BONE OR SOFT TISSUE HEALING AND FUSION ENHANCEMENT PRODUCTS

Guideline Number: MMG009.K **Effective Date**: April 1, 2019

Instructions for Use

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Related Medical Management Guidelines

- Ablative Treatment for Spinal Pain
- Discogenic Pain Treatment
- Platelet Derived Growth Factors for Treatment of Wounds
- Surgical Treatment for Spine Pain

COVERAGE RATIONALE

The following are proven and medically necessary:

- Autografts for bone fusion enhancement
- Demineralized bone matrix (DBM) allograft for bone fusion enhancement
- Allografts for bone fusion enhancement
- Bone Morphogenetic Protein-2 (rhBMP-2)
  - Infuse® Bone Graft for the enhancement of bone healing and/or fusion of the lumbar spine when the following criteria are met:
    - Implanted via an anterior or oblique approach and used in conjunction with an Infuse Bone Graft fusion device
    - Skeletally mature patient (18 years of age or older or radiographic evidence of epiphyseal closure) with degenerative disc disease at one level from L4–S1
    - No more than Grade I spondylolisthesis at the involved level
    - Failure of at least 6 months of non-operative treatment
  - The Infuse/MASTERGRAFT™ Posterolateral Revision Device system when used according to U.S. Food and Drug Administration (FDA) indications in members who meet all of the following criteria:
    - Implanted via a posterolateral approach
    - Presence of symptomatic posterolateral lumbar spine pseudoarthrosis
    - Skeletally mature patient (older than 21 years of age or radiographic evidence of epiphyseal closure)
    - Treatment of 2 or more levels of the lumbar spine
    - Autologous bone and/or bone marrow harvest is not feasible or is not expected to promote fusion. These individuals are diabetics and smokers.

The following are unproven and not medically necessary due to insufficient evidence of efficacy:

- Amniotic membrane products in the treatment of spine disease or in spine surgery
- Infuse® Bone Graft and The Infuse/MASTERGRAFT™ Posterolateral Revision Device for ALL other indications not included above
- Bone Morphogenetic Protein-7 (BMP-7)
  - OP-1™ Implant and OP-1 Putty for the enhancement of bone healing and/or fusion with or without use of other devices (including the PEEK device)
- Ceramic-based products such as beta tricalcium phosphate (b-TCP), calcium phosphate, calcium sulfate and bioactive glass used alone or in combination with other grafts including bone marrow aspirate for the enhancement of bone healing and/or fusion
- Cell-based products such as mesenchymal stem cells (MSC) for the enhancement of bone healing
- Platelet-rich plasma (e.g., autologous platelet derived growth factor) when used to enhance bone or soft tissue healing.

- The OptiMesh® deployable grafting system

DEFINITIONS

Overview

Allograft: An allograft is obtained from a person other than the surgical candidate. Harvested through a minimally invasive procedure, this allograft provides a population of osteoprogenitor cells and critical growth factors that help cell differentiation, leading to bone healing. It can include cadaveric bone and/or tissue from a bone bank. It may be used alone or in combination with another material. Even when used alone, allograft must be processed to decrease the likelihood of disease transmission and immunogenic response.

More recently, processing methods used for preparation of some allografts have been refined and products are now available that manufacturers claim retain higher concentrations of naturally occurring growth factors and/or stem cells. Human growth factors such as fibroblast growth factor, insulin-like growth factor, platelet-derived growth factor, transforming growth factor-beta, and microglobulin-B, are examples of osteogenic growth factors that are naturally found within the matrix of bone.

Amniotic Tissue Membrane: The innermost layer of the amniotic fetal membrane is considered a source of collagen that acts as a scaffold for the attachment of cells. Recently, amniotic membrane allografts have been investigated for various uses including use as bone void fillers during spinal and other orthopedic surgeries to enhance bone healing.

Anorganic Bone Graft Materials: Anorganic bone graft materials are a type of xenograft bone graft substitute made from other than human material, such as cow (i.e., bovine) or coral, and is typically used in combination with other types of bone graft materials, for example with collagen or a calcified matrix. The animal bone is processed to remove any organic components (i.e., anorganic bone material) reducing concerns of disease transmission or immunogenic reactions. Some of the anorganic type xenograft materials may be used as stand-alone graft material to enhance healing.

Autograft: An autograft is taken directly from the patient undergoing surgery. The usual site for an autograft harvest is the posterior iliac crest. When autograft material is of an insufficient volume, of poor quality, or cannot be used for any other reason, another type of material must be used for the bone graft.

Bone Morphogenetic Proteins (BMP) and Recombinant Human Bone Morphogenetic Proteins (rhBMP): RhBMP is a unique subgroup of graft substitutes. Bone morphogenetic proteins are naturally occurring proteins found in human bone and play an active role in bone formation. Recombinant human bone morphogenetic proteins act as an adjunct to autogenous bone grafts, and are used commonly with spinal instrumentation devices (i.e., cages) during lumbar fusion and for fracture repair.

Carrier systems: Function to maintain the concentration of the rhBMP at the treatment site, provide temporary scaffolding for osteogenesis and prevent extraneous bone formation. Carrier systems have included inorganic material, synthetic polymer, natural polymers and bone allograft. The rhBMP and carrier may be inserted via a delivery system, which may also function to provide mechanical support. The carrier and delivery system are important variables in the clinical use of rhBMPs.

Cell-Based Products: Bone graft substitutes that are cell-based use cells to generate new tissue either alone, with other biomaterials, or seeded onto a support matrix (e.g., in combination with allograft material). One material proposed for use in combination with allograft is mesenchymal stem cells (MSC), obtained from bone marrow aspirate. Potential uses of MSCs for orthopedic applications include treatment of damaged bone, cartilage, ligaments, tendons, and intervertebral discs.

Ceramic-Based Products: Ceramic-based bone graft substitutes include materials such as calcium phosphate, calcium sulfate and bioactive glass, used alone or in combination with other grafts. Some ceramic-based products (e.g., calcium phosphate-collagen composites, beta-tricalcium phosphate) are combined with collagen to augment healing; collagen composites may include bovine material similar to that used with cell-based products. Several types of calcium phosphates, including tricalcium phosphate, synthetic hydroxyapatite, and coralline hydroxyapatite are available in pastes, putties, solid matrices, and granules.

Combination Bone Graft Substitutes: A newer practice in the use of bone graft substitutes is to combine different materials, with the theory that each different property working together will work in synergy with another in the healing and grafting process.

Concentrated Bone Marrow Aspirate (CBMA): CBMA is produced from native BMA, usually obtained from the iliac crest or local vertebrae. The bone marrow aspirate contains stem cells that have been proposed to help with the healing of some bone and joint conditions.

Demineralized Bone Matrix (DBM): DBM is a type of allograft; it is produced by acid extraction of allograft bone (known as decalcification). Based on manufacturing techniques, DBM may be a freeze-dried powder, granules, gel, putty, or strips. After processing, the material contains 90% type I collagen and 10% noncollagen protein containing a variety of bone growth stimulators such as bone morphogenetic protein (BMPs). The bone growth stimulators induce osteoblast formation (osteoinduction) from the patient's osteogenic stem cells. Added materials provide a three-dimensional substance into which capillaries, osteogenic cells, and other tissue can migrate and produce new bone (osteoconduction). DBM is commonly used as a bone graft extender for posterolateral spinal fusion surgery.

Infuse™ Bone Graft: (**Infuse**™ Bone Graft is the premium product for autograft replacement due to its high osteoinductivity. Infuse bone graft is recombinant human bone morphogenetic protein-2 (rhBMP-2) applied to an absorbable collagen sponge carrier (ACS). One of the functions of the protein is to stimulate natural bone formation.

OptiMesh Grafting System®: OptiMesh is a conformable, porous, polymeric containment device that is inserted into the evacuated disc space and filled with a mixture of cortico-cancellous allograft with demineralized bone matrix, autograft, and bone marrow aspirate to aid traumatic fracture repair and interbody fusion.

Orthobiologics: Are designed to substitute for real bone, but they can also enhance bone-fracture healing or bone fusion by providing substances that are either osteoconductive or osteoinductive (described in further detail below). Some products may have both properties. Orthobiologics require an invasive surgical procedure to place the material in the bone void site or at the site of bone fusion.

- **Osteoconductive Matrix Materials**: Osteoconductive materials provide a three-dimensional substance into which capillaries, osteogenic cells, and other tissue can migrate and produce new bone. This material acts only as a scaffold into which the new bone cells grow.
- **Osteoinductive Bone Graft Substitutes**: Osteoinduction means that the product induces osteoblast formation from the patient's own osteogenic stem cells that are already present at the fusion site. The osteoinductive properties of bone tissue are attributed to bone morphogenetic proteins (BMPs).

Bone graft substitutes have overlapping properties and are made of a variety of materials such as polymers (degradable and nondegradable), ceramics and composites (calcium phosphate, calcium sulfate, and bioactive glass), factor-based techniques (recombinant growth factors) and cell-based techniques (mesenchymal stem cells).

Platelet-Rich Plasma: Platelet concentrate products are derived from platelet-rich plasma (PRP), which involves concentrating whole blood through a centrifugation process. Platelet rich plasma (plasma having a platelet concentration above baseline) is an approach being investigated for the treatment of bone healing. PRP is also referred to as autologous platelet derived growth factor, platelet enriched plasma, platelet-rich concentrate, and autogenous platelet gel or platelet releasate. When activated in the body, platelets release growth factors which accelerate healing, including platelet-derived growth factor, transforming growth factor beta (TGF-β) and insulin-like growth factor to name a few. Variability in processing methods, classification systems, and terminology has led to wide inconsistency in the results of its use in many orthopedic conditions, including bone healing.

RhBMP–7/ OP–1™ Putty:
A second type of human bone morphogenetic protein is rhBMP–7, marketed in the United States as OP–1™ Implant for use in healing fractures of the long bones, and OP–1™ Putty for use in spinal fusion. OP-1™ Putty is a recombinant human bone morphogenetic protein-7 (rhBMP-7) and type 1 bovine bone collagen matrix combined with the putty additive carboxymethylcellulose sodium. It is intended to aid in treating lumbar spine pseudoarthrosis.

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this guideline does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
0232T	Injection(s), platelet rich plasma, any site, including image guidance, harvesting and preparation when performed
20930	Allograft, morselized, or placement of osteopromotive material, for spine surgery only (List separately in addition to code for primary procedure)

CPT Code	Description
20931	Allograft, structural, for spine surgery only (List separately in addition to code for primary procedure)
20932	Allograft, includes templating, cutting, placement and internal fixation, when performed; osteoarticular, including articular surface and contiguous bone (List separately in addition to code for primary procedure)
20933	Allograft, includes templating, cutting, placement and internal fixation, when performed; hemicortical intercalary, partial (i.e., hemicylindrical) (List separately in addition to code for primary procedure)
20934	Allograft, includes templating, cutting, placement and internal fixation, when performed; intercalary, complete (i.e., cylindrical) (List separately in addition to code for primary procedure)
22558	Arthrodesis, anterior interbody technique, including minimal discectomy to prepare interspace (other than for decompression); lumbar
22585	Arthrodesis, anterior interbody technique, including minimal discectomy to prepare interspace (other than for decompression); each additional interspace (List separately in addition to code for primary procedure)
22899	Unlisted procedure, spine

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HCPCS Code	Description
Q4100	Skin substitute, not otherwise specified
Q4149	Excellagen, 0.1 cc
Q4186	Epifix, per sq cm
Q4187	Epicord, per sq cm

DESCRIPTION OF SERVICES

The composition of allograft and synthetic bone graft substitutes and their mechanism of action can vary widely. Bone graft materials are often combined to extend graft availability and enhance healing. Used alone or in combination, bone graft substitutes may be utilized for many orthopaedic applications including spinal fusion. The carrier and delivery system are important variables in the clinical use of rhBMPs, and different clinical applications, such as long bone nonunion, or interbody or intertransverse fusion, may require different dosages of rhBMP along with different carriers and delivery systems.

CLINICAL EVIDENCE

Bone Morphogenetic Protein (rhBMP or BMP)

Hayes (2018) the literature search identified a large body of moderate-quality evidence suggests that, compared with an autograft, use of rhBMP-2 for lumbar spinal fusion provides more rapid fusion and/or a somewhat greater likelihood of achieving fusion. Use of rhBMP-2 also appears reasonably safe for lumbar fusion over the short term. Furthermore, due to the limited duration of follow-up in almost all of the reviewed studies, it has not been possible to determine the clinical significance of more complete fusion with rhBMP-2, and it has not been possible to rule out certain serious long term risks of rhBMP-2, including a low potential risk of cancer. Additional long-term studies are needed to determine whether the benefits outweigh the potential risks.

ECRI (2017) reviewed the evidence of five clinical studies of anterior interbody lumbar fusion. The authors reported a consensus statement for ALIF and use of Infuse increased the fusion rate compared with iliac crest bone graft (ICBG) but suggested that patients be informed of potential complications associated with Infuse. Based upon the published literature, we conclude that rhBMP-2 is likely associated with an increased rate of radiographic arthrodesis when compared with ICBG [iliac crest bone graft]. However, this does not necessarily translate to an improvement in clinical outcomes. Although rhBMP-2 limits the morbidity associated with harvesting ICBG, which may explain the shorter operative times and less blood loss, patients should be counseled regarding the potential complications that are specific to rhBMP-2 utilization including osteolysis and retrograde ejaculation. rhBMP-2 may also be associated with lumbar plexopathy when utilized in the transpsoas lumbar fusion cases.

Faundez et al. (2016) conducted an extensive review of randomized controlled trials (RCTs) and controlled series. Review confirmed that the use of rhBMP-2 following FDA-approved recommendations (i.e. one-level ALIF surgery with an LT-cage) is safe. The rate of complications is low and the AEs had been identified by the FDA during the pre-marketing clinical trials. The clinical efficiency of rhBMP-2 is equal or superior to that of allogenic or autologous bone

graft in respect to fusion rate, low back pain disability, patient satisfaction and rate of re-operations. For all other off-label use, the safety and effectiveness of rhBMP-2 have not been established, and further RCTs with high level of evidence are required.

In a prospective, longitudinal cohort study of 688 patients from 3 studies, Burkus et al. (2011) analyzed antibody formation to BMP-2, bovine collagen, and human collagen after three prospective clinical studies investigating rhBMP. Neutralizing antibodies were assessed using a cell bioassay. The incidence of antibodies to bovine and human collagen was determined. Radiographic and clinical outcome data were assessed to determine whether antibodies were correlated to patient outcomes. The authors concluded that formation of anti-BMP-2 antibodies was low and transient. No neutralizing antibodies were observed. Formation of antibodies did not affect fusion success or appear to have clinical sequelae.

A systematic review by Agarwal et al. (2009) compared the efficacy and safety of osteoinductive bone graft substitutes using autografts and allografts in lumbar fusion. Of 732 potential studies, 17 studies met the inclusion criteria (nine examined rhBMP-2, three examined rhBMP-7, three examined demineralized bone matrix, and two examined autologous growth factor). Primary outcome measures were nonunion as defined by failure to fuse as demonstrated on CT scans or plain x-rays. Secondary outcome measures were failure to demonstrate improvement on the Oswestry Low-Back Pain Disability Questionnaire (or Oswestry Disability Index [ODI]). When compared with autologous iliac crest bone graft (AIBG), recombinant human BMP-2 significantly increased union as evidenced by radiographic imaging, while rhBMP-7 showed no difference in radiographic nonunion. Neither rhBMP-2 nor rhBMP-7 demonstrated a significant improvement on the Oswestry Disability Index when compared with (AIBG). The controlled trials of demineralized bone matrix or autologous growth factor in comparison with AIBG showed no significant differences in radiographic nonunion. The authors concluded that rhBMP-2 may be an effective alternative to facilitate lumbar fusion in single-level lumbar DJD compared to AIBG. However, the data is limited for rhBMP-7, demineralized bone matrix, and autologous growth factor. The authors note the following limitations: English only published studies were reviewed; there were no double blinded studies; analyses of the efficacy of bone graft substitutes other than rhBMP-2 was limited by the study size and number; and there is a potential for bias because device manufacturers sponsored several studies and more than one author reported conflicts of interest.

Bone Morphogenetic Protein-2 (BMP-2) Lumbar Spine

Rodgers et al. (2013) investigated published results of industry funded trials of recombinant human bone morphogenetic protein 2 (rhBMP-2) in spinal fusion matching underlying trial data by comparing three different data sources: individual participant data, internal industry reports, and publicly available journal publications and conference abstracts. Outcomes from 11 of the 17 manufacturer-sponsored studies were reported in 32 publications. The authors concluded that the published literature only partially represents the total data known to have been collected on the effects of rhBMP-2. This did not lead to substantially different results for meta-analysis of effectiveness outcomes. In contrast, reporting of adverse event data in trial publications was inadequate and inconsistent to the extent that any systematic review based solely on the publicly available data would not be able to properly evaluate the safety of rhBMP-2. Analysis of individual participant data enabled the most complete, detailed, and in-depth analysis and was not more resource intensive than extracting, collating, and analyzing aggregate data from multiple trial publications and conference abstracts. Confidential internal reports presented considerably more adverse event data than publications, and in the absence of individual participant data access to these reports would support more accurate and reliable investigation, with less time and effort than relying on incomplete published data.

In a systematic review and meta-analysis of randomized, controlled trials and cohort studies by Fu et al. (2013), the clinical effectiveness of BMP-2 in spine fusion was assessed. This review found that in spinal fusion, rhBMP-2 has no proven clinical advantage over bone graft and may be associated with important harms, making it difficult to identify clear indications for rhBMP-2. Earlier disclosure of all relevant data would have better informed clinicians and the public than the initial published trial reports did.

Simmonds et al. (2013) also conducted a systemic review of individual patient data from all of the studies sponsored by the manufacturer, related internal documents, Food and Drug Administration (FDA) documents, and other published research to assess the effectiveness and harms of rhBMP-2 in spinal fusion compared with iliac crest bone graft or other bone grafts. The authors concluded that rhBMP-2 was associated with a small increase in fusion but greater immediate postoperative pain compared with iliac crest bone graft (ICBG). At 2 years, rhBMP-2 offered no clinically important pain reduction and was associated with a possible increased risk for cancer. While rhBMP-2 recipients had nearly double the number of new cancers compared with ICBG recipients, the overall absolute risk for cancer was low in both groups. The investigators could not rule out a bias in pain assessment because participants were not blinded to the treatment received or their fusion status.

Burkus et al. (2009) reported 6 year outcomes of 222 patients (112 open; 110 laparoscopic) who received anterior lumbar interbody arthrodesis using interbody fusion cages and recombinant human bone morphogenetic protein-2 (rhBMP-2). Of the 222 enrolled patients, 146 patients (78 open; 68 laparoscopic) completed the 6 year clinical follow-

up evaluations with 130 patients having a complete radiographic follow-up at 6 years. Outcomes were measured utilizing the Oswestry Disability Index (ODI) scores, Short Form-36 health survey physical component summary scores, and back and leg pain scores preoperatively and at 6 weeks and 3, 6, 12, 24,48, and 72 months postoperatively. Plain radiographs and thin-cut computed tomography scans were used to assess fusion status. At follow-up, fusion was confirmed in 128 of the 130 patients undergoing radiographic follow-up. Twenty-five patients required a second surgery. Improvements were achieved by 6 weeks in both the open and laparoscopic groups and were sustained at 6 years in the Oswestry Disability Index scores, Short Form-36 health survey physical component summary scores, and back and leg pain scores. The authors concluded that the use of rhBMP-2 on an absorbable collagen sponge is effective for obtaining anterior intervertebral spinal fusion with use of a stand-alone interbody fusion device. The lack of comparison to iliac crest bone graft or other treatment is a limitation of the study.

Glassman et al. (2008) conducted a prospective randomized controlled trial of rhBMP-2/ACS (Infuse bone graft) versus iliac crest bone graft (ICBG) for posterolateral lumbar spine fusion in patients over 60 years of age. Patients were randomized to rhBMP-2/ACS (n = 50) or ICBG (n = 52). Two-year postoperative improvement in Oswestry Disability Index averaged 15.8 in the rhBMP-2/ACS group and 13.0 in the ICBG group. Mean improvement in Short Form-36 physical component score was 6.6 in the rhBMP-2/ACS group and 7.5 in the ICBG group. There were 20 complications in the ICBG group and 8 complications in the rhBMP-2/ACS group. Sixteen ICBG and 10 rhBMP-2/ACS patients required additional treatment for persistent back or leg symptoms. Two rhBMP-2/ACS patients had revision procedures, 1 for nonunion. Eight patients in the ICBG group had revision procedures, 5 for nonunion. Mean fusion grade on computed tomography scan was significantly better in the rhBMP-2/ACS (4.3) compared with the ICBG group (3.8). The investigators concluded that RhBMP-2/ACS is a viable ICBG replacement in older patients in terms of safety, clinical efficacy, and cost-effectiveness. The conclusions of this study are limited by small sample size.

Dimar et al. (2009) conducted a multicenter, prospective, randomized study of 463 patients at 29 sites. Patients had symptomatic single-level lumbosacral degenerative disease with no greater than grade-1 spondylolisthesis treated with single-level instrumented posterolateral arthrodesis through an open midline approach. Patients were randomly assigned to receive either the recombinant human bone morphogenetic protein-2 matrix group (239 patients) or the autogenous iliac crest bone-graft group (224 patients). Outcomes were evaluated with the Oswestry Disability Index, Short Form-36, and back and leg pain scores preoperatively and at 1.5, 3, 6, 12, and 24 months postoperatively. Radiographs and computed tomography scans were made at 6, 12, and 24 months postoperatively to evaluate for fusion. Of the 463 patients who had surgery, 410 (194 iliac crest bone graft group and 216 rhBMP-2 matrix group) were available for assessment at 2 years after surgery. Both groups showed similar improvements in clinical outcomes and reduced pain. Radiographic and computed tomography scans showed a greater incidence of fusion in the rhBMP-2 group. Patients requiring a second surgery was higher in the iliac crest bone graft group (36 patients vs. 20) than the rhBMP-2 group. The authors concluded that the use of recombinant human bone morphogenetic protein-2 in instrumented posterolateral lumbar arthrodesis produces earlier and higher fusion rates than does iliac crest bone graft.

Professional Societies

North American Spine Society (NASS)

The NASS (2014) has coverage recommendations for the recombinant human bone morphogenetic protein-2 (rhBMP-2). The Society notes that coverage recommendations do not represent a 'Standard of Care' nor are they intended as a fixed treatment protocol.

Complications of the Use of Bone Morphogenetic Proteins

Although early evidence supports safety and efficacy when used according to FDA indications, adverse events have been reported which include ectopic bone formation, bone resorption or remodeling at the graft site, hematoma, neck swelling, and painful seroma (Dural tears, bowel/bladder and sexual dysfunction, failure to fuse and paralysis have also been reported as well as carcinogenicity and teratogenic effects. Recently there has been concern more specifically safety and efficacy of rhBMP–2 used in spinal fusion surgeries. (Benglis et al. 2008).

The U.S. Food and Drug Administration reported a higher incidence of cancer in patients who had spinal arthrodesis and were exposed to a high dose of recombinant human bone morphogenetic protein-2 (rhBMP-2). The purpose of this study was to determine the risk of cancer after spinal arthrodesis with BMP. Kelly et al. (2014) performed a retrospective analysis of the incidence of cancer in 467,916 Medicare patients undergoing spinal arthrodesis from 2005 to 2010. Patients with a preexisting diagnosis of cancer were excluded. The main outcome measure was the relative risk of developing new malignant lesions after spinal arthrodesis with or without exposure to BMP. The relative risk of developing cancer after BMP exposure was 0.938. In the BMP group, 5.9% of the patients developed an invasive cancer compared with 6.5% of the patients in the control group. The relative risk of developing cancer after BMP exposure was 0.98 in males and 0.93 in females. The control group showed a higher incidence of each type of cancer except pancreatic cancer. The authors concluded that recent clinical use of BMP was not associated with a detectable increase in the risk of cancer within a mean 2.9-year time window.

Cole et al. (2014) performed a retrospective database study from 2006 to 2010. The authors identify 91,543 patients who underwent anterior cervical discectomy and fusion (ACDF) with or without cervical corpectomy. A total of 3197 patients were treated with rhBMP intraoperatively. Mean follow-up was 588 days in the non-treated cohort and 591 days in the rhBMP-treated cohort. Multivariate logistic regression as well as propensity score analysis were used to evaluate the association of rhBMP usage with postoperative complications. Authors reported an overall rate of postoperative complications in patients receiving rhBMP for cervical spinal fusion procedures compared with patients not receiving rhBMP. Hematoma or seroma, pulmonary complications, and dysphagia were also more common in the rhBMP cohort.

In mid-2013 two major meta-analyses were published based on individual subject data supplied by Medtronic, Inc. through Yale University Open Data Access (YODA) Project. This has prompted surgeons to reassess their use of the rhBMP-2 in spine fusion procedures. Two groups were selected by YODA in an open competition to synthesize evidence regarding the safety of rhBMP-2 (Fu, 2013; Simmonds, 2013). The analyses used de-identified data from industry-sponsored RCTs of rhBMP-2 vs. iliac crest bone graft when used during spinal fusion surgery for degenerative disc disease and related conditions. Additional data of similar populations from observational studies were also used for investigation of adverse events.

The meta-analysis conducted by the group led by Simmonds included subject-level data from 11 RCTs, regardless of spinal level or surgical approach. Adverse event data was also collected from an additional 35 observational studies. The authors reported that at 24 months, rhBMP-2 increased the rate of radiographic fusion by 12%, and improved mean scores on the ODI by 3.5%. The improvement in ODI did not reach the previously defined threshold for a clinically significant effect. Subjects who received rhBMP were reported to have a clearly higher incidence of leg and back pain in the immediate postoperative period. This contrasts with the data for 3 months postoperatively, where recipients of rhBMP had less pain than subjects who had allograft treatment. There was an almost 2-fold increased risk of cancer reported in subjects treated with rhBMP-2. However, due to the small number of events recorded, confidence intervals were large and definite conclusions could not be drawn. The overall risk of cancer was low with either rhBMP or autograft procedures. With regard to adverse events analysis from the observational studies, the risk of heterotopic bone formation, leg pain and radiculitis, retrograde ejaculation, and osteolysis were all more frequent in subjects receiving rhBMP during lumbar spinal fusion. Among subjects undergoing cervical spine procedures, dysphagia was more common in rhBMP subjects. The authors note that there was weak correlation between spinal fusion rates and reduction in pain scores.

The meta-analysis by Fu and colleagues included individual subject data from 13 RCTs and 31 cohort studies. They found that rhBMP-2 and iliac bone crest autograft resulted in similar effectiveness outcomes for both lumbar and cervical fusion. An increased risk of cancer was found, but data were not sufficient to determine if risk was related to dose, and increased risk was no longer significant at 48 months. Event rates were low, and the types of cancers recorded were heterogeneous. Pain was more common shortly after surgery with rhBMP-2. The authors concluded that the use of rhBMP provides no additional advantage over autologous bone grafting and may be associated with significant risk of harm. In their analysis on the quality of available data, they reported that there was significant reporting bias in the journal publications and they state, "Early journal publications misrepresented the effectiveness and harms through selective reporting, duplicate publication, and under-reporting."

A report by Glassman and colleagues describes a retrospective case review of 1037 subjects who underwent posterolateral spine fusion using rhBMP-2, with a focus on complication rates (2011). They reported that medical and surgical complications were observed in 190 of 1037 subjects, with 81 major complications and 110 minor complications. New or more severe postoperative radicular symptoms were noted in 7 subjects. Complications directly related to rhBMP-2 were observed in at least 1 and in a worst case analysis, in as many as 6 subjects. The authors concluded that, "there were extremely few complications directly attributed to rhBMP-2/ACS, and the overall complication rates were consistent with established norms."

Chrastil and others (2013) published a systematic review of the spectrum of complications reported in the literature after posterior interbody fusions of the lumbar spine augmented with BMP. Seventeen articles were identified and reviewed that addressed the use and complications of BMP use during PLIF and TLIF procedures. The studies ranged from level I prospective randomized trial to case reports of complications. The authors reported appreciable rates of BMP-specific complications, including heterotopic ossification within the epidural space or neuroforamina, postoperative radiculitis, and endplate osteolysis with interbody device subsidence. They conclude by stating, "High-quality clinical trials should be initiated to develop appropriate paradigms to maximize the safety and efficacy of BMP for posterior interbody fusions."

According to Carragee, et al. (2011), who in a systematic review compared conclusions regarding safety and efficacy published in the original rhBMP–2 industry-sponsored trials when used for spinal fusion to data published following the

FDA approval, the risk of adverse events associated with rhBMP–2 for spinal fusion was found to be "10 to 50 times the original estimates calculated from the industry-sponsored peer-reviewed publications."

Devine et al. (2012) performed a systematic review of the literature of articles published through January 2012. Results: Five published peer-reviewed studies and two FDA safety summaries reported the occurrence of cancer in patients treated with spinal fusion using rhBMP-2 or rhBMP-7. Cancer data for on-label use of rhBMP-2 (Infuse) were reported in the FDA data summary but not in one published pivotal study. The risk of cancer was the same in both the rhBMP-2 and control groups, 0.7% after 24 months. Off-label use of rhBMP for posterolateral fusion (PLF) was associated with a slightly higher risk of cancer compared with controls in three randomized controlled trials and one poorly conducted retrospective cohort study at various follow-ups. Conclusions: Cancer risk with BMP-2 may be dose dependent, illustrating the need to continue to study this technology and obtain longer follow-up on patients currently enrolled in the FDA trials. Additionally, refined guidelines regarding the routine use of BMPs should be developed, taking into account the FDA summary data that is not routinely scrutinized by the practicing surgeon.

A review by Epstein (2011) found that complications associated with the use of bone morphogenetic proteins in spinal surgery include excessive or abnormal placement of bone formation, paralysis (cord, nerve damage), dural tears, bowel bladder and sexual dysfunction, airway related complications such as obstruction, dyspnea, dysphagia and respiratory failure, inflammation of adjacent tissues, fetal developmental complications, scar, and excessive bleeding.

Dmitriev et al. (2011) studied the deleterious effects, at the cellular level, of exogenous high-dose rhBMP-2 on the central and peripheral nervous system. They conclude that although rhBMP-2 and similar growth factors may promote bone induction, the relative benefits of rhBMP-2 fusion rates compared with potential and observed complications have not been well reported or analyzed, particularly in off-label indications. The range of negative or adverse effects with the use of this product has only recently become the subject of systematic research. Although this study was performed in a rodent model, the authors raise some very important questions about the true impact of rhBMP-2 when applied around cells of the nervous system. Finally, although rhBMP-2 has certain specific indications, its dosage, delivery route, and carrier materials, and the mechanism of each contributing to observed complications, warrant significant further evaluation.

Carragee et al. (2011) conducted a retrospective review to evaluate the incidence of retrograde ejaculation in 243 male patients undergoing anterior lumbar interbody fusion (ALIF). Sixty nine patients had ALIF with rhBMP-2 while 174 patients underwent ALIF without BMP. Of the 69 patients in the rhBMP group, 6 developed retrograde ejaculation. At 1 year after surgery, 3 of the 6 affected subjects reported resolution of the retrograde ejaculation.

Original industry-supported studies reported positive outcomes with no unanticipated adverse events for the use of rhBMP-2 as a bone graft substitute. However, complications associated with this product are now being reported. Helgeson et al. (2011) retrospectively reviewed the incidence of osteolysis (the gradual disintegration of bone) following the use of rHBMP2 in posterior and transforaminal lumbar interbody fusions in 23 patients. The rate of osteolysis decreased at 1 year compared with 3 to 6 months, but only 24% of the vertebral bodies with evidence of osteolysis at 3 to 6 months completely resolved by 1 year. The area/rate of osteolysis did not appear to significantly affect the rate of fusion or final outcome with an overall union rate of 83%.

Carragee et al. (2011a) completed a comparative review of FDA documents and subsequent publications for originally unpublished adverse events and internal inconsistencies. From this review, an estimate of adverse events associated with rhBMP-2 use in spine fusion varies from 10% to 50% depending on approach. Anterior cervical fusion with rhBMP-2 has an estimated 40% greater risk of adverse events with rhBMP-2 in the early postoperative period, including life-threatening events. After anterior interbody lumbar fusion rates of implant displacement, subsidence, infection, and retrograde ejaculation were higher after using rhBMP-2 than controls. Posterior lumbar interbody fusion use was associated with radiculitis, ectopic bone formation, osteolysis, and poorer global outcomes. In posterolateral fusions, the risk of adverse effects associated with rhBMP-2 use was equivalent to or greater than that of iliac crest bone graft harvesting, and 15% to 20% of subjects reported early back pain and leg pain; higher doses of rhBMP-2 were also associated with a greater apparent risk of new malignancy. The authors concluded that Level I and Level II evidence from original FDA summaries, original published data, and subsequent studies suggest possible study design bias in the original trials, as well as a clear increased risk of complications and adverse events to patients receiving rhBMP-2 in spinal fusion. This risk of adverse events associated with rhBMP-2 is 10 to 50 times the original estimates reported in the industry-sponsored peer-reviewed publications.

A retrospective review by Yaremchuk et al. (2010) compared the incidence and severity of complications in patients undergoing cervical spinal procedures. A total of 775 patients were included. BMP was utilized in 260 of these patients. The authors found that patients in the BMP group had a higher incidence of acute airway obstruction. This was due to an extensive soft-tissue inflammatory reaction that is most likely to occur 2 to 7 days after surgery.

A systematic review by Mroz et al. (2010) compared rate of complications after the use of BMP in spine fusion surgery. Incidence rate: 44% resorption, 25% subsidence, and 27% interbody cage migration. The authors concluded that "The complication profile of BMP-2 for [anterior lumbar interbody fusion] ALIF with LT-CAGE is well characterized. Because of the lack of substantive data, the same is not true for other types of lumbar fusions, or for cervical or thoracic fusion applications. BMP has been associated with a variety of unique complications in the ventral cervical and lumbar spines. The published data on BMP fail to precisely profile this product's use in fusion surgery; hence, it should be used only after a careful consideration of the relevant data. Well-designed and executed studies are necessary to completely define the incidence of various complications relative to type of BMP, type and region of fusion, surgical technique, dose, and carrier, and importantly, to define the natural history and management of associated complications."

Bone Morphogenetic Protein-7 (BMP-7)

Evidence in the published scientific literature is limited. The studies available include small sample size and short-term follow-up does not lead to formation of evidence-based conclusions regarding safety, efficacy and improved clinical outcomes. Additionally these trials evaluated primary fusion surgery and not revision surgery as mentioned in the HDE approval, and are therefore not in agreement with FDA limitations. Studies evaluating safety and efficacy of on-label use in the peer-reviewed published scientific literature are lacking. Other variables precluding generalizations include inconsistency with regard to instrumentation; some procedures were instrumented while others were not. Additional studies are needed to assess clinical outcomes.

A prospective, randomized, controlled, multicenter clinical study of 36 patients by Delawi et al. (2010) evaluated the use of OP-1 Putty in single level posterolateral lumbar fusion. Patients were equally divided into 2 treatment groups (OP-1 Putty and autologous iliac crest bone graft) and followed for 1 year. Outcomes were measure by computed tomography scans to evaluate presence or absence of fusion, Oswestry Disability Index (ODI) and Visual Analog Scale (VAS). Eight patients were excluded from the final analysis due to protocol violations (n=4) and failure to complete 1 year follow-up (n=2). Fusion rates at 1 year were similar between the 2 groups (OP-1 group = 63%, bone graft group = 67%). There were no significant differences in ODI scores for both groups. Adverse events were experienced by 17 patients. The authors concluded that OP-1 Putty is as effective as iliac crest bone graft in posterolateral fusion while avoiding the morbidity associated with harvesting autogenous bone grafts from the pelvis. The study is limited by small sample size, short term follow-up, and different levels of fusion between the 2 groups.

A multicenter, prospective, 2:1 randomized controlled trial by Vaccaro et al. (2008) compared OP-1 Putty with iliac crest autograft in patients with symptomatic degenerative spondylolisthesis and spinal stenosis treated with decompression without a device for posterolateral arthrodesis. Patients were followed at 6-weeks, and 3, 6, 9, 12, 24-months. Outcomes were measured by Oswestry Low Back Pain Disability (ODI) questionnaire, Visual Analog Scale (VAS), Short-Form 36 (SF-36) outcomes survey and x-ray studies. In addition, serum samples were examined at regular intervals to assess the presence of antibodies to OP-1. At 24-months, patients were recruited to participate in a 36 month assessment. At 36 months, 202 of the original patients (144 OP-1 Putty patients and 58 autograft patients) underwent CT and flexion/extension x-ray studies to assess fusion success. By 36 months, 74.8% of the OP-1 patients and 77.4% of the autograft patients showed presence of new bone. Improvement from baseline in ODI was seen in 74.5% of OP-1 patients and 75.7% of autograft patients at 24 months and 68.6 % of OP-1 patients and 77.3% of autograft patients at 36 months. While neurologic improvements were noted, there was no difference between the groups by 36 months. Both groups reported significant decreases in pain on VAS; however there were no significant differences between the 2 groups in terms of VAS scores. Patients in the OP-1 Putty group showed early formation of anti-OP-1 antibodies, however this completely resolved in all patients by 24 months. The authors concluded that OP-1 Putty is comparable to iliac crest autograft and is an effective alternative for posterolateral spinal arthrodesis performed without a device for degenerative spondylolisthesis and symptomatic spinal stenosis. However, the study did not compare outcomes between the use of a fusion devices and no device.

Professional Societies/Technology Assessments

American Association of Neurological Surgeons and Congress of Neurological Surgeons (2014)
The guideline states that DBM has demonstrated efficacy as a graft extender when combined with local autograft for 1-and 2 –level instrumented posterolateral fusions. (Kaiser et al.)

The **American Academy of Orthopaedic Surgeons** does not have a formal position statement, the Orthopaedic Device Forum initially published a document addressing the use of bone graft substitutes.

The Agency for Healthcare Research and Quality (AHRQ) in 2010 concluded that the evidence supports the use of rhBMP-2 for fusion of the lumbo-sacral spine. However, there is insufficient evidence to make conclusions regarding the use of BMP-7 to aid fusion in the lumbar spine. There is moderate evidence that the use of rhBMP-2 in cervical spine fusion increases cervical swelling and related complications. The strength of the evidence on clinical outcomes is moderate for on-label use of rhBMP-2 to enhance bony fusion in acute open shaft tibial fractures if the device is

applied within 14 days of the initial fracture. BMP-7 may be used as an alternative to autograft in recalcitrant long-bone non-unions where use of an autograft is not feasible and alternative treatments have failed. The strength of the evidence is moderate that rhBMP-2 does not provide an advantage in prosthesis implantation and functional loading compared to autograft plus allograft bone for sinus augmentation.

PEEK (Polyetheretherketone)

Than et al. (2018) performed a retrospective review of 127 cases to compare the rates of pseudarthrosis, a lack of solid bone growth across the disc space, and the need for revision surgery with the use of grafts made of allogenic bone versus PEEK. Radiographic evidence of pseudarthrosis at follow-up was found in 51% patients with PEEK implants compared to 10% of patients with structural allograft. In addition, 7 patients with PEEK implants (24%) required a revision surgery for pseudarthrosis compared to 1 patient (14%) with structural allograft. Limitations of the study include the retrospective design, surgeries performed by multiple surgeons making standardization of findings difficult, and lack of objective clinical data. The results of this study demonstrate that the use of PEEK devices in 1-level ACDF is associated with a significantly higher rate of radiographically demonstrated pseudarthrosis and need for revision surgery compared with the use of allografts. Surgeons should be aware of this when deciding on interbody graft options, and reimbursement policies should reflect these discrepancies.

Kersten et al (2015) stated that polyetheretherketone (PEEK) cages have been widely used during the past decade in patients with degenerative disorders of the cervical spine. Still, limitations are seen such as pseudoarthrosis, subsidence, and migration of the cages. The authors stated that limited evidence on the clinical outcome of PEEK cages is found in the literature other than noncomparative cohort studies with only a few randomized controlled trials. The authors conducted a systematic evidence review to assess the clinical and radiographic outcome of PEEK cages in the treatment of degenerative disc disorders and/or spondylolisthesis in the cervical spine. The systematic review included all randomized controlled trials and prospective and retrospective nonrandomized comparative studies with a minimum follow-up of 6 months and all noncomparative cohort studies with a long-term follow-up of more than 5 years. The primary outcome variable was clinical performance. Secondary outcome variables consisted of radiographic scores. A total of 223 studies were identified, of which 10 studies were included. These comprised two randomized controlled trials, five prospective comparative trials, and three retrospective comparative trials. The authors found minimal evidence for better clinical and radiographic outcome for PEEK cages compared with bone grafts in the cervical spine. No differences were found between PEEK, titanium, and carbon fiber cages. The authors stated that future studies are needed to improve methodology to minimize bias. Publication of lumbar interbody fusion studies needs to be promoted because differences in clinical and/or radiographic scores are more likely to be demonstrated in this part of the spine.

Ceramic Based Products

ECRI (2018) conducted a literature review of synthetic bone graft substitutes versus autograft or allograft for treating lumbar spinal degenerative diseases. The review concluded that calcium phosphate and principal bone salt as well as Beta tricalcium phosphate (β-TCP) were effective in terms of fusion, functional outcomes, and complications for lumbar spinal degenerative disease. This review found the overall quality of the evidence was low with high potential for bias (few RCTs), small sample sizes, and high risk of bias in many studies because of variability in patient characteristics and lack of standardization and variability in reporting of outcomes; also, many studies lacked data on some important outcomes, such as infection. Thus, definitive conclusions or recommendations regarding the use of these synthetic materials should be made cautiously and within the context of the limitations of the evidence. (Buser et al. 2016).

Nickoli et al. (2014) performed a systematic view of thirty studies with 1,332 patients. The overall fusion rate for all ceramic products as a bone graft extender in the lumbar spine was 86.4%. Age, gender, method of evaluation (plain radiographs, computed tomography, or combination), or specific ceramic product did not significantly affect fusion rate. Ceramics used in combination with local autograft resulted in significantly higher fusion rates compared with all other adjuncts, and bone marrow aspirate and platelet concentrates resulted in significantly lower fusion rates. The authors concluded that ceramic-based bone grafts represent a promising bone graft extender in lumbar spine fusion when an osteoinductive stimulus, such as local bone graft is available. Although all studies included patients with a degenerative lumbar pathology, critical exclusion criteria were not standardized. As a result, important patient variability could have influenced fusion rates including cigarette smoking, immunosuppression, and medical comorbidities. Also, given the lack of standardization and variability in reporting, we were unable to obtain information on other important complications such as infection. In addition, radiographic reporting methods varied among studies, which could certainly affect outcomes. Finally, because volume and technique of ceramic use was so inconsistently reported, recommendations could not be drawn from these data.

Cell Based Products

The use of cell based bone graft substitutes has been and continues to be investigated for various procedures, including spinal fusion and for intervertebral disc regeneration. The lack of adequate controls, randomization and

blinding and the small sample sizes precludes definitive conclusions regarding the net health benefit of cell based therapy.

Hayes (2018) conducted cellular bone matrix product review. Current published literature regarding the requested cellular bone matrices was limited. A search of peer-reviewed literature yielded no head-to-head studies comparing these products. There was insufficient evidence to make a recommendation for or against the use of cellular bone matrix products.

Hayes (2018) Hayes conducted concentrated bone marrow aspirate (CBMA) for spinal surgery literature review. Overall, a low-quality body of evidence is available to evaluate the use of CBMA for spinal surgeries. The limited evidence suggests that the balance of benefits and harms of concentrated BMA are at least comparable with those of alternative available graft materials. There is a paucity of long-term safety data from the randomized controlled trials. The overall quality of the evidence was assessed taking into consideration the quality of individual studies; the precision, directness, and consistency of data; and the applicability of the data to general practice.

Several preclinical studies have been conducted to evaluate the effectiveness of Mesenchymal stem cells (MSCs) in tissue regeneration. Caudwell and colleagues (2014) conducted a systematic review of preclinical studies using MSC and scaffolds in the treatment of knee ligament regeneration. The authors concluded, based on their investigation of 21 articles, that preclinical evidence of ligamentous regeneration with MSC and scaffold use was established, but limited clinical evidence exists to support recently developed scaffolds.

Ammerman et al. (2012) conducted a retrospective chart review to identify all patients who had undergone a minimally invasive instrumented transforaminal lumbar interbody fusion (MITLIF) for degenerative lumbar conditions. 23 patients at 26 spinal levels underwent a MILTLIF. Twenty-one patients went on to achieve radiographic evidence of solid bony arthrodesis by 12 months post-op. The authors concluded that Osteocel plus results in robust and reproducible lumbar interbody fusion. The study is limited by retrospective study design. Additional studies, preferably long-term randomized controlled trials, are needed to further validate these results.

Kerr et al. (2011) conducted a retrospective review to analyze the clinical effectiveness of mesenchymal stem cells allograft (Osteocel") to achieve radiological arthrodesis in adult patients undergoing lumbar interbody fusion surgery for different indications. Fifty-two consecutive patients received lumbar interbody fusion at one (69%) or two contiguous (31%) levels of lumbar spine for various indications. Procedures performed were circumferential fusion (67%), ALIF (17%) and TLIF (16%). Follow-up radiographic data was analyzed to establish arthrodesis versus failure (pseudarthrosis), number of months until achievement of fusion, and possible factors affecting the fusion rate. Followup ranged from 8 to 27 (median, 14) months. Solid arthrodesis was achieved in 92.3% of patients at median follow up time of 5 months (95% Cl; range, 3 to 11 months). Kaplan-Meier survival curves and Mantle-Cox test were conducted to assess the effect of various factors on the rate of fusion. Statistics showed that increasing age (older than 50 years) and habitual smoking delayed the fusion time and increased the risk of pseudarthrosis. The use of Osteocel allograft is safe and effective in adult patients undergoing lumbar interbody spinal fusion procedure. Increased age and habitual smoking delays fusion but gender, previous surgery at the index level, type of procedure and number of levels do not affect the fusion rates. The study is limited by retrospective study design. Additional studies, preferably long-term randomized controlled trials, are needed to further validate these results.

Professional Societies

The American Academy of Orthopaedic Surgeons (AAOS,2007) provides information on stem cells: At this point, stem cell procedures in orthopaedics are still at an experimental stage. Most procedures are performed at research centers as part of controlled clinical trials.

Demineralized Bone Matrix (DBM)

ECRI (2017) performed literature review specific to use of demineralized bone matrix for orthopedic and spine procedures. ECRI reported that DBM is a safe and effective bone graft substitute for use in orthopedic and spine procedures.

Professional Societies

American Association of Neurological Surgeons, Congress of Neurological Surgeons

The American Association of Neurological Surgeons, Congress of Neurological Surgeons (2014) recommendations:

- The use of demineralized bone matrix (DBM) as a bone graft extender is an option for 1- and 2-level instrumented posterolateral fusions.
- The use of b-tricalcium phosphate (b-TCP)/local autograft as a substitute for autologous iliac crest bone (AICB) is an option for single-level instrumented posterolateral fusion due to comparable fusion rates and clinical outcomes.
- The use of calcium sulfate preparations mixed with local autograft, as a substitute for autologous iliac crest bone, (AICB), is an option for instrumented posterolateral fusions.

Platelet Rich Plasma (PRP)

Bone Healing and Fusion Enhancement

Evidence in the published scientific literature is inconsistent and does not lend strong support to the clinical utility of using PRP to augment bone grafting and fusion enhancement. There are few randomized controlled trials with comparison groups available to support routine use of PRP.

Hayes (2018) performed literature review specific to the use of platelet-rich plasma (PRP) to treat spinal ligaments or facet joints. Hayes concluded that here is insufficient published evidence to assess the safety and/or impact on health outcomes or patient management of the use of PRP to treat thoracic and lumbar spinal pain.

ECRI (2017) for platelet-rich plasma for orthopedic procedures concluded that many of the systematic reviews reported that the available evidence was of poor quality or limited in number of studies. Hsu et al. (2013) noted the limited clinical evidence for orthopedic applications and recommended better-quality RCTs to determine PRP's actual benefit for the many surgical applications in which it has been used.

Soft Tissue (Tendon, Joint, and Other Soft Tissue Areas of the Body)

There is lack of well-designed studies to support use of PRP in clinical settings in the management of tendon injuries. Overall the authors found a limited amount of basic science research on the influence of PRP on the inflammation and repair of connective tissue. There is a large amount of variability. The lack of standardization makes it difficult to establish an appropriate treatment standard. Additional studies are needed to resolve these issues.

An archived Hayes report(2017) for platelet-rich plasma for ligament and tendon injuries concluded that the research provided mixed and inconclusive evidence regarding the ability of injection of platelet-rich plasma (PRP) to improve outcomes or accelerate healing in patients who have tendon or ligament injuries.

The clinical and tissue effects of the coapplication of platelet rich plasma(PRP) injection with arthroscopic acromioplasty (AA) in patients with chronic rotator cuff tendinopathy was investigated by Carr et al (2015) in a RCT of 60 individuals. The authors reported there was no significant difference in the Oxford Shoulder Score between AA alone and AA + PRP at any time point in the study. The authors noted that PRP significantly alters the tissue characteristics in tendons after surgery with reduced cellularity and vascularity and increased levels of apoptosis and the coapplication of PRP may have potential deleterious effects on healing tendons.

Balasubramaniam et al (2015) systematically reviewed the literature regarding PRP therapy in chronic tendinopathy. A total of 389 articles were reviewed from Feb 2010 to April 2014, for possible inclusion. Of these articles, a total of 9 randomized controlled trials (RCTs) met the inclusion criteria. Each article was reviewed independently by 2 authors. Each article was analyzed using the Cochrane Criteria checklist. Where any discrepancy occurred in results, a 3rd independent reviewer was consulted. The review found that PRP was most effective in patellar and lateral epicondylar tendinopathy, with both RCTs in the patellar section of the study supporting the use of PRP in pain reduction at 3 and 12 months, whereas 2 of 4 studies in the lateral epicondylar section showed improvements in pain and disability at 6 and 12 months. There was a lack of evidence to support the use of PRP in Achilles and rotator cuff tendinopathy. The authors concluded that although the results of this review showed promise for the use of PRP in chronic tendinopathy, the analysis highlighted the need for more controlled clinical trials comparing PRP with placebo.

Mishra et al. (2014) conducted a randomized controlled trial of 230 patients with chronic lateral epicondylar tendinopathy who were treated at 12 centers over 5 years. All patients had at least 3 months of symptoms and had failed conventional therapy. No significant differences were noted between groups at 12 weeks (n=192, 83.5%). At 24 weeks (n=119, 51.8%), the PRP-treated subjects reported an improvement of 71.5% in their pain scores compared with 56.1% in the control group). Additionally, 29.1% of the PRP-treated group reported significant elbow tenderness versus 54.0% in the control group. Success rates for the subjects completing the 24 week follow-up period were 83.9% in the PRP group vs. 68.3% in the control group. No significant complications occurred in either group. The authors concluded that at 24 weeks clinically meaningful improvements were found in subjects treated with leukocyte-enriched PRP compared with an active control group. However, these results must be viewed with care, since the loss to follow-up was so large at 24 weeks (48.2%).

A systematic review published in 2014 by de Vos and Weir evaluated the available literature on PRP treatment for epicondylar tendinopathy. The authors included six studies that met inclusion criteria, of which four were considered to be of high-quality. Of these studies, three high-quality and two low-quality studies showed no significant benefit at the final follow-up measurement or in predefined primary outcome score when compared with a control group. Only one high-quality study showed a beneficial effect of a PRP injection when compared with a corticosteroid injection (corticosteroid injections are harmful in tendinopathy). The conclusion of this analysis was that there is strong evidence that PRP injections are not efficacious in chronic LE.

A review by Jiang and Wang (2013) assessed the use of PRP for the treatment of tendinopathy. They discuss the positive rationales for using PRP, but note "the efficacy of PRP treatment in enhancing the recovery of tendinopathic tendons has not been conclusively or consistently demonstrated in clinical trials." The authors call for more studies to investigate and better define the precise effects of PRP treatment.

In a RCT, Peerbooms and associates (2010) examined the effectiveness of PRP compared with corticosteroid injections in patients with chronic lateral epicondylitis. A total of 100 patients with chronic lateral epicondylitis were randomly assigned in the PRP group (n = 51) or the corticosteroid group (n = 49). A central computer system carried out randomization and allocation to the trial group. Patients were randomized to receive either a corticosteroid injection or an autologous platelet concentrate injection through a peppering technique. The primary analysis included VAS and DASH Outcome Measure scores (DASH: Disabilities of the Arm, Shoulder, and Hand). Successful treatment was defined as more than a 25 % reduction in VAS or DASH score without a re-intervention after 1 year. The results showed that, according to the VAS, 24 of the 49 patients (49 %) in the corticosteroid group and 37 of the 51 patients (73 %) in the PRP group were successful, which was significantly different. Furthermore, according to the DASH scores, 25 of the 49 patients (51 %) in the corticosteroid group and 37 of the 51 patients (73 %) in the PRP group were successful, which was also significantly different. The corticosteroid group was better initially and then declined, whereas the PRP group progressively improved. The authors concluded that treatment of patients with chronic lateral epicondylitis with PRP reduces pain and significantly increases function, exceeding the effect of corticosteroid injection. They stated that future decisions for application of the PRP for lateral epicondylitis should be confirmed by further follow-up from this trial and should take into account possible costs and harms as well as benefits.

A systematic review by Rabago et al. (2009) reviewed existing evidence for prolotherapy, polidocanol, autologous whole blood, and platelet-rich plasma (PRP) injection therapies for lateral epicondylosis (LE) and found 5 prospective case series and 4 controlled trials (3 prolotherapy, 2 polidocanol, 3 autologous whole blood and 1 PRP) which suggested each of the 4 therapies is effective for LE. The authors concluded that there is strong pilot-level evidence supporting the use of prolotherapy, polidocanol, autologous whole blood, and PRP injections in the treatment of LE. However, rigorous studies of sufficient sample size, assessing these injection therapies using validated clinical, radiological and biomechanical measures, and tissue injury/healing-responsive biomarkers, are needed to determine long-term safety and effectiveness, and whether these techniques can play a definitive role in the management of LE and other tendinopathies.

de Vos et al. (2010) conducted a randomized controlled trial of 54 patients with chronic achilles tendinopathy. Patients were equally divided to receive either an injection of platelet rich plasma or saline. All patients completed a questionnaire consisting of standardized outcome measures for pain and activity levels at 6, 12, and 24 weeks. Upon completion of the study, there were no significant differences in the pain or activity levels between the two groups.

Professional Societies/Guidance Recommendations/ *Technology Assessments*

A formal position statement supporting platelet rich plasma for enhancement of bone healing from the American Academy of Orthopaedics (AAOS) could not be found. The AAOS does provide general information regarding PRP and suggests that further studies are needed to define the role of PRP and to determine for which settings PRP may be valuable. There is a lack of compelling evidence and the balance of clinical benefit and harm has not been established.

Guidance from the **National Institute for Health and Clinical Excellence (NICE)** on PRP for tendinopathy (Jan 2013) reported, "The evidence on autologous blood injection for tendinopathy raises no major safety concerns. The evidence on efficacy remains inadequate, with few studies available that use appropriate comparators. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research." NICE encourages further research comparing autologous blood injections (with or without techniques to produce platelet-rich plasma) against established non-surgical methods for managing tendinopathy. Trials should clearly describe patient selection (including the site of tendinopathy, duration of symptoms and any prior treatments) and document whether a 'dry needling' technique is used. Outcomes should include specific measures of pain, quality of life and function, and whether subsequent surgical intervention is needed.

In 2016 the Washington State Health Care Authority (WSHCA) conducted a technology assessment to evaluate the safety and efficacy of the use of PRP and/or autologous blood injection (ABI), for the treatment of various musculoskeletal and orthopedic conditions. As part of the technology assessment a total of 54 randomized controlled trials and eight cohort studies were included and reviewed. Limitations of the studies noted by the Committee generally included small sample populations, short-term follow-up, inconsistency of measured outcomes, potential for risk bias, and lack of high quality evidence. The authors concluded there was insufficient evidence to draw strong conclusions regarding safety and efficacy. Moreover, the Committee reported despite its current use, standardization of PRP preparation is lacking, and although the technology to obtain PRP is FDA-approved, PRP is currently not indicated for direct injection (WSHCA, 2016).

Zheng et al. (2010) evaluated the biomechanics of lumbar motion segments instrumented with stand-alone OptiMesh system augmented with posterior fixation using facet or pedicle screws and the efficacy of discectomy and disc distraction. The filled mesh bag serves as the interbody device providing structural support to the motion segment being fused. Twenty-four fresh human cadaveric lumbar motion segments were divided into two groups. In the control group, multidirectional flexibility testing was conducted after an intact condition and standard transforaminal lumbar interbody fusion (TLIF) procedure. In the OptiMesh group, testing was performed following intact, stand-alone OptiMesh procedure, OptiMesh with facet screws (placed using the transfacet approach), and OptiMesh with pedicle screws and rods. Range of motion (ROM) was calculated for each surgical treatment. The lordosis and disc height change of intact and instrumented specimens were measured in the lateral radiographs to evaluate the disc space distraction. The OptiMesh system offers large volume of bone graft in the disc space with small access portals. The OptiMesh system had similar construct stability to that of standard TLIF procedure when posterior fixation was applied. However, the amount of distraction was limited without additional distraction tools. With the anterior support provided by the expandable meshed bag, facet screws had comparable construct stability to that of pedicle screws.

Amniotic Tissue Membrane

A search of the peer-reviewed medical literature databases of amniotic tissues in orthopedic applications show a need for future research. There is limited evidence that amniotic tissue membrane improves health outcomes when used in lumbar spine fusion. Long term safety and efficacy have not been established. The function, structure, and characteristics of human amnion have been widely studied; however, there are very little research data to support the benefits of these tissues for orthopedic problems. (Hayes, 2017)

No professional guidelines offered recommendations regarding the use of amniotic-derived tissues for the treatment of orthopedic conditions.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Allografts are considered tissues for transplantation. FDA: "Minimally manipulated human bone for transplantation: Human cells or tissue intended for implantation, transplantation, infusion, or transfer into a human recipient is regulated as a human cell, tissue, and cellular and tissue-based product or HCT/P." If combined with other materials, the resulting product is considered a device and regulated by the FDA as a medical device.

Products used for bone growth and bone grafts products are extensive. See the following website for more information and search by product name in device name section:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm (Accessed January 15, 2019)

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GUIDELINE HISTORY/REVISION INFORMATION

Date	Action/Description

04/01/2019	• Updated list of related policies; added reference link to the policy titled *Platelet Derived Growth Factors for Treatment of Wounds*
	• Updated coverage rationale; replaced reference to "patients" with "individuals"
	• Updated definitions:
	  ○ Added definition of:
	  ▪ RhBMP–7/ OP–1™ Putty
	  ▪ Concentrated Bone Marrow Aspirate (CBMA)
	  ▪ Orthobiologics
	  ○ Modified definition of:
	  ▪ Amniotic Tissue Membrane
	  ▪ Bone Morphogenetic Proteins (BMP) and Recombinant Human Bone Morphogenetic Proteins (rhBMP)
	  ▪ Carrier Systems
	  ▪ Cell-Based Products
	  ▪ Ceramic-Based Products
	  ▪ Infuse™ Bone Graft
	  ▪ OptiMesh Grafting System®
	  ▪ Platelet-Rich Plasma
	• Updated supporting information to reflect the most current description of services, clinical evidence, and references
	• Archived previous policy version MMG009.J

INSTRUCTIONS FOR USE

This Medical Management Guideline provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard benefit plan. In the event of a conflict, the member specific benefit plan document governs. Before using this guideline, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as

necessary. This Medical Management Guideline is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare West Medical Management Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Member benefit coverage and limitations may vary based on the member's benefit plan Health Plan coverage provided by or through UnitedHealthcare of California, UnitedHealthcare Benefits Plan of California, UnitedHealthcare of Oklahoma, Inc., UnitedHealthcare of Oregon, Inc., UnitedHealthcare Benefits of Texas, Inc., or UnitedHealthcare of Washington, Inc.