical options, including grafting, for symptomatic individuals 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 reconstruction, issuing a strong recommendation based on high-quality evidence to prefer autografts over allografts in young or active individuals 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 or hamstring autografts by balancing lower risks of graft failure and infection with bone-patellar tendon-bone against reduced anterior or kneeling pain with hamstring grafts. The guideline also strongly advocates reconstruction over repair for Anterior Cruciate Ligament tears requiring surgery, citing lower revision risks. These recommendations emphasize the superiority of autografts in Anterior Cruciate Ligament 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., 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 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.

Ambrosio (2025) conducted a systematic review and network meta-analysis of 43 randomized controlled trials (n = 3,823) comparing osteobiologics with autologous iliac crest bone graft in lumbar spinal fusion. Recombinant human bone morphogenetic protein-2 was associated with significantly higher fusion rates (odds ratio 3.71; 95% confidence interval 2.59 to 5.32;  $P < .0001$ ), lower complication rates (odds ratio 0.30; 95% confidence interval 0.13 to 0.68;  $P < .0001$ ), shorter operative time, and lower blood loss. Evidence certainty was moderate for recombinant human bone morphogenetic protein-2 but low to very low for most other osteobiologics, limiting conclusions for non-recombinant human bone morphogenetic protein-2 products.

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% confidence interval: 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 Computed Tomography fusion rates (odds ratio 0.95, 95% confidence interval: 0.69–1.31,  $I^2 = 0\%$ ), American Orthopaedic Foot & Ankle Society functional scores (standardized mean difference 0.03, 95% confidence interval: -0.13–0.18,  $I^2 = 27\%$ ), or surgical complications (odds ratio 1.03, 95% confidence interval: 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.,

$\beta$ -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%  $\beta$ -tricalcium phosphate ratio after 6 months, though limited trial numbers prevented meta-analysis.

Thomas (2026) systematically reviewed 18 clinical studies comparing alloplastic and biologic grafts for maxillary sinus augmentation. Autografts demonstrated the highest effectiveness, followed by xenografts and allografts. Alloplastic grafts had lower new bone formation and regenerative potential than biologic grafts but showed acceptable safety, high implant survival, and potential utility when avoiding donor-site morbidity, immunologic risk, or infection-related concerns is clinically important.

Saghiri (2025) performed a systematic review and meta-analysis comparing bioactive glass with autogenic bone grafts in maxillofacial reconstruction. Bioactive glass showed greater total bone volume retention at six months, lower graft resorption, and higher residual biomaterial retention, while new bone formation was comparable to autogenic grafts. The authors concluded that bioactive glass may be a viable alternative when autograft harvesting is impractical or associated with high donor-site morbidity, though small sample sizes, heterogeneous indications, and limited long-term outcomes warrant cautious interpretation.

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,  $P = .83$ ). Ambrosio (2026) updated the network meta-analysis for posterior lumbar spinal fusion, including 35 randomized controlled trials ( $n = 2,298$ ). Recombinant human bone morphogenetic protein-2 showed significantly higher fusion rates than autologous iliac crest bone graft (odds ratio 3.86; 95% confidence interval 2.60 to 5.74;  $P < .0001$ ) and lower osteobiologic-related complication risk (odds ratio 0.50; 95% confidence interval 0.34 to 0.73;  $P = .0004$ ). Pain and disability outcomes were comparable across treatments. Other osteobiologics showed favorable trends but did not demonstrate consistent superiority, reinforcing recombinant human bone morphogenetic protein-2 as the best-supported biologic in posterior lumbar fusion while leaving uncertainty for other agents.

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% confidence

interval, 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 recombinant human bone morphogenetic protein-2 compared to iliac crest autografts. Liu (2020) and Xiao (2020) confirmed equivalent outcomes for recombinant human bone morphogenetic protein-2 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% confidence interval, -4.14 to 1.67) between recombinant human bone morphogenetic protein-2 ( $61.11\% \pm 24.6\%$ ) and iliac crest grafts ( $59.12\% \pm 18.59\%$ ), though iliac crest grafts achieved higher bone height ( $78.65\% \pm 14.38\%$  vs.  $67.5\% \pm 5.45\%$ ). 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 (2023) reviewed 14 studies ( $n = 1,782$ ) on long bone non-union, finding recombinant human bone morphogenetic protein-2 had higher healing rates and shorter healing times than autologous grafts in moderate-quality studies. Xie (2022), 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.

In 2026, we updated the findings section with new systematic reviews and network meta-analyses on lumbar spinal fusion, posterior lumbar fusion, maxillary sinus augmentation, and bioactive glass in maxillofacial reconstruction (Ambrosio, 2025; Ambrosio, 2026; Saghiri, 2025; Thomas, 2026). We also updated the background and coverage rationale to reflect recent U.S. Food and Drug Administration activity for INFUSE Bone Graft and selected 510(k)-cleared bone graft substitute products (U.S. Food and Drug Administration, 2023; U.S. Food and Drug Administration, 2026).

## References

On April 19, 2026, 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.

Alawami EAA, Alomari F, Aloqaybi SA, et al. Efficacy of recombinant human bone morphogenetic protein-2 in alveolar cleft treatment for children: systematic review and meta-analysis. *Life* (Basel). 2025;15(2):185. Doi:10.3390/life15020185.

Al-Moraissi EA, Oginni FO, Mahyoub Holkom MA, Mohamed AAS, Al-Sharani HM. Tissue-engineered bone using mesenchymal stem cells versus conventional bone grafts in the regeneration of maxillary alveolar bone: A systematic review and meta-analysis. *Int J Oral Maxillofac Implants*. 2020;35(1):79–90. Doi: 10.11607/jomi.7682.

Ambrosio L, Muthu S, Sakai D, Vadalà G, Denaro V. Comparative efficacy and safety of osteobiologics in posterior lumbar fusion: a network meta-analysis of randomized controlled trials. *Global Spine J*. Published online 2026. Doi:10.1177/21925682261447888

Ambrosio L, Schol J, Tamagawa S, et al. Efficacy and safety of osteobiologics for lumbar spinal fusion: a systematic review and network meta-analysis. *J Bone Joint Surg Am*. 2025;107(22):2110-2121. Doi:10.2106/JBJS.24.01205

American Academy of Orthopaedic Surgeons. Management of anterior cruciate ligament injuries: evidence-based clinical practice guideline. Published 2022. <https://www.aaos.org/aclcp>

American Academy of Orthopaedic Surgeons. Clinical Practice Guideline: Management of Anterior Cruciate Ligament Injuries. AAOS.org. Published March 13, 2023. <https://www.aaos.org/quality/clinical-practice-guidelines/anterior-cruciate-ligament/>

American Academy of Orthopaedic Surgeons. Clinical Practice Guideline: Management of Osteochondritis Dissecans. AAOS.org. Published June 8, 2023. <https://www.aaos.org/quality/clinical-practice-guidelines/osteochondritis-dissecans/>

American Orthopaedic Foot & Ankle Society. Position Statement: Use of Osteochondral Transplantation for Treatment of Osteochondral Lesions of the Talus. AOFAS.org. Published September 2022. <https://www.aofas.org/advocacy/position-statements/use-of-osteochondral-transplantation-for-treatment-of-osteochondral-lesions-of-the-talus/>

Amini Z, Lari R. A systematic review of decellularized allograft and xenograft-derived scaffolds in bone tissue regeneration. *Tissue Cell*. 2021;69:101494. Doi: 10.1016/j.tice.2021.101494.

Avila-Ortiz G, Chambrone L, Vignoletti F. Effect of alveolar ridge preservation interventions following tooth extraction: A systematic review and meta-analysis. *J Clin Periodontol*. 2019;46 Suppl 21:195-223. Doi: 10.1111/jcpe.13057.

Biddau DT, Wang ZA, Faulks CR, Mobbs RJ, Malham GM. Bone graft substitutes used in anterior lumbar interbody fusion: a contemporary systematic review of fusion rates and complications. *J Spine Surg*. 2024;10(3):548-561. Doi:10.21037/jss-24-24.

Brophy RH, Lowry KJ. American Academy of Orthopaedic Surgeons clinical practice guideline summary: management of anterior cruciate ligament injuries. *J Am Acad Orthop Surg*. 2023;31(11):531-537. Doi:10.5435/JAAOS-D-22-01020.

Campana V, Milano G, Pagano E, et al. Bone substitutes in orthopaedic surgery: From basic science to clinical practice. *J Mater Sci Mater Med*. 2014;25(10):2445-2461. Doi: 10.1007/s10856-014-5240-2.

- Chu CR, Rodeo S, Bhutani N, et al. Optimizing clinical use of biologics in orthopaedic surgery: consensus recommendations from the 2018 AAOS/NIH U-13 conference. *J Am Acad Orthop Surg*. 2019;27(2):e50-e63. Doi:10.5435/JAAOS-D-18-0030.
- Cicciu M, Cervino G, Herford AS, et al. Facial bone reconstruction using both marine or non-marine bone substitutes: Evaluation of current outcomes in a systematic literature review. *Mar Drugs*. 2018;16(1);27. Doi: 10.3390/md16010027.
- Cottrill E, Premananthan C, Pennington Z, et al. Radiographic and clinical outcomes of silicate-substituted calcium phosphate (SiCAP) bone grafts in spinal fusion: Systematic review and meta-analysis. *J Clin Neurosci*. 2020;81:353-366. Doi: 10.1016/j.jocn.2020.09.073.
- Deandra FA, Sulijaya B, Sudjarmika DA, Harsas NA. Selection of bone graft material and proper timing of periodontal surgery for orthodontic patients: a systematic review. *Heliyon*. 2024;10(1):e24201. Doi:10.1016/j.heliyon.2024.e24201.
- Dragonas P, Schiavo JH, Avila-Ortiz G, Palaiologou A, Katsaros T. Plasma rich in growth factors (PRGF) in intraoral bone grafting procedures: A systematic review. *J Craniomaxillofac Surg*. 2019;47(3):443-453. Doi: 10.1016/j.jcms.2019.01.012.
- Fischer CR, Cassilly R, Cantor W, Edusei E, Hammouri Q, Errico T. A systematic review of comparative studies on bone graft alternatives for common spine fusion procedures. *Eur Spine J*. 2013;22(6):1423-1435. Doi: 10.1007/s00586-013-2718-4.
- Fitzgerald A, McCool R, Carr E, et al. A systematic review of bone graft products used in lumbar interbody fusion procedures for degenerative disc disease. *N Am Spine Soc J*. 2025;21:100579. Doi:10.1016/j.xnsj.2024.100579.
- Fu R, Selph S, McDonagh M, et al. Effectiveness and harms of recombinant human bone morphogenetic protein-2 in spine fusion: A systematic review and meta-analysis. *Ann Intern Med*. 2013;158(12):890-902. Doi: 10.7326/0003-4819-158-12-201306180-00006.
- Grabowski M, Gregory D; Cornett A. Bone graft and bone graft substitutes in spine surgery: Current concepts and controversies. *J Am Acad Orthop Surg*. 2013;21(1):51-60. Doi: 10.5435/jaaos-21-01-51.
- Hartman H, Butler JJ, Calton M, et al. Limited evidence to support demineralized bone matrix in foot and ankle surgical procedures: a systematic review. *World J Orthop*. 2025;16(1):16-26. Doi:10.5312/wjo.v16.i1.16.
- Hoveidaei AH, Ghaseminejad-Raeini A, Esmaeili S, et al. Effectiveness of synthetic versus autologous bone grafts in foot and ankle surgery: a systematic review and meta-analysis. *BMC Musculoskelet Disord*. 2024;25(1):539. Doi:10.1186/s12891-024-07676-8.
- Kelly MP, Vaughn OL, Anderson PA. Systematic review and meta-analysis of recombinant human bone morphogenetic protein-2 in localized alveolar ridge and maxillary sinus augmentation. *J Oral Maxillofac Surg*. 2016;74(5):928-939. Doi: 10.1016/j.joms.2015.11.027.
- Killington K, Mafi R, Mafi P, Khan WS. A systematic review of clinical studies investigating mesenchymal stem cells for fracture non-union and bone defects. *Curr Stem Cell Res Ther*. 2018;13(4):284-291. Doi: 10.2174/1574888x12666170915121137.
- Krishnakumar GS, Roffi A, Reale D, Kon E, Filardo G. Clinical application of bone morphogenetic proteins for bone healing: A systematic review. *Int Orthop*. 2017;41(6):1073-1083. Doi: 10.1007/s00264-017-3471-9.
- Laurencin C, Khan Y, El-Amin SF. Bone graft substitutes. *Expert Rev Med Devices*. 2006;3(1):49-57. Doi: 10.1586/17434440.3.1.49.

- Lee HR, Lee DH, Seok SY, Kim IH, Cho JH, Hwang CJ. Meta-analysis on efficacy and complications of bone morphogenetic protein-2 for posterior fusion of cervical spine. *World Neurosurg.* 2024;183:e3-e10. Doi:10.1016/j.wneu.2023.09.035.
- Lin GH, Lim G, Chan HL, Giannobile WV, Wang HL. Recombinant human bone morphogenetic protein 2 outcomes for maxillary sinus floor augmentation: A systematic review and meta-analysis. *Clin Oral Implants Res.* 2016;27(11):1349-1359. Doi: 10.1111/clr.12737.
- Liu R, Yan M, Chen S, et al. Effectiveness of platelet-rich fibrin as an adjunctive material to bone graft in maxillary sinus augmentation: A meta-analysis of randomized controlled trials. *BioMed Res Int.* 2019;2019:7267062-7267062. Doi: 10.1155/2019/7267062.
- Liu S, Wang Y, Liang Z, Zhou M, Chen C. Comparative clinical effectiveness and safety of bone morphogenetic protein versus autologous iliac crest bone graft in lumbar fusion: A meta-analysis and systematic review. *Spine.* 2020;45(12):E729-e741. Doi: 10.1097/brs.0000000000003372.
- Mariscal G, Nuñez JH, Barrios C, Domenech-Fernández P. A meta-analysis of bone morphogenetic protein-2 versus iliac crest bone graft for the posterolateral fusion of the lumbar spine. *J Bone Miner Metab.* 2020;38(1):54-62. Doi: 10.1007/s00774-019-01025-9.
- McNamara IR, Smith TO, Shepherd KL, et al. Surgical fixation methods for tibial plateau fractures. *Cochrane Database Syst Rev.* 2015;(9):CD009679. Doi: 10.1002/14651858.CD009679.pub2.
- Mendes VV, Martins FV, de Santana CMM, de Santana RB. Do recombinant, purified or concentrated growth factors enhance the regenerative potential of particulate bone graft substitutes in maxillary sinus floor augmentation? A systematic review and meta-analysis. *Int J Oral Maxillofac Implants.* 2023;0(0):1-36. Doi: 10.11607/jomi.10553.
- Mohanasatheesh S, Balaji A, Subramaniam D, Ganapathy V, Rajendran KP, Farjana N. Biphasic calcium phosphate in the extraction socket preservation: a systematic review. *J Pharm Bioallied Sci.* 2024;16(Suppl 2):S1007-S1011. Doi:10.4103/jpbs.jpbs\_1003\_23.
- North American Spine Society. Diagnosis and treatment of degenerative lumbar spondylolisthesis. 2nd ed. Burr Ridge, IL: North American Spine Society. <https://www.spine.org/ResearchClinicalCare/QualityImprovement/ClinicalGuidelines.aspx>. Published 2014.
- Papageorgiou SN, Papageorgiou PN, Deschner J, Gotz W. Comparative effectiveness of natural and synthetic bone grafts in oral and maxillofacial surgery prior to insertion of dental implants: Systematic review and network meta-analysis of parallel and cluster randomized controlled trials. *J Dent.* 2016;48:1-8. Doi: 10.1016/j.jdent.2016.03.010.
- Poorman GW, Jalai CM, Boniello A, et al. Bone morphogenetic protein in adult spinal deformity surgery: A meta-analysis. *Eur Spine J.* 2017;26(8):2094-2102. Doi: 10.1007/s00586-016-4841-5.
- Saghiri MA, Saini RS, Okshah A, Binduhayyim RIH, Heboyan A, Muradyan AA. Efficacy of bioactive glass versus traditional bone grafts in maxillofacial reconstruction: a systematic review and meta-analysis of clinical outcomes. *Cell Transplant.* 2025;34:9636897251379572. Doi:10.1177/09636897251379572
- Simmonds MC, Brown JV, Heirs MK, et al. Safety and effectiveness of recombinant human bone morphogenetic protein-2 for spinal fusion: A meta-analysis of individual-participant data. *Ann Intern Med.* 2013;158(12):877-889. Doi: 10.7326/0003-4819-158-12-201306180-00005.
- Song W, Zhou R, Liu P, et al. Surgical treatment of congenital pseudarthrosis of the tibia in children: CPAM-LRC consensus and guidelines. *Int J Surg.* 2025;111(2):1689-1698. Doi:10.1097/JS9.0000000000002211.

- Stumbras A, Krukis MM, Januzis G, Juodzbalsys G. Regenerative bone potential after sinus floor elevation using various bone graft materials: A systematic review. *Quintessence Int.* 2019;50(7):548-558. Doi: 10.3290/j.qi.a42482.
- Thomas JV, Martande S, et al. Comparative effectiveness of alloplastic and biologic grafts in maxillary sinus augmentation: a systematic review. *BDJ Open.* 2026;12:46. Doi:10.1038/s41405-026-00435-y.
- Trimmel B, Gede N, Hegyi P, et al. Relative performance of various biomaterials used for maxillary sinus augmentation: A Bayesian network meta-analysis. *Clin Oral Implants Res.* 2021;32(2):135-153. Doi: 10.1111/clr.13690.
- U.S. Food and Drug Administration. AdaptosFuse Bone Graft: 510(k) premarket notification K253524. Decision date February 17, 2026. [https://www.accessdata.fda.gov/cdrh\\_docs/pdf25/K253524.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf25/K253524.pdf).
- U.S. Food and Drug Administration. FDA human cell and tissue establishment registration — public query database. [https://www.accessdata.fda.gov/scripts/cber/CFAppsPub/tiss/Index.cfm?fuseaction=fuse\\_DisplaySearch&CFID=23091837&CFTOKEN=985566c088c8989f-1F22E2A5-CD46-2D0D-FE6C7A28B417F791](https://www.accessdata.fda.gov/scripts/cber/CFAppsPub/tiss/Index.cfm?fuseaction=fuse_DisplaySearch&CFID=23091837&CFTOKEN=985566c088c8989f-1F22E2A5-CD46-2D0D-FE6C7A28B417F791). Updated April 11, 2024.
- U.S. Food and Drug Administration. Fibergraft BG Matrix Bone Graft Substitute: 510(k) premarket notification K253147. Decision date October 22, 2025. <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K253147>.
- U.S. Food and Drug Administration. FG Bone Graft M: 510(k) premarket notification K244006. Decision date September 17, 2025. <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K244006>.
- U.S. Food and Drug Administration. INFUSE® Bone Graft. Pre-market approval letter P050053. [https://www.accessdata.fda.gov/cdrh\\_docs/pdf5/P050053A.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf5/P050053A.pdf). Published March 9, 2007.
- U.S. Food and Drug Administration. INFUSE® Bone Graft. Pre-market approval letter P000054. [https://www.accessdata.fda.gov/cdrh\\_docs/pdf/p000054c.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf/p000054c.pdf). Published April 30, 2004. U.S. Food and Drug Administration. INFUSE™ Bone Graft/LT-CAGET" Lumbar Tapered Fusion Device. Pre-market approval letter P000058. [https://www.accessdata.fda.gov/cdrh\\_docs/pdf/P000058A.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf/P000058A.pdf). Published July 2, 2002.
- Vaishya R, Pokhrel A, Agarwal AK, Vijay V. Current status of bone cementing and bone grafting for giant cell tumour of bone: A systematic review. *Ann R Coll Surg Engl.* 2019;101(2):79-85. Doi: 10.1308/rcsann.2019.0004.
- Wu Z, Zhou B, Chen L, Wang X, Abdelrahim MEA, Wei C. Bone morphogenetic protein-2 against iliac crest bone graft for the postlateral fusion of the lumbar spine: A meta-analysis. *Int J Clin Pract.* 2021;75(4):e13911. Doi: 10.1111/ijcp.13911.
- Xiao WL, Jia KN, Yu G, Zhao N. Outcomes of bone morphogenetic protein-2 and iliac cancellous bone transplantation on alveolar cleft bone grafting: A meta-analysis. *J Plast Reconstr Aesthet Surg.* 2020;73(6):1135-1142. Doi: 10.1016/j.bjps.2020.01.011.
- Xie C, Wang C, Huang W, et al. Recombinant human bone morphogenetic protein is a valid alternative to autologous bone graft for long bone non-unions: A systematic review and meta-analysis. *Surgeon.* 2023;S1479-666X(22)00134-2. (a)
- Xie C, Wang C, Huang Y, et al. Therapeutic effect of autologous bone grafting with adjuvant bone morphogenetic protein on long bone nonunion: A systematic review and meta-analysis. *J Orthop Surg Res.* 2022;17(1):298. Doi: 10.1186/s13018-022-03185-3. (b)

Zadegan SA, Abedi A, Jazayeri SB, et al. Bone morphogenetic proteins in anterior cervical fusion: A systematic review and meta-analysis. *World Neurosurg.* 2017;104:752-787. Doi: 10.1016/j.wneu.2017.02.098.

Zhang G, Brion A, Willemin AS, et al. Nacre, a natural, multi-use, and timely biomaterial for bone graft substitution. *J Biomed Mater Res A.* 2017;105(2):662-671. Doi: 10.1002/jbm.a.35939.

## 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.

5/2026: Policy references updated.

## Related codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy CCP.1232 This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

| Code        | Code description                                                        |
|-------------|-------------------------------------------------------------------------|
| 20900       | CPT - Bone graft harvest/procedure, minor or small.                     |
| 20902       | CPT - Bone graft harvest/procedure, major or large.                     |
| 20930       | CPT - Spine add-on for morselized allograft or osteopromotive material. |
| 20931       | CPT - Spine add-on for structural allograft.                            |
| 20936-20939 | CPT - Spine autograft and bone marrow aspirate add-on code family.      |
| 20999       | CPT - Unlisted musculoskeletal procedure.                               |
| 21208       | CPT - Facial bone augmentation with graft or implant material.          |
| 21210       | CPT - Bone graft to nasal, maxillary, or malar area.                    |
| 21499       | CPT - Unlisted musculoskeletal procedure, head.                         |
| 22558       | CPT - Anterior lumbar interbody arthrodesis context.                    |
| 22585       | CPT - Additional interspace for anterior interbody arthrodesis.         |

| <b>Code</b> | <b>Code description</b>                                                            |
|-------------|------------------------------------------------------------------------------------|
| 22630-22634 | CPT - Posterior lumbar interbody or posterolateral arthrodesis code family.        |
| 22853       | CPT - Interbody biomechanical device insertion add-on.                             |
| 27759       | CPT - Tibial shaft fracture treatment with intramedullary implant.                 |
| 27899       | CPT - Unlisted leg or ankle procedure.                                             |
| 31299       | CPT - Unlisted accessory sinus procedure.                                          |
| C1602       | HCPCS - Antimicrobial-eluting absorbable bone void filler.                         |
| C1734       | HCPCS - Orthopedic/device/drug matrix for bone-to-bone or soft tissue-to-bone use. |
| C1762       | HCPCS - Human connective tissue, including fascia lata.                            |
| C1889       | HCPCS - Implantable or insertable device, not otherwise classified.                |
| C9359       | HCPCS - Porous purified collagen matrix bone void filler, putty, per 0.5 cc.       |
| C9362       | HCPCS - Porous purified collagen matrix bone void filler, strip, per 0.5 cc.       |
| L8699       | HCPCS - Prosthetic implant, not otherwise specified.                               |