Clinical Policy Bulletin:
Bone and Tendon Graft Substitutes and Adjuncts

Number: 0411

Policy

I. Osteogenic Protein-1 (OP-1) Implant

Aetna considers the osteogenic protein-1 (OP-1) implant (also known as bone morphogenic, or morphogenetic protein-7, BMP-7) medically necessary for use as an alternative to autograft in recalcitrant long-bone non-unions or for spinal fusion where the (i) use of autograft is unfeasible (see I., A., below) and (ii) for nonunions only, alternative treatments have failed (see I., B., below).

A. Use of an autograft may be deemed unfeasible for any of the following reasons:

1. Member has received a previous autograft and is not a candidate for further autograft procedures because the tissue is no longer available; or
2. There is insufficient autogenous tissue for the intended purpose; or
3. Member is deemed an unacceptable candidate for autograft for any of the following reasons:
   a. Advanced age (over 65 years of age); or
   b. Excessive risk of anatomic disruption (including fracture) from harvesting autograft from donor site; or
   c. Member has concurrent medical conditions and co-morbidities that increase the risk of autograft; or
   d. Member's bone is of poor quality (osteoporosis); or
   e. Obesity; or
   f. Presence of morbidity (infection, or fracture) preventing harvesting at autograft donor site.

B. For nonunions, alternative treatments should include the following, as appropriate:

1. Autograft;
2. Bone growth stimulation (ultrasonic or electrical);
3. Cadaveric allograft;
4. Cast immobilization or other non-operative approaches;
5. Compression;
6. Dynamization;
7. Fixation (internal and external);
8. Revision of fixation.
C. The OP-1 Implant has no proven value in persons with any of the following contraindications:

1. Persons with history of malignancy;
2. Persons with known hypersensitivity to the OP-1 Implant or to collagen;
3. Persons who are skeletally immature (less than 18 years of age or no radiographic evidence of closure of epiphyses);
4. Pregnant women.

D. Aetna considers the OP-1 Implant experimental and investigational if it is to be applied at the site of a resected tumor that is at or near the vicinity of the nonunion because its use for these indications is less effective than bone autograft.

E. Aetna considers the OP-1 Implant experimental and investigational for all indications other than those listed above because its effectiveness for indications other than the ones listed above has not been established.

II. INFUSE Bone Graft (Bone Morphogenic Protein-2)

Aetna considers the INFUSE Bone Graft/LT-CAGE Lumbar Tapered Fusion Device medically necessary for spinal fusion procedures in skeletally mature patients with degenerative disc disease only for a single level from the fourth lumbar vertebra (L4) to the first sacral vertebra (S1), in persons who meet the following criteria:

A. INFUSE Bone Graft/LT-CAGE device is to be implanted via an anterior approach; and
B. Member does not have greater than Grade I spondylolisthesis at the involved level; and
C. Member has degenerative disc disease, defined as discogenic back pain with degeneration of the disc confirmed by patient history and radiographic studies; and
D. Member has had at least 6 months of non-operative treatment prior to treatment with the INFUSE Bone Graft/LT-CAGE device; and
E. Use of autograft or cadaveric allograft is unfeasible for one of more of the reasons listed in Section I above

The INFUSE Bone Graft is considered medically necessary for treating skeletally mature persons with acute, open tibial shaft fractures that have been stabilized with intramedullary nail fixation after appropriate wound management, when INFUSE Bone Graft is applied within 14 days after the initial fracture.

Aetna considers the INFUSE Bone Graft experimental and investigational for all other indications, including its use in cervical fusions, and multiple levels because its effectiveness for indications other than the ones listed above has not been established.

Note: The INFUSE Bone Graft is also known as bone morphogenic, or morphogenetic protein-2, BMP-2.

III. Pro Osteon Porous Hydroxyapatite Bone Graft Substitute

Aetna considers the Pro Osteon Porous Hydroxyapatite Bone Graft Substitute experimental and investigational for repair of metaphyseal fracture defects or repair of long bone cyst and tumor defects, because it has not been shown to be more effective than autograft or cadaveric allograft for these indications.

Aetna considers the Pro Osteon Bone Graft Substitute experimental and investigational for use in spinal fusion, epiphyseal fractures or other indications because its effectiveness for these indications has not been established.

IV. Platelet-Rich Plasma

Aetna considers the use of platelet-rich plasma, alone or in conjunction with bone grafting materials, experimental and investigational for augmentation procedures (e.g., for dental implants and for the floor of the maxillary sinus) or indications (e.g., soft tissue injuries) other than thrombocytopenia because its effectiveness has not been established.
See also CPB 0244 - Wound Care (stating that autologous platelet-rich plasma, autologous platelet gel, and autologous platelet-derived growth factors (e.g., Procuren) are considered experimental and investigational for chronic wound healing).

V. Porcine Intestinal Submucosa Surgical Mesh

Aetna considers a surgical mesh composed of porcine intestinal submucosa experimental and investigational because its clinical value in rotator cuff repair surgery, repair of anorectal fistula, and for other indications has not been established.

VI. Allograft for Spinal Fusion

Aetna considers cadaveric allograft and demineralized bone matrix (Accell, AlloFuse, Allogor DBM, Allomatrix, DBX, DynaGraft, DynaGraft, Exactech Resorbable Bone Paste, Grafton DBM, Intergro DBM, Magnifuse, Optefil, Opteform, Origen DBM, OrthoBlast, Ostefil, OsteoSelect, OsteoSponge, and Progenix) medically necessary for spinal fusions.

VII. Bone Void Fillers for Nonunions

Aetna considers bone void fillers experimental and investigational for the treatment of delayed unions and nonunions because they have not been proven effective for these indications.

Note: Bone void fillers (e.g., Allomatrix putty, Integra Mozaik Osteoconductive Scaffold putty, Opteform, a demineralized bone matrix-based allograft, and Vitoss bioactive bone graft) are most commonly used in orthopedic surgery for filling osteochondral defects; their use as such is considered a medically necessary part of the surgical procedure.

VIII. Polymethylmethacrylate (PMMA) Antibiotic Beads

Aetna considers PMMA antibiotic beads medically necessary for use in conjunction with intravenous antibiotics in the treatment of chronic osteomyelitis.

IX. Mesenchymal Stem Cell Therapy/Bone Marrow Aspirate

Aetna considers the use of mesenchymal stem cell therapy (e.g., AlloStem, Osteocel, Osteocel Plus, Ovation, Regenexx, and Trinity Evolution) experimental and investigational for all orthopedic applications including repair or regeneration of musculoskeletal tissue, spinal fusion, and bone nonunions because there is insufficient evidence to support its use for these indications, especially its safety and long-term outcomes.

Aetna considers bone marrow injections medically necessary in the treatment of bone cysts (unicameral/simple). Aetna considers the use of bone marrow aspirate experimental and investigational for all other orthopedic applications including nonunion fracture, repair or regeneration of musculoskeletal tissue, osteoarthritis, and as an adjunct to spinal fusion because there is insufficient evidence to support its use for these indications.

X. Aetna considers hydroxyapatite bone substitute (e.g., OtoMimix) medically necessary for middle ear surgery.

XI. Aetna considers the following interventions experimental and investigational because there is insufficient evidence to support their use for these indications (not an all-inclusive list):

- Acellular human dermal allograft (e.g., Alloderm and Arthrex allograft) for nasal septal repair
- Actifuse silicated calcium sulphate as bone graft substitute
- Anterior cruciate ligament-derived stem cells for ligament tissue engineering
- Arthrex biopaste (BioCartilage) for glenoid osteochondral defects and other indications
- Autologous stem cells for use after screw removal in orthopedic surgery
- BIO MatrX as bone graft substitute
- Ceramic-based products (e.g., beta tri-calcium phosphate (b-TCP) when used alone or with bone marrow aspirate for the enhancement of bone healing and/or fusion
- ChronOS bone graft substitute
- Cook anal fistula plug
Bone and Tendon Graft Substitutes and Adjuncts

DeNovo NT natural tissue (allogeneic minced cartilage) graft
Gore anal fistula plug
Gracilis cadaveric graft for hallux valgus repair
Human growth factors (e.g., fibroblast growth factor, insulin-like growth factor) to enhance bone healing
Knee Creation nanocrystalline calcium phosphate bone substitute
Ligament and Joint Regeneration and Neuuro-generation Medicine (LaJRaN)
Mastergraft putty in spinal surgeries
NanOss Bioactive/nanOss Bioactive 3D in spinal surgeries
OssiMend putty in spinal surgeries
ProDense (calcium sulfate/calcium phosphate composite) as bone graft substitute
Surgisis collagen plug for the treatment of anal fistulas
Tendon Wrap Tendon Protector.

See also CPB 0743 - Spinal Surgery: Laminectomy and Fusion.

Background

Osteogenic proteins, also referred to as bone morphogenetic, or morphogenic proteins (BMPs), are a family of bone-matrix polypeptides isolated from a variety of mammalian species. Implantation of OPs induces a sequence of cellular events that lead to the formation of new bone. Some of the potential clinical applications of OPs are: (i) as a bone graft substitute to promote spinal fusion and to aid in the incorporation of metal implants, (ii) to improve the performance of autograft and allograft bone, and (iii) as an agent for osteochondral defects.

Recombinantly produced human osteogenic protein-1 (OP-1), also known as BMP-7, was developed by Stryker Biotech (Hopkinton, MA), a division of Stryker Corporation. The OP-1 Implant was approved by the Food and Drug Administration (FDA) as a Humanitarian Use Device (HUD). As defined in the Federal Food, Drug and Cosmetic Act (21 CFR 814.124), a HUD “is a device that is intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect or is manifested in fewer than 4,000 individuals in the United States per year.” The FDA developed the HUD categorization to provide an incentive for the development of devices for use in the treatment or diagnosis of diseases affecting small patient populations.

The manufacturer submitted to the FDA results from a multi-center Long Bone Treatment Study, where 10 patients with long bone nonunions having prior failed autograft were treated with OP-1 implant. Seven of the 10 patients had clinical healing (pain and function), and 2 of 10 had radiographic healing (bridging in 3 or 4 cortices).

The manufacturer also submitted the results of the multi-center Tibial Nonunion Study, where a subset of 14 patients with prior failed autograft was treated with the OP-1 Implant, and 13 patients were treated with autograft. Twelve of patients receiving the OP-1 Implant had clinical resolution (pain and function) of their nonunion, and 8 patients had radiographic healing (bridging in three views). By comparison, 12 of 13 patients receiving autograft had clinical resolution of their nonunion, and 12 of 13 had radiographic healing. The FDA concluded that, although the OP-1 implant was an effective treatment for nonunions, the implant was not as effective as autograft. Therefore, the FDA product labeling states that the OP-1 bone morphogenetic protein is indicated “for use as an alternative to autograft in recalcitrant long bone nonunions where use of autograft is unfeasible and alternative treatments have failed” (emphasis added).

Friedlaender et al. (2001) reported on the results of a randomized, controlled, single-blind multi-center clinical trial where 122 patients with 124 tibial nonunions were assigned to either OP-1 Implant or bone autograft. The OP-1 Implant was found to be less effective than bone autograft. After 9 months of treatment, 81% of the OP-1-treated nonunions and 85% of patients receiving autogenous bone were judged by clinical criteria to have been treated successfully, and 75% of OP-1 treated patients and 84% of autograft-treated patients had healed fractures by radiographic criteria.

In a randomized study, Johnsson et al (2002) examined whether OP-1 (BMP-7) in the OP-1 Implant yields better stabilizing bony fusion than autograft bone in patients undergoing posterolateral fusion...
between L5 and S1. A total of 20 patients were randomized to fusion with either OP-1 Implant (n = 10) or autograft bone from the iliac crest (n = 10). The patients were instructed to keep the trunk straight for 5 months after surgery with the aid of a soft lumbar brace. At surgery 0.8-mm metallic markers were positioned in L5 and the sacrum, enabling radio-stereometric follow-up analysis during 1 year. No significant difference was observed between the radio-stereometric and radiographic results of fusion with the OP-1 Implant and fusion with autograft bone. Thus, the OP-1 Implant did not yield better stabilizing bony fusion than autograft bone.

Sandhu et al (2003) stated that OP-1 has been studied in limited pilot studies of posterolateral fusion. It is unclear whether the addition of OP-1 ensures arthrodesis in this application.

Vaccaro et al (2008) examined the safety and the clinical and radiographical efficacy of OP-1 (rhBMP-7) Putty as compared with an iliac crest bone autograft control in un-instrumented, single-level posterolateral spinal arthrodesis. A total of 335 patients were randomized in 2:1 fashion to receive either OP-1 Putty or autograft for degenerative spondylolisthesis and symptomatic spinal stenosis. Patients were observed serially with radiographs, clinical examinations, and appropriate clinical indicators, including Oswestry Disability Index (ODI), Short-Form 36, and visual analog scale scores. Serum samples were examined at regular intervals to assess the presence of antibodies to OP-1. The primary end point, “overall success”, was analyzed at 24 months. The study was extended to include additional imaging data and long-term clinical follow-up at 36+ months. At the 36+ month time point, CT scans were obtained in addition to plain radiographs to evaluate the presence and location of new bone formation. Modified overall success, including improvements in ODI, absence of re-treatment, neurological success, absence of device-related serious adverse events, angulation and translation success, and new bone formation by CT scan (at 36+ months), was then calculated using the 24-month primary clinical endpoints, updated retreatment data, and CT imaging and radiographical end points. OP-1 Putty was demonstrated to be statistically equivalent to autograft with respect to the primary end point of modified overall success. The use of OP-1 Putty when compared to autograft was associated with statistically lower intra-operative blood loss and shorter operative times. Although patients in the OP-1 Putty group demonstrated an early propensity for formation of anti-OP-1 antibodies, this resolved completely in all patients with no clinical sequelae. The authors concluded that OP-1 Putty is a safe and effective alternative to autograft in the setting of un-instrumented posterolateral spinal arthrodesis performed for degenerative spondylolisthesis and symptomatic spinal stenosis.

Bone morphogenetic protein-2 (BMP-2) was approved by the FDA as a bone graft substitute in anterior lumbar interbody fusions. It has also been used off-label in anterior cervical fusions. Smucker and colleagues (2006) examined if BMP-2 is associated with an increased incidence of clinically relevant post-operative pre-vertebral swelling problems in patients undergoing anterior cervical fusions. A total of 234 consecutive patients (aged 12 to 82 years) undergoing anterior cervical fusion with and without BMP-2 over a 2-year period at one institution comprised the study population. The incidence of clinically relevant pre-vertebral swelling was calculated. The populations were compared and statistical significance was determined. A total of 234 patients met the study criteria, 69 of whom underwent anterior cervical spine fusions using BMP-2; 27.5 % of those patients in the BMP-2 group had a clinically significant swelling event versus only 3.6 % of patients in the non-BMP-2 group. This difference was statistically significant (p < 0.0001) and remained so after controlling for other significant predictors of swelling. The authors concluded that off-label use of BMP-2 in the anterior cervical spine is associated with an increased rate of clinically relevant swelling events.

In a systemic review, Mussano et al (2007) examined if BMPs are more effective in treating bone defects than traditional techniques, such as grafting autologous bone. An electronic search was made in the databases of MEDLINE, EMBASE (through MeSH and Emtree), and the Cochrane Central Register of Controlled Trials with no linguistic restrictions. Randomized controlled trials (RCTs) that compared bone regeneration achieved through BMPs versus that obtained by traditional methods entered the study. The 17 publications that met the criteria, divided into subgroups by type of bone, were tabulated by salient characteristics and evaluated through the items proposed by van Tulder et al. However, as the studies differed widely (in terms of site, sample size, dosage of active principle, carrier, clinical and radiological data recording), it was possible to carry out a meta-analysis of clinical and radiological outcome only for the subgroup that evaluated the vertebrae, where it was observed that BMPs offer a slightly but statistically significant greater efficacy than do traditional techniques. The authors concluded that the use of BMPs at the vertebrae can eliminate the need for surgery to harvest autologous bone. The only large study carried out on the other sites suggested that BMPs should be
used at a concentration of 1.5 mg/ml to treat fractures of the tibia. The authors stated that further RCTs of good methodological quality are needed to clarify the effectiveness of BMPs in clinical practice.

The Pro Osteon Bone Graft Substitute (Interpore International) is a hydroxyapatite bone allograft material made from marine coral. The product was approved by the FDA in 1992 as a bone void filler for repair of metaphyseal defects and long bone cyst and tumor defects. The product is to be used in conjunction with rigid internal fixation, as the Pro Osteon does not possess sufficient strength to support the reduction of a defect site prior to hard tissue ingrowth. External stabilization is not sufficient.

Pro Osteon coralline hydroxyapatite is not indicated for spinal fusion or fractures of the epiphyseal plate. A prospective randomized controlled clinical study directly compared coralline hydroxyapatite to iliac crest grafts in spinal fusion and found that the coralline graft “does not possess adequate structural integrity to resist axial loading and maintain disc height or segmental lordosis during cervical interbody fusion” (McConnell et al, 2003).

The INFUSE Bone Graft/LT-CAGE Lumbar Tapered Fusion Device (Medtronic Sofamor Danek) includes recombinant human bone morphogenic protein 2 (rhBMP-2) in a collagen absorbable sponge and a tapered titanium spinal cage, and has been approved for spinal fusion in persons with single-level degenerative disc disease from L4 to S1, where the patient has had at least 6 months of nonoperative treatment, and the device is to be used via an anterior approach. Studies submitted to the FDA compared the INFUSE Bone Graft to autogenous iliac crest bone graft in patients with degenerative lumbar disc disease. These studies showed clinically equivalent fusion rates between the 2 groups, with similar outcomes in terms of back pain, leg pain, disability and neurological status. The primary advantage of use of the device is that it does not require harvesting of autologous bone.

The California Technology Assessment Forum (CTAF) (Feldman, 2005) concluded that rhBMP-2 carried on a collagen sponge used in conjunction with an FDA approved device meets CTAF criteria for the treatment of patients undergoing single level anterior lumbar interbody spinal fusion for symptomatic single level degenerative disease at L4 to S1 of at least 6 months duration that has not responded to non-operative treatments. The California Technology Assessment Forum concluded that all other uses of rhBMP-2 including its use in cervical spinal fusions and for treatment of open tibial fracture do not meet CTAF criteria.

An evidence review prepared for the Ontario Ministry of Health and Long-Term Care (2004) found that “[t]he largest number of spinal fusion cases using BMP devices has been for anterior lumbar interbody fusion. Although radiologic fusion occurs at a consistently faster rate among recipients of the BMP device than among recipients of autologous bone grafts, clinical outcomes (pain and disability) appear no different. Regardless of technique, improvements in pain and disability are reported by similar proportions of participants in all the arms of all the trials.”

In a study on occipito-cervical fusion using recombinant human BMP-2, Shahaie and Kim (2008) stated that INFUSE should not be routinely used for occipito-cervical fusion. They noted that further studies are needed to determine if modified techniques such as intra-operative steroids and extended post-operative use of wound drains, can improve safety of its use in the posterior cervical region.

On July 1, 2008, the FDA issued a Public Health Notification to health care providers regarding life-threatening complications arising from off-label use of INFUSE Bone Graft in cervical spinal fusion. These complications included swelling of the neck and throat tissue that caused difficulty breathing, swallowing or speaking. People who suffered these adverse events needed respiratory support with intubation, medication or tracheotomy.

http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm062000.htm

Platelet-Rich Plasma

Regeneration of guided bone is an established procedure used in implant dentistry to increase the quality and quantity of the host bone in sites of localized alveolar defects. Improvement in the osteoinductive properties of currently available grafting materials is needed because of the lack of predictability in osseous regenerative procedures with these materials. Platelet-rich plasma (PRP), a modification of fibrin glue derived from autologous blood, is being used to deliver growth factors in high concentration to areas requiring osseous grafting. Growth factors released from the platelets include
platelet-derived growth factor, transforming growth factor beta, platelet-derived epidermal growth factor, platelet-derived angiogenesis factor, insulin-like growth factor 1, and platelet factor 4. These factors signal the local mesenchymal and epithelial cells to migrate, divide, and increase collagen and matrix synthesis. PRP, as an adjunctive material with bone grafts during augmentation procedures, has been suggested to increase quality of bone regeneration and the rate of bone deposition.

In a randomized controlled study (n = 10), Kassolis and Reynolds (2005) compared bone formation after sub-antral maxillary sinus augmentation with freeze-dried bone allograft (FDBA) plus PRP versus FDBA plus resorbable membrane. The authors reported that the combination of FDBA and PRP enhanced the rate of formation of bone compared with FDBA and membrane, when used in sub-antral sinus augmentation. The investigators concluded, however, that more studies are needed to determine if such incremental enhancements in bone formation affect clinical outcome.

In a randomized controlled study, Camargo et al (2005) compared the clinical effectiveness of a combination therapy consisting of bovine porous bone mineral (BPBM), guided tissue regeneration (GTR), and PRP in the regeneration of periodontal intra-bony defects in humans. Twenty-eight paired intra-bony defects were surgically treated using a split-mouth design. Defects were treated with BPBM, GTR, and PRP (experimental), or with open-flap debridement (control). Clinical parameters evaluated included changes in attachment level, pocket depth, and defect fill as revealed by re-entry at 6 months. Pre-operative pocket depths, attachment levels, and trans-operative bone measurements were similar for the 2 groups. Post-surgical measurements taken at 6 months revealed that both treatment modalities significantly decreased pocket depth and increased clinical attachment and defect fill compared to baseline. The differences between the experimental and control groups were 2.22 (+/- 0.39) mm on buccal and 2.12 (+/- 0.34) mm on lingual sites for pocket depth, 3.05 (+/- 0.51) mm on buccal and 2.88 (+/- 0.46) mm on lingual sites for gain in clinical attachment, and 3.46 (+/- 0.96) mm on buccal and 3.42 (+/- 0.02) mm on lingual sites for defect fill. These differences between groups were statistically significant in favor of the experimental defects. The combined therapy was also clinically more effective than open-flap debridement. The authors stated that the superiority of the experimental group could not be attributed solely to the surgical intervention and was likely a result of the BPBM/GTR/PRP application. The authors concluded that combining BPBM, GTR, and PRP was an effective modality of regenerative treatment for intra-bony defects in patients with advanced periodontitis.

Lekovic and colleagues (2003) examined the effectiveness of PRP, BPBM and GTR used in combination as regenerative treatment for grade II molar furcation defects in humans (n = 52). These investigators concluded that the PRP/BPBM/GTR combined technique is an effective modality of regenerative treatment for mandibular grade II furcation defects. Moreover, they stated that further studies are necessary to elucidate the role played by each component of the combined therapy in achieving these results.

Recent reviews have reached contradictory findings regarding the effectiveness of PRP for bone grafting. Marx (2004) stated that PRP remains the only effective growth factor preparation available to oral and maxillofacial surgeons as well as other dental specialists for outpatient use. In contrast, Freymiller and Aghaloo (2004) stated: “Practitioners involved with bone grafting have high hopes that PRP will be proven to be of benefit in bone graft healing. However, at this early stage of investigation, the results are inconclusive. There is still much to learn regarding PRP before this adjunctive material should be considered for routine use. Unfortunately, this has not been the case because an entire industry has developed to manufacture the equipment and supplies needed for surgeons to prepare PRP in the office or operating room. Courses are being offered throughout the United States touting the benefits of PRP. Considering the meager volume and contradictory nature of the currently available evidence, there appears to be a disproportionate use of PRP in clinical practice.” These authors concluded that more research (especially well-designed, rigorous, standardized human trials) is needed before evidence-based surgeons can feel confident in recommending this procedure/material to their patients.

These conclusions are in agreement with the observations of Sanchez et al (2003) and Grageda (2004). Sanchez et al (2003) stated that “there is clearly a lack of scientific evidence to support the use of PRP in combination with bone grafts during augmentation procedures. This novel and potentially promising technique requires well-designed, controlled trials to provide evidence of effectiveness.” Grageda (2004) stated that since the introduction of PRP, several investigators have examined its
effectiveness using various bone grafting materials. There have been different protocols as well as different types of clinical cases. The author concluded that "there is an urgent need not just for more, but for standardized research studies in this subject to provide evidence-based dentistry to patients. Without the standardization of these protocols, it will be extremely difficult to ascertain whether PRP enhances bone healing when it is used alone or in conjunction with bone grafting materials."

A systematic evidence review of surgical techniques for placing dental implants prepared for the Cochrane Collaboration (Coulthard et al, 2003) concluded that there is no strong evidence that the use of PRP or other variations in surgical technique described in the review for placing implants have superior success rates.

Devices to prepare PRP have been cleared by the FDA based on 510(k) premarket notification. The FDA has required that the product labeling for one such device state that "[t]he Platelet Rich Plasma prepared by this device has not been evaluated for any clinical indications" (Golding, 2004).

Recent studies also produced contradictory findings on the clinical value of PRP. While Okuda et al (2005) reported that treatment with a combination of PRP and porous hydroxyapatite (HA) compared to HA with saline led to a significantly more favorable clinical improvement in intra-bony periodontal defects (n = 70), and Sammartino et al (2005) found that PRP is effective in inducing and accelerating bone regeneration for the treatment of periodontal defects at the distal root of the mandibular second molar after surgical extraction of a mesioangular, deeply impacted mandibular third molar (n = 18), results from other studies indicated that PRP does not provide any added benefits.

In a randomized controlled study (n = 24), Huang et al (2005) examined the effects of PRP in combination with coronally advanced flap (CAF) for the treatment of gingival recession. These investigators concluded that the application of PRP in CAF root coverage procedure provides no clinically measurable enhancements on the final therapeutic outcomes of CAF in Miller's Class I recession defects. Furthermore, in a controlled clinical trial (n = 10), Monov et al (2005) found that the instillation of PRP during implant placement in the lower anterior mandible did not add additional benefit. These findings are in agreement with the observation of Raghoebard et al (2005) who noted that no beneficial effect of PRP on wound healing and bone remodeling of autologous bone grafts used for augmentation of the floor of the maxillary sinus.

In a review on the role of PRP in sinus augmentation, Boyapati and Wang (2006) stated that although the lateral wall sinus lift is a predictable clinical procedure to increase vertical bone height resulting in implant success rates comparable to that of native bone, the issue of extended healing periods remains troublesome. Clinicians and researchers have investigated several methods, including addition of growth factors and peptides, to reduce this healing time and enhance bone formation within the subantral environment. Platelet-rich plasma is an autologous blood product containing high concentrations of several growth factors and adhesive glycoproteins. The incorporation of PRP into the sinus graft has been proposed as a method to shorten healing time, enhance wound healing, and improve bone quality. These investigators noted that currently, the literature is conflicting with respect to the adjunctive use of PRP in sinus augmentation. Factors that may contribute to this variability include variable/inappropriate study design, under-powered studies, differing platelet yields, and differing graft materials used. In addition, methods of quantifying bone regeneration and wound healing differ between studies. Currently, because of limited scientific evidence, the adjunctive use of PRP in sinus augmentation cannot be recommended. The authors stated that further prospective clinical studies are urgently needed.

In a randomized controlled trial, de Vos et al (2010) examined if a PRP injection would improve outcome in chronic mid-portion Achilles tendinopathy. A stratified, block-randomized, double-blind, placebo-controlled study at a single center of 54 randomized patients aged 18 to 70 years with chronic tendinopathy 2 to 7 cm above the Achilles tendon insertion were carried out. The trial was conducted between August 28, 2008, and January 29, 2009, with follow-up until July 16, 2009. Subjects received eccentric exercises (usual care) with either a PRP injection (PRP group) or saline injection (placebo group). Randomization was stratified by activity level. Main outcome measure was the validated Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire, which evaluated pain score and activity level; and was completed at baseline and 6, 12, and 24 weeks. The VISA-A score ranged from 0 to 100, with higher scores corresponding with less pain and increased activity. Treatment group effects were evaluated using general linear models on the basis of intention-to-treat. After randomization into the PRP group (n = 27) or placebo group (n = 27), there was complete follow-up of
The mean VISA-A score improved significantly after 24 weeks in the PRP group by 21.7 points (95% confidence interval [CI]: 13.0 to 30.5) and in the placebo group by 20.5 points (95% CI: 11.6 to 29.4). The increase was not significantly different between both groups (adjusted between-group difference from baseline to 24 weeks, -0.9; 95% CI: -12.4 to 10.6). This CI did not include the pre-defined relevant difference of 12 points in favor of PRP treatment. The authors concluded that among patients with chronic Achilles tendinopathy who were treated with eccentric exercises, a PRP injection compared with a saline injection did not result in greater improvement in pain and activity.

In a decision memorandum, the Centers for Medicare & Medicaid Services (CMS, 2008) determined that the evidence is inadequate to conclude that autologous PRP for the treatment of chronic non-healing cutaneous wounds, acute surgical wounds when the autologous PRP is applied directly to the closed incision, or dehiscent wounds improves health outcomes. Therefore, CMS determined that PRP is not reasonable and necessary for the treatment of these indications. Consequently, CMS issued a non-coverage determination for acute surgical wounds when the autologous PRP is applied directly to the closed incision and for dehiscent wounds. CMS also maintained the current non-coverage for chronic, non-healing cutaneous wounds.

In a systematic review on the safety and effectiveness of the use of autologous PRP for tissue regeneration, Martínez-Zapata et al. (2009) concluded that PRP improves the gingival recession but not the clinical attachment level in chronic periodontitis. In the complete healing process of chronic skin ulcers, the results are inconclusive. There are little data regarding the safety of PRP. There are several methodological limitations and, consequently, future research should focus on strong and well-designed RCTs that evaluate the safety and effectiveness of PRP.

Guidelines from the Work Loss Data Institute (2008) on work-related disorders of the elbow state that platelet-rich plasma and autologous blood donation are under study and are not specifically recommended.

An assessment by the Institute for Clinical Effectiveness and Health Policy (IECS, 2008) concluded that, "although in vitro, PRP has demonstrated to release growth factors and to improve tendon structure, so far, there is no evidence supporting its use in human beings."

Porcine Intestinal Submucosa Surgical Mesh

The rotator cuff is comprised of four muscles (i.e., infraspinatus, subscapularis, supraspinatus and teres minor) that originate from the scapula. The tendons of these muscles form a single tendon unit, which inserts onto the greater tuberosity of the humerus. These "structures" combine to form a "cuff" over the head of the humerus. The rotator cuff helps to lift and rotate the arm as well as to stabilize the ball of the shoulder within the joint.

Tears of the rotator cuff tendons are one of the most common causes of pain, loss of motion, and disability in adults. Traditional treatments include conservative interventions (e.g., rest and limited overhead activity, use of a sling, non-steroidal anti-inflammatory drugs, oral glucocorticoid, strengthening exercise and physical therapy, intra-articular or subacromial glucocorticosteroid injection), and surgery (arthroscopic or open). Non-surgical treatments, which may take several weeks or months, produce pain relief in approximately 50% of patients and no improvement in strength at long-term follow-up, whereas surgical intervention results in pain relief in about 85% of patients and a better return of strength (Ruotolo and Nottage, 2002). Following rotator cuff repair surgery, the arm is immobilized to allow the tear to heal. The length of immobilization is usually dependent on the severity of the tear. Furthermore, patients' commitment/compliance to rehabilitation is important to attain a good surgical outcome.

Recent developments in rotator cuff repair surgery include newer arthroscopic and mini-open surgical techniques. These new techniques are intended to allow for smaller, less painful incisions and faster recovery time. Many of these advances use dissolvable anchors, which hold sutures in place or hold sutures down to bone until the repair has healed and then are absorbed by the body. There is also ongoing research on orthobiologic tissue implants that is intended to enhance healing and promote growth of new tissue.

A surgical mesh composed of porcine small intestinal submucosa (Restore Orthobiologic Soft Tissue Implant, DePuy Orthopaedics, Inc., Warsaw, IN) was cleared for marketing based on a FDA 510(k) premarket notification in December 2000. The implant is manufactured from 10 layers of small
intestine submucosa derived from porcine small intestine and is mainly composed of water and collagen. According to the FDA, this surgical mesh implant is intended for use in general surgical procedures for reinforcement of soft tissue where weakness exists. The device is intended to act as a resorbable scaffold that initially has sufficient strength to assist with a soft tissue repair, but then resorbs and is replaced by the patient's own tissue. In addition, the implant is intended for use in the specific application of reinforcement of the soft tissues, which are repaired by suture or suture anchors, limited to the supraspinatus, during rotator cuff surgery. According to the manufacturer, this surgical mesh implant is intended to give the surgeon a less invasive treatment when the rotator cuff tissue is of poor quality or the repair needs reinforcement.

Although the Restore orthobiologic implant has been cleared by the FDA for marketing, there is a lack of adequate evidence on the effectiveness of this implant in rotator cuff repair. Malcarney et al (2005) presented a case series of 25 patients who underwent rotator cuff repair by one surgeon using this implant to augment the repaired tendon or fill a defect. Four of 25 patients (16 %) experienced an overt inflammatory reaction at a mean of 13 days post-operatively. All patients underwent open irrigation and debridement of the rotator cuff and the implant. The authors concluded that these porcine surgical mesh implants should be used with caution and with the understanding that an early post-operative non-specific inflammatory reaction can occur that may cause breakdown of the repair. Furthermore, these investigators stated that more studies are needed to further characterize the reaction and determine which patients are susceptible.

Zheng et al (2005) stated that the small intestinal submucosa (SIS) that is used in this implant is not an acellular collagenous matrix, and contains porcine DNA. They suggested that further studies should be conducted to evaluate the clinical safety and effectiveness of SIS implant biomaterials.

The most frequent side effects encountered in soft tissue repair include infection, adhesions, sterile effusion, instability, increased stiffness post-operatively, and general risks associated with surgery and anesthesia such as neurological, cardiac, and respiratory deficit. Potential device-related risks include stretching or tearing of the device, stiffness, chronic synovitis or effusion, prolonged post-operative rehabilitation, delayed or failed incorporation of the device as well as immunological reaction. Moreover, the porcine surgical mesh implant is contraindicated in patients with massive chronic rotator cuff tears that cannot be mobilized, or where the muscle tissue has undergone substantial fatty degeneration.

Fibrin glue has been used to treat anorectal fistulas in an attempt to avoid more radical surgical intervention. Fibrin glue treatment is simple and repeatable; failure does not compromise further treatment options; and sphincter function is preserved. However, reported success rates vary widely. Suturable bioprosthetic plugs (Surgisis, Cook Surgical, Inc.) have been employed to close the primary opening of fistula tracts. Surgisis is a new 4- or 8-ply bioactive, prosthetic mesh for hernia repair derived from porcine SIS. In a review on resorbable extra-cellular matrix grafts in urological reconstruction, Santucci and Barber (2005) noted that recent problems with inflammation following 8-ply pubo-vaginal sling use and failures after 1- and 4-ply SIS repair of Peyronie's disease underscore the need for research before wide adoption.

In a prospective cohort study, Johnson and Armstrong (2006) compared fibrin glue versus the anal fistula plug. Patients with high trans-sphincteric fistulas, or deeper, were prospectively enrolled. Patients with Crohn's disease or superficial fistulas were excluded. Age, gender, number and type of fistula tracts, and previous fistula surgeries were compared between groups. Under general anesthesia and in prone jack-knife position, the tract was irrigated with hydrogen peroxide. Fistula tracts were occluded by fibrin glue versus closure of the primary opening using a Surgisis anal fistula plug. A total of 25 patients were prospectively enrolled: 10 patients underwent fibrin glue closure, and 15 used a fistula plug. Patient's age, gender, fistula tract characteristics, and number of previous closure attempts was similar in both groups. In the fibrin glue group, 6 patients (60 %) had persistence of one or more fistulas at 3 months, compared with 2 patients (13 %) in the plug group (p < 0.05, Fisher exact test). The authors concluded that closure of the primary opening of a fistula tract using a suturable biologic anal fistula plug is an effective method of treating anorectal fistulas. The method seems to be more reliable than fibrin glue closure. The greater efficacy of the fistula plug may be the result of the ability to suture the plug in the primary opening, therefore, closing the primary opening more effectively. These investigators noted that further prospective, long-term studies are warranted.
A guidance document from the National Institute for Health and Clinical Excellence (NICE, 2006) found insufficient evidence to support the use of porcine intestinal submucosa plugs for repair of anorectal fistula. The NICE assessment concluded: "Current evidence suggests that there are no major safety concerns associated with the closure of anal fistula (fistula in ano) using a suturable bioprosthesis plug. However, evidence on the efficacy of the procedure is not adequate for it to be used without special arrangements for consent and for audit or research." The specialist advisors to NICE commented that there was uncertainty about recurrence rates and the long-term outcomes of this procedure.

Schwandner and Fuerst (2009) analyzed the efficacy of the Surgisis(R) AFP(TM) anal fistula plug and the Surgisis(R) mesh for the closure of complex fistulas in Crohn's disease. All patients with peri-rectal Crohn's disease suffering from trans-sphincteric and recto-vaginal fistulas who underwent surgery using the Surgisis(R) anal fistula plug or the Surgisis(R) mesh were prospectively enrolled in this study. Inclusion criteria included trans-sphincteric single-tract fistulas and recto-vaginal fistulas. Surgery was performed using a standardized technique, including irrigation of the fistula tract, placement and internal fixation of the Surgisis(R) anal fistula plug, and combined trans-anal/trans-vaginal excision of recto-vaginal fistula with trans-vaginal placement of the mesh. Success was defined as closure of both internal and external (peri-anal or vaginal) openings, absence of drainage without further intervention, and absence of abscess formation. Follow-up information was obtained from clinical examination 3, 6, 9, and 12 months post-operatively. Within the observation period, a total of 16 procedures were performed. After a mean follow-up of 9 months and 1 patient lost to follow-up, the overall success rate was 75%. For trans-sphincteric fistulas, the success rate was 77%, whereas it was 66% in recto-vaginal fistulas associated with Crohn's disease. All 4 patients with failure had re-operation. Rate of stoma reversal in those patients who had fecal diversion was 66%. No deterioration of continence was documented. The authors concluded that the short-term success rates are promising; further analysis is needed to explain the definite role of this technique in comparison with traditional surgical techniques.

Safar et al (2009) analyzed the efficacy of the Cook Surgisis AFP anal fistula plug for the management of complex anal fistulas. This was a retrospective review of all patients prospectively entered into a database at the authors' institution who underwent treatment for complex anal fistulas using Cook Surgisis AFP anal fistula plug between July 2005 and July 2006. Patient demographics, fistula etiology, and success rates were recorded. The plug was placed in accordance with the inventor's guidelines. Success was defined as closure of all external openings, absence of drainage without further intervention, and absence of abscess formation. A total of 35 patients underwent 39 plug insertions (22 men; mean age of 46 (range of 15 to 79) years). Three patients were lost to follow-up, therefore, 36 procedures to be analyzed. The fistula etiology was crypto-glandular in 31 (88.6%) patients and Crohn's disease associated in the other 4 (11.4%). There were 11 smokers and 3 patients with diabetes. The mean follow-up was 126 days (standard = 69.4). The overall success rate was 5 of 36 (13.9%). One of the 4 Crohn's disease-associated fistulas healed (25%) and 4 of 32 (12.5%) procedures resulted in healing of crypto-glandular fistulas. In 17 patients, further procedures were necessary as a result of failure of treatment with the plug. The reasons for failure were infection requiring drainage and seton placement in 8 patients (25.8%), plug dislodgement in 3 (9.7%), persistent drainage tract and need for other procedures in 20 patients (64.5%). The authors concluded that the success rate for Surgisis AFP anal fistula plug for the treatment of complex anal fistulas was (13.9%), which is much lower than previously described. They stated that further analysis is needed to explain significant differences in outcomes.

**Deminerlized Bone Matrix**

Autologous Iliac Crest Bone Grafting (ICBG) is considered the gold-standard graft choice for spinal arthrodesis; however, it is associated with donor site morbidity and a limited graft supply.

Deminerlized bone matrix products are a class of commercially available grafting agents that are prepared from allograft bone. There is some evidence for the use of deminerlized bone matrix products in spinal fusions as an alternative to allograft. Cammisa, et al. (2004) conducted a prospective equivalency trial of Grafton DBM and iliac crest autograft in spine fusion, with each patient serving as his own control. The investigators stated that, while autograft remains the preferred graft material to facilitate spine fusion, the supply is limited and harvesting produces may have undesirable clinical consequences. A total of 120 patients underwent posterolateral spine fusion with pedicle screw fixation and bone grafting. Iliac crest autograft was implanted on one side of the spine and a Grafton...
DBM/autograft composite was implanted on the contralateral side in the same patient. An independent, blinded reviewer evaluated anteroposterior and lateral flexion-extension radiographs. The fusion mass lateral to the instrumentation on each side was judged fused or not, and the mineralization of the graft was rated absent, mild, moderate, or extensive. The degree of correspondence in outcomes between sides was estimated by computing the percentage agreement and kappa statistic. The investigators reported that nearly 70% of patients (81 of 120) provided complete 24-month radiographic studies. The bone graft mass was fused in 42 cases (52%) on the Grafton DBM side and in 44 cases (54%) on the autograft side. The overall percentage agreement for fusion status between sides was approximately 75% (61 of 81), indicating moderately strong statistical correspondence (kappa = 0.51, P < 0.0001). Bone mineralization ratings also were similar between treated sides. Perfect agreement was realized in almost 60% of patients (48 of 81) with moderate statistical correspondence (weighted kappa = 0.54, P < 0.0001). The authors concluded that Grafton DBM can extend a smaller quantity of autograft than is normally required to achieve a solid spinal arthrodesis. Consequently, a reduced amount of harvested autograft may be required, potentially diminishing the risk and severity of donor site complications.

Kang, et al. (2012) conducted a 2-year prospective, multicenter, randomized controlled clinical trial comparing the outcomes of Grafton demineralized bone matrix (DBM) Matrix with local bone with that of iliac crest bone graft (ICBG) in a single-level instrumented posterior lumbar fusion. Forty-six patients were randomly assigned (2:1) to receive Grafton DBM Matrix with local bone (30 patients) or autologous ICBG (16 patients). The mean age was 64 (females [F] = 21, males [M] = 9) in the DBM group and 65 (F = 9, M = 5) in the ICBG group. An independent radiologist evaluated plain radiographs and computed tomographic scans at 6-month, 1-year, and 2-year time points. Clinical outcomes were measured using Oswestry Disability Index (ODI) and Medical Outcomes Study 36-Item Short Form Health Survey. The investigators reported that 41 patients (DBM = 28 and ICBG = 13) completed the 2-year follow-up. Final fusion rates were 86% (Grafton Matrix) versus 92% (ICBG) (P = 1.0 not significant). The Grafton group showed slightly better improvement in ODI score than the ICBG group at the final 2-year follow-up (Grafton [16.2] and ICBG [22.7]); however, the difference was not statistically significant (P = 0.2346 at 24 mo). Grafton showed consistently higher physical function scores at 24 months; however, differences were not statistically significant (P = 0.0823). Similar improvements in the physical component summary scores were seen in both the Grafton and ICBG groups. There was a statistically significant greater mean intraoperative blood loss in the ICBG group than in the Grafton group (P < 0.0031). The investigators concluded that, at 2-year follow-up, subjects who were randomized to Grafton Matrix and local bone achieved an 86% overall fusion rate and improvements in clinical outcomes that were comparable with those in the ICBG group.

Aghdasi, et al. (2013) conducted a systematic review of the evidence for demineralized bone matrix for spinal fusion. The authors found that demineralized bone matrix has been evaluated in animal models and human clinical trials of spine fusion. Results of animal studies indicate variation in performance within and among demineralized bone matrix products. The majority of human clinical trials report high fusion rates when DBM is employed as a graft extender or a graft enhancer. The authors found that few prospective randomized controlled trials have been performed comparing DBM to autologous iliac crest bone graft in spine fusion. The authors concluded that, although many animal and human studies demonstrate comparable efficacy of DBM when combined with autograft or compared to autograft alone, additional high level of evidence studies are required to clearly define the indications for its use in spine fusion surgeries and the appropriate patient population that will benefit from DBM.

**Bone Void Fillers for Nonunions**

Minimally invasive injectable graft (MIIG) (Wright Medical Technology, Inc., Arlington, TN) is an example of a bone void filler, and is a paste made with calcium sulphate (plaster of Paris). It is injected into osseous defects that are created surgically or as a result of trauma. The paste cures in-situ, resorbs, and then is replaced with bone during the healing process. The cured paste provides a temporary support media for bone fragments during the surgical procedure but does not provide structural support during the healing process. Injection of MIIG is usually performed in conjunction with another procedure, such as reduction of a fracture. Minimally invasive injectable graft was cleared by the FDA through the 510(k) process since it is substantially equivalent to other bone void fillers on the market.

Integra Mozaik Osteoconductive Scaffold (OS) putty (Integra LifeSciences Corp., Plainsboro, NJ) is a synthetic bone void filler manufactured from beta tri-calcium phosphate and type I bovine collagen.
Combined with bone marrow aspirate, Integra Mozaik OS is intended for use as a bone void filler of the skeletal system in the extremities, spine, and pelvis. Integra Mozaik OS putty was cleared by the FDA through the 510(k) process since it is substantially equivalent to another bone void filler on the market. According to the FDA 510(k) letter to the manufacturer, it is specifically indicated for use in the treatment of surgically treated osseous defects or osseous defects created from traumatic injury to the bone. Following placement in the body void or gap (defect), Integra Mozaik putty is resorbed and replaced with bone during the healing process.

There is insufficient evidence to support the use of MIIG, Integra Mozaik OS putty, or other bone void fillers as a treatment for delayed union or nonunions. Furthermore, a technology assessment prepared by ECRI for Agency for Healthcare Research and Quality (2005) concluded that there is no reliable evidence to support the use of calcium sulphate or other bone void fillers as treatments for delayed fracture healing.

A retrospective case series examined the use of AlloMatrix injectable putty in nonunions in multiple bone types (Wilkins and Kelly, 2003). The nonunions were also treated using standard internal/external fixation techniques. The publication did not report prior treatment or the duration of the nonunions prior to the AlloMatrix putty treatment. A technology assessment prepared by the ECRI Institute (Schoelles et al, 2005) for the Agency for Healthcare Research and Quality, commenting on this study, stated that "[w]ithout this information, interpretation of the results is difficult". The study also did not report whether all consecutively treated patients were included or if dropouts occurred during the treatment period. The reported healing rate was 30 of 35 (85 %) in an average of 3.5 months, but healing rates per bone type were not reported.

A subsequent study by Ziran and colleagues (2007) reported on an unacceptably high rate of complications with the use of AlloMatrix for nonunions. A consecutive series of patients requiring bone grafting for atrophic/avascular nonunions were retrospectively studied. Patients were monitored for healing and adverse effects, which included local or systemic reactions, wound problems, infection, and any secondary surgery caused by graft complications. The investigators reported that over half of the patients (51 %) developed post-operative drainage. Of the 41 patients, 13 (32 %) had drainage that required surgical intervention and 14 (34 %) developed a deep infection. Eleven patients with deep infections also required surgical treatment of drainage. In addition, 19 (46 %) patients did not heal and required secondary surgical intervention. The investigators reported that there were correlations between infection and a history of previously treated infection (p < 0.007), as well as wound drainage (p < 0.001). Failure of treatment correlated to the presence of a post-operative infection (p < 0.001). Other analyses were not performed because of the small sample size, which was because of early termination of the study. The investigators concluded that the use of AlloMatrix putty as an alternative for autogenous bone graft in the treatment of nonunions resulted in an unacceptably high rate of complications. The investigators stated: "[a]lthough we recommend further study, we do not recommend the use of AlloMatrix for the treatment of nonunions, especially if there is a large volumetric defect or a history of any prior contamination of the tissue bed".

Mesenchymal Stem Cell

Mesenchymal stem cells or MSCs are multipotent stem cells that can differentiate into a variety of cell types. Mesenchymal stem cells have been classically obtained from the bone marrow, and have been shown to differentiate into various cell types, including osteoblasts, chondrocytes, myocytes, adipocytes, and neuronal cells.

Helm and colleagues (2001) stated that although autologous bone remains the gold standard for stimulating bone repair and regeneration, the advent in molecular biology as well as bioengineering techniques has produced materials that exhibit potent osteogenic activities. Recombinant human osteogenic growth factors (e.g., BMP) are now produced in highly concentrated and pure forms and have been shown to be extremely potent bone-inducing agents when delivered in vivo in rats, dogs, primates, and humans. They noted that the delivery of MSCs, derived from adult bone marrow, to regions requiring bone formation is also compelling, and it has been shown to be successful in inducing osteogenesis in many pre-clinical animal studies. Finally, the identification of biological and non-biological scaffolding materials is a crucial component of future bone graft substitutes, not only as a delivery vehicle for bone growth factors and MSCs, but also as an osteo-conductive matrix to stimulate bone deposition directly.
Recently, MSCs has been studied for its use in orthopedic application (e.g., healing long bone defects, intervertebral disc repair and regeneration as well as spinal arthrodesis procedures). Acosta et al (2005) noted that although important obstacles to the survival and proliferation of MSCs within the degenerating intervertebral disc need to be overcome, the potential for this therapy to slow or reverse the degenerative process remains substantial. Leung et al (2006) stated that in the past several years, significant progress has been made in the field of stem cell regeneration of the intervertebral disc. Autogenic MSCs in animal models can arrest intervertebral disc degeneration or even partially regenerate it, and the effect is suggested to be dependent on the severity of degeneration. Mesenchymal stem cells are able to escape alloantigen recognition which is an advantage for allogenic transplantation. A number of injectable scaffolds have been described and various methods to pre-modulate MSCs’ activity have been tested. They noted that more work is needed to address the use of MSCs in large animal models as well as the fate of the implanted MSCs, especially the long-term outcomes.

Mclain et al (2005) noted that successful arthrodesis in challenging clinical scenarios is facilitated when the site is augmented with autograft bone. The iliac crest has long been the preferred source of autograft material, but graft harvest is associated with frequent complications and pain. Connective tissue progenitor cells aspirated from the iliac crest and concentrated with allograft matrix and demineralized bone matrix provide a promising alternative to traditional autograft harvest. The vertebral body, an even larger reservoir of myeloproliferative cells, should provide progenitor cell concentrations similar to those of the iliac crest. In this study, a total of 21 adults (11 men and 10 women with a mean age of 59 +/- 14 years) undergoing posterior lumbar arthrodesis and pedicle screw instrumentation underwent transpedicular aspiration of connective tissue progenitor cells. Aspirates were obtained from two depths within the vertebral body and were quantified relative to matched, bilateral aspirates from the iliac crest that were obtained from the same patient at the same time. Histochemical analysis was used to determine the prevalence of vertebral progenitor cells relative to the depth of aspiration, the vertebral level, age, and gender, as compared with the iliac crest standard. The cell count, progenitor cell concentration (cells/cc marrow), and progenitor cell prevalence (cells/million cells) were calculated. Aspirates of vertebral marrow demonstrated comparable or greater concentrations of progenitor cells compared with matched controls from the iliac crest. Progenitor cell concentrations were consistently higher than matched controls from the iliac crest (p = 0.05). The concentration of osteogenic progenitor cells was, on the average, 71% higher in the vertebral aspirates than in the paired iliac crest samples (p = 0.05). With the numbers available, there were no significant differences relative to vertebral body level, the side aspirated, the depth of aspiration, or gender. An age-related decline in cellularity was suggested for the iliac crest aspirates. The authors concluded that the vertebral body is a suitable site for aspiration of bone marrow for graft augmentation during spinal arthrodesis. They also stated that future clinical studies will attempt to confirm the ability to obtain fusion using only this source of connective tissue progenitor cells.

Anderson and colleagues (2005) reviewed the rationale and discussed the results of cellular strategies that have been proposed or investigated for disc degeneration. These investigators noted that although substantial work remains, the future of cellular therapies for symptomatic disc degeneration appears promising. They concluded that continued research is warranted to further define the optimal cell type, scaffolds, and adjuvants that will allow successful disc repair in human patients.

Risbud and colleagues (2006) evaluated the osteogenic potential of MSCs isolated from the bone marrow of the human vertebral body (VB). Marrow samples from VB of patients undergoing lumbar spinal surgery were collected; marrow was also harvested from the iliac crest (IC). Progenitor cells were isolated and the number of colony forming unit-fibroblastic (CFU-F) determined. The osteogenic potential of the cells was characterized using biochemical and molecular biology techniques. Both the VB and IC marrow generated small, medium, and large sized CFU-F. Higher numbers of CFU-F were obtained from the VB marrow than the IC (p < 0.05). Progenitor cells from both anatomic sites expressed comparable levels of CD166, CD105, CD49a, and CD63. Moreover, progenitor cells from the VB exhibited an increased level of alkaline phosphatase activity. MSCs of the VB and the IC displayed similar levels of expression of Runx-2, collagen Type I, CD44, ALCAM, and ostecalcin. The level of expression of bone sialoprotein was higher in MSC from the IC than the VB. VB and IC cells mineralized their extracellular matrix to a similar extent. The authors concluded that their findings show that CFU-F frequency is higher in the marrow of the VB than the IC. Progenitor cells isolated from both sites respond in a similar manner to an osteogenic stimulus and express common immunophenotypes.
Based on these findings, these researchers proposed that progenitor cells from the lumbar vertebral marrow would be suitable candidates for osseous graft supplementation in spinal fusion procedures. They stated that studies must now be conducted using animal models to ascertain if cells of the VB are as effective as those of the IC for the fusion applications.

Minamide et al (2007) examined the ability of BMP and basic fibroblast growth factor (FGF) to enhance the effectiveness of bone marrow-derived MSCs in lumbar arthrodesis. They found that MSCs cultured with BMP-2 and basic FGF act as a substitute for autograft in lumbar arthrodesis. This technique may yield a more consistent quality of fusion bone as compared to that with autograft. They stated that these results are encouraging and warrant further studies with the suitable dose of BMP-2 and basic FGF, and may provide a rational basis for their clinical application.

AlloStem is partially demineralized allograft bone combined with adipose derived mesenchymal stem cells; it is similar to autograft bone. http://www.allosource.org/products/allostem-cellular-bone-allograft/

Neman et al (2013) noted that arthrodesis is a critical component of spine surgery for both degenerative and oncologic pathologies with durable clinical benefits requiring successful bony fusion. The gold standard for bone grafting remains the autograft, optimally from the iliac crest. However, the effectiveness of an autograft varies due to the inconsistent quality of the bone procured as well as risks of donor site morbidity. Several technologies exist as alternatives to autograft, either as a graft extender or replacement. These include treatment with bone morphogenetic protein (BMP-2), use of synthetic ceramics, demineralized bone matrix (DBM), and allografts; all with varying strengths and weaknesses in terms safety and/or efficacy. Alternatively, stem cells have become increasingly popular as cell-based therapeutics for musculoskeletal applications. Mesenchymal stem cells (MSCs) have been obtained from adipose tissue, bone marrow, peripheral blood, and synovial fluid, then combined with various osteo-conductive scaffolds. The rationale for their use is to add an osteogenic component to enhance formation of new bone via differentiation into osteoblasts. However, despite the appeal of this approach, there is a paucity of data supporting the efficacy of using stem cells in a clinical setting for spinal surgery. Furthermore, the best method for incorporating this technology into spinal surgery has not yet been determined. One approach has been to process an allograft such that endogenous progenitor cells are retained during the processing of freshly procured cadaveric bone. This approach has the advantage that cells potentially benefit from micro-environmental cues derived from maintaining their attachment to the native cancellous bone scaffold. Indeed, signaling in terms of chemical and mechanical cues between the cell and its scaffold is critically important for new bone formation. While cellularized allografts are known to harbor endogenous cells, the identity of these cells remains obscure, largely due to the lack of bona fide markers for stem and progenitor cells. In this study, these investigators hypothesized that a cellular allograft bone matrix (Osteocel Plus) contains a population of mesenchymal stem and bone progenitor cells, the former capable of self-renewal and multi-lineage differentiation. Currently, no single cell marker can unequivocally distinguish stem cells from progenitor cells. The use of cell surface marker combinations allows for enrichment of the stem cell population but is inadequate for prospective isolation. A novel use of lineage mapping allowed identification of highly proliferative clones and permitted us to determine whether cells endogenous to a cellular allograft undergo extensive self-renewal-a functional hallmark of stem cells. Further, these researchers used genetic and proteomic profiling as well as functional assays to examine whether these cells in the Osteocel Plus allograft are capable of multi-potential differentiation (the second functional hallmark of stem cells). They postulated that the use of these 2 functional hallmarks could enable us to establish corroborative evidence for the existence of a stem and progenitor cell population in cellular allografts. They also stated that "As of the date of this publication, there have been no well-controlled prospective clinical studies published on the effectiveness of Osteocel Plus .... Taken together, these data provide corroborative evidence that Osteocel Plus cellular allograft contains a heterogeneous cell population with some cells demonstrating extensive self-renewal and multipotent differentiation in vitro -- the hallmarks for progenitor/stem cell state. In-vivo investigation is constrained to the use of small immune- deficient animals, because cellular allografts have retained human cells that would be rejected in immune-competent models. Small animal models, such as rodents, have limited translation to human biology. Ultimately, determining whether allografts containing a viable population of stem cells function comparably to autograft will require further study".

In a prospective, multi-center, non-randomized, institutional review board-approved clinical and radiographic study, Eastlack et al (2014) evaluated and summarized the 2-year outcomes of patients
treated with Osteocel Plus cellular allograft as part of an anterior cervical discectomy and fusion procedure. A total of 182 patients were treated with anterior cervical discectomy and fusion using Osteocel Plus in a PEEK (polyetheretherketone) cage and anterior plating at 1 or 2 consecutive levels. Clinical outcomes included visual analog scale (VAS) for neck and arm pain, neck disability index, and SF-12 physical and mental component scores. Computed tomography and plain film radiographic measures included assessment of bridging bone, disc height, disc angle, and segmental range of motion (ROM). A total of 249 levels were treated in 182 patients. Mean procedure time was 100 minutes, blood loss was less than 50 ml in 93 % of patients, and hospital stay was 1 day or less in 84 % of patients. Significant (p < 0.05) average improvements in clinical outcomes from pre-operatively to 24 months included the following: neck disability index: 21.5 %; VAS neck: 34 mm; VAS arm: 35 mm; SF-12 physical component score: 11.2; SF-12 mental component score: 6.8. At 24 months, 93 % of patients were satisfied with their outcome. In patients treated at a single level with a minimum of 24-month follow-up, 92 % (79/86) of levels achieved solid bridging and 95 % of levels demonstrated ROM of less than 3°. In combined single- and 2-level procedures, 87 % (157/180) of levels achieved solid bridging and 92 % (148/161) had ROM of less than 3° at 24 months. No patient required revision for pseudarthrosis. The authors concluded that improvements in clinical results at 2 years, high patient satisfaction, and high radiographic and clinical fusion rates provided confidence in Osteocel Plus as an effective alternative to structural allograft or autograft in anterior cervical discectomy and fusion procedures. The level of evidence was “4”. These findings need to be confirmed in well-designed randomized controlled trials with longer follow-up periods.

Further investigation is needed to study the value of MSC therapy in orthopedic applications before it can be used in the clinical setting.

Miscellaneous Interventions:

Cheng et al (2010) had previously isolated and identified stem cells from human anterior cruciate ligament (ACL). The purpose of this study was to evaluate the differences in proliferation, differentiation, and extracellular matrix (ECM) formation abilities between bone marrow stem cells (BMSCs) and ACL-derived stem cells (LSCs) from the same donors when cultured with different growth factors, including basic fibroblast growth factor (bFGF), epidermal growth factor, and transforming growth factor-beta 1 (TGF-beta1). Ligament tissues and bone marrow aspirate were obtained from patients undergoing total knee arthroplasty and ACL reconstruction surgeries. Proliferation, colony formation, and population doubling capacity as well as multi-lineage differentiation potentials of LSCs and BMSCs were compared. Gene expression and ECM production for ligament engineering were also evaluated. It was found that BMSCs possessed better osteogenic differentiation potential than LSCs, while similar adipogenic and chondrogenic differentiation abilities were observed. Proliferation rates of both LSCs and BMSCs were enhanced by bFGF and TGF-beta1. TGF-beta1 treatment significantly increased the expression of type I collagen, type III collagen, fibronectin, and alpha-smooth muscle actin in LSCs, but TGF-beta1 only up-regulated type I collagen and tenasin-c in BMSCs. Protein quantification further confirmed the results of differential gene expression and suggested that LSCs and BMSCs increase ECM production upon TGF-beta1 treatment. In summary, in comparison with BMSCs, LSCs proliferate faster and maintain an undifferentiated state with bFGF treatment, whereas under TGF-beta1 treatment, LSCs up-regulate major tendinous gene expression and produce a robust amount of ligament ECM protein, making LSCs a potential cell source in future applications of ACL tissue engineering.

Steinert et al (2011) noted that when ruptured, the ACL of the human knee has limited regenerative potential. However, the goal of this report was to show that the cells that migrate out of the human ACL constitute a rich population of progenitor cells and these researchers hypothesized that they display mesenchymal stem cell (MSC) characteristics when compared with adherent cells derived from bone marrow or collagenase digests from ACL. They showed that ACL outgrowth cells are adherent, fibroblastic cells with a surface immunophenotype strongly positive for cluster of differentiation (CD)29, CD44, CD49c, CD73, CD90, CD97, CD105, CD146, and CD166, weakly positive for CD106 and CD14, but negative for CD11c, CD31, CD34, CD40, CD45, CD53, CD74, CD133, CD144, and CD163. Staining for STRO-1 was seen by immunohistochemistry but not flow cytometry. Under suitable culture conditions, the ACL outgrowth-derived MSCs differentiated into chondrocytes, osteoblasts, and adipocytes and showed capacity to self-renew in an in vitro assay of ligamentogenesis. MSCs derived from collagenase digests of ACL tissue and human bone marrow were analyzed in parallel and displayed similar, but not identical, properties. In situ staining of the ACL suggests that the MSCs
Bone and Tendon Graft Substitutes and Adjuncts

The authors concluded that the cells that emigrate from damaged ACLs are MSCs and that they have the potential to provide the basis for a superior, biological repair of this ligament.

According to information from the manufacturer, BIO MatrX Structure is a highly porous, synthetic bone graft substitute that sets hard upon implantation for a complete defect fill. The manufacturer states that the resulting osteoconductive scaffold provides inter-connected porosity and high surface area to facilitate cell mediated remodeling and new bone growth. BIO MatrX Generate is a combination of osteoconductive nano-crystalline calcium phosphate and Demineralized Bone Matrix (DBM) that is tested for osteoinductive potential by lot, after sterilization, in an in-vivo athymic nude rodent muscle pouch model. The viscous putty sets hard after closure providing an osteoconductive scaffold to facilitate new bone growth. The manufacturer states that both materials are FDA-cleared to be hydrated with saline or blood; and are indicated as bone void fillers of the pelvis, extremities and the posterolateral spine.

The use of minced cartilage techniques are in the early stages of development. According to the manufacturer, DeNovo NT was developed as a consequence of the need for expanded treatment options for the treatment of cartilage lesions. DeNovo NT (natural tissue) graft and DeNovo ET live chondral engineered tissue graft (Neocartilage) are produced by ISTO Technologies (St. Louis, MO), and exclusively distributed by Zimmer, Inc. (Warsaw, IN). DeNovo NT consists of manually minced cartilage tissue pieces obtained from juvenile allograft donor joints. The tissue fragments are mixed intra-operatively with fibrin glue before implantation. It is thought that mincing the tissue helps with cell migration. As there are no chemicals used and minimal manipulation, it is regulated as an allograft tissue rather than a biological implant. Thus, the allograft tissue does not require FDA approval for marketing. DeNovo NT is currently available in the U.S. Neocartilage uses juvenile allogeneic cartilage cells that are isolated and expanded in-vitro, similar to other ACI techniques. Neocartilage is currently being studied in human clinical trials under an FDA-approved investigational new drug (IND) application. The FDA approved ISTO's IND application in 2006, which allowed them to pursue clinical trials of the product in humans. There are no studies evaluating the DeNovo ET tissue graft in the published medical literature.

There are no studies evaluating the DeNovo NT graft in the published medical literature. The manufacturer of DeNovo NT has initiated a post-market, multi-center, longitudinal data collection study to collect clinical outcomes of subjects implanted with DeNovo NT. Data are to be obtained either retrospectively or prospectively from patients implanted or to be implanted with DeNovo NT for the treatment of lesion in the ankle. Data to be collected include details of the operative procedure as well as subjects' pain, function, activity levels, and healthcare resource use through a 5-year post-operative follow-up period. Four U.S. sites are participating in this manufacturer-sponsored observational study with 25 subjects; the study began in 2006 and is expected to be completed in 2013.

Ky et al (2008) evaluated the effectiveness of the Surgisis (Anal Fistula Plug) in multiple patients and presented early clinical results along with notable clinical observations from their experience. This was a prospective analysis of all patients who received the Anal Fistula Plug for treatment of anorectal fistulas between April 2006 and February 2007. All tracts were irrigated with peroxide, the plug was inserted in the tract, and buried at the internal opening with 2-0 vicryl and mucosal advancement flap. Statistical analysis was performed with Fisher's exact test. A total of 45 patients were treated with the Anal Fistula Plug and 1 patient was lost to follow-up. There were 27 males and 17 females with average age of 44.1 years treated for simple (n = 24) or complex (n = 20) fistulas. Preliminary results indicated an 84 % healing rate by 3 to 8 weeks post-operatively, which progressively declined from 72.7 % at 8 weeks to 62.4 % at 12 weeks and 54.6 % at a median follow-up of 6.5 (range of 3 to 13) months. Long-term Anal Fistula Plug closure rate was significantly higher in patients with simple than complex fistulas (70.8 versus 35 %; p < 0.02) and with non-Crohn's disease versus Crohn's disease (66.7 versus 26.6 %; p < 0.02). Patients with 2 successive plug placements had significantly lower closure rates than patients who underwent placement of the plug once (12.5 versus 63.9 %; p < 0.02). No significant difference in closure rates were found between patients with 1 versus multiple fistula tracts. Post-operative complications included peri-anal abscess in 5 patients (3 Crohn's disease, 2 non-Crohn's disease). The authors concluded that Anal Fistula Plug is most successful in the treatment of simple anorectal fistulas but is associated with a high failure rate in complex fistula and particularly in patients with Crohn's disease. Repeat plug placement is associated with increased failure. Given the relatively low morbidity associated with the procedure, Anal Fistula Plug should be considered as a first option for the treatment of anorectal fistulas.
-line treatment for patients with simple fistulas and as an alternative in selected patients with complex fistulas. Drawbacks of this study were: (i) small sample size, (ii) short duration of follow-up, and (iii) high failure rate.

Buchberg et al (2010) compared the Cook Surgisis AFP plug and the newer Gore Bio-A plug in the management of complex anal fistulas. A retrospective chart review of patients treated with Cook and Gore fistula plugs between August 2007 and December 2009 was performed. Success was defined as closure of all external openings and absence of drainage and abscess formation. Twelve Cook patients underwent 16 plug insertions and 10 Gore patients underwent 11 plug insertions. The overall procedural success rate in the Gore group was 54.5 % (6 of 11) versus 12.5 % (2 of 16) in the Cook group. The reasons for failure were unknown in the majority of patients and plug dislodgement in 2 patients. These short-term results with the Gore fistula plug suggested a higher procedural success rate in comparison to the Cook plug. The authors concluded that patients should be cautioned regarding potentially high failure rates; however, longer follow-up and a larger patient population are needed to confirm significant differences in fistula plug efficacy.

According to the manufacturer, Ovation, a novel cellular repair matrix, is derived from placental mesenchyme. It provides the 3 essential components of periosteum -- (i) extracellular matrix, (ii) endogenous mesenchymal stem cells and (iii) a replenishing source of growth factors -- without the need for autografting. There is currently insufficient evidence to support the use of mesenchymal stem cell therapy for orthopedic applications including repair or regeneration of musculoskeletal tissue, spinal fusion, and long bone nonunions.

An UpToDate review on “Hallux valgus deformity (bunion)” (Ferrari, 2013) does not mention the use of grafting as a therapeutic option.

Goebel et al (2005) described the advantages of using Mimix hydroxyapatite (HA) bone cement in reconstructing a variety of ossicular chain abnormalities. A total of 25 cases of HA reconstruction were included in this series (ages of 23 to 74; mean of 47 years). The examples presented include (i) HA as the sole reconstructive material for incus erosion, (ii) HA for securing total or partial ossicular replacement prosthesis, (iii) incus augmentation after crimping for revision stapedotomy with incus erosion, (iv) HA in primary stapedotomy to fix the crimped prosthesis to an intact incus, and (v) other unique situations. Pre-operative and post-operative audiograms were evaluated for 4-tone pure tone average (PTA), speech reception thresholds, word recognition scores, and air-bone gaps (ABGs). Mean follow-up was 11 months (range of 2 to 22 months). The mean PTA improved from 57 dB to 37 dB, whereas the mean ABGs decreased from 33 dB to 16 dB. There were no cases of infection or extrusion. The authors concluded that hydroxyapatite bone cement is an excellent adjunct or alternative to ossiculoplasty with preformed prostheses. Easily malleable, rapidly setting, and rapidly hardening, Mimix is particularly well-suited for middle ear work. Definitive fixation with bone cements during difficult ossicular chain reconstruction may ensure a more enduring successful outcome.

Elsheikh et al (2006) analyzed the results obtained from HA bone cement repair of ossicular discontinuity between the incus and stapes during surgery of retraction pockets. A total of 62 previously untreated patients (82 ears) with retraction pockets were studied. Hydroxyapatite bone cement was used to repair defects at the incudo-stapedial connection in 82 ears with retraction pockets. The ears were divided into 2 groups: group 1 included 48 ears with a small defect in the long process of the incus; group 2 included 34 ears with a large defect in the long process of the incus. In addition, 20 control patients underwent surgery using Plastipore partial ossicular replacement prostheses. Hearing results were reported in 4 frequencies (0.5, 1, 2, and 3 kHz). Analysis of the results was performed using the paired t-test with significance level at 0.05. Main outcome measures were anatomic and audiologic results. Significant post-operative improvement of pure-tone air conduction threshold averages and air-bone gap (ABG) averages were reported in the 3 studied groups. The post-operative air-bone gap averages showed significantly better outcome in groups 1 and 2 compared with controls (p < 0.001), while there was no statistically significant difference between groups 1 and 2 (p > 0.05). The authors concluded that bone cement ossiculoplasty offered cost-effective and significant improvement in conductive hearing loss. It provided an excellent alternative to ossiculoplasty with preformed prostheses. They believed the indications for bone cement were validated by these results.

Redaelli de Zinis et al (2008) reported hearing results using a titanium ossicular replacement prosthesis during canal wall down mastoidectomy with tympanoplasty to treat cholesteatoma. Patients with
cholesteatoma treated with primary or revision canal wall down mastoidectomy with tympanoplasty in a single-stage. Patients with implanted HA prostheses composed a matched control group. Medical records were reviewed for type of ossicular condition, type of prosthesis, and hearing threshold at 1-year follow-up. Results were reported as the 5-frequency average air conduction gain, bone conduction gain, and ABG. The malleus handle was present in 24 patients, and the stapes superstructure in 22 patients. Mean (SD) air conduction gain was 7.6 (14.7) dB (p = 0.001); it was 8.7 (12.0) dB in the group with titanium prostheses and 6.3 (17.4) dB in the group with HA prostheses (p = 0.54). Bone conduction gain was 1.1 (4.9) dB (p = 0.19). No patients experienced post-operative impairment of bone threshold greater than 5 dB. Post-operative air-bone gap was 26.5 (15.3) dB; it was 23.8 (15.7) dB in the titanium group and 29.8 (14.6) dB in the HA group (p = 0.18). Air-bone gap closure was 40 %; it was 46.2 % in the titanium group and 33.3 % in the HA group (p = 0.35). The authors concluded that titanium is a satisfactory material for use in ossicular reconstruction and is comparable to HA, although at present, no definitive conclusion about the superiority of titanium can be drawn.

Kawano and co-workers (2010) noted that many cases of tympano-sclerotic stapes fixation are accompanied by fixation or erosion of malleus and/or incus. This status of the ossicular chain is one of the reasons that ossiculoplasty for tympano-sclerotic stapes fixation is more difficult than that for otosclerosis. These investigators conducted a retrospective review of 7 patients who were operated on for tympano-sclerotic stapes fixation between 2002 and 2006. All of the patients had abnormal conditions of the malleus and/or incus and underwent stapedectomy and total ossiculoplasty with HA prosthesis (Apaceram T-7 type), which has a planar-like head portion that contacts a piece of cartilage. Post-operative hearing results were assessed in all 7 patients after at least 1 year. The post-operative ABG was closed within 10 dB in 2 of 7 patients, and was less than 20 dB in 6 of 7 patients. The mean post-operative ABG was closed within 10 dB at 1 and 2 kHz and less than 20 dB at low frequencies (0.25 and 0.5 Hz). There was almost no hearing improvement at high frequencies (4 and 8 kHz). There were no patients with post-operative SNHL. The authors concluded that the present study showed that stapedectomy and total ossiculoplasty with cartilage-connecting HA prosthesis is effective and safe for stapes fixation accompanied by fixation or erosion of the malleus and/or incus.

Van Rompaey et al (2011) studied hearing outcome in revision stapedotomy cases where extensive erosion of the long process of the incus was observed in a consecutive series where a malleo-vestibular prosthesis was used versus a consecutive series where HA bone cement was used to re-build the eroded long process of the incus and integrate the prosthesis. This study examined a total of 20 revision cases of surgically treated oto-sclerosis where extensive incus erosion was observed during revision surgery. In the earlier consecutive series, 10 cases were treated with malleo-vestibular prostheses. In the later consecutive series, 10 cases were treated with HA bone cement to re-build the incus-prosthesis interface. Air-bone gap, bone-conduction thresholds, and air-conduction thresholds were evaluated pre-operatively and at 1 to 3 months. Last audiometry available also was reported (median of 12 months). Pure-tone averages were calculated according to the guidelines of the Committee on Hearing and Equilibrium for the evaluation of conductive hearing loss. Raw data were displayed in an Amsterdam Hearing Evaluation Plot. Six male patients and 14 female patients were included. Age varied from 34 to 75 years (median of 53 years). The median post-operative ABG at last follow-up audiometry was 15.6 in the malleo-vestibular prosthesis group and 13.1 dB in the HA bone cement group. No short-term or intermediate-term adverse reactions or unsuspected bone conduction deteriorations were seen. The authors concluded that HA bone cement can be successfully used to reconstruct the long process of the incus in case of extensive erosion of the long process. Intermediate-term hearing outcome is comparable to the outcome of a series of similar cases treated with malleo-vestibular prostheses. Because the placement of a malleo-vestibular prosthesis is technically more difficult and presents a high risk to the inner ear, the authors thought HA bone cement can be a useful alternative in these difficult cases.

Somers et al (2012) compared the hearing outcome using HA bone cement to bridge the incudo-stapedia l gap versus incus re-modelling for ossiculoplasty in case of incudo-stapedial discontinuity. A non-randomized retrospective study was conducted at a tertiary referral otorologic center. The intervention in 24 primary cases of conductive hearing loss was subsequent middle ear inspection where incudo-stapedial discontinuity was observed. Hydroxyapatite bone cement was used in 10 consecutive cases, and incus re-modelling was performed in 14 consecutive cases. Air-bone gap, bone-conduction (BC) thresholds, and air-conduction (AC) thresholds were evaluated pre-operatively and at 3, 6 and 12 months post-operatively. No patients were lost to follow-up. Pure-tone averages
Bone and Tendon Graft Substitutes and Adjuncts

were calculated according to the guidelines of the Committee on Hearing and Equilibrium for the evaluation of conductive hearing loss. The Amsterdam Hearing Evaluation Plots are presented. The postoperative ABG closure to within 20 and 10 dB at 12 months was, respectively, 80 and 40 % in the HA bone cement group and 57.1 and 28.6 % in the standard ossiculoplasty group (no statistically significant difference). However, these researchers observed a statistically significant difference in ABG gain at 6 and 12 months favoring the HA bone cement cases. No short-term or intermediate-term adverse reactions were observed. The authors concluded that HA bone cement bridging ossiculoplasty offers a better intermediate-term ABG gain than standard ossiculoplasty. This new technique is a valuable alternative to conventional ossiculoplasty and presents the practical advantage of being easier and faster.

Ayshford et al (2003) noted that nasal septal perforations present a distinct challenge to the otolaryngologist and a significant cause of symptoms to affected patients. Many surgical techniques for the repair of septal perforations have been described. Connective tissue autografts are commonly used as inter-positional grafts between the septal flaps. Recently acellular human dermal allograft has been used with success. In this study, a total of 17 patients with symptomatic anterior nasal septal perforations that had failed conservative treatment underwent a closed endoscopic repair of their perforations with acellular human dermal allograft (AlloDerm) and an anteriorly based inferior turbinate flap; 13 patients had a successful closure of the perforation, 2 patients, despite initial success, re-perforated as a result of persistent crust picking and, in 2 patients, the graft failed. The authors concluded that with appropriate patient selection and stringent post-operative care this technique offers a good surgical outcome for the closure of septal perforations. The findings of this small study need to be validated by well-designed studies.

Chhabra and Houser (2012) noted that the closure of nasal septal perforations can be challenging based on the etiology, location, and method of closure. These researchers reported on a novel method of closure for nasal septal perforations using a unilateral mucosal rotational flap and acellular dermal interposition graft. A total of 20 patients with nasal septal perforations of various etiologies underwent this novel method of repair through a closed, endonasal approach. Out of 20 patients, 17 demonstrated successful closure of their septal perforations, consistent with an 85 % success rate. Based upon size, closure rates were 89 % for small perforations (less than 1 cm), 80 % for medium perforations (1 to 2 cm), and complete closure for a single large perforation (greater than 2 cm). Of 20 patients, 19 were completely asymptomatic following surgical intervention, and of the 3 with failed repairs, only 1 patient required revision surgery for persistent symptoms. The authors concluded that nasal septal perforations may cause bothersome symptoms and present a significant reconstructive challenge. Native septal tissue is advantageous due to a rich vascular supply and proximity to the defect, while interposition grafts act as a scaffold for the migration of respiratory mucosa. The findings of this small study need to be validated by well-designed studies.

An UpToDate review on "Osteonecrosis (avascular necrosis of bone)" (Jones and Mont, 2014) states that "Bone grafting of the lesion, which has also been used to treat small- to medium-sized lesions. Outcomes for patients treated with impaction grafting have demonstrated promising results. The objective Knee Society Score after a mean follow-up of approximately four years (range of two to eight years) was 89 (range of 70 to 100), and the functional score was 81 (range of 50 to 100). None of the patients were revised. One study reported that a graft matrix of allogeneic cancellous bone chips augmented with enriched autogenous bone marrow aspirate yielded promising results in three patients with large lesions at two years of follow-up".

Le Huec et al (1997) presented the results of a comparative study of 2 series of postero-lateral arthrodeses for scoliosis performed using COTREL DUBOUSSET instrumentation. A total of 54 consecutive patients underwent surgery for idiopathic scoliosis using the same technique -- 30 received a graft consisting of a mixture of cortico-cancellous autologous and allogenic bone frozen at -80 degrees, and 24 patients were grafted with a mixture of cortico-cancellous autologous bone and sticks of tri-calcium phosphate (TCP, Biosorb, SBM, Lourdes, France). All patients were seen at 3, 6 and 12 months, then once a year for at least 4 years with clinical and radiological evaluation at each visit. At the final follow-up visit, no radiologic signs of pseudoarthrosis were found in either group with a minimum follow-up of 4 years. The appearance of bone callus was considered satisfactory at 6 months in all cases; moreover callus seemed to be more important in the TCP series, although this assessment was subjective. Tri-calcium phosphate resorption was total after 2 years, while allograft fragments were visible on x-rays after 2 years. Minor mechanical complications occurred but did not influence the
results. Loss of correction was 8 % of that initially obtained in the allograft group and 2 % in the TCP group. Loss of correction did not progress after 6 months in the TCP group and after 2 years in the allograft group. Based upon this experience, the use of synthetic bone substitutes such as TCP would appear to be a valuable alternative to allografts in posterolateral spinal arthrodesis for idiopathic scoliosis, and it would eliminate the risk of viral contamination inherent to allograft implantation. The authors stated that there had been no previous comparative studies concerning the use of TCP versus allograft in the literature.

Kanayama et al (2006) evaluated the osteo-inductive property of OP-1 or BMP-7 and fusion rate in human instrumented posterolateral lumbar fusion through radiographic examination, surgical exploration, and histologic assessment. A total of 19 patients with L3 to L4 or L4 to L5 degenerative spondylolisthesis underwent posterolateral lumbar fusion using pedicle screw instrumentation. The patients were randomized to receive either OP-1 putty (3.5 mg OP-1/g of collagen matrix per side) alone (n = 9), or local autograft with HA-TCP granules (n = 10). Fusion status was evaluated using plain radiography and CT scan. Radiographic fusion criteria included less than 5 degrees of angular motion, less than 2 mm of translation, and evidence of bridging bone in the posterolateral lumbar area in which the graft materials were placed following decortication. After a minimum 1-year follow-up, the patients who showed radiographic evidence of fusion underwent instrumentation removal and surgical exploration of the fusion site. Biopsy specimens were taken from the fusion mass and evaluated histologically. Radiographic fusion rate was 7 of 9 OP-1 patients and 9 of 10 control patients. Based on surgical exploration of these 16 patients, new bone formation was macroscopically observed in the posterolateral lumbar region in all cases; however, solid fusion was observed in 4 of 7 OP-1 and 7 of 9 HA-TCP/autograft patients. Histologic assessment demonstrated viable bone in 6 of 7 OP-1 patients. All the control (HA-TCP/autograft) specimens contained viable bone and fibrous tissue surrounding ceramic granules, suggesting slow incorporation of the graft material. The authors concluded that in a human posterolateral lumbar spine trial, OP-1 reliably induced viable amounts of new bone formation, but the fusion success rate evaluated by surgical exploration was only 4 of 7.

In a pilot study, Lerner et al (2009) compared the clinical and radiographic results of ultraporous beta-TCP (b-TCP) versus autogenous iliac crest bone graft (ICBG) as graft extenders in scoliosis surgery. In the posterior correction of scoliosis, local bone resected as part of the procedure is used as the base bone graft material. Supplemental grafting from the iliac crest is considered the gold-standard in posterior spinal fusion. However, autograft is not available in unlimited quantities, and bone harvesting is a source of significant morbidity. Ultraporous b-TCP might be a substitute for ICBG in these patients and thus eliminate donor site morbidity. A total of 40 patients with adolescent idiopathic scoliosis (AIS) were randomized into 2 treatment groups and underwent corrective posterior instrumentation. In 20 patients, ICBG harvesting was performed whereas the other half received b-TCP (VITOSS) to augment the local bone graft. If thoracoplasty was performed, the resected rib bone was added in both groups. Patients were observed clinically and radiographically for a minimum of 20 months post-operatively, with a mean follow-up of 4 years. Overall pain and pain specific to the back and donor site were assessed using a visual analog scale (VAS). As a result, both groups were comparable with respect to the age at the time of surgery, gender ratio, pre-operative deformity, and hence length of instrumentation. There was no significant difference in blood loss and operative time. In 9 patients of the b-TCP group and 8 patients of the ICBG group, thoracoplasty was performed resulting in a rib graft of an average 7.9 g in both groups. Average curve correction was 61.7 % in the b-TCP group and 61.2 % in the ICBG group at hospital discharge (p = 0.313) and 57.2 and 54.3 %, respectively, at follow-up (p = 0.109). Loss of curve correction amounted on average 2.6 degrees in the b-TCP group and 4.2 degrees in the comparison group (p = 0.033). In the ICBG group, 4 patients still reported donor site pain of on average 2/10 on the VAS at last follow-up. One patient in the b-TCP group was diagnosed with a pseudarthrosis at the caudal end of the instrumentation. Revision surgery demonstrated solid bone formation directly above the pseudarthrosis with no histological evidence of b-TCP in the biopsy taken. The authors concluded that the use of b-TCP instead of ICBG as extenders of local bone graft yielded equivalent results in the posterior correction of AIS. They stated that the promising early results of this pilot study supported that b-TCP appears to be an effective bone substitute in scoliosis surgery avoiding harvesting of pelvic bone and the associated morbidity.

Larsson (2010) noted that a number of different calcium phosphate compounds such as calcium phosphate cements and solid b-TCP products have been introduced during the past 10 years. The chemical composition mimics the mineral phase of bone and as a result of this likeness, the materials seem to be re-modeled as for normal bone through a cell-mediated process that involves osteoclastic
activity. This is a major difference when compared with, for instance, calcium sulphate compounds that after implantation dissolve irrespective of the new bone formation rate. Calcium phosphates are highly biocompatible and in addition, they act as synthetic osteo-conductive scaffolds after implantation in bone. When placed adjacent to bone, osteoid is formed directly on the surface of the calcium phosphate with no soft tissue interposed. Remodeling is slow and incomplete, but by adding more and larger pores, like in ultraporous b-TCP, complete or nearly complete resorption can be achieved. The indications explored so far include filling of metaphyseal fracture voids or bone cysts, a volume expander in conjunction with inductive products, and as a carrier for various growth factors and antibiotics. The authors concluded that calcium phosphate compounds (e.g., calcium phosphate cement and b-TCP) will most certainly be part of the future armamentarium when dealing with fracture treatment.

Larsson and Hannink (2011) stated that more than a decade has passed since the first injectable bone substitutes were introduced for use in orthopedic trauma, and over recent years the number of commercial products has increased dramatically. Despite the fact that these bone substitutes have been on the market for many years, knowledge among potential users on how and when they might be useful is still fairly limited. Most injectable bone substitutes belong to one of two major groups: by far the largest group contains products based on various calcium phosphate (CP) mixtures, whilst the smaller group consists of calcium sulphate (CS) compounds. Following mixing, the CP or CS paste can be injected into—for instance—a fracture space for augmentation as an alternative to bone graft, or around a screw for augmentation if the bone is weak. Within minutes an in-situ process makes the substitute hard; the mechanical strength in compression resembles that of cancellous bone, whereas the strength in bending and shear is lower. Over time, CP products undergo remodeling through a cell-mediated process that seems to mimic the normal bone remodeling, while CS products are dissolved through a faster process that is not cell-mediated. For CP, a number of clinical studies have shown that it can be useful for augmentation of metaphyseal fractures when a space is present. Randomized studies have verified that CP works especially well in tibial plateau fractures when compared with conventional bone grafting. So far the number of clinical studies on CS products is very low. Development at present seems to be heading towards premixed or directly mixed products as well as new compounds that contain fibers or other components to enhance bending and shear strength. Products that are based on combinations of CP and CS and are also being developed to combine the fast-dissolving CS with the stronger and more slowly remodeling CP. Injectable bone substitutes, and especially CS, have also been targeted as potentially good carriers for antibiotics and growth factors.

In summary, there is currently a lack of good quality RCTs on the use of ceramic-based products (e.g., b-TCP) bone void fillers.

Buchberg et al (2010) noted that treatment of complex anal fistulas presents an ongoing challenge to colorectal surgeons. The anal fistula plug is an attractive definitive option due to its minimal risk of incontinence, simple design, and easy application. These researchers compared the Cook Surgisis AFP plug and the newer Gore Bio-A plug in the management of complex anal fistulas. A retrospective chart review of patients treated with Cook and Gore fistula plugs between August 2007 and December 2009 was performed. Success was defined as closure of all external openings and absence of drainage and abscess formation. Twelve Cook patients underwent 16 plug insertions and 10 Gore patients underwent 11 plug insertions. The overall procedural success rate in the Gore group was 54.5% (6 of 11) versus 12.5% (2 of 16) in the Cook group. The reasons for failure were unknown in the majority of patients and plug dislodgement in 2 patients. These short-term results with the Gore fistula plug suggested a higher procedural success rate in comparison to the Cook plug. The authors concluded that patients should be cautioned regarding potentially high failure rates; moreover, they stated that longer follow-up and a larger patient population are needed to confirm significant differences in fistula plug efficacy.

O’Riordan et al (2012) summarized the anal fistula plug literature for Crohn’s and non-Crohn’s fistula-in-ano in a homogenous patient population. PubMed, MEDLINE, Embase, and Cochrane medical databases were searched from 1995 to 2011. Abstracts from the American Society of Colon and Rectal Surgeons, the Society for Surgery of the Alimentary Tract, the European Society of Coloproctology, and the Association of Coloproctology of Great Britain and Ireland meetings between 2007 and 2010 were also evaluated. Studies were included if results for patients with and without Crohn’s disease could be differentiated. Patients with recto-vaginal, ano-vaginal, recto-urethral, or ileal-pouch vaginal fistulas were excluded as were studies where the mean or median follow-up was less
than 3 months. Two researchers independently selected studies matching the inclusion criteria. The primary outcomes measured were the overall fistula closure rates and length of follow-up. A total of 76 articles or abstracts were identified from the title as being of relevance; 20 studies (2 abstracts, 18 articles) were finally included. Study sample size ranged from 4 to 60 patients; 530 patients were included in all studies (488 non-Crohn's and 42 Crohn's patients). The plug extrusion rate was 8.7% (46 patients). The proportion of patients achieving fistula closure varied widely between studies for non-Crohn's, ranging from 0.2 (95% confidence interval [CI] 0.04 to 0.48) to 0.86 (95% CI: 0.64 to 0.97). The pooled proportion of patients achieving fistula closure in patients with non-Crohn's fistula-in-ano was 0.54 (95% CI: 0.50 to 0.59). The proportion achieving closure in patients with Crohn's disease was similar (0.55, 95% CI: 0.39 to 0.70). The authors concluded that fistula closure is achieved by using the anal fistula plug in approximately 54% of patients without Crohn's disease. The anal fistula plug has not been adequately evaluated in the Crohn's population.

Abrams et al (2013) stated that osteochondritis dissecans lesions occur frequently in children and adolescents. Treatment can be challenging and depends on the status of the articular cartilage and subchondral bone. Injection of calcium phosphate bone substitute into the area of subchondral bone edema (Subchondroplasty; Knee Creations, West Chester, PA) may be an option. These researchers presented a case of a lateral tibial plateau osteochondritis dissecans lesion treated with subchondral injection of nanocrystalline calcium phosphate. Pre-operative magnetic resonance imaging is used to determine the area of subchondral edema, and intra-operative fluoroscopy is used to localize this area with the injection cannula. Calcium phosphate is injected by use of a series of syringes until the appropriate fill is obtained. Treatment of concomitant cartilage defects may also be carried out at this time. The authors noted that potential challenges in using this technique are accurate localization of the lesion intra-operatively. Fluoroscopy is often not able to show the lesion at the time of the procedure. Because of this, these investigators regularly had the pre-operative MRI scan available in the operating room to reference to be able to properly match the location of the cannula with the area of maximal T2 signal intensity based on the MRI scan. In addition, when this technique is used in skeletally immature individuals, there is the potential for physeal injury because of the proximity of the calcium phosphate. The findings of this single case study need to be validated by well-designed studies.

Miscellaneous Interventions:

AlloStem is partially demineralized allograft bone combined with adipose derived mesenchymal stem cells.

Shin et al (2014) noted that focal chondral lesions of the glenohumeral joint, though less common than chondral defects in the knee or ankle, can be a significant source of pain in an active population. For patients in whom non-surgical management fails, promising results have been reported after arthroscopic microfracture surgery to treat such lesions. However, microfracture leads to growth of fibrocartilage tissue and is biomechanically less durable than native hyaline cartilage. Recently, augmentation of the microfractured defect with micronized allogeneic cartilage and PRP has been described to restore hyaline-like cartilage and potentially protect the subchondral bone from post-surgical fracture biology within the base of the defect. In a single-case study, these investigators presented a simple arthroscopic technique of implanting dehydrated, micronized allogeneic cartilage scaffold to treat an isolated chondral lesion of the glenoid. The authors noted that "Data regarding outcomes of BioCartilage use in human subjects are limited to expert opinion, but controlled human trials examining outcome differences between standard microfracture and BioCartilage techniques are currently under way .... Ongoing clinical studies will determine the effectiveness of augmented microfracture compared with standard microfracture alone".

In a case-report, Desai (2014) stated that although talar dome osteochondral lesions (OCLs) are common injuries, OCLs of the tibial plafond are relatively infrequent. These lesions have historically been managed in a similar manner to talar OCLs, with most treated with debridement and marrow stimulation. This treatment has had mixed results. The present case report described a patient who underwent an all-arthroscopic surgical technique consisting of debridement and marrow stimulation with application of micronized allograft cartilage matrix (BioCartilage™, Arthrex, Naples, FL). This was a single case study on the use of BioCartilage™ for a tibial osteochondral defect; not a glenoid defect.

Muller et al (2010) noted that grafts generated by cultivation of progenitor cells from the stromal vascular fraction of human adipose tissue have been proven to have osteogenic and vasculogenic
properties in-vivo. However, in-vitro manufacture of such implants is challenged by complex, impractical and expensive processes, and requires implantation in a separate surgery. This study investigated the feasibility of an intra-operative approach to engineer cell-based bone grafts with tissue harvest, cell isolation, cell seeding onto a scaffold and subsequent implantation within a few hours. Freshly isolated adipose tissue cells from a total of 11 donors, containing variable fractions of mesenchymal and endothelial progenitors, were embedded at different densities in a fibrin hydrogel, which was wrapped around bone substitute materials based on beta-tricalcium phosphate (ChronOS), hydroxyapatite (Engipore), or acellular xenograft (Bio-Oss). The resulting constructs, generated within 3 hours from biopsy harvest, were immediately implanted ectopically in nude mice and analyzed after 8 weeks. All explants contained blood vessels formed by human endothelial cells, functionally connected to the recipient's vasculature. Human origin cells were also found within osteoid structures, positively immune-stained for bone sialoprotein and osteocalcin. However, even with the highest loaded cell densities, no frank bone tissue was detected, independently of the material used. These results provided a proof-of-principle that an intra-operative engineering of autologous cell-based vasculogenic bone substitutes is feasible, but highlighted that -- in the absence of in-vitro commitment -- additional cues (e.g., low dose of osteogenic factors or orthotopic environmental conditions) are likely needed to support complete osteoblastic cell differentiation and bone tissue generation.

Ondrus et al (2011) tested the hypothesis that the application of tricalcium phosphate (TCP) mixed with autologous bone marrow can achieve better and faster healing of benign bone lesions than the application of tricalcium phosphate granules alone. The prospective study included 2 groups, each consisting of 10 patients, treated for benign cystic bone lesions at the Department of Paediatric Surgery, Orthopaedics and Trauma Surgery from July 1, 2008 to June 30, 2010. The bone cysts involved non-ossifying fibroma, enchondroma, fibrous dysplasia, aneurysmal bone cyst and juvenile bone cyst. One group was treated using ChronOS(TM) Beta-Tricalcium Phosphate (Synthes GmbH, Switzerland) granules mixed with autologous bone marrow harvested during surgery (BM group). The other (CH group) received treatment with ChronOS granules alone. Relevant clinical data were obtained from all 20 patients treated for one of the bone cyst forms mentioned above. The patients were followed up till the end of 2010. TCP application was a 1-step procedure in both groups. In the BM group, bone regeneration ad integrum (Neer 1) was achieved, with only an occasional very small residue of the cyst seen on radiographs (Neer 2). None of the patients reported any problems, not even at 6 months after surgery. In the CH group, 2 patients required further surgical treatment because of insufficient bone healing (Neer 3) and 2 other patients reported pain persisting at the site of the lesion at 6 months post-operatively. In these patients TCP was used to fill a defect after excochleation of an aneurysmal bone cyst or fibrous dysplasia. The rest of the patients showed satisfactory healing. The main objective of the use of synthetic biocompatible materials in surgical treatment of benign bone cysts requiring filling of the lesion is to reduce the post-operative stress of pediatric patients as much as possible. Although their first results were not statistically significant to give unambiguous support to the hypothesis that lesions would heal better with the use of synthetic tricalcium phosphate mixed with autologous bone marrow, there is plenty of evidence that further development of cell technologies will result in a more exact definition of bone substitute materials in both their components, i.e., well-defined cells and non-biological scaffolds close in structure to inorganic compounds of bone, i.e., biodegradable osteo-inductive materials. The authors concluded that patients with benign bone lesions treated by TCP mixed with autologous bone marrow showed neither recurrent disease nor complications. The group treated with TCP alone had recurrent lesions in 2 and persisting pain also in 2 patients. Other complications were not recorded.

Currently, there is insufficient evidence to support the use of ChronOS bone graft substitute.

Appendix

Bone and Tendon Graft Substitutes considered medically necessary when criteria are met (not an all-inclusive list):

- 3D ProFuse Bioscaffold
- Accell Connexus
- Accell Evo 3
- Accell TBM
- AlloFlex
- AlloFuse
<table>
<thead>
<tr>
<th>Bone and Tendon Graft Substitutes and Adjuncts</th>
</tr>
</thead>
<tbody>
<tr>
<td>AlloGro DBM</td>
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<tr>
<td>AlloPac</td>
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<tr>
<td>AlphaGraft DBM</td>
</tr>
<tr>
<td>AlloQuent</td>
</tr>
<tr>
<td>Autograft (patient)</td>
</tr>
<tr>
<td>Auxano DBM</td>
</tr>
<tr>
<td>Bacterim DBM sponge</td>
</tr>
<tr>
<td>BioMet Boost DBM</td>
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<tr>
<td>BioMet DBM putty</td>
</tr>
<tr>
<td>BioMet EBI DBM</td>
</tr>
<tr>
<td>BonePlast Quick Set</td>
</tr>
<tr>
<td>Bone Void Fillers</td>
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<tr>
<td>Cadaveric Allograft</td>
</tr>
<tr>
<td>CeSpace Bone</td>
</tr>
<tr>
<td>Cornerstone-SR Allograft Tissue</td>
</tr>
<tr>
<td>Demineralized Bone Matrix</td>
</tr>
<tr>
<td>Dynagraft</td>
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<tr>
<td>Equivabone graft</td>
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<tr>
<td>Featherbone C-spine compressible bone matrix (DBM)</td>
</tr>
<tr>
<td>Fortitude Duo</td>
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<tr>
<td>Globus Maintain cervical allograft</td>
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<tr>
<td>Globus Xemplifi DBM</td>
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<tr>
<td>Grafton A-flex</td>
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<tr>
<td>Grafton Crunch</td>
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<tr>
<td>Grafton Flex</td>
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<tr>
<td>Grafton Gel</td>
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<tr>
<td>Grafton Matrix PLF</td>
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<tr>
<td>Grafton Matrix Scoliosis Strips</td>
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<tr>
<td>Grafton Orthobrand Large Defect</td>
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<tr>
<td>Grafton Orthobrand Small Defect</td>
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<tr>
<td>Grafton Putty</td>
</tr>
<tr>
<td>Healos Bone Graft Replacement</td>
</tr>
<tr>
<td>Healos Sponge</td>
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<tr>
<td>IC Graft Chamber</td>
</tr>
<tr>
<td>INFUSE Bone Graft (Bone Morphogenic Protein-2)</td>
</tr>
<tr>
<td>MTF cube</td>
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<tr>
<td>Optecure DBM</td>
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<tr>
<td>Optefil</td>
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<tr>
<td>Optium DBM</td>
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<tr>
<td>Osprey Biomedical Allograft</td>
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<tr>
<td>Osteofil DBM</td>
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<tr>
<td>Osteogenic Protein-1 (OP-1)</td>
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<tr>
<td>OsteoSparx DBM</td>
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<tr>
<td>Osteosurge 100 DBM</td>
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<tr>
<td>Pinnacle DBM sponge</td>
</tr>
<tr>
<td>Polymethylmethacrylate (PMMA) Antibiotic Beads</td>
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<tr>
<td>Progenix Plus</td>
</tr>
<tr>
<td>Progenix Putty</td>
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<tr>
<td>Promote Osteostrip</td>
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<tr>
<td>PureBone</td>
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<tr>
<td>Puros DBM</td>
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<tr>
<td>RTI Biologics BioSet Allograft Paste</td>
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<tr>
<td>Sterisponge</td>
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<tr>
<td>Staygraft DBM</td>
</tr>
<tr>
<td>Triad Allograft</td>
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<tr>
<td>Vertigraft</td>
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<tr>
<td>VG2 cervical allograft</td>
</tr>
<tr>
<td>Xemplifi DBM</td>
</tr>
</tbody>
</table>

06/04/2015
Wright Allomatrix
Wright Allomatrix RCS
Wright Allopure
Wright Ignite

Bone and Tendon Graft Substitutes considered experimental and investigational (not an all-inclusive list):

Acuity Allostem
Actifuse
Activize Nucel
Advanced Biologics OsteoAmp
AlloGro Stem Cell Bone Growth Substitute
Allosource AlloStem
Alphatec Allograft
Alphatec VELOSSITY Moldable Synthetic Bone Graft
Amniofix
AmnioShield
Arteriocyte \ Magellan Platelet Separator Systems
Bio AVS graft
Bioactive graft (nano-structured hydroxyapatite material)
BioD factor
Biogennix RPC
Bone XTRUDABLE
BonePlast
Calceon 6
Cellentra Allograft CONDUIT
TCP Granules CopiOs Bone
Void Filler CopiOs Cancellous
Bone Graft
Cyclone Bone Marrow Concentrate system
Formagraft
Cymbicyte
Globus Matrix ceramic
Globus Medical conduct
Globus NuBone
Graston Allograft
H-Genin DBM
Inductaputty (hydroxapatite)
Integra Mozaik
InterGro
InterGro DBM Plus
Magnifuse
Mastergraft Granules
Mastergraft Putty
Mastergraft Strip
Matrix Ovation Stem Cell
Mesenchymal Stem Cell Therapy
MTX DBX
Nanoss bioactive bone void filler
NextGraft
NEXoss
Norian SRS
Norian SRS Fast Set Putty
Novabone
Opteform
OpteMx
Optimesh
Optium DBM Gel
Orthospine Allostem or Osteostem
OsteoBlast II
Osteocel
Osteocel Plus
OsteoMatrix
Osiris Therapeutics Ovation
PiatForm DBM
Porcine Intestinal Submucosa Surgical Mesh
Pro Osteo Porous Hydroxyapatite Bone Graft SubstitutePurBone PurGEN
Regeneration BioSet
Regenexx PL-Disc
RTI Tissue Bank Bio DBM
RTI Tissue Bank BioSet Allograft
SKYE Liquid Gel
Spineology Optimesh
Stryker Biotech OP-1
Stryker Spine Lifenet DBM
TriCore
Trinity Elite
Trinity Evolution
Viagraf
Vitoss
Wright Cancelllo-Pure
Wright Cellplex
Wright MIIGX3
Wright Osteoset
WRight Pro-Dense
Wright Pro-Stim

CPT Codes / HCPCS Codes / ICD-9 Codes

**Bone and Tendon Graft Substitutes and Adjuncts:**

**Other CPT codes related to the CPB:**

<table>
<thead>
<tr>
<th>Code Range</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>20690 - 20694</td>
<td>Uniplane and multiplane fixation systems</td>
</tr>
<tr>
<td>20900</td>
<td>Bone graft, any donor area; minor or small (e.g., dowel or button)</td>
</tr>
<tr>
<td>20902</td>
<td>major or large</td>
</tr>
<tr>
<td>20955</td>
<td>Bone graft with microvascular anastomosis; fibula</td>
</tr>
<tr>
<td>20962</td>
<td>other than fibula, iliac crest, or metatarsal</td>
</tr>
<tr>
<td>20974</td>
<td>Electrical stimulation to aid bone healing, noninvasive (nonoperative)</td>
</tr>
<tr>
<td>20975</td>
<td>invasive (operative)</td>
</tr>
<tr>
<td>20979</td>
<td>Low intensity ultrasound stimulation to aid bone healing, noninvasive (nonoperative)</td>
</tr>
<tr>
<td>22548 - 22819</td>
<td>Arthrodesis, spine [spinal fusion]</td>
</tr>
<tr>
<td>22851</td>
<td>Application of intervertebral biomechanical device(s) (e.g., synthetic cage(s), methylmethacrylate) to vertebral defect or interspace (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>27301 - 27499</td>
<td>Femur (thigh region) and knee joint surgery</td>
</tr>
</tbody>
</table>
29065 - 29085  Application cast; upper extremity
29305 - 29355  Lower extremity casts
77072  Bone age studies

**HCPCS codes not covered for indications listed in the CPB:**

C1763  Connective tissue, non-human (includes synthetic)

**Other HCPCS codes related to the CPB:**

E0747  Osteogenesis stimulator, electrical, noninvasive, other than spinal applications
E0749  Osteogenesis stimulator, electrical, surgically implanted
Q4001 - Q4048  Casting supplies

**Osteogenic Protein-1 (OP-1):**

**Other CPT codes related to the CPB:**

22548 - 22819  Arthrodesis, spine [spinal fusion]

**ICD-9 codes covered if selection criteria are met:**

170.2  Malignant neoplasm of vertebral column, excluding sacrum and coccyx
192.3  Malignant neoplasm of spinal meninges
198.3 - 198.5  Secondary malignant neoplasms of brain, spinal cord, bone and bone marrow
225.3 - 225.4  Benign neoplasm of spinal cord and meninges
237.5 - 237.6  Neoplasm of uncertain behavior of brain, spinal cord and meninges
238.0  Neoplasm of uncertain behavior of bone and articular cartilage
724.02  Spinal stenosis, lumbar region
733.13  Pathologic fracture of vertebrae
733.82  Nonunion of fracture [long bone]
737.30 - 737.39  Kyphoscoliosis and scoliosis
737.42  Lordosis, curvature of spine associated with other conditions
738.4  Acquired spondylolisthesis
756.12  Spondylolisthesis
805.4 - 805.5  Fracture of vertebral column without mention of spinal cord injury, lumbar
806.4 - 806.5  Fracture of vertebral column with spinal cord injury, lumbar
810.00 - 810.13  Fracture of clavicle (nonunion)
812.00 - 813.93  Fracture of humerus, radius and ulna (nonunion)
815.00 - 815.19  Fracture of metacarpal bone(s) (nonunion)
820.00 - 821.39  Fracture of femur (nonunion)
823.00 - 825.35  Fracture of tibia and fibula, ankle, tarsal and metatarsal (nonunion)
839.20  Dislocation of lumbar vertebra, closed
839.30  Dislocation of lumbar vertebra, open
V45.4  Arthrodesis status [nonunion of prior fusion]

**ICD-9 codes not covered for indications listed in the CPB:**

640.00 - 648.94  Complications mainly related to pregnancy
V10.0 - V10.9  Personal history of malignant neoplasm
V22.0 - V23.9  Supervision of pregnancy
V24.0 - V24.2  Postpartum care

**Other ICD-9 codes related to the CPB:**

733.14  Pathological fracture of neck of femur
808.41  Fracture of ilium, closed
808.51  Fracture of ilium, open
996.40 - 996.49  Complications of bone grafts
996.67  Infection and inflammatory reaction due to other internal orthopedic device, implant, and graft
996.78  Complications due to internal orthopedic graft
996.79  Other complications of internal (biological) (synthetic) prosthetic device, implant, and graft

**InFuse Bone Graft (Bone Morphogenic Protein-2):**

**ICD-9 codes covered if selection criteria are met:**

722.52  Degeneration of lumbar or lumbosacral intervertebral disc
823.30  Fracture of the tibia and fibula shaft, open [for skeletally mature persons stabilized with intramedullary nail fixation after appropriate wound management and applied within 14 days after the initial fracture]

**Pro Osteon Hydroxyapatite Bone Graft Substitute:**

**ICD-9 codes not covered for indications listed in the CPB:**

170.4  Malignant neoplasm of scapula and long bones of upper limb
170.7  Malignant neoplasm of long bones of lower limb
198.5  Secondary malignant neoplasm of bone and bone marrow
213.4  Benign neoplasm of scapula and long bones of upper limb
213.7  Benign neoplasm of long bones of lower limb
565.1  Anal fistula
722.4 - 722.73  Degeneration of intervertebral disc
722.80 - 722.83  Postlaminectomy syndrome
733.20 - 733.29  Cyst of bone
733.82  Nonunion of fracture
737.0 - 737.9  Curvature of spine
738.4  Acquired spondylolisthesis
754.2  Certain congenital musculoskeletal deformities of spine
756.11  Spondylolysis, lumbosacral region
756.12  Spondylolisthesis
756.19  Other anomalies of spine
805.00 - 805.9  Fracture of vertebral column without mention of spinal cord injury
806.00 - 806.9  Fracture of vertebral column with spinal cord injury
812.44, 813.43, 820.01, 820.11, 821.22  Epiphyseal fractures
839.00 - 839.59  Dislocation of vertebra

Platelet-Rich Plasma:

CPT codes not covered for indications listed in the CPB:

0232T  Injection(s), platelet rich plasma, any tissue, including image guidance, harvesting and preparation when performed

HCPCS codes covered if selection criteria are met:

P9020  Platelet rich plasma, each unit

HCPCS codes not covered for indications listed in the CPB:

S9055  Procuren or other growth factor preparation to promote wound healing

ICD-9 codes covered if selection criteria are met:

287.30 - 287.5  Thrombocytopenia

Porcine Intestinal Submucous Surgical Mesh:

CPT codes not covered for indications listed in the CPB:

46707  Repair of anorectal fistula with plug (e.g., porcine small intestine submucosa [SIS])

Allograft for Spinal Fusion:

CPT codes covered if selection criteria are met:

20930  Allograft for spine surgery only; morselized
20931  Allograft for spine surgery only; structural

Bone Void Fillers for Nonunions:

HCPCS codes not covered for indications listed in the CPB:

C9359  Porous purified collagen matrix bone void filler (Integra Mozaik Osteoconductive Scaffold Putty, Integra OS Osteoconductive Scaffold Putty), per 0.5 cc [actifuse silicate calcium sulphate]

C9362  Porous purified collagen matrix bone void filler (Integra Mozaik Osteoconductive Scaffold Strip), per 0.5 cc [actifuse silicate calcium sulphate]

ICD-9 codes not covered for indications listed in the CPB:
733.81  Malunion of fracture
733.82  Nonunion of fracture

**Polymethylmethacrylate (PMMA) Antibiotic beads:**

CPT codes covered if selection criteria are met:

- 11981  Insertion, non-biodegradable drug delivery implant
- 19182  Removal, non-biodegradable drug delivery implant
- 19183  Removal with reinsertion, non-biodegradable drug delivery implant

ICD-9 codes covered if selection criteria are met:

- 730.10 - 730.19  Chronic osteomyelitis [PMMA antibiotic beads are covered when used with IV antibiotics in the treatment of chronic osteomyelitis]

**Mesenchymal Stem Cell Therapy/Bone Marrow Aspirate:**

CPT codes not covered for indications listed in the CPB:

- 38220  Bone marrow; aspiration only
- 38232  Bone marrow harvesting for transplantation; autologous
- 38240 - 38241  Bone marrow or blood derived peripheral stem cell transplantation

Other CPT codes related to the CPB:

- 20615  Aspiration and injection for treatment of bone cyst
- 22548 - 22819  Arthrodesis, spine

HCPCS codes not covered for indications listed in the CPB:

- G0364  Bone marrow aspiration performed with bone marrow biopsy through the same incision on the same date of service
- S2142  Cord blood-derived stem-cell transplantation, allogeneic
- S2150  Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre- and post-transplant care in the global definition

ICD-9 codes covered if selection criteria are met:

- 733.20 - 733.29  Cyst of bone

ICD-9 codes not covered for indications listed in the CPB:

- 733.81  Malunion of fractures
- 733.82  Nonunion of fracture
- V45.4  Arthrodesis status

**Hydroxyapatite bone substitute (e.g., OtoMimix) for middle ear surgery:**

No specific code

**Experimental and investigational Substitutes and Adjuncts:**
Bone and Tendon Graft Substitutes and Adjuncts

HCPCS codes not covered for indications listed in the CPB:

Q4116  AlloDerm, per square centimeter

Tendon Wrap Tendon Protector:

HCPCS codes not covered for indications listed in the CPB:

C9356  Tendon, porous matrix of cross-linked collagen and glycosaminoglycan matrix (Tenoglide Tendon Protector Sheet), per square centimeter [Tendon Wrap Tendon Protector]

The above policy is based on the following references:

Bone Graft Substitutes:


**Platelet-Rich Plasma:**


Porcine Intestinal Submucosa Surgical Mesh


**Demineralized Bone Matrix**


**Bone Void Fillers for Nonunions:**


**Mesenchymal Stem Cell Therapy:**

Miscellaneous Interventions:

5. Ferrari J. Hallux valgus deformity (bunion). Last reviewed February 2013. UpToDate Inc. Waltham, MA.
23. Jones LC, Mont MA. Osteonecrosis (avascular necrosis of bone). UpToDate [serial online]. Waltham, MA: UpToDate; reviewed February 2014.


