Spinal Fusion and Bone Healing Enhancement Products

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Instructions for Use

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Application

This Medical Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

State	Policy/Guideline
Idaho	Spinal Fusion and Bone Healing Enhancement Products (for Idaho Only)
Indiana	None
Kansas	Spinal Fusion and Bone Healing Enhancement Products (for Kansas Only)
Kentucky	Spinal Fusion and Bone Healing Enhancement Products (for Kentucky Only)
Nebraska	Spinal Fusion and Bone Healing Enhancement Products (for Nebraska Only)
New Jersey	Spinal Fusion and Bone Healing Enhancement Products (for New Jersey Only)
New Mexico	Spinal Fusion and Bone Healing Enhancement Products (for New Mexico Only)
North Carolina	Spinal Fusion and Bone Healing Enhancement Products (for North Carolina Only)
Ohio	Spinal Fusion and Bone Healing Enhancement Products (for Ohio Only)
Pennsylvania	Spinal Fusion and Bone Healing Enhancement Products (for Pennsylvania Only)
Tennessee	Spinal Fusion and Bone Healing Enhancement Products (for Tennessee Only)

Coverage Rationale

The following are proven and medically necessary for the enhancement of spinal fusion:

- Autografts [including Bone Marrow Aspirate (BMA) used for bone grafting]
- Demineralized Bone Matrix (DBM) without added products listed below as unproven and not medically necessary
- Allograft-based products not listed below as unproven and not medically necessary
- InFUSE® Bone Graft [recombinant human bone morphogenetic protein-2 (rhBMP-2)] of the lumbar spine when the following criteria are met:
  - The approach is anterior or oblique and used in conjunction with an FDA-approved interbody fusion device
  - Skeletally mature individual (18 years of age or older or radiographic evidence of epiphyseal closure) with degenerative disc disease (DDD)

    - The fusion involves vertebral bodies L2-S1, without or with spondylolisthesis of no more than grade 1 (25% displacement) at the involved level
    - The fusion is single level
- The InFUSE/MASTERGRAFT™ Posterolateral Revision Device System (or InFUSE BMP used with MASTERGRAFT) when used according to U.S. Food and Drug Administration (FDA) indications, contraindications, warnings, and precautions in individuals who meet all of the following criteria:
    - Implanted via a posterolateral approach; and
    - Presence of symptomatic posterolateral lumbar spine pseudoarthrosis; and
    - Skeletally mature patient (older than 21 years of age or radiographic evidence of epiphyseal closure); and
    - Autologous bone and/or bone marrow harvest is not feasible or is not expected to promote fusion

The following are unproven and not medically necessary for the enhancement of spinal fusion and bone healing due to insufficient evidence of efficacy and/or safety:

- Allograft-based products:
    - Cell-based [e.g., mesenchymal stem cells (MSC)]
    - Human amniotic tissue materials, including amniotic fluid stem cell substitutes
    - Recombinant human bone morphogenetic protein-2 (e.g., rhBMP-2, InFUSE) and InFUSE/MASTERGRAFT™ (or InFUSE BMP used with MASTERGRAFT or MASTERGRAFT alone) Posterolateral Revision Device for all other indications not included above
    - Ceramic-Based Products [e.g., beta tricalcium phosphate (b-TCP), calcium phosphate, calcium sulfate] used alone or in combination with other grafts and/or graft components including Bone Marrow Aspirate (BMA)
- Bioactive Glass used alone or in combination with other grafts including Bone Marrow Aspirate (BMA)
- Expandable Interbody Fusion System

Medical Records Documentation Used for Reviews

Benefit coverage for health services is determined by federal, state, or contractual requirements, and applicable laws that may require coverage for a specific service. Medical records documentation may be required to assess whether the member meets the clinical criteria for coverage but does not guarantee coverage of the service requested; refer to the guidelines titled Medical Records Documentation Used for Reviews.

Definitions

Allograft: The transplant of an organ or tissue from one individual to another of the same species with a different genotype. Also known as an allogeneic graft or a homograft (MedicineNet, 2022).

Autograft: Tissue grafted into a new position in the body of the same individual (Elsevier, 2022).

Bioactive Glass: Silicate glass-based materials with osteoconductive and osteoinductive properties (Gomez, 2021).

Bone Marrow Aspiration: Bone marrow is the soft tissue inside bones that helps form blood cells. It is found in the hollow part of most bones. Bone Marrow Aspiration is the removal of a small amount of this tissue in liquid form for examination (A.D.A.M., 2024).

Bone Morphogenetic Proteins (BMP) and Recombinant Human Bone Morphogenetic Proteins (rhBMP): Naturally occurring osteoinductive proteins that initiate a cascade resulting in the differentiation of local host MSCs into osteoblasts. Recombinant DNA technology allows the production of large and highly purified quantities of BMP (Pinter, 2022).

Ceramic-Based Products: Mineral salts produced at high temperatures to create various structures with osteoconductive properties. Ceramic-based bone graft substitutes include hydroxyapatite, calcium phosphate, tricalcium phosphate, calcium sulfate, and Bioactive Glass (ECRI, 2022).

Demineralized Bone Matrix (DBM): DBM is a type of Allograft; it is produced by dissolving the mineralized portion of bone and leaving behind only the collagen matrix and growth factors. The collagen matrix provides weak osteoconductive capacity, while the retained growth factors are osteoinductive. DBM must be combined with a carrier that serves as a more potent osteoconductive scaffold (Pinter, 2022).

Duo™ Ti Expandable Interbody Fusion System: An implant that is designed to provide mechanical support of the intradiscal space as an adjunct to fusion. The implant is designed with a porous central cavity for graft containment, a rounded nose to aid in implant insertion, and rigid teeth to resist migration (FDA, 2021).

Human Amniotic Tissue Membrane: A multilayer tissue forming the innermost layer of the amniotic sac that surrounds the developing fetus. It is comprised of 5 layers, from the inside out: a single layer of epithelial cells, a thick basement membrane, a compact layer, a fibroblast layer, and a spongy layer that abuts the surrounding chorion (Heckman, 2016).

InFUSE™ Bone Graft: A bone graft that helps stimulate natural bone formation and remodeling and avoids the need for harvesting bone from other parts of a patient's body. Infuse contains rhBMP-2 and is approved for use in certain spine, dental, and trauma indications (Medtronic, 2018).

OptiMesh® Expandable Interbody Fusion System: A device that is intended to maintain the relative position of bone graft material within a vertebral body defect (FDA). The implant expands in three dimensions when filled to create an anatomy-conforming interbody fusion implant (Spineology, 2021).

Osseointegration: Is the stable anchorage of an implant achieved by direct bone to implant contact (Albrektsson, 2001).

Osteoconduction: Bone grows on the surface. This phenomenon is regularly seen in the case of bone implants (Albrektsson, 2001).

Osteoinduction: The process by which osteogenesis is induced. The recruitment of immature cells and the stimulation of these cells to develop into pre-osteoblasts. In bone healing such as a fracture, the majority of bone healing is dependent on Osteoinduction (Albrektsson, 2001).

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 policy 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 federal, state, or contractual requirements 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
0814T	Percutaneous injection of calcium-based biodegradable osteoconductive material, proximal femur, including imaging guidance, unilateral
20930	Allograft, morselized, or placement of osteopromotive material, for spine surgery only (List separately in addition to code for primary procedure)
20931	Allograft, structural, for spine surgery only (List separately in addition to code for primary procedure)
20939	Bone marrow aspiration for bone grafting, spine surgery only, through separate skin or fascial incision (List separately in addition to code for primary procedure)
22899	Unlisted procedure, spine

Description of Services

Autologous iliac bone grafting has long been the gold standard for bone grafting in spinal fusion due to its osteoconductive, osteoinductive, and osteogenic abilities, however, it is associated with donor site morbidity. Biological products such as Bone Marrow Aspirate (BMA), recombinant human bone morphogenetic protein-2 (rhBMP-2), and Demineralized Bone Matrix (DBM) may improve spinal fusion success rates and enhance bone healing. Some biological products such as human amniotic membrane derivatives, and cell-based products, as well as synthetics such as Ceramic-Based Products and Bioactive Glass, are being investigated for their ability to improve outcomes.

Clinical Evidence

Allograft-Based Products

Cell-Based Products

There is insufficient evidence in published clinical literature to determine the safety and efficacy of cell-based allograft products. Cell-based products contain native bone cells such as MSC, osteoblasts, or pre-osteoblasts, and are often combined with cancellous allograft chips and/or DBM. The use of cell-based bone graft substitutes continues to be investigated for various procedures, including spinal fusion and intervertebral disc regeneration. The literature for cell-based products contains limited cohort trials, with minimal time for follow-up. Studies were biased due to the manufacturer sponsoring the trials and there were limitations in outcomes studied. Large prospective clinical trials are needed to substantiate the findings.

Calodney et al. (2024) conducted a multi-center, prospective, single arm study to evaluate the safety and efficacy of utilizing a minimally invasive sacroiliac posterior fusion allograft implant (LinQ Fusion DBM Implant); (PainTEQ, Tampa, FL) for management of chronic, low back pain associated with sacroiliac disease. One-hundred and fifty-nine (159) participants were enrolled across 16 investigational sites in the U.S. between January 2020 and March 2022. One hundred and twenty-two (122) participants were implanted. At the 1-month follow-up, 82 participants satisfied all criteria for the composite responder endpoint, representing 73.2% of the study cohort. These results stayed consistent across the remaining study timepoints with 66.0%, 74.4%, and 73.5% of participants classified as responders at the 3-, 6- and 12-month follow-up visits, respectively. VAS scores were significantly reduced ($p < 0.0001$) and ODI scores were significantly improved ($p < 0.0001$). All domains of the PROMIS 29 were also improved (all $p < 0.0001$). Only one procedure-related serious AE was reported in the study. The authors concluded that these results suggest that the posterior approach LinQ Implant System is a safe and effective treatment for sacroiliac joint dysfunction at 12 months, with results that are favorable compared to outcomes reported for an FDA-cleared lateral approach. The lack of a control group and the partial cohort in this analysis are limitations to the generalizability of these results. In addition, features of the therapy prohibit blinding, so a traditional randomized-controlled trial was not possible. Twenty-four implanted participants were lost to follow-up within the course of this study. Patient outreach and in-person follow-up were very likely impacted by the COVID pandemic, beginning in March of 2020, with limitations on patient retention due to mandatory lockdown across all study sites. The study limitations include possible conflict of interest related to funding by the manufacturer, PainTEQ, and several investigators who conducted the study either serve on the advisory board, or as consultants, for PainTEQ. Further research with RCTs is needed to validate these findings.

Jain et al. (2024) performed a systematic review evaluating postoperative fusion rates for anterior cervical discectomy and fusion (ACDF) using structural allograft vs various interbody devices augmented with different osteobiologic materials. Included studies were those that reported results of 1-4 levels ACDF using pure structural allograft compared with a mechanical interbody device augmented with an osteobiologic. Excluded studies were those that reported on ACDF with cervical corpectomy; anterior and posterior cervical fusions; circumferential (360° or 540°) fusion or revision ACDF for nonunion or other conditions.. Eight articles reporting fusion rates of structural allograft and an interbody device/osteobiologic pair were included. All included studies compared fusion rates following ACDF among structural allograft vs. non-allograft interbody device/osteobiologic pairs. Fusion rates were reported between 84% and 100% for structural allograft, while fusion rates for various interbody device/osteobiologic combinations ranged from 26% to 100%. Among non-allograft cage groups, fusion rates varied from 73-100%. One study found polyetheretherketone (PEEK) cages filled with combinations of autograft, allograft, and DBM to have an overall fusion rate of 26%. In one study comparing plate and zero-profile constructs, there was no difference in fusion rates for two-level fusions. The authors concluded there was limited data comparing fusion outcomes of patients undergoing ACDF using structural allograft vs. interbody devices augmented with osteobiologic materials to support superiority of one method. This systematic review has several limitations. Risk of bias was determined using the Cochrane review guidelines. A meta-analysis was not performed due to heterogeneity in the reviewed studies, especially in the definition of fusion. While this systematic review was comprehensive and performed in alignment with PRISMA guidelines, the lack of any level I randomized studies on this topic limits quantitative conclusions from being drawn when comparing fusion rates among allograft vs the various comparison groups. There are many important clinical outcomes aside from fusion rate. The authors chose not to examine these as part of this systematic review given that clinical outcomes reporting is likely to be even more varied than fusion rate which can be more objectively and reproducibly assessed. Prospective, randomized studies are necessary to study this topic further as none were identified in the literature.

An ECRI Clinical Evidence Assessment (2022) was performed to determine the safety and efficacy of cellular bone allograft (CBA) for cervical spine fusion compared with those of iliac crest bone graft (ICBG) and other alternative bone graft materials. ICBG is the gold standard for spinal fusion because it has osteogenic properties (provides osteoblast precursor cells) as well as being osteoconductive and osteo-inductive. CBA may be a viable bone graft substitute that

stimulates new bone growth similar to autograft bone but avoids ICBG-related morbidities. Per The Evidence Bar™ conclusions, evidence is inconclusive and very low quality. Per ECRI, one systematic review (SR), one non-randomized comparison study, and one case series provide very-low-quality evidence and do not enable conclusions about CBA's comparative effectiveness and safety for cervical spinal fusion. Well-designed and -conducted randomized controlled trials (RCTs) comparing CBA with ICBG and other bone substitute materials are needed to determine how well CBA works compared with alternative methods to increase fusion rates, pain relief, and function.

An ECRI Clinical Evidence Assessment (2022) was performed to determine the safety and efficacy of cellular bone allograft (CBA) for lumbar spinal fusion compared with those of iliac crest bone graft (ICBG) and other alternative bone graft materials. ICBG is the gold standard for spinal fusion because it has osteogenic properties (provides osteoblast precursor cells) as well as being osteoconductive and osteo-inductive. CBA is derived from donated human bones and processed to preserve bone-forming cells. Per The Evidence Bar™ conclusions, evidence is inconclusive and very low quality. Per ECRI, available evidence suggests CBAs are safe and may aid lumbar fusion, but whether CBAs are as effective as ICBG or other bone graft materials cannot be determined because available studies provide very-low-quality evidence and assess too few patients treated with CBAs. The evidence base is limited primarily to case series at high risk of bias due to small sample size, retrospective design, single center focus, and lack of randomization, blinding, and control groups. Function and pain outcomes are not reported as often as fusion rates. These limitations do not permit firm conclusions about CBA's efficacy for lumbar fusion surgery. Additional research, preferably using well-designed and -conducted randomized controlled trials (RCTs) comparing CBAs with ICBG, is needed to determine CBA efficacy for lumbar fusion.

An ECRI Clinical Evidence Assessment (2022) was performed to determine the safety and efficacy of Trinity Elite, a cryopreserved, living-cell allograft used during lumbar fusion procedures. The authors reviewed full text of one non-randomized comparative study and one case series reporting on 164 patients. Per The Evidence Bar™ conclusions, evidence is very low quality. Evidence from one nonrandomized comparative study and one before-and-after study is too limited in quantity and quality to permit conclusions on Trinity Elite's safety and effectiveness as an allograft for lumbar fusion procedures. Studies are at high risk of bias due to three or more of the following: small size, lack of randomization and blinding, retrospective design, and lack of control groups. Studies varied in the approach to lumbar fusion, which may influence result generalization. Studies also used Trinity Elite as the primary graft, but adjunct graft substances used may have confounded results. Large multicenter randomized controlled trials (RCTs) that compare Trinity Elite to other allografts and bone graft substitutes for patients undergoing the same approach of lumbar fusion are needed to validate current findings on effectiveness and safety.

A 2022 ECRI clinical evidence assessment entitled OsteoAMP Bone Graft (Bioventus, LLC.) for Cervical Spinal Surgery, reported on the safety and effectiveness of OsteoAMP and how it compares with other bone graft substitutes for cervical spine surgery. OsteoAMP is an allogeneic bone graft substitute processed from human cadaver bone and undergoes proprietary processing techniques to preserve BMPs and other growth factors. Two case series totaling 259 patients, had a high risk of bias due to retrospective design and lack of controls and randomization. Neither reported on patient-oriented outcomes, and only one reported on adverse events (AEs). No comparative data was available to assess how well OsteoAMP works compared with other bone graft substitute options. Large prospective studies comparing OsteoAMP with bone autograft and with autograft alternatives are needed.

Hayes (2020, updated in 2023) conducted a health technology assessment on the use of concentrated bone marrow aspirate (CBMA) for spinal surgery. Ten studies addressed lumbar spinal fusion, and two addressed cervical spinal fusion. Overall, a low-quality body of evidence is available to evaluate the use of CBMA for spinal surgeries, and substantial uncertainty exists regarding the benefits of CBMA as an adjunct for spinal fusion. There is a lack of consensus on the optimal enrichment technique, delivery method and the CBMA preparations, and additional well-designed studies are needed to establish whether use of CBMA is associated with inferior fusion success compared with other approaches for lumbar spinal fusion.

Hsieh et al. (2019 - included in ECRI clinical evidence assessment below) conducted a systematic comparative review of the evidence regarding the use of allogenic stem cell products for spine fusion when compared with other bone graft materials in patients with degenerative disease of the cervical or thoracolumbar spine. Eleven studies met the inclusion criteria, the majority were retrospective case series and only 2 retrospective cohort studies were identified, one on lumbar fusion and one on cervical fusion. Both were considered a moderately high risk of bias. No evidence on the impact of patient or intervention characteristics on effectiveness or safety was available for any of the studies included. Across case series, allogenic stem cell products appeared to be associated with improved pain and function, however in the absence of methodologically sound comparative studies, conclusions regarding effectiveness or safety cannot be drawn. While the use is promising, there is a lack of high-quality studies and further research is needed.

A 2019 ECRI clinical evidence assessment, updated in 2022, entitled Bio4 Viable Bone Matrix (Osiris Therapeutics, Inc.) for Lumbar Fusion Procedures identified no published studies that examined the safety and efficacy of Bio4, or how it compares to similar products. Bio4 is derived from donated human bone and is minimally processed to preserve bone-forming cells.

A 2019 ECRI clinical evidence assessment, updated in 2022, entitled PrimaGen Advanced Allograft (Zimmer Biomet) for Lumbar Fusion Procedures identified no published studies that examined the safety and efficacy of the PrimaGen Advanced Allograft, or how it compares to similar products. PrimaGen is derived from donated human bone and is minimally processed to preserve bone-forming cells.

A 2016 ECRI clinical evidence assessment, updated in 2022, entitled OsteoAMP Bone Graft (Bioventus, LLC.) for Lumbar Spine Surgery reported on the safety and effectiveness of OsteoAMP, and how it compares with other bone graft substitutes for lumbar spine surgery. Four studies were identified that provided data, but none compared OsteoAMP to bone autograft, or other substitutes other than one that compared it to the Infuse® Bone Graft. It was concluded that the evidence is too limited in quality and quantity to determine if OsteoAMP works as well as, or better than other bone graft substitutes, and large prospective studies are needed.

Kerr et al. (2011) conducted a retrospective review to analyze the clinical effectiveness of mesenchymal stem cells allograft (Osteocel, NuVasive, Inc.) 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. Follow up 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% CI; 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.

Human Amniotic Tissue

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 in human models that amniotic tissue membrane improves health outcomes when used in lumbar spine fusion. Long term safety and efficacy have not been established.

Recombinant Bone Morphogenetic Protein (rhBMP or BMP)

Recombinant bone morphogenetic protein (rhBMP or BMP) showed trials with limited methodologies yielding conflicting results, and a lack of higher quality evidence showing a beneficial impact on outcomes in patients using osteobiologics. Moreover, short term follow-up and small sample size made it difficult to extrapolate the finding to the general population.

Fitzgerald et al. (2025) conducted a systematic review to validate and consolidate the existing evidence base supporting bone graft materials related to lumbar interbody fusion procedures for degenerative disc disease (DDD), specifically anterior lumbar interbody fusion (ALIF) and oblique lumbar interbody fusion (OLIF). Clinical and economic studies of adults with DDD in regions L2 to S1 undergoing lumbar interbody fusion with Infuse™, allograft, synthetic bone grafts, DBMs or cell-based matrices were eligible for inclusion. Twenty-one studies (reported in 25 publications) were included in the review. Eighteen studies (reported in 22 publications) reported clinical outcomes, while four studies reported economic outcomes. Nine studies (in five publications) investigated Infuse™, including three randomized controlled trials (RCTs), one cohort study and four case series. Ten studies investigated allograft bone, bone harvested from the vertebral spur combined with apacerum powder, or tricalcium phosphate soaked in autologous BMA, including one RCT, two cohort studies, and seven case series. The authors concluded the systematic review shows that Infuse™ offers comparable results to iliac crest bone graft with the benefit of not requiring harvested bone and offers significant benefits in surgical time and blood loss. This systematic review has limitations. The scope and depth of the systematic review were constrained by the limited number and methodological shortcomings of existing studies, especially for those bone grafts that were only supported by single arm evidence. Despite exhaustive searches across multiple databases and reference lists, the review only revealed A1 evidence supporting the use of Infuse™ in adults with DDD in regions L2 to S1 undergoing lumbar interbody fusion. An overall lack of high-quality, comparative trials means that the superiority of any single bone graft product over another cannot be concluded. Variability in study design, patient characteristics,

interventions, and outcomes further complicated the interpretation and application of the findings. Due to the lack of comparative evidence for any other bone grafts identified in this systematic review, there remains a need for further well-designed studies to be conducted in this area.

Biddau et al. (2024) conducted a systematic review to examine recent studies on fusion rates and postoperative complications associated with bone graft substitutes used in anterior lumbar interbody fusion (ALIF). The authors conducted a systematic review of the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, MEDLINE, and PubMed databases, to critically examine a decade of research on the effectiveness and safety of various bone graft substitutes in ALIF. This timeframe was chosen to build on a previous systematic review published in 2013. The PRISMA guidelines were used. In total, 27 articles met inclusion and exclusion criteria. A substantial portion of these studies (67%) focused rhBMP-2 and highlighted its efficacy for achieving high fusion rates. However, the literature presents a dichotomy regarding the association of rhBMP-2 with increased postoperative complications. Notably, the methodologies for evaluating spinal fusion varied across studies. Only one-third of studies employed computed tomography to assess interbody fusion at 12 months postoperatively, highlighting the urgent need to establish uniform fusion criteria to facilitate more accurate comparative analyses. Moreover, there was considerable variability in the criteria used for diagnosing and detecting postoperative complications, significantly influencing the reported incidence rates. The authors concluded that this review underscores the need for continued research into bone graft substitutes, particularly focusing on assessment of long-term complications. Future research endeavors should concentrate on developing comprehensive clinical guidelines to aid in the selection of the most suitable bone graft substitutes for use in ALIF, thereby enhancing patient outcomes and surgical efficacy.

Chung et al. (2024) conducted a systematic review to determine how osteobiologic choice affects fusion rates in patients undergoing anterior cervical discectomy and fusion (ACDF). The study's secondary objectives were to 1) determine the optimal timing of fusion assessment following ACDF and 2) determine if osteobiologic type affects the timing and optimal modality of fusion assessment. A systematic search of PubMed/MEDLINE was conducted for literature published from 2000 through October 2020 comparing anterior fusion in the cervical spine with various osteobiologics. Both comparative studies and case series of ≥ 10 patients were included. A total of 74 studies met the inclusion criteria. Seventeen studies evaluated the efficacy of autograft on fusion outcomes, and 23 studies assessed the efficacy of allograft on fusion outcomes. Three studies evaluated the efficacy of DBM, and seven assessed the efficacy of rhBMP-2 on fusion outcomes. Other limited studies evaluated the efficacy of ceramics and bioactive glasses on fusion outcomes, and four assessed the efficacy of stem cell products. Most studies utilized dynamic radiographs for the assessment of fusion. Overall, there was a general lack of supportive data to determine the optimal timing of fusion assessment meaningfully or if osteobiologic type influenced fusion timing. The authors concluded that achieving fusion following ACDF appears to remain an intricate interplay between host biology and various surgical factors, including the selection of osteobiologics. While alternative osteobiologics to autograft exist and may produce acceptable fusion rates, limitations in study methodology prevent any definitive conclusions from existing literature. This systematic review has several limitations. Lack of stratification in regard to the number of levels fused and lack of standardized surgical techniques, use of numerous adjunctive biologics in conjunction with studied biologics, are significant confounding factors that critically limit the quality of data to date. Effective comparisons between homogenous groups at equivalent timepoints were not possible, as exclusion of poorer quality of data would have further limited the number of data points for comparison. There is a lack of high-quality evidence demonstrating a beneficial impact of osteobiologics on health outcomes in patients undergoing ACDF. Further investigation is needed before clinical usefulness of this procedure is proven.

Hoffman et al. (2024) conducted a systematic literature review to assess evidence for the use of osteobiologics in single vs. multi-level anterior cervical discectomy and fusion (ACDF) in patients with cervical spine degeneration. The primary objective was to compare fusion rates after single and multi-level surgery with different osteobiologics. Secondary objectives were to compare differences in patient reported outcome measures (PROMs) and complications. After a global team of reviewers was selected, a systematic review using different repositories was performed, confirming to PRISMA and GRADE guidelines. In total 1,206 articles were identified and after applying inclusion and exclusion criteria, 11 articles were eligible for analysis. Extracted data included fusion rates, definition of fusion, patient reported outcome measures, types of osteobiologics used, complications, adverse events, and revisions. Fusion rates ranged from 87.7% to 100% for bone morphogenetic protein 2 (BMP-2) and 88.6% to 94.7% for DBM, while fusion rates reported for other osteobiologics were lower. All included studies showed PROMs improved for each osteobiologic. However, no differences were reported when comparing osteobiologics, or when comparing single vs. multi-level surgery specifically. The authors concluded the highest fusion rates after 2-level ACDF for cervical spine degeneration were reported when BMP-2 was used. However, PROMs did not differ between the different osteobiologics. Further blinded randomized trials should be performed to compare the use of BMP-2 in single vs. multi-level ACDF specifically. A limitation of the current review is the lack of studies reporting specifically on the effect of osteobiologics on single vs. multi-level ACDF. Most included studies did not specify results based on levels treated, except for earlier discussed results, plus the number of results on 3-level or more than 3-level fusions were very limited. This precludes making stringent recommendations. Furthermore, the included

studies almost uniformly possessed a moderately high to high risk of bias. Lastly, the heterogeneity of outcome parameters made performing a meta-analysis impossible.

Muthu et al. (2024) conducted a systematic review to analyze the literature and describe the evidence supporting osteobiologic use in revision anterior cervical discectomy and fusion (ACDF) surgery. A systematic search of PubMed/MEDLINE, EMBASE, Cochrane library, and ClinicalTrials.gov databases was conducted for literature reporting the use of osteobiologics in revision ACDF. The authors searched for studies reporting outcomes of using any osteobiologic use in revision ACDF surgeries (independently of the number of levels) in the above databases. There are currently no studies in the literature describing the outcome and comparative efficacy of diverse osteobiologic agents in the context of revision ACDF surgery. A majority of the current evidence is based only upon studies involving primary ACDF surgery. The authors concluded the current study highlights the paucity of literature evidence on the role of diverse osteobiologics in revision ACDF and foregrounds the need for high-quality evidence on this subject.

An ECRI Clinical Evidence Assessment (2022) was performed to determine the safety and efficacy of recombinant human bone morphogenetic protein 2 (rhBMP-2) for cervical spine fusion and how it compares with those of autograft and other bone substitutes. Recombinant human bone morphogenetic protein 2 (rhBMP-2) is an osteoinductive growth factor that can be applied to osteoconductive implants to promote their integration into bone. The only FDA-approved spinal fusion product containing rhBMP-2 is Infuse Bone Graft (Medtronic plc.), an absorbable collagen sponge coated in rhBMP-2 and used instead of a graft, alongside an interbody fusion cage. In the United States, Infuse is approved only for lumbosacral spine fusion (L2 to S1). RhBMP-2 is intended to achieve vertebral fusion by promoting natural bone growth, eliminating the need for autologous bone graft harvest (usually from the iliac crest) and its associated side effects and risks (e.g., pain, infections). Per The Evidence Bar™ conclusions, evidence raises concerns. Per ECRI, two systematic reviews (SRs) and one additional randomized controlled trial (RCT) show rhBMP-2 use during cervical fusion promotes bone fusion but results in a higher rate of adverse events (AEs) than other bone substitutes, and risks may outweigh benefits. The FDA has warned that off-label use of Infuse for cervical fusion can cause life-threatening AEs (e.g., compression of the airway and/or neurologic structures in patients' necks). The two SRs and four individual clinical studies reviewed found higher fusion rates with rhBMP-2 than with plain bone substitutes, but the largest SR and the RCT examining AEs in > 1,500,000 patients reported higher AE rates with rhBMP-2. Three smaller, nonrandomized comparison studies reported no statistical difference in AEs between those treated with or without rhBMP-2, but these results are inconclusive because the studies have a very high risk of bias due to retrospective design and lack of randomization and blinding.

Im et al. (2022) conducted a prospective, single-institution, therapeutic investigative clinical study to explore the effectiveness and feasibility of injectable Escherichia coli-derived recombinant human bone morphogenetic protein-2 (injectable E-rhBMP-2, a combination of E. coli-derived recombinant human bone morphogenic protein-2 and a hydrogel type beta-tricalcium phosphate carrier) as a bone substitute for anterior lumbar interbody fusion (ALIF) of the lumbosacral junction in adult spinal deformity (ASD) patients. Twenty patients (average age: 69.1 years; 19 female and one male; average fusion level: 7.95) diagnosed with ASD with sagittal imbalance who underwent surgical treatment including ALIF at the lumbosacral junction from December 2017 to January 2019 were evaluated. Injectable E-rhBMP-2 was prepared by dissolving 3 mg of E. coli-derived recombinant human bone morphogenetic protein-2 in 1.5 ml H_2O and mixing in situ with 9 g hydrogel type beta-tricalcium phosphate. This bone graft substitute was loaded onto a metal ALIF cage and L5–S1 ALIF was performed in a routine manner. Then posterior column osteotomy with multilevel oblique lumbar interbody fusion or pedicle subtraction osteotomy with accessory rod technique was performed to restore sagittal balance. Patients were followed up for 12 months. CT-based fusion rates were examined at 6 and 12 months after surgery. Also, clinical outcomes [Oswestry Disability Index (ODI), Visual Analog Scale (VAS) score of the back and leg] were evaluated at 6 and 12 months after surgery. All postoperative adverse events were evaluated for the association with injectable E.BMP-2. Of the 20 patients, loss to follow-up occurred with one patient at 6 months after surgery and one patient at 12 months after surgery, resulting in a total of 18 patients who were available for follow-up. Six months after surgery, 68.4% patients achieved solid fusion. Twelve months after surgery, 100% fusion rate was achieved. Compared to baseline values, ODI scores improved to 45.8% and 63.7%, VAS (back) improved to 69.2% and 72.8%, and VAS (leg) improved to 49.2% and 64.8%, respectively, at 6 and 12 months after surgery ($p < 0.001$ for all). Ten cases of adverse events occurred; however, no adverse events were associated with injectable E-rhBMP-2. The authors concluded injectable E-rhBMP-2 will be an effective bone graft substitute when achieving solid interbody fusion in the lumbosacral junction. Limitations include a small sample size making it difficult to decide whether these conclusions can be generalized to a larger population. In addition, the short-term follow-up did not allow for assessment of intermediate and long-term outcomes. Further research with randomized controlled trials is needed to validate these findings.

Meng et al. (2022) conducted a retrospective study evaluating the clinical and radiographic effect of rhBMP-2 in pars repair of lumbar spondylolysis. Direct pars repair and pedicle screw fixation was performed, which were added with 1 mg of rhBMP-2 and iliac crest bone graft in the study group (rhBMP-2 group, n = 32) and iliac crest bone graft alone in the autograft group (n = 36). Patients completed the visual analog scale and the Oswestry Disability Index pre-operation, 3, 6,

and 12 months after the operation. Computed tomography scans with axial and sagittal reconstructions were performed at 6, 9, 12, 18, and 24 months postoperatively. Baseline demographic data showed no difference between the 2 groups. There were differences for the Oswestry Disability Index score at 3- and 6-months post-operatively, which were higher in the autograft group. There was no difference between the groups with respect to the overall union status. As for union speed, the trabecular bone appeared earlier and union rates were higher in rhBMP-2 group than in the autograft group at 9, and 12 months post-operatively. No complications were identified in either group. One case in the rhBMP-2 group and 2 cases in the autograft group underwent revision surgery. The authors concluded that when compared with iliac crest bone graft alone, the use of rhBMP-2 can accelerate fusion in pars repair for young patients with spondylolysis. The union rates were different at 9 and 12 months after surgery. This study showed no clinical difference when adding rhBMP-2 compared with iliac crest bone graft alone. The limitations of this study include bias because of retrospective, single-center and nonrandomized study, as well as the small sample size, which may weaken the study's ability to detect differences between study subgroups and determine the significance of these differences. Further research with randomized controlled trials is needed to validate these findings.

A Hayes (2018; updated 2022) comparative effectiveness review identified a large body of moderate-quality evidence that suggests that compared with an autograft, the use of rhBMP-2 for lumbar spinal fusion provides more rapid fusion and/or a somewhat greater likelihood of achieving fusion, but this did not consistently result in reduced pain or disability or better QOL. Use of rhBMP-2 also appears reasonably safe for lumbar fusion over the short term. Similar results were seen in studies related to cervical fusion, however the small number and quality of studies as well as varied treatment protocols limit reliability of the findings. There is a lack of studies regarding the use of rhBMP-2 for thoracic fusion and the efficacy and safety cannot be determined. 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.

Liu et al. (2020) conducted a systematic review and meta-analysis regarding the comparative clinical effectiveness and safety of rhBMP versus autologous iliac crest bone graft (ICBG) in lumbar fusion. Twenty randomized controlled trials identified through May 2019, with a total of 2,185 patients met the inclusion criteria of age 18 to 80 years, suffering from lumbar degenerative diseases requiring lumbar fusion, and the RCT compared rhBMP with ICBG (patients with spinal deformities, fractures, tumors or infections, cases demonstrated spondylolisthesis classified higher than Meyerding Grade II, follow-up was < 12 months, and there were incomplete follow-up data were excluded). The primary outcomes assessed included fusion success, improvement on the Oswestry disability index (ODI), improvement on short form 36 (SF-36), improvement on the Numeric Rating Scale (NRS) for back pain and leg pain, adverse events, and reoperation. Secondary outcomes included operation time, intraoperative blood loss, and duration of hospital stay. The overall results showed improvement across all primary outcomes. The fusion success rate for rhBMP-2 was approximately 5.5 times higher than that observed in ICBG, with reoperation rates about 60% of ICBG. Adverse events and complications showed no significant differences. The authors acknowledged that the quality of evidence in this meta-analysis is limited by the low quality of the original studies. Most evaluated studies did not report their randomization or allocation methods. Nearly all studies failed to use independent blinding. The authors concluded that evidence is still lacking to support rhBMP superiority to ICBG, and future research should address using more rigorous methods including accurate reporting of pre- and post-operative scores and follow up of long-term complications.

In 2017, James et al. presented a review article regarding the side effects of rhBMP-2. Since its FDA approval in 2002, increased use has resulted in a growing and well- documented body of side effects that include postoperative inflammation (and associated adverse effects), ectopic bone formation, osteoclast-mediated bone resorption, and inappropriate adipogenesis. Additionally, several large-scale studies have confirmed the relative frequency of adverse events associated when used for cervical spine fusions, and in 2008, the FDA issued a public health notification regarding the life-threatening complications associated with recombinant human bone morphogenetic protein for this use. The authors stress that the use of rhBMP-2 in appropriately selected patients with impaired fusion capacity can result in better overall long-term outcomes, however there are risks when the product is used off label or for inappropriate indications, and dosing.

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.

Ceramic-Based Products

There is insufficient evidence in published clinical literature to determine the safety and efficacy of ceramic-based products. Ceramic-based products include a variety of biologically inert compounds and components. They vary widely based on differences in composition, manufacturing, porosity, and structure which ultimately affect their outcomes and success rates. Future well-designed trials with higher quality comparison groups and long-term outcomes are necessary.

An ECRI Clinical Evidence Assessment (2024) was performed for resorbable, biphasic calcium phosphate bone graft substitute, MagnetOs EasyPack Putty (Kuros Biosciences A.G.) for lumbar fusion. Per The Evidence Bar™ conclusions, no data available. ECRI literature searches of Embase and PubMed did not identify any relevant clinical studies, published as full articles, to inform decisions about how well MagnetOs EasyPack Putty works for lumbar fusion or how it compares to similar bone graft substitutes.

Hasan et al. (2024) conducted a systematic review to determine the efficacy and overall outcomes of iFactor/ABM/P-15 following lumbar spine surgery. The primary outcomes of interest were fusion rates and iFactor efficacy after lumbar surgery in patients who received iFactor. Secondary outcomes included patient-reported outcomes and complication rates. A total of 766 titles were initially screened. After inclusion criteria were applied, five studies (388 patients) were included, which measured overall outcomes of iFactor/ABM/P-15 following lumbar spine surgery. These studies showed acceptable reliability for inclusion based on the Methodical Index for Non-Randomized studies and Critical Appraisal Skills Program assessment tools. iFactor/ABM/P-15 facilitated faster bone development in various procedures while maintaining favorable clinical outcomes compared to traditional grafts. The authors concluded this systematic review found that iFactor/ABM/P-15 use for lumbar spine surgery maintains similar managing patient-reported outcomes relative to other grafting methods. Regarding rates of fusion, iFactor/ABM/P-15 showed a faster rate of fusion when compared to traditional grafts including allograft, autograft, DBM, and rhBMP-2. This systematic review has limitations. The heterogeneity observed spans different surgical procedures and varied outcome measurements, making direct comparisons and meta-analyses challenging. In addition, four out of the five studies included in this review were sponsored, either directly or indirectly, by Cerapedics, the manufacturers of iFactor. Such financial ties raise concerns about potential biases in the study outcomes and interpretations. Low sample sizes observed in some of the studies limit the power of the findings. Small cohorts can lead to overestimations or underestimations of the true effect sizes. The predominance of single-center studies in our review further narrows the generalizability of the results, as findings from a single institution might not be representative of broader clinical practices. iFactor grafting methods were also variable among studies, posing another limitation. Some studies utilized iFactor independently while others combined it with either allograft or autograft. Future multi-center randomized control trials with larger sample sizes are recommended to further assess iFactor/ABM/P-15 efficacy in lumbar spine surgery.

Stempels et al. (2024) conducted a multi-center randomized controlled noninferiority trial with intra-patient comparisons to determine noninferiority of a slow resorbable biphasic calcium phosphate with submicron microplasty (BCP < µm, MagnetOs Granules) as an alternative for autograft in instrumented posterolateral fusion (PLF). Adults indicated for instrumented PLF (one to six levels) were enrolled at five participating centers. After bilateral instrumentation and fusion-bed preparation, the randomized allocation side (left or right) was disclosed. Per segment 10 cc of BCP < µm granules (1 to 2 mm) were placed in the posterolateral gutter on one side and 10 cc autograft on the contralateral side. Fusion was systematically scored on one-year follow-up CT scans. The study was powered to detect > 15% inferiority with binomial paired comparisons of the fusion performance score per treatment side. Of the 100 patients (57 ±12.9 y, 62% female), 91 subjects and 128 segments were analyzed. The overall posterolateral fusion rate per segment (left and/or right) was 83%. For the BCP < µm side only the fusion rate was 79% versus 47% for the autograft side (difference of 32 percentage points, 95% CI, 23-41). Analysis of the primary outcome confirmed the noninferiority of BCP < µm with an absolute difference in paired proportions of 39.6% (95% CI, 26.8-51.2; p < 0.001). The authors concluded that this clinical trial demonstrates noninferiority and indicates superiority of MagnetOs Granules as a standalone ceramic when compared to autograft for posterolateral spinal fusion. These results challenge the belief that autologous bone is the most optimal graft material. This study has limitations. First, the authors used an outcome measure that at best only indicates if the intended fusion has been achieved. Even if this leads to an improved clinical outcome after one year, the intra-patient model does not allow for comparison of patient reported outcomes. To really demonstrate clinical benefit, thousands of patients are needed, probably with a much longer follow-up. Second, the intra-patient design only assessed unilateral fusion, which underestimates the fusion rate when any fusion (left and/or right) would be regarded as a fusion. Third, the reliability of the thin-slice CT assessment for fusion determination is not fully established, as highlighted in a recent systematic review and reflected by the moderate interobserver reliability. Fourth, because of the slower absorption rate of this BCP < µm, the authors are not completely sure that the fusion observed in this condition always represents bone and is not a remnant of BCP < µm that perfectly mimics bone. Finally, a fifth limitation is that in many cases the observers could not be truly blinded. Given the radiological resemblance between ceramics and bone, it will be very difficult to completely exclude the human factor for this assessment. Conducting fusion assessments after a longer follow-up period would afford the BCP < µm more time to dissolve but reduces the graft related component of fusion.

A 2022 ECRI clinical evidence assessment entitled Bicera Bone Graft Substitute (Wiltrom Corp. Ltd.) for Filling Bone Defects reported on the safety and effectiveness of Bicera compared to bone grafts and other natural or synthetic bone substitutes. Bicera is a biocompatible ceramic composed of hydroxyapatite and beta-tricalcium. Evidence from one nonrandomized comparison study and two small case series is too limited in quantity and quality to determine how well Bicera works compared with autografts, allografts, or other bone graft materials bone fillers. Large well-designed studies are needed.

A 2022 ECRI clinical evidence assessment entitled Ceramic Bone Graft Substitutes for Spinal Fusion and Long Bone Voids reported on the effectiveness and safety of ceramic bone graft substitutes for spinal fusion and long bone void filling compared to ICBG and other alternative materials. Based on the results for spinal fusion, one SR reported that cages filled with nanocrystalline HA or homologous bone had similar fusion rates and function outcomes after anterior lumbar interbody fusion. For cervical fusion, one RCT reported ceramic-based synthetics used alone had the lowest fusion rate compared with other bone graft material, and when combined with allograft the fusion rates were slightly higher. Another RCT reported polyetheretherketone cages filled with allograft produced significantly better fusion rates than cages filled with tricalcium phosphate, and another reported polyetheretherketone cages with or without tricalcium phosphate filler produced better than 97% fusion at 24 months. It was concluded ceramic bone graft substitutes are safe and may aid cervical and lumbar fusion and long bone void repair, but due to the mixed results of the studies, the superiority to ICBG or other bone graft materials cannot be determined, and large well-designed and conducted RCTs comparing specific ceramic and ceramic/bone graft material combinations with ICBG, and other bone graft materials are needed.

Menezes et al. (2022) conducted a prospective, parallel, randomized, single-center study to evaluate the clinical success of a commercial ceramic bone graft substitute (CBGS) for autograft in extreme Lateral Interbody Fusion (XLIF) procedures. Forty-five adult subjects were consecutively enrolled and randomized into a single-level XLIF procedure using either CBGS or iliac crest bone graft autograft (30 and 15 subjects, respectively). The primary outcome was fusion rate at 12, 18, and 24 months. Secondary outcomes were pain and disability measured by HRQOL questionnaires. The fusion rates for both CBGS and autograft groups at the 24-month follow-up were 96.4% and 100%, respectively. For the CBGS group, mean ODI, mean back pain, and mean worst leg pain improved at the 24-month follow-up by 76.7% (39.9-9.3), 77.6% (7.3-1.6), and 81.3% (5.1-1.0), respectively. For the autograft group, mean ODI, mean back pain, and mean worst leg pain improved during the same time period by 77.1% (35.9-8.2), 75.6% (6.1-1.5), and 86.0% (6.6-0.9), respectively (all time points between groups, $p < 0.05$). The authors concluded that the results of this prospective, randomized study support the use of CBGS as a standalone bone graft substitute for autograft in single-level XLIF surgery. The clinical performance and safety outcomes reported here are consistent with published evidence on CBGS. Improvements in patient-reported back pain, leg pain, and disability outcomes were comparable between the CBGS and autograft groups. A small sample size makes it difficult to decide whether these conclusions can be generalized to a larger population.

Griffoni et al. (2022) conducted a prospective pilot clinical study to evaluate the degree of fusion and new bone formation achieved by the use of moldable ceramic paste bone graft substitute, SINTLife, an Mg-doped hydroxyapatite (HA) product. From February 2017 to September 2019, a total of 16 individuals who had indications of single- or multiple-level postero-lateral spinal fusion due to degenerative lumbar spine diseases were included in this study and followed up for 18 months. Three individuals dropped out due to adverse events post-surgery. Results showed a successful degree of fusion of about 62% at the 12-month follow-up and an improvement of quality of life and health status following surgery, as evaluated by clinical scores (ODI, VAS, and EQ-5L). No adverse events related to the material were reported. Considering all the patients, the VAS score at baseline was 7.2 ±1.8, and it decreased to 4.7 ±1.69 at 6-month follow-up, while it remained stable at 12–18-month follow-up (4.8 ±2.4), with a statistically significant difference between baseline and follow-up scores, starting from 6 months after surgery ($p < 0.0004$). The Oswestry Disability Index at baseline was 48.3 ±14.5, and it decreased to 31.6 ±14.7 at 6-month follow-up and remained stable at 12-18-month follow-up (33.3 ±18.3), with a statistically significant difference between baseline and follow-up scores, starting from 6 months after surgery ($p < 0.0006$) (Figure 5). The EQ-5L score at baseline was 45 ±15, and it increased to 62 ±13 at 6-month follow-up, and it was 64.5 ±22 at 12-18-month follow-up, with a statistically significant difference between baseline and follow-up scores, starting from 6 months after surgery ($p < 0.0003$). Differences between ODI, VAS, and EQ-5D scores at 12–18-month follow-up, as compared to 6-month FU values, were not statistically significant, and a sensitive analysis performed by considering only those patients who underwent all three follow-up visits (n = 13) confirmed the trend. Three adverse events (i.e., inflammatory reactions) were recorded in the follow-up period, with one requiring surgical debridement and the remaining treated with anti-inflammatory agents The authors concluded that this pilot study shows the effectiveness and the safety profile of an Mg-doped HA bone graft substitute used to achieve postero-lateral fusion in the treatment of degenerative spine diseases, laying down the basis for further larger clinical investigations.

In a 2020 systematic review and meta-analysis, Cottrill et al. (included in ECRI ceramic based bone graft substitutes clinical evidence assessment above) reported on the results in the published literature regarding silicate-substituted calcium phosphate (SiCaP) bone grafts and improved spinal fusion rates. Ten studies that included 694 patients were

included. The primary endpoint was radiographic fusion rate and patient reported outcomes (PROs) in VAS and ODI at last follow up. The results showed that across all studies, the mean fusion rate for patients treated with SiCaP bone grafts was 93%. There was no significant difference in fusion rates reported by case series and RCTs, or between single-center and multicenter studies. Fusion was achieved at 100% is adolescent idiopathic scoliosis (AIS) patients. Fusion rates were similar across interbody fusion, posterior/posterolateral fusion, and circumferential cervical fusion procedures, and between patients treated with SiCaP alone and SiCaP used in conjunction with bone marrow aspirate (BMA) and/or autograft. In studies that examined interbody fusion, titanium interbody devices had higher fusion rates than PEEK devices, and rates of fusion did not significantly differ between single or multi-level, or cervical or thoracic columbar procedures. Among the three RCTs included, there was no difference in fusion rates among patients that received SiCaP vs. those that received grafts supplemented with rhBMP-2. PROs showed patients that received SiCaP reported significant improvement in VAS back and leg pain, and ODI. The authors concluded that SiCaP achieved successful fusion in 93% of patients treated. The SR is limited by the high heterogeneity of the included studies, as well as comparison to other graft materials. Further high-quality research is needed to validate these findings.

Lehr et al. (2020) conducted a patient- and observer-blinded, multicenter, randomized, noninferiority trial with intra-patient comparisons to determine noninferiority of a biphasic calcium-phosphate (AttraX Putty) as a bone graft substitute for autograft in instrumented posterolateral fusion (PLF). This study included 100 nontraumatic adults who underwent a primary, single- or multilevel, thoracolumbar, instrumented PLF. After instrumentation and preparation for grafting, the randomized allocation side of AttraX Putty was disclosed. Autograft was applied to the contralateral side of the fusion trajectory, so each patient served as his/her own control. For the primary efficacy outcome, PLF was assessed at one-year follow-up on computed tomography scans. Each segment and side were scored as fused, doubtful fusion, or nonunion. After correction for multilevel fusions, resulting in a single score per side, the fusion performance of AttraX Putty was tested with a noninferiority margin of 15% using a 90% confidence interval (CI). There were 49 males and 51 females with a mean age of 55.4 ±12.0 (range 27-79) years. Two-third of the patients underwent a single-level fusion and 62% an additional interbody fusion procedure. The primary analysis was based on 87 patients, including 146 instrumented segments. The fusion rate of AttraX Putty was 55% versus 52% at the autograft side, with an overall fusion rate of 71%. The 90% CI around the difference in fusion performance excluded the noninferiority margin (difference = 2.3%, 90% CI = 9.1% to + 13.7%). The authors concluded that the results of this noninferiority trial support the use of ceramic-based, synthetic bone void filler, AttraX Putty, as a standalone bone graft substitute for autograft in instrumented thoracolumbar PLF. A limitation of an intra-patient design is that clinical outcomes like PROMs and adverse events cannot be attributed separately to the treatment conditions. These outcomes were therefore mainly collected to confirm a general treatment effect as expected based on control populations. In an effort to evaluate safety, all unexpected, undesirable medical experiences, whether or not considered related to the spinal fusion, were registered prospectively. Long-term evaluations of the results and prospective randomized studies are still needed before clinical usefulness of this procedure is proven.

Lehr et al. (2020) conducted a two-year clinical and radiographic follow-up of a double-blind, multicenter, randomized, intra-patient controlled, non-inferiority trial comparing a bone graft substitute (AttraX Putty) with autograft in instrumented posterolateral fusion (PLF) surgery between one and two years of follow-up and between graft types, and to explore the role of bone grafting based on the location of the PLF mass. A total of 100 adult patients underwent a primary, single- or multilevel, thoracolumbar PLF. After instrumentation and preparation for grafting, the randomized allocation side of AttraX Putty was disclosed. The contralateral posterolateral gutters were grafted with autograft. At one-year follow-up, and in case of no fusion at two years, the fusion status of both sides of each segment was blindly assessed on CT scans. Intertransverse and facet fusion were scored separately. Difference in fusion rates after one and two years and between grafts were analyzed with a Generalized Estimating Equations (GEE) model ($p < 0.05$). The two-year PLF rate (66 patients) was 70% at the AttraX Putty and 68% at the autograft side, compared to 55% and 52% after one year (87 patients). GEE analysis demonstrated an increase for both conditions (odds ratio 2.0, 95% confidence interval 1.5-2.7, $p < 0.001$), but no difference between the grafts ($p = 0.595$). Ongoing bone formation was only observed between the facet joints. The authors concluded that this intra-patient-controlled trial demonstrated an increase in PLF rate between one and two years after instrumented thoracolumbar fusion, but no difference between AttraX Putty and autograft. Based on the location of the PLF mass, this increase is most likely the result of immobilization instead of grafting. This study has some limitations. To limit the exposure to ionizing radiation, only patients without fusion at all of the instrumented segments were scheduled for an additional CT-scan at two years. For logistical reasons, this decision was made by the treating physician. Fourteen patients were not re-assessed as the treating physician, unlike the blinded observers, qualified these as complete fusions. Another limitation is the assumption that successful fusions can be extrapolated. However, of the 43 patients that were re assessed, only 6.5% of the segment sides that were scored as fused at one year were scored differently at two years. This is most likely the result of variance in (re-)assessment, as also reflected in the 72% interobserver agreement at one year. Furthermore, the contribution of the bone grafts to the fusion process during the first and second year after surgery was only explored visually based on the location of the PLF mass. Imaging-based quantification of bone (graft) resorption and remodeling over time is still in its infancy. Last, the intra-patient design limits the separate attribution of adverse events to the treatment conditions. Well designed, adequately powered, prospective,

controlled clinical trials using ceramic-based, synthetic bone void filler, AttraX Putty, are needed to further clinical outcomes with safety and efficacy.

A 2018 ECRI clinical evidence assessment, updated in 2021 entitled i-Factor Bone Graft (Cerapedics, Inc.) for Lumbar Fusion Procedures, reported on the efficacy of the i-Factor bone graft and how it compares to autograft and allograft bone. i-Factor is a biologic bone graft made of a small peptide (P-15 Osteogenic Cell Binding Peptide), bound to an anorganic bone mineral. Limited evidence suggests that i-Factor is safe and effective, however too few patients have been included to determine its superiority to autografts, allografts, or other bone graft materials. Two ongoing randomized controlled trials expected to be completed in 2027 are likely to address this gap.

Bioactive Glass

Bioactive glasses are a class of synthetic silica-based bioactive materials that have unique bone forming properties and have been introduced as bone graft substitutes. Typically composed of 4 different oxide materials: SiO_2, CaO, Na_2O, and P_2O_5, they have unique properties when compared to other synthetic bioresorbable bioactive ceramics [i.e., calcium phosphates, hydroxyapatite (HA), and tricalcium phosphate (TCP)]. They are claimed to exhibit faster rates of hydroxyl carbonated apatite (HCA) and bone bonding formation, and higher osteoconductivity. There is insufficient high-quality evidence to come to conclusions on the efficacy and safety of these products on health care outcomes, and how they compare with established procedures.

Courvoisier et al. (2023) conducted a retrospective study to evaluate and compare the post-operative safety and efficiency of stand-alone bioactive glass putty and granules in posterior spine fusion for scoliosis in a pediatric cohort. A total of 43 children and adolescents were included retrospectively. Each patient's last follow-up was performed at 24 months and included clinical and radiological evaluations. Pseudarthrosis was defined as a loss of correction measuring > 10° of Cobb angle between the pre-operative and last follow-up measurements. There was no significant loss of correction between the immediate post-operative timepoint and the 24-month follow-up. There was no sign of non-union, implant displacement or rod breakage. The authors concluded that bioactive glass in the form of putty or granules is an easily handled biomaterial but still a newcomer on the market. This study shows that the use of bioactive glass in posterior fusion, when combined with proper surgical planning, hardware placement and correction, is effective in providing good clinical and radiological outcomes. The retrospective nature and uncontrolled design of this study are its main limitations. While these observations confirmed the efficacy and safety of stand-alone bioactive glass 45S5 as an alternative to autologous bone grafts, further studies will be required to compare the available materials and assess possible differences among the various compounds.

A 2022 ECRI clinical evidence assessment entitled Bioactive Glass Bone Graft Substitutes for Spinal Fusion and Long Bone Voids reported on the effectiveness and safety of bioactive glasses (BGs) for spinal fusion and long bone void filling compared to ICBG and other alternative materials. Due to insufficient, very low-quality evidence whether BG is as effective as ICBG or other bone graft materials cannot be determined, and RCTs comparing specific BGs and BG/graft combinations to the current gold standard ICBG are needed.

Gomez and Westerland (2021, included in the ECRI clinical evidence assessment) conducted a retrospective case series review of 39 patients who underwent primary multilevel instrumented fusions for degenerative cervical disc disease treated with a porous PEEK interbody spacer and a third-generation bioactive glass synthetic bone graft substitute (BioSphere® Putty, Synergy Biomedical, Wayne, PA, USA). Patients were assessed using accepted standard outcome measurements including VAS and neck disability index, immediately following surgery, and at 3-, 6-, 12-, and 24-months post operatively. The mean follow-up period was 16 months. Lateral radiographs were used to assess sagittal alignment, disc space height, arthrodesis status, osseous integration, and implant migration. Sagittal plane angulation was measured by Cobb's criteria. Seventeen patients (43%) underwent a two-level fusion; 12 (31%) underwent a three-level fusion; 9 (23%) underwent a four-level fusion; and 1 (3%) underwent a five-level fusion. The results showed significant improvements in VAS and neck disability index, and these were maintained up to one year follow up. All patients improved or maintained neurological status up to one year. Radiographic outcomes showed that all patients demonstrated osseous integration of the interbody spacers to the vertebral endplates and trabeculated new bone formation across the fused interspace. No radiographic lucencies developed, and dynamic flexion/extension radiographs showed was no motion, migration of the implants, broken screws, or plates. There was a significant improvement in the fusion segment lordosis, C2-C7 lordosis angle, as well as T1 slope and disc height remained unchanged. Statistically significant improvement was not shown for sagittal vertical axis or proximal and distal adjacent segment lordosis. No adverse events were reported. The authors concluded that third generation bioactive glass is a promising and effective method to enhance spinal fusion. This study is limited by a small number of participants and larger, well-designed studies are needed to validate these findings.

Lee et al. (2020) conducted a prospective, stratified randomized, multicenter, follow-up study aimed to evaluate the long-term clinical efficacy and safety of CaO-SiO2-P2O5-B2O3 glass ceramics (BGS-7) spacers in 1-level posterior lumbar interbody fusion (PLIF) at a 4-year follow-up. According to 1-year follow-up results, BGS-7 spacer showed similar fusion rates and clinical outcomes compared with titanium cage. A long-term follow-up study beyond 2 years is necessary to investigate the status of intervertebral bone graft volumes. Moreover, longer follow-up is necessary to evaluate the safety and efficacy of BGS-7 spacers as they remain in the intervertebral space for a long time. Evaluation of 62 of the 74 patients who underwent 1-level PLIF was performed. During 1-level PLIF, titanium cages filled with autologous local bone were inserted into the control group patients and BGS-7 spacers were inserted to the experimental group patients. Bone fusion was evaluated by plain radiography and thin section computed tomography. Visual Analog Scale (VAS), the Oswestry Disability Index (ODI), Short Form-36 Health Survey (SF-36), and evaluation of safety were conducted after 48 months. Computed tomography scan showed a bone fusion rate of 90.6% in the BGS-7 spacer group and 93.3% in the control group, with no differences between groups. The BGS-7 spacer group showed a larger area directly fused to the endplate than the control group ($p < 0.001$). The BGS-7 spacer group showed an increase in the fused area compared with the titanium group at 1- and 4-year follow-up. The ODI, SF-36, back pain, and lower limb pain in both groups showed improvement after surgery, and no differences were observed between the groups. Both groups showed no additional adverse events. The authors concluded that the 4-year follow-up study showed similar fusion rates and clinical outcomes in both the BGS-7 spacer and autologous bone with a titanium cage in 1-level PLIF. However, the BGS-7 spacer implants showed a larger area of fusion with the endplates than that of autologous bone with a titanium cage. Therefore, the results demonstrated that the BGS-7 spacer can be considered as a novel intervertebral spacer to achieve successful spinal fusion without safety concerns for long-term use. A limitation to this study focused on the safety of the BGS-7 should be analyzed beyond 4 years, because BGS7 spacers would remain in the intervertebral spaces for a long period of time. Further research is needed to determine the clinical relevance of these findings.

Westerland and Borden (2020) conducted a retrospective clinical case series to evaluate the use of a novel, spherical bioactive glass bone graft (BioSphere® Putty) as a graft material for cervical and lumbar interbody fusion. Data was gathered for a combined 248 patients who underwent 115 anterior cervical decompression and fusion (ACDF), 103 transforaminal lumbar interbody fusion (TLIF), and 30 anterior lumbar interbody fusion (ALIF) procedures by a single surgeon. BioSphere Putty was used in combination with cancellous allograft (ACDF and ALIF) or in combination with autograft (TLIF). Successful clinical outcomes were determined by a combination of the presence of complete radiographic fusion and a decrease in VAS at 1-year and 1- and 2-year follow-up. Only 43 of the 248 patients were followed for 2 years. At follow up, radiographically all patients demonstrated fusion, and there were no clinically adverse events. One-year VAS scores demonstrated significant decreases in pre-operative pain for both ACDF patients (78% decrease) and lumbar patients (66% decrease TLIF/ALIF). Over 2 years, VAS scores continued to drop with significant decreases for the ACDF patients (96%), TLIF patients (82%), and ALIF patients (80%). Combined with the 100% radiographic fusion rates for patients, this resulted in a clinical success rate of 93% for the ACDF patients and 89% for the TLIF/ALIF patients. The authors concluded that Biosphere Putty demonstrates successful outcomes in cervical and lumbar interbody fusion surgeries. This study is limited by the retrospective design, high risk of bias, and small number of participants evaluated for 2 years. Further well-designed high-quality research is warranted.

Expandable Interbody Fusion Systems

Expandable interbody fusion systems are unproven due to a lack of prospective randomized controlled trials with larger sample size and longer-term follow-up to determine clinical efficacy.

An ECRI Clinical Evidence Assessment (2024) was performed to determine how well Aprevo patient-specific titanium interbody fusion implants work compared with other treatments for lumbar interbody fusion. Aprevo spine implants are intended to provide structural stability to treat degenerative disc disease (DDD) and other painful spine conditions. Per The Evidence Bar™ conclusions, very low-quality data exists. One multicenter, retrospective cohort study with a high risk of bias is insufficient to determine how well the Aprevo spine implant works and how it compares with standard lumbar spinal fusion procedures. The study reported fusion with Aprevo achieved segmental alignment that was close to the planned goals but did not report patient-oriented outcomes (e.g., pain relief, patient functional status, quality of life), which are necessary to assess treatment success. This report updates the 2021 clinical evidence assessment. The Evidence Bar™ did not change

Johnson et al. (2024) conducted a systematic review and meta-analysis aimed to compare clinical and radiological outcomes between lumbar arthrodesis with a synthetic interbody spacer (cage) versus structural bone graft alone (autograft or allograft) in patients with degenerative spine disease. A systematic review of the literature was performed to identify studies directly comparing outcomes of lumbar interbody arthrodesis with and without interbody cage use. The outcomes of individual studies were synthesized in meta-analyses using random-effects models. Twenty studies with 1,508 patients (769 with an interbody cage and 739 without an interbody cage) were included. Interbody cage placement was associated with a greater increase in disc height after surgery (4.0 mm vs. 3.4 mm, $p < 0.01$). There was a greater

reduction of back pain [visual analog scale (VAS) score] in cases in which an interbody cage was used (5.4 vs. 4.7, p = 0.03). Fusion rates were 5.5% higher in the cage group (96.3% vs. 90.8%) and reached statistical significance (p = 0.03). The authors stated no statistically significant differences were identified between the two groups regarding all-cause reoperation rates, complication rates, or improvement in Oswestry Disability Index score or leg pain (VAS score). The authors concluded that these results suggest that implantation of an interbody cage is associated with higher rates of fusion, more effective maintenance of disc height, and greater improvement of back pain. This study underlines the clinical value of interbody cages in lumbar arthrodesis for patients with degenerative spine disease. This systematic review and meta-analysis have limitations. First, as with all meta-analyses using observational studies, the conclusions are liable to confounders and selection bias. More specifically, patient allocation to a group may be influenced by patient characteristics, surgeon preference, and socioeconomic status mediated by insurance payor. In this scenario, interbody cages may have been utilized in cases with more severe deformity, a confounder the authors were unable to adjust for. To moderate the impact of heterogeneity in practices among different studies, the authors conducted the meta-analyses via random-effects models. Additionally, not all studies reported every outcome of interest, and the follow-up period of the included studies was not homogeneous, which may have impacted clinical, radiological, and patient-reported outcomes. Although the authors utilized random-effects models for their analyses, it is unclear how patient heterogeneity within the individual studies affected the results of our study.

Kucharzyk et al. (2023) conducted a retrospective study to review and analyze collected perioperative, radiographic, and clinical outcome data following treatment with either a static or minimally invasive expandable transforaminal lumbar interbody fusion (TLIF) device for the treatment of spondylolisthesis, degenerative disc disease, spinal stenosis, disc herniation, or degenerative scoliosis. Patients treated with either static or expandable transforaminal lumbar interbody fusion devices (ProLift® Expandable Spacer System) for the treatment of spondylolisthesis, degenerative disc disease, spinal stenosis, disc herniation, or degenerative scoliosis at L4-L5 or L5-S1 were chosen from retrospective data. Outcomes included radiographic and spinopelvic changes, patient-reported outcomes, and incidence of nonunion and revision surgery. One hundred patients were included (Static: 50; Expandable: 50). Demographics between groups were similar, with some differences in comorbidities and spinal disease diagnosis. Radiographically, changes in disc height, foraminal height, and lordosis were improved in the Expandable group up to 2 years ($p < 0.001$). Improvements in patient reported outcomes were more favorable in the Expandable group. The authors concluded patients who underwent transforaminal lumbar spinal fusion via minimally invasive surgery, the Expandable device group, demonstrated improved radiographic, and patient reported outcomes compared to a static cage over 2 years. Prospective randomized controlled trials, with larger sample sizes and long-term patient follow-up are needed to validate these findings.

Lee et al. (2023) conducted a systematic review and meta-analysis to determine the effectiveness of expandable cages by analyzing studies that compared the surgical outcomes between the use of expandable cages and static cages. The preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were used to conduct this meta-analysis and systematic review. The primary outcomes of this study were anterior disc height, posterior disc height, segmental lordosis (SL), lumbar lordosis (LL), subsidence rate, numeric rating scale (NRS) scores for back and leg pain, and Oswestry Disability Index (ODI). Thirteen studies with 1,700 patients were included in the meta-analysis. Compared with static cages for LIFs, expandable cages increased the anterior disc height [standardized mean difference 0.478, 95% confidence interval (CI) 0.088-0.867, p = .0162] and segmental lordosis (sMD 0.307, 95% CI 0.159-0.454, p < .0001). There were no differences in the posterior disc height, lumbar lordosis, subsidence rate, back pain, leg pain, or ODI between the two groups. The authors concluded that expandable cages show no clear clinical benefit over static cages. This systematic review has several limitations. First, the level of evidence was low because only retrospective studies have been conducted to date on expandable cages. Second, various factors affect the results of LIF, such as procedure technique, cage position, cage design, and approach; however, due to the lack of information on the environment of each study included in this review, these factors could not be controlled in the analysis. Therefore, in future studies, it is necessary to conduct a subgroup analysis of these factors. Finally, only a few studies have compared the parameters of sagittal balance, such as pelvic incidence (PI), sagittal vertical axis, and PI-LL mis match between the two groups; therefore, it is impossible to analyze differences in the overall sagittal balance. Further research with RCTs is needed to validate these findings.

Kucharzyk and Miller (2020) conducted a retrospective, single-center study to evaluate the two-year clinical safety and effectiveness outcomes of a multi-expandable interbody fusion device (Luna 3D Interbody Fusion System) in patients undergoing posterior or transforaminal lumbar interbody fusion. Key patient-reported outcomes included back pain severity, leg pain severity, and the Oswestry Disability Index (ODI). Radiographic assessments included disc height (anterior, posterior, and average), foraminal height, segmental lordosis, subsidence, implant migration, and pseudarthrosis. A total of 50 consecutive patients were treated with transforaminal lumbar interbody fusion (TLIF) using the multidimensional expandable implant and followed at regular intervals over two years post-procedure. Procedural blood loss was minimal (median 200 ml), and the mean hospital stay was 2.1 days. Perioperative complications were reported in three patients and included a dural tear, postoperative ileus, and end-plate violation. All complications were

successfully managed conservatively. There were no nerve root injuries or perioperative infections. Over the two-year follow-up period, one case of subsidence and one case of implant migration were noted on radiographic imaging but required no treatment. Comparing the values reported at baseline and two years, the mean ODI score decreased by 61%, back pain severity decreased by 67%, and leg pain severity decreased by 80% (all $p < 0.001$). One case of non-union was observed and the corresponding two-year fusion rate was 98%. The authors concluded that the utilization of a minimally invasive, multidimensional, expandable interbody implant was safe and effective over two years of clinical follow-up. The implant allows the surgeon to re-establish sagittal balance and to provide a larger surface area for fusion as compared to traditional minimally invasive interbody devices. This study is limited by its retrospective observations, single-center patient population, and lack of a controlled comparator group. The findings of this study need to be validated by well-designed studies.

Clinical Practice Guidelines

American Academy of Neurological Surgeons (AANS)

In a 2014 updated guideline (Kaiser et al.) for the performance of fusion procedures for degenerative disease of the lumbar spine, the AANS makes the following recommendations:

- The use of DBM as a bone graft extender is an option for 1- and 2-level instrumented posterolateral fusions.
- The use of b-TCP/local autograft as a substitute for AICB is an option for single-level instrumented posterolateral fusion due to comparable fusion rates and clinical outcomes (Kaiser et al., 2014).

Hydroxyapatite/Calcium Extenders

- The use of hydroxyapatite (HA) with local autograft/BMA as a substitute for AICB in an option for instrumented posterolateral fusion due to comparable fusion rates and clinical outcomes.
- The use of HA can be considered an option as a graft extender when mixed with AICB for instrumented posterolateral fusions.
- There is insufficient evidence to recommend for or against the use of a HA-glass/BMA composite as an autograft substitute for posterolateral fusion.
- The use of calcium sulfate preparations mixed with local autograft, as a substitute for AICB, is an option for instrumented posterolateral fusions.

rhBMP-2

The use of rhBMP-2 as a graft option has been associated with unique complications that the surgeon should be aware of when considering its use.

Interbody Fusion

- As a substitute for AICB for anterior lumbar interbody fusion (ALIF) with threaded interbody cages is an option due to similar fusion rates and clinical outcome
- As a substitute for AICB for single-level posterior lumbar interbody fusion (PLIF) is an option due to similar fusion rates and clinical outcomes; however, formation of heterotopic bone has been observed
- As a bone graft extender can be considered as an option when performing a transforaminal lumbar interbody fusion (TLIF) procedure with a structural interbody graft
- There is insufficient evidence to make a recommendation regarding the use of rhBMP-2 as a supplement for stand-alone ALIF procedures using femoral ring allograft or with a resorbable spacer when performing TLIF procedures

Posterolateral Fusion

- Supplemented with 15% HA/85% b-TCP matrix as a substitute for AICB is an option in single-level posterolateral instrumented fusions given the consistent observation of comparable fusion rate and clinical outcomes
- Supplemented with graft extenders as an alternative to AICB is an option for single level, instrumented posterolateral fusions in patients older than 60 years
- As a graft extender with either AICB or local bone is an option in patients undergoing either instrumented or non-instrumented posterolateral fusions

There is insufficient evidence to formulate a recommendation regarding the use of rhBMP-2/local bone as a substitute for AICB when performing revision posterolateral fusions or the use of rh- BMP-2/calcium-based extenders for single level posterolateral fusions in patients who smoke and elect to undergo surgery for lumbar spondylosis.

North American Spine Society (NASS)

In a 2017 evidence-based coverage policy recommendation for allograft and demineralized bone matrix for spinal fusion, the NASS identified the following scope and clinical indications:

Structural Allograft

Structural cortical or corticocancellous allograft bone (fresh-frozen or freeze-dried), with or without additional autograft, is indicated for use in anterior cervical spinal reconstruction in the following clinical scenarios:

- Anterior cervical discectomy and fusion
  - Uninstrumented single level
  - Instrumented single-level
  - Instrumented multilevel
- One or more level cervical corpectomy

Posterior Cervical Fusion

Structural allograft is indicated for posterior upper cervical and occipitocervical instrumented fusion:

- Nonstructural allograft bone
- DBM may be indicated for anterior cervical spinal reconstruction and fusion for cervical radiculopathy and/or myelopathy in the following clinical scenarios:
  - Anterior cervical discectomy and fusion
  - Cervical corpectomy
  - Posterior cervical fusion
  - Thoracolumbar spine fusion
    - Structural cortical and corticocancellous allograft bone (with or without additional autograft)
      - Interbody fusion [including transforaminal (TLIF), posterior (PLIF) and anterior (ALIF) lumbar interbody fusion]
      - Anterior corpectomy and fusion
    - Nonstructural allograft (with or without additional autograft)
      - Posterior instrumentation and fusion
      - In combination with structural allograft or synthetic cages for thoracolumbar interbody fusion

DBM combined with autograft is indicated for use in posterior instrumented fusion. There is no significant evidence at this time for use as a stand-alone product in non-instrumented posterior fusion or anterior fusions.

Iliac crest bone autograft (ICBG) remains the “gold standard” material for structural and nonstructural bone graft in cervical and thoracolumbar spine fusion, though the morbidity associated with its harvest, including fracture, infection, neurologic injury, and chronic pain at the harvest site, have led to allograft becoming a more frequently used non-autogenous bone graft material in spine surgery.

In a 2014 evidence-based coverage policy recommendation for rhBMP-2, the NASS states rhBMP-2 may be considered as an adjunct to spinal fusion for the following diagnoses:

- Stand-alone anterior lumbar interbody fusion (ALIF) in all patient groups except males with a strong reproductive priority
- Posterolateral lumbar fusion in patients at high risk for nonunion with autogenous bone graft or in those with inadequate or poor-quality autogenous bone available
- Posterior lumbar interbody fusion (PLIF and TLIF) in patients at high risk for nonunion with autogenous bone graft or in those with inadequate or poor-quality autogenous bone available
- Posterior cervical or thoracic fusions
  - In pediatric patients at very high risk for fusion failure (e.g., neuromuscular scoliosis, occipitocervical pathology)
  - In adult patients at high risk for nonunion, for example, revision surgery
- Anterior cervical fusion in patients at high risk for nonunion

The society also states that rhBMP-2 should not be used for the following:

- Routine anterior and posterior cervical fusion procedures
- Single level posterior/posterolateral fusions in healthy adults
- Routine pediatric spine fusion procedures (e.g., adolescent idiopathic scoliosis)

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

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. Refer to the following website for more information: https://www.fda.gov/vaccines-blood-biologics/tissue-tissue-products. (Accessed July 23, 2025)

Products used for bone growth and bone grafts products are extensive. Refer to 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 July 23, 2025)

In 2018, the FDA granted 501K premarket approval for the Bicera® Resorbable Bone Substitute. Refer to the following website for more information: https://www.accessdata.fda.gov/cdrh_docs/pdf17/K172237.pdf. (Accessed July 23, 2025)

In July 2002, the FDA granted 510K premarket approval for the InFUSE™ Bone Graft/LT-CAGE™. It has several supplements. Refer to the following website for more information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P000058. (Accessed July 23, 2025)

In November 2015, the FDA granted 510 (k) premarket approval for the i-FACTOR® peptide enhanced bone graft. Refer to the following website for more information: https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?db=pma&id=320591. (Accessed July 23, 2025)

In October 2008, the FDA granted the InFUSE/MASTERGRAFT Humanitarian Device Exemption. Refer to the following website for more information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfHDE/hde.cfm?id=375525. (Accessed July 23, 2025)

In November 2003, the FDA granted 510(k) premarket approval for the OptiMesh® Expandable Interbody Fusion System for maintaining the relative position of bone graft material within a vertebral body defect that does not impact the stability of the vertebral body and does not include the vertebral endplates. Refer to the following website for more information: https://www.accessdata.fda.gov/cdrh_docs/pdf/K014200.pdf. (Accessed July 23, 2025)

In September 2020, the OptiMesh® Expandable Interbody Fusion System was granted De Novo classification for expanded indications allowing the use with bone graft and supplemental posterior fixation in lumbar interbody fusion. Refer to the following website for more information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/denovo.cfm?id=DEN200010. (Accessed July 23, 2025)

In February 2021, the FDA granted 510(k) premarket approval for the Duo™ Expandable Interbody Fusion System for intervertebral body fusion at one level, or two contiguous levels in the lumbar spine from L2 to L5 in patients with degenerative disc disease with up to Grade I spondylolisthesis at the involved level. Refer to the following website for more information: https://www.accessdata.fda.gov/cdrh_docs/pdf21/K210155.pdf. (Accessed July 23, 2025)

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Policy History/Revision Information

Date	Summary of Changes
04/01/2026	**Template Update** • Removed content/language pertaining to the state of Louisiana

12/01/2025	**Coverage Rationale**
	• Added language to clarify Ceramic-Based Products [e.g., beta tricalcium phosphate (b-TCP), calcium phosphate, calcium sulfate] used alone or in combination with other grafts *and/or graft components*, including Bone Marrow Aspirate (BMA), are unproven and not medically necessary
	Medical Records Documentation Used for Reviews
	• Added language to indicate:
	  ○ Benefit coverage for health services is determined by the federal, state, or contractual requirements, and applicable laws that may require coverage for a specific service
	  ○ Medical records documentation may be required to assess whether the member meets the clinical criteria for coverage but does not guarantee coverage of the service requested; refer to the guidelines titled Medical Records Documentation Used for Reviews
	Definitions
	• Added definition of:
	  ○ Osseointegration
	  ○ Osteoconduction
	  ○ Osteoinduction
	• Updated definition of:
	  ○ Allograft
	  ○ Autograft
	  ○ Bone Marrow Aspiration
	Supporting Information
	• Updated *Clinical Evidence*, *FDA*, and *References* sections to reflect the most current information
	• Archived previous policy version CS009.U

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

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