Clinical Policy Title: Bone graft substitutes

Clinical Policy Number: 14.02.09

Effective Date: July 1, 2016
Initial Review Date: May 18, 2016
Most Recent Review Date: May 18, 2016
Next Review Date: May 2017

Policy contains:
- Bone graft substitutes.

Related policies:

CP# 14.02.06 Bone marrow transplant
CP# 03.03.03 Spinal surgeries

ABOUT THIS POLICY: 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 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

Keystone First considers the use of the following bone graft substitutes, alone or in combination, to be clinically proven and, therefore, medically necessary for enhancement of bone healing.

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

Note: Refer to the chart on page three in this policy for the list of bone graft substitutes.
Limitations:

Keystone First considers all other uses of bone graft substitutes to be investigational and, therefore, not medically necessary.

- Mesenchymal stem cell therapy is considered investigational for all orthopedic applications, including, but not limited to, use in repair or regeneration of musculoskeletal tissue.
- Allograft bone products containing viable stem cells is considered investigational for all orthopedic applications, including, but not limited to, DBM with stem cells.
- Cms.gov: Local Coverage Determination (LCD) L33382 Lumbar Spinal Fusion for Instability and Degenerative Disc Conditions does not address lumbar spinal fusion techniques, devices, and instrumentation or bone graft substitutes. Some of the emerging techniques and associated tools (e.g., devices, spinal instrumentation and bone graft substitutes) are investigational, and this LCD does not endorse such procedures. The scope of this LCD is the indications and medical need of lumbar spinal fusion for instability and degenerative disc conditions.

Note: The following CPT/HCPCS codes are not listed in the Pennsylvania Medicaid fee schedule:

C9359 - Porous purified collagen matrix bone void filler (Integra Mozaik Osteoconductive Scaffold Putty, Integra OS Osteoconductive Scaffold Putty) per 0.5 cc

C9362 - Porous purified collagen matrix bone void filler (Integra Mozaik Osteoconductive Scaffold Strip) per 0.5cc

Alternative covered services:

None.

Background

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

The Centers for Disease Control and Prevention (CDC) gave an update: allograft-associated bacterial infections — United States, 2002. Tissue allografts are commonly used in orthopedic surgical procedures; in 1999, approximately 650,000 musculoskeletal allografts were distributed by tissue processors. A rare complication of musculoskeletal allografts is bacterial infection.

After the reported death of a recipient of an allograft contaminated with Clostridium spp. (an anaerobic spore and toxin-forming organism), CDC investigated this case and solicited additional reports of allograft-associated infections; 26 cases have been identified.

This report summarizes the investigation of these cases and describes additional steps given to a tissue processor to enhance tissue transplant safety.

Classification of bone grafts based on material groups:
- Allograft-based bone graft involves allograft bone, used alone or in combination with other materials (e.g., Grafton or OrthoBlast).
- Factor-based bone graft are natural and recombinant growth factors, used alone or in combination with other materials such as transforming growth factor-beta (TGF-beta), platelet-derived growth factor (PDGF), fibroblast growth factors (FGF), and bone morphogeneic protein (BMP).
- Cell-based bone grafts use cells to generate new tissue alone or are added onto a support matrix, such as mesenchymal stem cells.
- Ceramic-based bone graft substitutes include calcium phosphate, calcium sulphate and bioglass used alone or in combination, such as Osteograft, ProOsteon or OsteoSet.
- Polymer-based bone graft uses degradable and nondegradable polymers alone or in combination with other materials, such as open-porosity polylactic acid polymer.

The past and existing bone grafts, graft substitutes and the clinical evidence to support their use in the management of orthopedic cases are reviewed as also future direction of research (Table 1).

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Examples</th>
<th>Properties of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autograft based</td>
<td>Used alone</td>
<td></td>
<td>Osteoconductive, Osteoinductive, Osteogenic</td>
</tr>
<tr>
<td>Allograft based</td>
<td>Allograft bone used alone or in combination with other materials</td>
<td>Allegro, Orthoblast, Grafton</td>
<td>Osteoconductive, Osteoinductive</td>
</tr>
<tr>
<td>Factor based</td>
<td>Natural and recombinant growth factors used alone or in combination with</td>
<td>TGF-β, PDGF, FGF, BMP</td>
<td>Osteoinductive, Both osteoconductive and osteoinductive</td>
</tr>
<tr>
<td></td>
<td>other materials</td>
<td></td>
<td>with carrier materials</td>
</tr>
<tr>
<td>Cell based</td>
<td>Cells used to generate new tissue alone or seeded onto a support matrix</td>
<td>Mesenchymal stem cells</td>
<td>Osteogenic, Both osteogenic and osteoconductive with</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>carrier materials</td>
</tr>
<tr>
<td>Ceramic based</td>
<td>Includes calcium phosphate, calcium sulfate, and bioactive glass used alone</td>
<td>Osteograf, Osteoset, NovaBone</td>
<td>Osteoconductive, Limited osteoinductive when mixed with</td>
</tr>
<tr>
<td></td>
<td>or in combination</td>
<td></td>
<td>bone marrow</td>
</tr>
<tr>
<td>Polymer based</td>
<td>Includes degradable and nondegradable polymers used alone and in combination</td>
<td>Cortoss, OPLA, Immix</td>
<td>Osteoconductive, Biodegradable in degradable polymer</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Coral hydrogel-hydroxyapatite (HA) granules, blocks and composite</td>
<td>ProOsteon</td>
<td>Osteoconductive, Biodegradable</td>
</tr>
</tbody>
</table>

(Laurencin C, 2006)

**Types and tissue sources of bone graft substitute:**

When a block graft will be performed, autogenous bone is the most preferred material because there is less risk of graft rejection as the graft is originated from the patient’s body. It would be osteoinductive and osteogenic, as well as osteoconductive. A disadvantage of autologous grafts is that an additional surgical site is required, which is another location for potential postoperative pain and complications.
**Synthetic variants:**

Flexible HA composite is a variant that has a mineral-to-organic matrix ratio approximating that of human bone.

Artificial bone can be created from ceramics, such as calcium phosphates (e.g., HA and tricalcium phosphate), bioglass, and calcium sulphate that are biologically active depending on solubility in physiological environment. These materials combine with growth factors, ions such as strontium, or are mixed with bone marrow aspirate to increase biological activity. The presence of elements such as strontium can result in higher bone mineral density (BMD) and enhanced osteoblast proliferation.

Xenografts are bone grafts from a species other than human, such as a bovine species, and are used as a calcified matrix.

**Alloplastic grafts:** Alloplastic grafts may be made from hydroxyapatite, a naturally occurring mineral (main mineral component of bone), made from bioactive glass. Hydroxyapatite is a synthetic bone graft, which is the most used now due to its osteoconduction, hardness and acceptability by bone. Some synthetic bone grafts are made of calcium carbonate, which starts to decrease in usage because it is completely resorbable in a short time and makes breaking of the bone easier. Finally used is the tricalcium phosphate in combination with hydroxyapatite and thus giving effect of both osteoconduction and resorbability.

**Ceramic-based bone graft substitutes:** The majority of bone grafts available involve ceramics, either alone or in combination with another material (e.g., calcium sulfate, bioactive glass or calcium phosphate). Ceramics like calcium phosphates use calcium hydroxyapatite, which is osteoconductive and osteointegrative and, in some cases, osteoinductive. Ceramics require high temperatures for scaffold formation and have brittle properties.

**Growth factors:** Growth factors-enhanced grafts are produced using recombinant DNA technology. They consist of either human growth factors or morphogens (BMPs in conjunction with a carrier medium, such as collagen).

**Polymer-based bone graft substitutes:** These can be divided into natural polymers and synthetic polymers, and subclassified into degradable and nondegradable types. Polymer-based bone graft substitutes include:

- Healos, a natural polymer-based product and polymer-ceramic composite consisting of collagen fibers coated with hydroxyapatite and indicated for spinal fusions.
- Cortoss, an injectable resin-based product with applications for load-bearing sites.

The most common use of bone grafting is in application of dental implants to restore the edentulous area of a missing tooth. In general, bone grafts are either used in block (such as from chin or ascending ramus area of lower jaw) or particulated to be able 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. The periosteum and nutrient artery are generally removed with a piece of bone so the graft will remain alive and grow when transplanted into a new host site. Once the transplanted bone is secured into its new location, it generally restores blood supply to the bone on which it has been attached.

Besides the main use of bone grafting in dental implants, this procedure is used to fuse joints to prevent movement, repair broken bones that have bone loss, and repair broken bones that have not yet healed.
**Searches**

Keystone First searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on April 2, 2016. Search terms were: “allograft, autograft, bone reconstruction, bone repair, calcium sulphate, ceramic, hydroxyapatite, implant, polymer.”

We included:
- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

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 their 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. 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.


**Summary of clinical evidence:**
<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grabowski, Gregory, M.D.; Cornett, Chris A., M.D. (2013)</td>
<td><strong>Key points:</strong></td>
</tr>
<tr>
<td></td>
<td>• Bone grafting is frequently used to augment bone healing with the numerous approaches to reconstructing or replacing skeletal defects. Autologous cancellous bone graft remains the most effective grafting material because it provides the three elements required for bone regeneration: osteoconduction, osteoinduction and osteogenic cells.</td>
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<tr>
<td></td>
<td>• Autologous cortical bone graft provides these three components to a limited extent as well and also provides the structural integrity important in reconstruction of larger defects. However, because autogenous grafting is associated with several shortcomings and complications, including limited quantities of bone for harvest and donor-site morbidity, alternatives have been used in a wide range of orthopedic pathologic conditions.</td>
</tr>
<tr>
<td></td>
<td>• Grafting substitutes currently available include cancellous and cortical allograft bone, ceramics, demineralized bone matrix, bone marrow, and composite grafts. No single alternative graft material provides all three components for bone regeneration.</td>
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<tr>
<td></td>
<td>• The clinical applications for each type of material are dictated by its particular structural and biochemical properties. Composite grafts consisting of several materials are often used to maximize bone healing, especially where the grafting site is compromised.</td>
</tr>
<tr>
<td>Kirkpatrick, JS, et al. (2010)</td>
<td><strong>Key points:</strong></td>
</tr>
<tr>
<td></td>
<td>• For this technology overview, the tools of evidence-based medicine were used to summarize information on the effectiveness and clinical outcomes related to the usage of bone void fillers — specifically, synthetic graft materials.</td>
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<td></td>
<td>• Comprehensive literature searches were conducted to address five key questions, which the task force that prepared the report posed as follows:</td>
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<tr>
<td></td>
<td>o Question 1 addressed the use of synthetic bone void fillers alone.</td>
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<tr>
<td></td>
<td>o Question 2 was designed to determine whether synthetic bone void fillers could successfully serve as graft extenders and eliminate the need for iliac crest bone graft.</td>
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<tr>
<td></td>
<td>o Questions 3, 4 and 5 addressed the use of allografts as a comparison with synthetic fillers because clinical results with allografts are perceived as being much closer to autografts in these areas of the spine.</td>
</tr>
<tr>
<td>Bucholz RW, et al. (1989)</td>
<td><strong>Key points:</strong></td>
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<tr>
<td></td>
<td>• The metaphyseal defects in 40 patients with displaced tibial plateau fractures necessitating surgical repair were filled with either cancellous autograft or interporous hydroxyapatite.</td>
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<td></td>
<td>• Roentgenographic and clinical assessments at follow-up periods averaging 15.4 months (autograft) and 34.5 months (hydroxyapatite) demonstrated no significant differences in the two groups.</td>
</tr>
<tr>
<td></td>
<td>• Interporous hydroxyapatite is a safe, effective alternative to autogenous cancellous bone for the filling of metaphyseal defects associated with tibial plateau fractures.</td>
</tr>
</tbody>
</table>
Key points:

- The morbidity associated with autogenous bone graft harvest and the recent concern regarding the transmission of live virus through the use of allografts have been the impetus for research into a variety of materials that could take the place of these standard materials for bone grafting.
- The positive results reported with various ceramics and/or bone derivatives suggest the possibility of a material with osteoconductive and/or osteoinductive properties for use with or in place of bone graft. This review discusses a variety of bone graft and bone graft substitute materials.
- Among the osteoconductive materials outlined are the hydroxyapatite and tricalcium phosphate ceramics as well as some reportedly osteoactive polymers.
- While osteoconduction is a favorable quality, much interest has focused on the use of osteoinductive or osteogenic materials such as demineralized bone matrix or bone derivatives, that is, BMP osteogenin and others.
- It is increasingly apparent that these materials require a carrier vehicle for optimal expression of osteoactivity. Therefore, the review finishes with a comparison of the various materials suggested for use as carriers.

Glossary

Allografts — Allograft is derived from humans. The difference from autografts is that allograft is harvested from an individual other than the one receiving the graft. Allograft bone is taken from cadavers that have donated their bone so it can be used for living people who need it. It is typically sourced from a bone bank.

Autograft — Autologous or autogenous bone grafting uses bone obtained from the individual receiving the graft. Bone can be harvested from nonessential bones, such as from iliac crest, mandibular symphysis (chin area), and anterior mandibular ramus (coronoid process).

Osteoconduction — Occurs when bone graft material serves as a scaffold for new bone growth, which is perpetuated by the native bone. Osteoblasts from the margin of defect that is being grafted use the bone graft material as a framework on which to spread and generate new bone. A bone graft material should be at least osteoconductive.

Osteogenesis — This occurs when vital osteoblasts originating from bone graft material contribute to the growth of new bone along with bone formation.

Osteoinduction — Involves stimulation of osteoprogenitor cells to differentiate into osteoblasts and then begin formation of new bone. The most widely studied type of osteoinductive cell mediators are BMPs. A bone graft material that is osteoconductive and osteoinductive will not only serve as a scaffold for currently existing osteoblasts, but will also trigger formation of new osteoblasts, promoting faster integration of the graft.

Osteopromotion — Involves enhancement of osteoinduction without possession of osteoinductive properties. For example, enamel matrix derivative enhances the osteoinductive effect of demineralized freeze-dried bone allograft (DFDBA), but will not stimulate bone growth alone.

References

Professional society guidelines/other:


Peer-reviewed references:


2006;3:49–57. [pubmed].


Clinical trials:

Searched clinicaltrials.gov on April 4, 2016, using terms bone graft substitutes | Open Studies. 30 studies
found, four relevant.

Ohio Health, Columbus, Ohio. Efficacy of a human amniotic tissue-derived allograft, NuCel, in patients
undergoing posterolateral lumbar fusions for degenerative disc disease. ClinicalTrials.gov website.


Others can be found at the following ClinicalTrials.gov websites:

- Prospective, Multicenter, Randomized Study Investigating the Use of CERAMENT™|BONE VOID
  FILLER as Bone Graft Substitute in Tibia Plateau Fractures.
  https://clinicaltrials.gov/ct2/show/NCT01828905?term=bone+graft+substitutes&recr=Open&n
  o_unk=Y&rank=1.
- Clinical Evaluation of GENEX® DS in Instrumented Posterolateral Fusion.
  o_unk=Y&rank=6.
- Outcome Comparison of Allogenic Cancellous Bone and a New Synthetic Bone Substitute
  (geneX®) in Filling the Bone Defect Created with Medial Open Wedge High Tibial Osteotomy.
  o_unk=Y&rank=10.

CMS National Coverage Determinations (NCDs):

No NCDs identified as of the writing of this policy.

Local Coverage Determinations (LCDs):

No LCDs identified as of the writing of this policy.

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

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<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>Comments</th>
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<td>Diagnoses too numerous</td>
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<tr>
<th>HCPCS Code</th>
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<th>Comments</th>
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<td>C9359</td>
<td>Porous purified collagen matrix bone void filler (Integra Mozaik Osteoconductive Scaffold Putty, Integra OS Osteoconductive Scaffold Putty) per 0.5 cc</td>
<td></td>
</tr>
<tr>
<td>C9362</td>
<td>Porous purified collagen matrix bone void filler (Integra Mozaik Osteoconductive Scaffold Strip) per 0.5cc</td>
<td></td>
</tr>
</tbody>
</table>