# Bone Grafts and Bone Graft Substitutes

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## Abstract

Bone grafting has been uniquely practiced since the early 1600s. Historically, bone grafting includes autologous bone, a variety of allograft bone, and synthetic based-materials utilized in surgical interventions to treat spinal diseases or fractures. One of the most common uses of bone grafts is in spinal surgery to promote fusion between two functional vertebral segments. During a spinal surgery procedure wherein host bone is prepared, bone grafts are employed to optimize the biological environment to augment healing of the bony tissues for a desired outcome of a solid union – successful spinal fusion. State-of-the art bone graft materials have been effectively used to enhance bone induction and healing, providing more predictable outcomes resulting in spinal fusion.

Autograft has traditionally been recognized as the gold standard for bone grafts. However, differing grafting modalities are currently replacing autograft as the standard of care due to patient donor site morbidity, limitation to autograft, and the cessation of training young surgeons in the technique of autograft harvest. This has led to the research and development of various next-generation osteoconductive, osteoinductive, and osteogenic materials. In this chapter, various options to augment or replace autograft bone have been reviewed. Current options for spinal fusion discussed herein include autografts, allografts, and osteoconductive, osteoinductive, osteogenic, and osteostimulative materials. Further, novel materials such as engineered bioactive glass and peptide-based materials are presented. Choice of graft material with consideration of anatomical location, surgical application, spinal fusion technique, and patient characteristics will optimize bone healing and clinical outcomes.

## Keywords

Autograft · Allograft · Synthetic bone grafts · Viable bone grafts · Cell-based bone grafts · Bioactive glass · Growth differentiation factors · Bone graft extenders · Substitutes · Combination products · Osteoconductive · Osteoinductive · Osteogenic · Interbody fusion · Posterolateral fusion · Posterior fusion · BMP · rhBMP-2 · rhBMP-7 · P-15

## Abbreviations

| | |
|---|---|
| AATB | American Association of Tissue Bank |
| ABM | Anorganic bone matrix |
| ACDF | Anterior cervical discectomy and fusion |
| ACS | Absorbable collage sponge, used as a carrier |
| AIBG | Autologous iliac bone graft |
| ALIF | Anterior lumbar interbody fusion |
| Allograft | Graft derived from unrelated human donor and transplanted to another person/patient, cadaver via bone bank; live donor patients undergoing removal, i.e., hip replacement |

| | |
|---|---|
| APC, PRP | Autologous platelet concentrate, serum derived from patient himself is concentrated via centrifugation (contains cytokines, growth factors; theorized to promote fusion) |
| Autograft, Autologous | Bone harvested from patient self from one site of the body and implant to another site of same patient |
| BAG, BG | Bioactive glass, a ceramic, biologically compatible synthetic material of crystalline components |
| BCG | Biocompatible glass |
| BCP | Biphasic calcium phosphate |
| BIC | Bone-implant contact |
| BMA | Bone marrow aspirate |
| BMC | Bone marrow concentrate |
| BMP, rhBMP-2, rhBMP-7 | Bone morphogenetic protein, recombinant human bone morphogenetic protein |
| βTCP, β-TCP | Beta-tricalcium phosphate |
| Cage | Cages are cylindrical or square-shaped devices usually threaded. Used as instrumentation/fixation and to hold graft material in a surgical site, employed for interbody fusion, i.e., LT-Cage |
| Cell-based | Bone grafts with viable cells preserved or substitutes wherein cells are added |
| CGTP | Current Good Tissue Practice |
| CHO | Chinese hamster ovary (used to derive rhBMP-2) |
| Collagen Carrier | ACS, bovine type I collagen matrix |
| CS | Calcium sulfate, synthetic ceramic material composed of calcium-sulfate (1:1) |
| DBM powder | Demineralized bone matrix powder (human derived) |
| DBM, hDBM | Demineralized bone matrix (allograft), bone powder (allograft), hDBM (human derived) |
| DBM-based product | Demineralized bone matrix-based product, DBM powder (human derived) mixed with other material substances, or carriers |
| DFBA | Freeze-dried bone allograft |
| E.BMP, E.BMP-2 | Escherichia coli-derived BMP-2 (used to derive rhBMP-2) |
| ECM | Extracellular matrix |
| Enhancer | Acts to add properties of osteogenicity or osteoinductivity to a graft material |
| Extender | Bone graft extender, osteoconductive material, compounds, scaffolds added to other grafting materials (ideally inductive or osteogenic), to increase the volume of graft. May add structural support |
| FDA CFR | Code of Federal Regulations |
| FDA, US-FDA | Food and Drug Administration, US FDA |

| | |
|---|---|
| Growth factors/ growth Differentiation factors | BMP, rhBMP-2, rhBMP-7, bone morphogenetic protein, recombinant human bone morphogenetic protein |
| GvHD | Graft-versus-host disease |
| h | Human-derived or human-like version |
| HA | Hydroxyapatite, calcium-containing porous crystal, accounts for a majority of bone natural mineral component |
| HCO | Bicarbonate (Bae to review) |
| HCT/P | Human cell and tissue product |
| ICBG | Iliac crest bone graft, autograft – bone morsels harvested from iliac crest |
| ISO | International Organization for Standardization |
| LBG, LAG | Local bone graft, local autograft – bone morsels harvested from the surgical dissection site |
| LLIF | Lateral lumbar interbody fusion |
| MED | Minimally effective dose |
| MIS | Minimally Invasive Surgery |
| MRI | Magnetic resonance imaging |
| MSC | Mesenchymal stem cell |
| ncHA | Nanocrystal hydroxyapatite |
| OIF | Osteoinductive factor |
| OLIF | Oblique lumbar interbody fusion |
| Osteoconductive | Provides structural scaffolding upon which matrix-producing cells deposit new bone |
| Osteogenic | Presence of osteoblast precursor cells that contribute to new bone growth |
| Osteoinductive | Presence of molecular growth factors that stimulate precursors cells to migrate to graft site, mature into osteoid-producing cells, increase production of bone matrix |
| PEEK | Polyetheretherketone synthetic material, hydrophobic material to which cells have a limited ability to bond (polyaryletherketone family colorless organic thermoplastic polymer), used to fabricate spinal devices such as cages |
| Peptides/growth factors/growth differentiation factors | BMP, rhBMP-2, rhBMP-7 (OP-1 osteogenic protein), bone morphogenetic protein, recombinant human bone morphogenetic protein |
| rh | Recombinant human form |
| PLF | Posterolateral fusion |
| PLIF | Posterior lumbar interbody fusion |
| PLLF | Posterolateral lumbar fusion |
| PRP | Platelet-rich plasma (PRP) platelets (thought to have target |

| | |
|---|---|
| | growth factors) from patients' own blood |
| Segment, spinal segment | Spinal segment of the spine includes a superior vertebral body, disc, inferior vertebral body. Upper vertebral body, target vertebral body, lower vertebral body |
| Substitute | Graft substitute used instead of autologous bone grafting |
| TCP | Tricalcium phosphate, synthetic ceramic material composed of calcium and phosphate (3:2) |
| TI | Titanium (Ti) |
| TLIF | Transforaminal lumbar interbody fusion |
| TNF | Tumor necrosis factor |
| UDI | FDA rule that requires medical device manufacturers to update products with a unique device identifier |
| Xenograft | Grafted from one species to another species (i.e., bovine to human; porcine to human) |

## Introduction

Bone grafts and graft substitutes are materials that are used to rapidly induce or support biologic bone remodeling after surgical procedures to reconstruct bony structures and correct deformities and/or to provide initial structural support (Wang and Yeung 2017). In the spine, bone grafts are most often used to support biological healing with bony union of vertebral segments after a spinal fusion surgical procedure.

Bone grafts may come from a patient's own bone (autograft), may come from a human cadaver or living donor via bone bank (allograft), or may be fabricated from a synthetic material such as ceramics or bioactive glass. Furthermore, combination materials including composites of allografts, growth factors, osteogenic cells, synthetic materials of ceramic and/or cements, bioactive glass, and peptide-based materials have been developed and are offered for clinical use in spine fusion. See Table 1 for a description of sources of grafting materials and their associated bone-forming properties.

## Design Requirements for Engineered Biomaterials (Table 2)

The selection of bone graft alternatives to be used for spinal fusion should be conducted carefully by considering the different healing environments, reviewing the preclinical and clinical data, and also considering the regulatory burden of proof for products not subjected to high levels of regulation (Boden 2002).

The development of products used for bone regeneration has followed the basic criteria of providing a biocompatible three-dimensional scaffold with controlled architecture capable of stimulating or supporting bone growth in the natural in vivo environment. The ability of the material to be amalgamated with cellular and signal (differentiation/growth factors)-based products is a key strategy in maximizing the efficacy and likely success of fusion. The primary characteristics and significance of bone graft substitutes is shown in Table 2.

## Spinal Fusion

Spinal fusion is usually performed to provide stability to the spine when its biomechanics have been disturbed or altered. The surgical concept underlying spinal fusion is to reduce clinically important abnormal motion and add immediate and long-term stability, therefore decreasing or

**Table 1** Description of specific graft materials and bone forming properties

| Grafting material | Grafting material (typical abbreviation) | Grafting material category and description | Variability | Osteogenic | Osteo inductive | Osteo conductive | Immunogenicity/ disease transmission | Strength (immediate) | Donor site morbidity |
|---|---|---|---|---|---|---|---|---|---|
| *Autograft* | | | | | | | | | |
| Autograft | Iliac crest bone graft (ICBG) | More cancellous (mercerized and/or strut form) | Patients' own bone quality | +++ | ++ | +++ | – | +++ | ++ |
| Autograft | Local bone (LB, LAG) | More cortical (mostly mercerized form) | | +/– | + | + | – | +/– | +/– |
| Autograft | Bone dust (Gao et al. 2018; Street et al. 2017) | Generated via high-speed burr on bone surface | | +/– (less than local bone) | +/– (less than local bone) | +/– (less than local bone) | – | – | +/– |
| Autograft | PRP (platelet-rich plasma) (Elder et al. 2015) | Plasma preparation with increased platelet concentration | Patients' own health status | +/– | ++ (Elder et al. 2015) (activation of growth factors) | – | – | – | – |
| Autograft/bone marrow aspirate (Robbins et al. 2017) | Osteogenic cell with growth factors | Most common source of MSC | | + (variable according to donor's condition) | + (variable according to donor's condition) | – | – | – | + |

| *Allograft* | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Allograft | Fresh (Meyers 1985) | 1. Living donor (patient to patient transfer)<br>2. Cadaveric donor (harvested within 12 h and allotransplantation within 72 h)<br>➔ Femoral head (as osteochondral form) | Lot-to-lot variability donor's bone condition + sterilization processing techniques | ? (no data for osteogenic graft for human) | ? (no data for osteogenic graft for human) | ? (no data for osteogenic graft for human) | +++ (generally causes an unacceptable host immune reaction as osteogenic graft)<br>➔ Not used commercially, only animal studies | | |
| Allograft | Fresh (osteochondral graft) (Rauck et al. 2019) | 1. Living donor (patient to patient transfer)<br>2. Cadaveric donor (harvested within 12 h and allotransplantation within 24 h)<br>➔ Femoral head (as osteochondral form) (Torrie et al. 2015) | | +/– (only chondrocyte viability remains) | – | ++ | + (reduced/mild immune reaction by cartilaginous portion of graft)<br>+ (infection risk due to storage media) | ++ (grafted at articular portion for weight supporting) | |
| Allograft | Fresh-frozen (Kawaguchi and Hart 2015) | From:<br>1) Living donor<br>2) Cadaveric donor | | – | – | ++ (less than autogenous bone) (Miyazaki et al. 2009) | + (reported cases) | ++ (Kawaguchi and Hart 2015) | – |
| Allograft | Freeze-dried | From:<br>1) Living donor<br>2) Cadaveric donor | | – | – | ++ | +/– | +/– (significantly affected by drying process) (Wheeless 2013) | – |
| Allograft | Gamma sterilization | | | – | – | ++ | +/– | + (by radiation effect) (Hamer et al. 1999) | |

(continued)

**Table 1** (continued)

| Grafting material | Grafting material (typical abbreviation) | Grafting material category and description | Variability | Osteogenic | Osteo inductive | Osteo conductive | Immunogenicity/ disease transmission | Strength (immediate) | Donor site morbidity |
|---|---|---|---|---|---|---|---|---|---|
| Allograft | Demineralized bone matrix (Morris et al. 2018) | Mostly cadaveric donors | Demineralization processes + particle sizes | – | +/– | ++ | +/– | – | – |
| Selective cell retained allografts | Osteogenic cell | | Patient characteristics | + | +/– | – | | – | – |
| *Differentiation factors* | | | | | | | | | |
| Differentiation/ growth factor (Burke and Dhall 2017) | rhBMP-2 | Differentiation/ growth factor | High manufacturing consistency | – | +++ | – | – | – | – |
| | rhBMP-7 | Differentiation/ growth factor | | – | +++ | – | – | – | – |
| Peptides | B2A (Glazebrook and Young 2016) | Bioactive synthetic peptide | | – | – | ++ | – | – | – |
| | P15 (Hsu et al. 2017) | Bioactive synthetic peptide | | – | – | ++ | – | – | – |
| *Synthetic ceramics* | | | | | | | | | |
| Tricalcium phosphate | TCP | Synthetic ceramics | | – | – | ++ | – | – | – |
| Hydroxy apatite | HA | Synthetic ceramics | | – | – | ++ | – | +/– | – |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Biphasic calcium phosphate | BCP | Synthetic ceramics | | – | – | ++ | – | +/– | – |
| Calcium sulfate | CS | Synthetic ceramics | | – | – | ++ | – | – | – |
| *Synthetic bioactive glasses* | | | | | | | | | |
| Synthetic bioactive glass | 45S5 | Bioactive glass with 45% silicate | | – | + | ++ | – | +/– (Hench and Jones 2015) | – |
| | S53P4 | Bioactive glass with 53% silicate | | | + | + (less bioactive than 45S5) (Hench and Jones 2015) | | | |
| *Others* | | | | | | | | | |
| Xenograft | Xenograft | From nonhuman species, mainly bovine-based bone graft | Donor variability | – | +/– (according to sterilization process) | + | +++ (more than allograft) (Shibuya and Jupiter 2015) | ++ (in spine, foot, and ankle and trauma part) (Shibuya and Jupiter 2015) | – |
| Type I collagen | Xenograft carrier (bovine) | Osteoconductive scaffold/ hemostasis | Anatomic source location and species | – | – | + | – | +/– | – |

+++ Characteristic is definitely observed from biologic, clinical, and preclinical studies
++ Characteristic is somewhat observed from biologic, clinical, and preclinical studies
+ Suggested by clinical and preclinical studies. There may be some controversy, or effect is minimal
+/– Debate status
– None/no effect

**Table 2** Optimal characteristics of engineered biomaterials (O'Brien 2011)

| Characteristic/*sub-characteristic* | Significance |
|---|---|
| **Biocompatibility** | The very first criterion of any biomaterials for tissue engineering is biocompatibility. Cells must adhere, function normally, and migrate onto the surface and eventually through the scaffold and begin to proliferate before laying down new matrix. The host's immune reaction to the material must be negligible in order to allow for proper healing |
| *Capacity to bind cells or growth factors* | For this purpose, collagen often used as a method to enhance cell and growth factor attachment |
| **Biodegradability** | The biomaterials must be biodegradable to allow cells to produce their own extracellular matrix. The by-products of this degradation should also be nontoxic and able to exit the body without interference with other organs |
| *Resorption rate balanced with rate of bone formation* | The biomaterials must resorb and allow formation of new bone. Otherwise material may remain and become an inert obstacle to fusion or healing |
| **Mechanical properties** | The biomaterials should have mechanical properties consistent with the anatomical site into which it is to be implanted |
| *Intraoperative handling* | From a practical perspective, it must be strong enough to allow surgical handling during implantation |
| *Ability to visualize by fluorography intraoperatively* | Radio-density important to visualize location and to determine healing with subsequent x-rays |
| **Biomaterials architecture** | The biomaterials should have an interconnected pore structure and high porosity to ensure cellular penetration and adequate diffusion of nutrients to cells and of waste products out of the scaffold |
| *Controlled architecture,* i.e.*, porosity, interconnected pores, and pore size that permits cell ingrowth* | Cells need to be allowed to interact with each other and have continuity |
| *Promotes revascularization and bone ingrowth* | Essential in aiding bone healing |
| **Manufacturing technology** | In order for a particular tissue-engineered construct to become clinically and commercially available, it should be safe and cost-effective, manufactured following GMP, GLP, US-FDA, EU-EMA, and WHO International Conference of Harmonization technology standards (ISO) for scale-up from research laboratory-based small batch to large scale production lot reproducibility, maintaining reliability, stability, with optimized production processes meeting manufacturing requirements of country of manufacture and distribution |

For the USA, PHS Act (Public Health Service Act), FDA-established regulations for Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), set forth in Title 21, Code of Federal Regulations, Part 1271 (21 CFR 1271), Public Health Service Act (42 USC 264), Good Manufacturing Practices (GMP), Good Laboratory Practices (GLP), GTP, Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products etc. HCT/Ps to prevent the introduction, transmission, and spread of communicable diseases. These regulations can be found in 21 CFR Part 1271, section 361 (US FDA 2017, 2018)

eliminating pain thought to be aggravated by the abnormal motion (Herkowitz et al. 2004; Adams 2013). Spinal fusion is performed in patients with degenerative diseases like spinal instability, vertebral fractures, degenerative disc disease, and scoliosis. After a surgical decompression procedure has been performed to relieve pressure on the nerve roots or spinal cord, a fusion procedure may be completed as well to address the instability and provide long-term bony stability and structural reinforcement. The two main types of spinal fusion procedures are posterolateral fusion (PLF) and interbody fusion (IBF) performed from among a large variety of surgical approaches and techniques (Makanji et al. 2018; Morris et al. 2018).

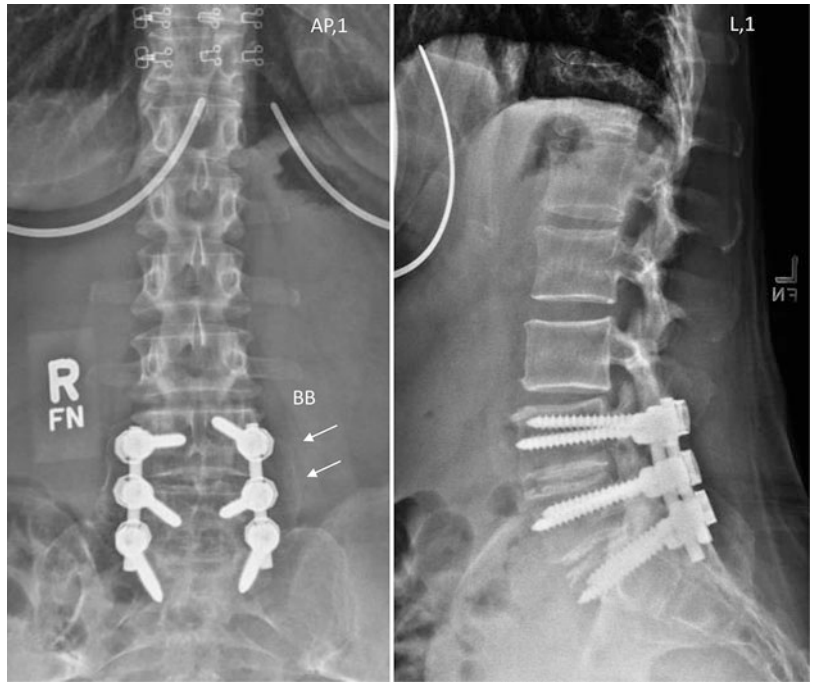


**Fig. 1** Example of posterolateral fusion with consolidated bone mass (BB) approximately 1 year after spinal fusion procedure with instrumentation and autograft placed in the posterolateral bed

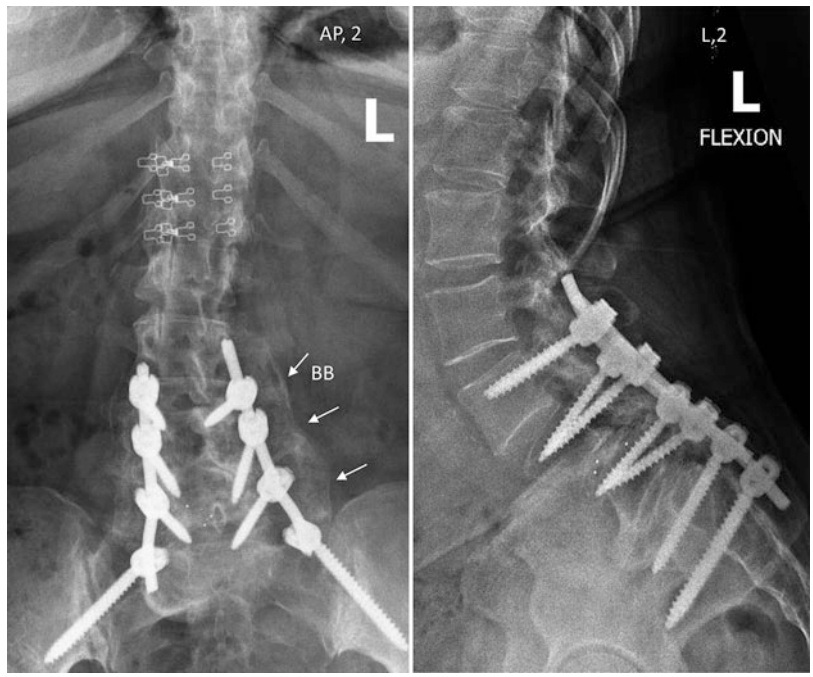


**Fig. 2** Example of four-level posterolateral fusion with dense solid bone mass (BB) bilaterally at 1 year after posterior spinal fusion procedure with instrumentation and grafting with Fibergraft (Prosidyan), allografts, and bone marrow aspirate (BMA)

Radiographic images of example patients after surgical fusion procedures in lumbar and cervical spine are provided (Figs. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 11).

In posterolateral fusion (PLF), the bone graft or bone graft substitute is surgically placed between the transverse processes, lateral to the side of the superior vertebral body and inferior vertebral

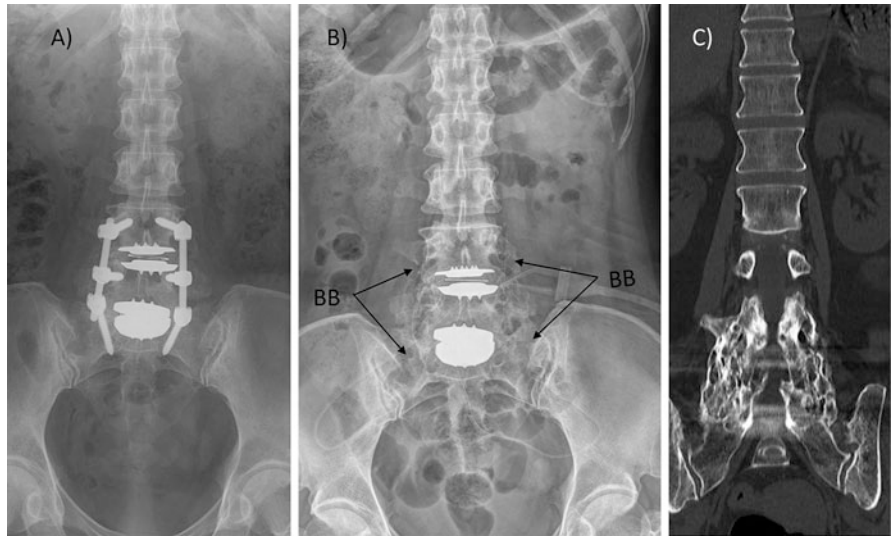


**Fig. 3** A 59-year-old female patient was surgically treated for failed artificial disc in the lumbar spine. For treatment, a posterolateral fixation was performed with allograft cancellous chip bone (Medtronic) mixed with autologous local bone and pedicle screw fixation device (Medtronic). A radio-dense bone bridge *was not* observed between transverse process between L3 and S1 on the initial postoperative anterior-posterior radiographs (A). On radiographs taken at 3-year follow-up after removal of pedicle screws, there was a radio-dense bone bridge (BB black arrows) on anterior-posterior (AP) radiographs. On CT image (C), definitive radio-dense bone (BB) was observed with contact between transverse process, facet joint, and grafted bone

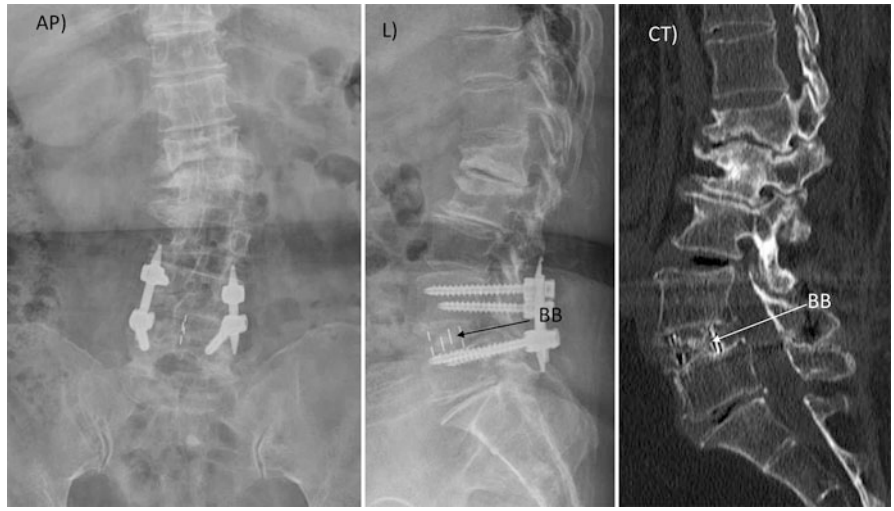


**Fig. 4** A 60-year-old female patient was surgically treated with a diagnosis of spinal-stenosis L4-L5. Surgery: an indirect decompression of spinal nerve and fusion via oblique interbody fusion (OLIF) technique with PEEK cage containing DBM-based product (Medtronic). A hemilaminectomy via MIS surgery technique was performed using percutaneous screw fixation. On anterior-posterior (AP), lateral (L) radiographs taken at 1.5-year follow-up, a radio-dense bony line was observed between upper and lower vertebral body through the inserted cage. On sagittal CT view, a dense bridge (bony incorporation) was formed at fusion site. Wedge-shaped vertebral deformation of L1 and L2 compression fracture was observed. L2 fracture was treated with PMMA bone cement

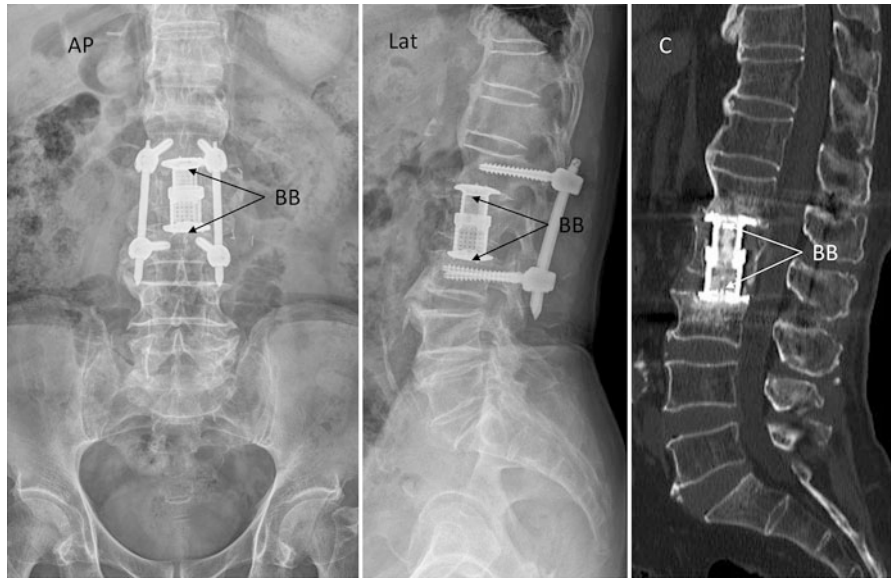


**Fig. 5** A 78-year-old male patient was surgically treated for TB spondylitis in L2. The infected vertebrae were removed through corpectomy process. Fusion procedures were performed using a distractible cage (DePuy Synthes) with allograft cancellous chip bone (Medtronic) mixed with autologous local bone and a percutaneous pedicle screw fixation device (Medtronic). Titanium distractible cage with keel on contact surface with vertebral endplate was used for load bearing architecture. On anterior-posterior (AP), lateral (L) radiographs taken at 2-year follow-up, a radio-dense bone bridge (black BB) was observed between upper and lower vertebral body. On CT image (C), definitive radio-dense bone (white BB) was observed connecting through the cage between the two vertebral endplates (white arrows indicate endplates)

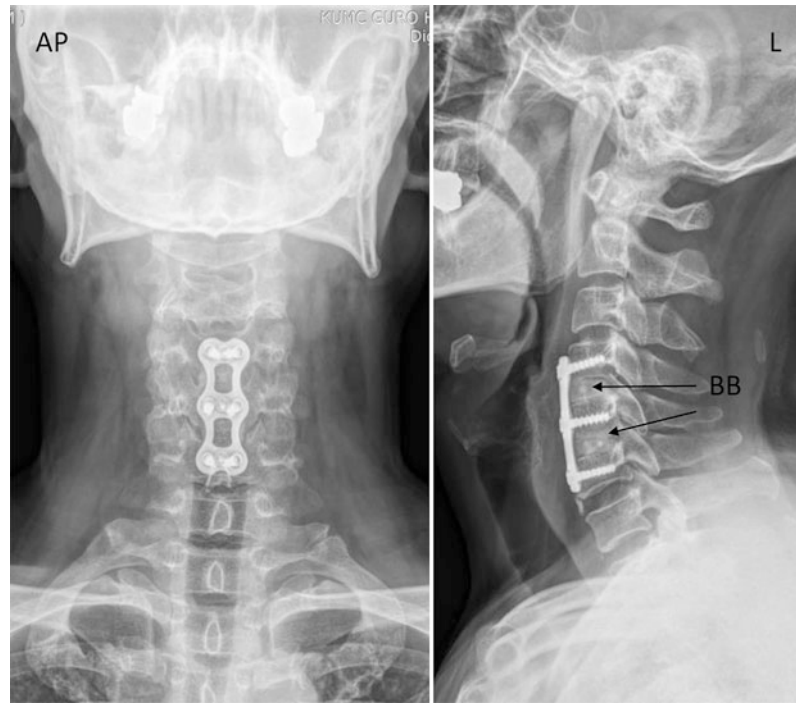


**Fig. 6** A 49-year-old male patient was surgically treated for herniated intervertebral disc C4–C5, C5–C6. A total discectomy was performed for decompression through an anterior surgical approach. A machined cortico-cancellous allograft (Medtronic) and cervical plate (Medtronic) were used in the fusion procedure. On anterior-posterior (AP), lateral (L) radiographs taken at 1-year follow-up, a radio-dense bone bridge (BB) was observed between upper and lower vertebral bodies though the inserted machined cortico-cancellous allograft

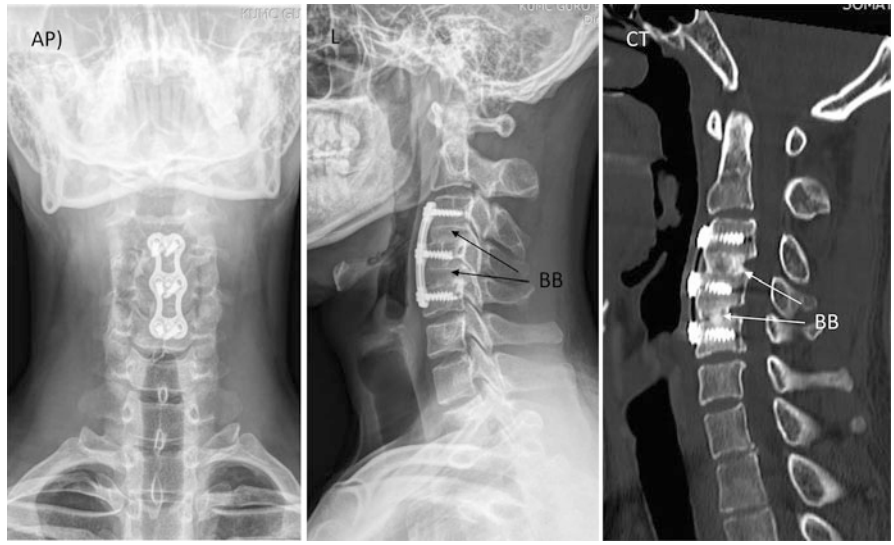


**Fig. 7** A 34-year-old male patient was surgically treated for two-level herniated intervertebral disc C3–C4, C4–C5. A total discectomy was performed for decompression through an anterior approach. For the fusion procedure, iliac autogenous bone graft and a cervical plate (Medtronic) were used. On anterior-posterior (AP), lateral (L) radiographs taken at 1-year follow-up, a radio-dense bone bridge (BB) was observed between upper and lower vertebral body through the inserted iliac autogenous bone graft. On sagittal CT view, there is bone formed and complete incorporation of C3–C4–C5 (BB) at the fusion site

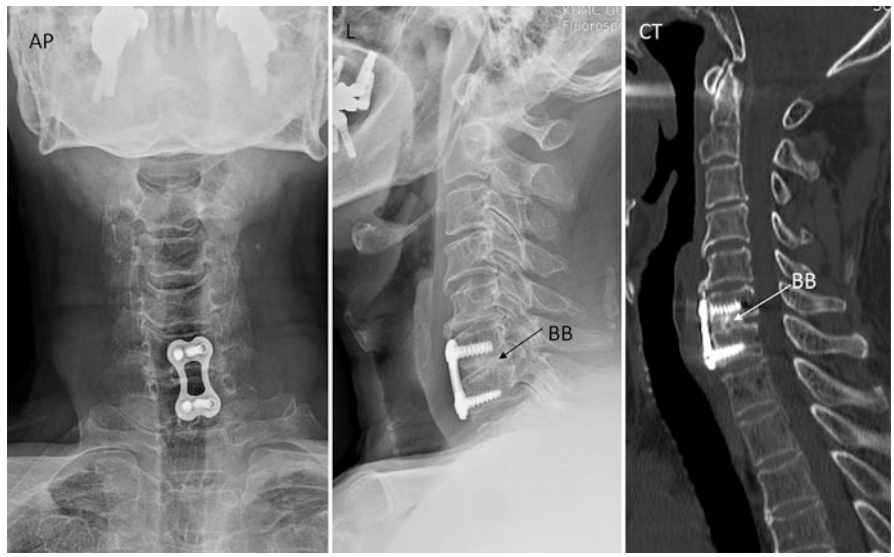


**Fig. 8** A 64-year-old male patient was surgically treated for herniated intervertebral disc C6–C7. A total discectomy was performed for decompression through an anterior surgical approach. For fusion procedure, a machined corticocancellous allograft (Medtronic) and a cervical plate (Medtronic) were used. On anterior-posterior (AP), lateral (L) radiographs taken at 1.5-year follow-up, a radio-dense bone bridge (BB) was observed between upper and lower vertebral body through the inserted machined corticocancellous allograft. On sagittal CT view, a bone bridge (BB, complete bony incorporation) was formed at fusion site

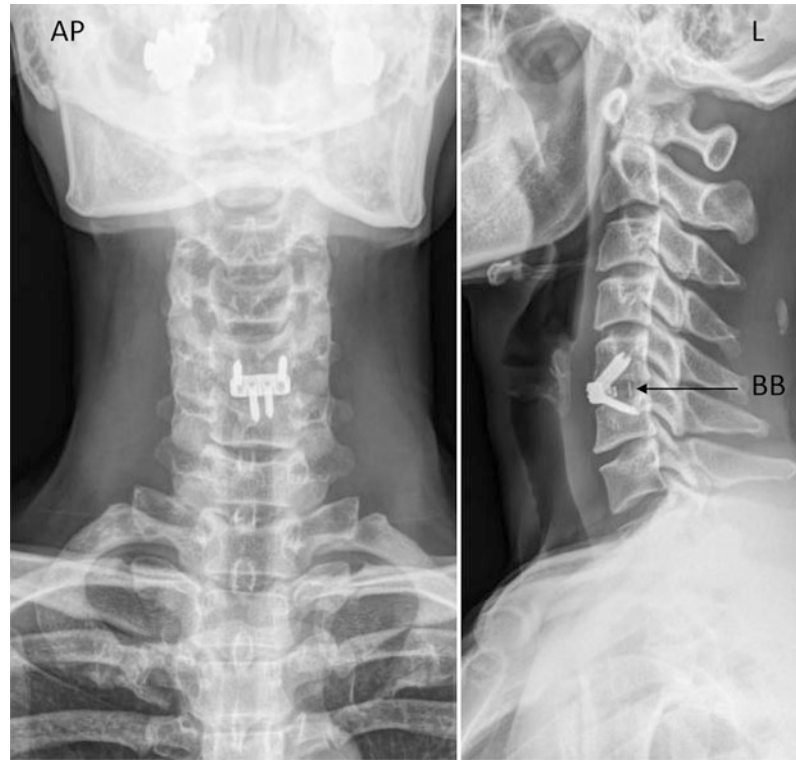


**Fig. 9** A 49-year-old female patient was surgically treated for herniated intervertebral disc at C5–C6. A total discectomy was performed for decompression through the anterior approach. For the fusion procedure, a Zero-p system (DePuy Synthes) and DBM-based putty (DBX, DePuy Synthes) were used. On anterior-posterior (AP) and lateral (L) radiographs taken at 2-year follow-up, a radio-dense bone bridge (BB) was observed between upper and lower vertebral body

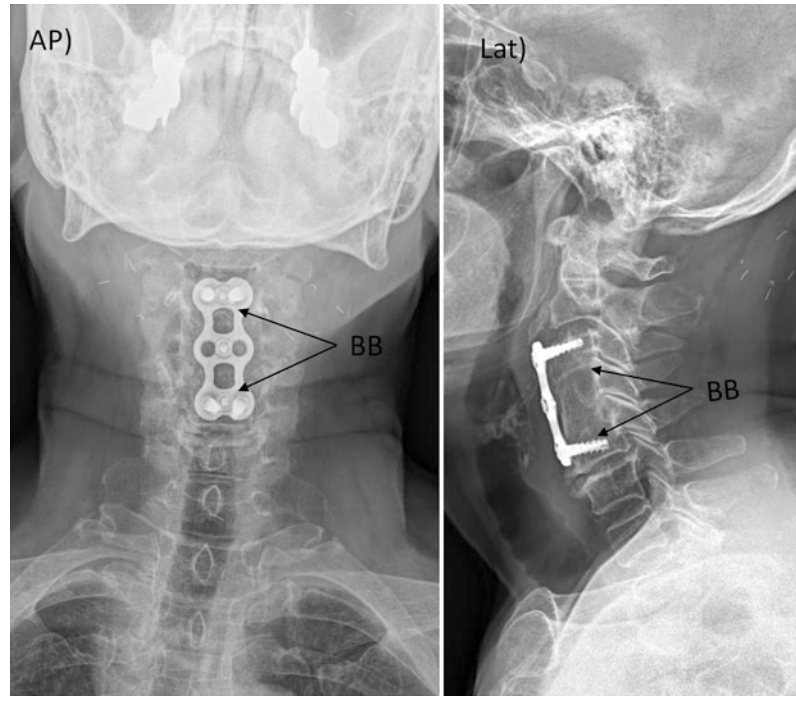


**Fig. 10** A 59-year old patient was surgically treated for fracture dislocation injury at C3 vertebrae after fall from height. Treatment of fracture was performed by a decompression through corpectomy and fusion using auto-iliac crest strut bone graft with cervical metal plate fixation spanning C3–4–5). On anterior-posterior (AP), lateral (L) radiographs taken at 3-year follow-up, a radio-dense bone bridge (black BB) was observed between upper and lower vertebral bodies (C3–C5 a solid bone unit). Note no radio-opaque gap between graft material and endplate of adjacent vertebral bodies

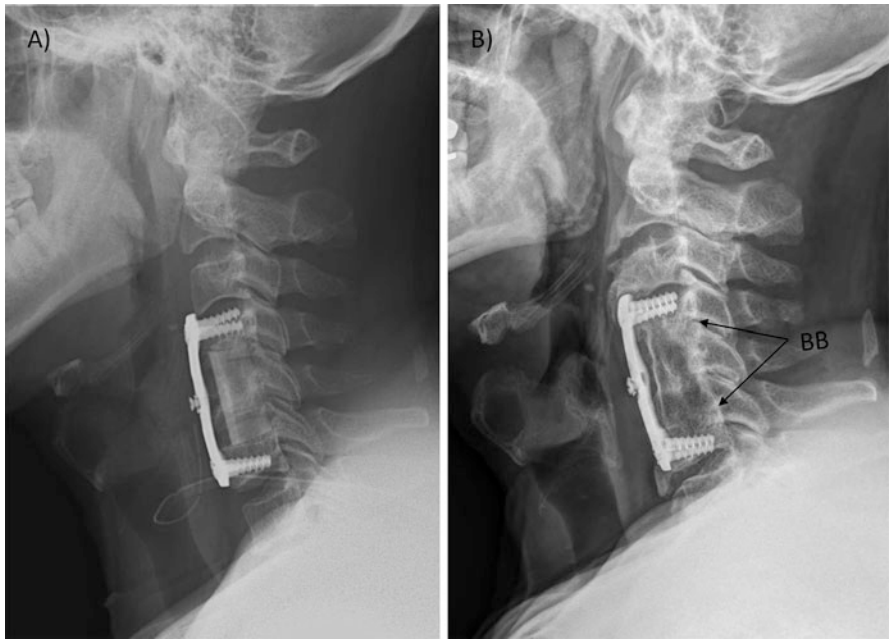


**Fig. 11** A 62-year-old male patient was surgically treated for OPLL from C4 to C6 cervical spine. Decompression of the spinal cord was performed through removal of vertebral body of C5 and C6. Fusion was performed using allograft strut fibula bone with a cervical metal plate (Medtronic). After initial postoperative radiography, a radio-opaque gap is seen between grafted material and endplate vertebral body. At 1-year follow-up, a complete incorporation between allograft and host bone is observed as a solid bone unit – no radio-opaque gap between grafted material and vertebral endplates. There is radio-density of grafted material indicating bony consolidation and incorporation with fusion from C4-C7

body. During the healing process, the graft material is remodeled and incorporated into a solid bony "bridge" (BB) between the transverse processes and lamina. Once healed, the spine segment is stabilized, and motion between vertebral functional segments is eliminated or reduced (Fig. 1, example lumbar spine).

In interbody spinal fusion, compared to PLF, the bone grafts or bone graft substitutes are placed between the endplates of two adjacent vertebrae (e.g., Figs. 4 and 5, lumbar spine; Figs. 6, 7, 8, 9, 10, and 11, cervical spine). The bone graft's and/or instrument with graft's contact with the endplates of the adjacent vertebral bodies resists relatively high loading forces.

Due to these biomechanical differences in graft sites, interbody fusion bone grafts are commonly placed with cages that hold the graft in place and are designed to withstand the compressive forces of the vertebrae. When the bone graft or bone graft in a cage is placed between the endplates of the vertebral body, it creates a framework of mechanical support during the early time of graft incorporation. This mechanical fixation and support eventually aids in the biologic bony union connecting one vertebral body to the other. Similarly to posterolateral fusion, once the vertebrae are fused, the spine is stabilized, and movement between operated spine segments should disappear. A systematic recent review of 12 studies (565 IBF-treated patients) by Baker et al. (2017) concluded that interbody fusion was a good surgical option in spondylolisthesis patients with instability. Interbody fusion can be performed by several different surgical approaches and techniques such as anterior (anterior lumbar interbody fusion (ALIF)), posterior (posterior lumbar interbody fusion (PLIF)), transforaminal (transforaminal lumbar interbody fusion (TLIF)), and lateral (lateral lumbar interbody fusion (LLIF)).

After a fusion procedure, the bone healing process occurs in different phases: inflammation,

soft callus formation, hard callus formation, and bone remodeling.

This includes hematoma formation, release of native growth factors/cytokines, and recruitment of inflammatory cells (e.g., macrophages and bone-forming cells); cell differentiation to bone-forming cells and mineralization of the extracellular matrix (ECM); bone resorption and remodeling; and formation of lamellar bone and hematopoietic marrow cavities (Rausch et al. 2017). These complex biologic processes of consolidation of grafted materials into new bone and remodeled into mature bone can be negatively affected by various systemic and local factors. Typical host or patient-based negative factors are advanced age (Ajiboye et al. 2017), concomitant use of tobacco or other drugs, poor nutritional status, and metabolic comorbidities (e.g., diabetes or osteoporosis) (Campbell et al. 2012; Ajiboye et al. 2017). Negative local factors are remaining structural instability, poor vascularity around surgical site, revision surgery, previous or current infection, and other local/surgical site considerations including surgical technical factors such as inadequate preparation of host bone, lack of fixation, inadequate bone graft volume and preparation, and improper use of graft materials (Yoo et al. 2015). Critical challenges for both interbody and posterolateral fusion are the excessive distances for the cells to migrate within and between host bone beds in order to attach to targeted neighboring anatomic bony structures; the limited durability of concentrations of growth factors, peptides, exogenous cells, biochemical, and other agents; and the biomechanical stability. These biologic challenges are particularly deterring in geriatric spine patients with severe osteoporosis.

To achieve successful bone fusion in the spine, surgeons vigilantly adhere to the requirements of bone regeneration and fracture healing mentioned above in deciding use of grafting materials. Bone formation requires three critical elements: osteoconduction, osteoinduction, and osteogenesis. *Osteoconduction* relies on a scaffold that supports cell ingrowth, facilitates vascularization, and provides a network for cells to attach. *Osteoinduction* relies on the provision of signals that act on the precursor cells and encourage cell migration, proliferation, and differentiation into bone-forming cells leading to rapid bone formation. *Osteogenesis* relies on the immediate provision of viable cells emanating from the host to the defect site differentiating into bone-forming cells. Autograft or autogenous bone possesses all three properties essential for bone formation and is therefore considered to be the gold standard graft material for inducing bone healing, consolidation, and fusion of the spine.

## Current Materials for Spinal Fusion

The graft material used in spinal fusion procedures can be generally categorized into three main types of materials: autogenous bone graft (autograft) from the patient's own body, allograft from human cadavers and/or living donors, and synthetic bone graft or substitutes (Table 1).

The use of autogenous bone graft has been a standard practice in spine surgery for over a century. The first reported use of autogenous bone graft for spine fusion was reported in 1911 when Fred Albee, MD, placed a tibia between spinal lamina in order to fuse and stabilize the spine (Albee 2007). Autograft has been considered the "gold standard" of bone grafting primarily because it contains all the elements required for successful fusion mentioned above: osteoconductive matrix, osteoinductive factors, and pluripotent bone-forming cells (Gupta and Maitra 2002; Whang and Wang 2003).

### Autografts

Autograft for spinal fusion can be obtained via different surgical approaches and dissection methods. Firstly, resected lamina, spinous process, facet, and osteophytes during the surgical decompression process yield bone graft which is then morselized – "local bone graft" (LBG). Local bone is commonly limited in amount and quality as mixture consists of mostly cortical bone vs. cancellous bone (Tuchman et al. 2016). Secondly, a bone graft can be obtained from iliac crest

using a separate surgical incision and various dissections (White and Hirsch 1971), which then can be used as strut or morselized bone. Iliac crest bone graft (ICBG) is relatively abundant, providing good-quality graft (mainly cancellous bone). However, iliac bone and local bone autografts have similar effectiveness in terms of fusion rates, pain scores, and functional outcomes in view of lumbar spine fusion (Tuchman et al. 2016).

Autograft bone is safe to use due to the low risk of disease transmission and offers the optimal chance of acceptance and effectiveness in the transplant site without immune reaction (Campana et al. 2014). However, the limitations with autogenous iliac bone graft such as relatively limited quantity, increased surgical time, and donor site morbidity are well recognized (Vaccaro et al. 2002). Due to these limitations, the use of autograft has declined.

The reduction in the use of autograft from the iliac crest in the recent practice has led to the increase in the use of local bone graft and has created new demands for the identification of cost-effective biologic materials that will "extend" the bone healing effects of local autograft (Ito et al. 2013). To achieve optimal outcomes, these materials should be biocompatible and biodegradable and have beneficial mechanical properties and microarchitecture that facilitates the biological healing process (Table 2).

## Allografts

Allografts are primarily osteoconductive with minimal osteoinductive potential and traditionally not osteogenic because the donor cells are eradicated during processing (Campana et al. 2014; Duarte et al. 2017). Allografts have the advantage for a surgeon of easy procurement (off-the-shelf), availability (commercially available), and many varieties of structural and non-structural form. However, allografts consist of nonviable tissue and cannot stimulate bone formation without the addition of bone-stimulating factors and cells (Goldberg and Stevenson 1993; Garbuz et al. 1998; Stevenson 1999). These limitations lead to slower and less complete incorporation with native bone. Additionally, allografts have potential risk of disease transmission even if the incidence is very low and the risk can be controlled during procurement and sterilization process (Campana et al. 2014).

### Allo-bone Graft: Cortico-cancellous Allograft (Table 3)

Allograft bone obtained from cadaver sources is added to the most widely used substitute or extender for autogenous bone graft. In the 1980s, femoral head from living donors (after total hip replacement surgery) was also introduced as another form of allograft and has demonstrated good clinical results in lumbar spine fusion (Urrutia and Molina 2013).

Allograft bone may be morselized to various sizes of particulate (i.e., chip bone) formed or machined to create structural spacers and then applied to site of desired bone formation. Cortical allograft is most often used as mechanical strut graft and is suited for interbody fusion, while cancellous allograft serves as a useful osteoconductive scaffold for bone formation.

The efficacy of allograft alone has been shown to have more clinical variability and lower fusion rates in challenging animal models and human studies of spinal fusion (Morris et al. 2018). These overall clinical results suggest that allograft be cautiously used in conjunction with either autograft or osteogenic material (e.g., bone marrow aspiration) to achieve good fusion rates and clinical outcomes (Morris et al. 2018). However, while the actual risk of transmission is negligible, issues of immunogenicity are present (Manyalich et al. 2009).

### Allo-bone Graft: Demineralized Bone Matrix (DBM)-Based Product (Table 4)

The DBM technology is based on the observation by Urist MR (Urist 1965) that soluble signals contained within the organic phase of bone were capable of promoting bone formation. The processing of transforming ground cortical bone into DBM powder base involves the use of hydrochloric acid to progressively remove mineral while attempting to preserve the organic phase containing type 1 collagen, non-collagenous

**Table 3** Commercially available structural and/or nonstructural allograftsural[a]

| Company | Allograft spinal graft products | Formulation product composition | | Clinical evidence ClinicalTrials.gov ongoing study | Regulatory clearance/approvals US by FDA registered tissue bank establishments 21CFR1270, CFR 1271 AATB; US; Pharmacopoeia USP standard 71 |
|---|---|---|---|---|---|
| AlloSource®, Centennial, Co, USA, 1995 Allosource.org | AlloFuse® | | Cortical/cancellous spacers<br>Cancellous cervical spacers<br>Cortical cervical spacers | n/a | Regulated human tissue CFR 1270, 1271 |
| | Spinal grafts freeze-dried | | Bicortical blocks<br>Dowel<br>Patella wedge<br>Cervical spacers, parallel spacer/textured lordotic<br>Femoral rings<br>Fibular rings, radial rings, ulna rings | n/a | Regulated human tissue CFR 1270, 1271 |
| | Spinal grafts freeze-dried/frozen | | Cortical strut<br>TriCortical Ilium Wedges, Strips | n/a | Regulated under CFR 1270, 1271 as a human tissue http://activize.com/wp-content/uploads/2014/05/Allograft-Catalog.pdf |
| ATEC, Carlsbad, CA | AlphaGRAFT® structural allografts | | Vacuum level allograft designed to hydrate | n/a | AATB standards and Good Tissue Practices |
| Aziyo, Richmond, CA | OsteSpine | | Structural cortical (femur, tibia, cortical shafts/struts)/cancellous spacers, (OsteSpine) precision-machined allografts | n/a | Regulated under CFR 1270, 1271 as a human tissue |
| Bone Bank Allografts, Texas, USA | SteriSorb™ | [a] | Osteoconductive Sponge Allografts (100% cancellous bone)<br>Characteristics of a sponge by absorbing saline, blood, or bone marrow aspirate | n/a | Bone Bank Allografts Registration – FDA<br>BBA Manufacturing Registration – FDA (previously THB)<br>Bone Bank Allografts – Accreditation<br>American Association of Tissue Banks (AATB)<br>CTO Registration Certificate – Bone Bank Allografts (International Registration) |
| | SteriFlex™ | | Wrappable Bone Allografts (100% cortical bone)<br>Can be bent, contoured, rolled, trimmed, molded, or sewn, making this flexible bone material | n/a | |

(continued)

**Table 3** (continued)

| Company | Allograft spinal graft products | Formulation product composition | Clinical evidence ClinicalTrials.gov ongoing study | Regulatory clearance/approvals US by FDA registered tissue bank establishments 21CFR1270, CFR 1271 AATB; US; Pharmacopoeia USP standard 71 |
|---|---|---|---|---|
| | SteriGraft™ – Cervical ACF<br>SteriGraft™ – ACF Cortical-Cancellous Spacer<br>SteriGraft™ – ALIF<br>SteriGraft™ – PLIF<br>SteriGraft™ – Unicortical Dense Cancellous Block<br>SteriGraft™ – Dense Cancellous Block | Fully machined. Constructed of 100% human cortical bone (femur or tibia)<br>Fully machined. Constructed of 100% human cortical bone with an internal cancellous plug (femur or tibia)<br>Fully machined. Constructed of 100% human cortical bone (femur)<br>Fully machined. Constructed of 100% human cortical bone (femur or tibia)<br>Unicortical Dense Cancellous Block (femoral head, patella, distal tibia, talus, or calcaneus)<br>Dense Cancellous Block (femoral head, patella, distal tibia, talus, or calcaneus) | n/a | |
| | Traditional bone/ cancellous bone allografts<br>Traditional bone/ cortical-cancellous bone allografts | Traditional-type cancellous bone chip or tricortical allo-iliac bone | n/a | |
| DePuy Synthes Spine | Zero-P Natural Plate System | Zero-Profile Plate with Allograft Spacer (cervical spine) | n/a | 21 CFR 888.3060, K152239, 2015 Dec<br>FDA 510(k) cleared |
| Hospital Innovations Ltd. Pontyclum, Wales, UK | Ilium Tricortical strips<br>Bone blocks<br>Whole and hemi shaft | Traditional cortical/cancellous bone graft<br>Available freeze-dried (FD) or frozen (FZ)<br>Sterilized SAL $10^{-6}$ | n/a | #22512, CF729FG, 2014 Jul [Regulation 7(1) Schedule 2 of Human Tissue Authority (Quality and Safety for Human Application (non-departmental public body, Department of Health and Social Care, UK) Regulations, 20070] |

| | | | | | |
|---|---|---|---|---|---|
| Globus Medical Inc | FORGE®<br>FORGE® Oblique | | Fully machined corticocancellous spacer (cervical spine fusion)<br>Fully machined cortical spacer designed to provide a natural option for transforaminal lumbar fusion | n/a | FDA 510(k) cleared<br>K153203, 2015 Dec |
| LifeLink Tissue Bank | Cortical Cancellous Spacer | | Fully machined cortical-cancellous spacer (from femur and tibia) for cervical spine | | AATB<br>FDA<br>Florida, California, and New York<br>Holds a permit to provide tissue in Maryland |
| Mountain States Medical<br>➔ Merged into Zimmer | OsteoStim® | | Fully machined cortical spacer (from femur and tibia) for cervical spine | | Processed at an AATB-accredited facility |
| Medtronic Spinal and Biologics | Allograft structural<br>Cornerstone SR<br>Cornerstone™ ASR<br>Cornerstone-Reserve™ | | Fully machined cortical block (from femur or tibia) with capital D shape<br>Fully machined cortical lateral wall with a cancellous center with capital D shape<br>Fully machined cortical ring with cancellous plug | ClinicalTrials.gov Identifier: NCT01491399, no results posted | AATB standards, FDA regulations, and applicable Public Health Service Guidelines for donor screening |
| | Cornerstone™ tricortical<br>Cornerstone™ bicortical<br>Cornerstone™ unicortical<br>Cornerstone™ dense cancellous block | | Freeze-dried cortical/cancellous (iliac crest)<br>Freeze-dried cortical/cancellous (iliac crest)<br>Freeze-dried anterior cortical wall with cancellous center<br>Freeze-dried dense cancellous with capital D shape | | AATB standards, FDA regulations, and applicable Public Health Service Guidelines for donor screening |
| | Cornerstone™ selective/cortical wedge | | Freeze-dried cortical ring | | AATB standards, FDA regulations, and applicable Public Health Service Guidelines for donor screening |
| Orthofix® | AlloQuent-s, Monolithic Cortical Structural allograft | | Structural allograft (cervical fusion, lumbar fusion)<br>Different sizes and shapes (ALIF, PLIF, TLIF) | NCT00637312, has results posted – cervical disc: Trial was stopped. Approval not being pursued for device (clinicaltrial.gov) | unk |

(continued)

**Table 3** (continued)

| Company | Allograft spinal graft products | Formulation product composition | Clinical evidence ClinicalTrials.gov ongoing study | Regulatory clearance/approvals US by FDA registered tissue bank establishments 21CFR1270, CFR 1271 AATB; US; Pharmacopoeia USP standard 71 |
|---|---|---|---|---|
| RTI Surgical® | Elemax® Cortical Spacer Allograft<br>Elemax® Cortical Spacer Allograft<br>Elemax® PLIF Allograft | Precision-machined cortical spacer for anterior cervical discectomy and fusion procedures<br>Fully machined cortical lateral wall with a cancellous center with capital D shape for anterior cervical discectomy and fusion procedures<br>Fully machined cortical spacer designed to provide a natural option for PLIF | n/a | AATB Accreditation Certificate – (Florida)<br>FDA Establishment Registration and Listing for Human Cells (FDA-HCT/Ps)<br>Florida, USA<br>Tutogen Medical, GmbH (Germany)<br>International Organization of Standards (ISO)<br>Tutogen Medical, GmbH (Germany)<br>CMDCAS – RTI Surgical (Florida)<br>CE Certificates<br>Pioneer Surgical Technology (Michigan)<br>International Facility Registrations<br>Health Canada CTO Registration<br>State Tissue Banking Licenses<br>California, Florida, Maryland, New York, Oregon, Illinois, Delaware |
| | AlloWedge® Bicortical Allograft Bone | Options for approaching opening wedge osteotomies in the foot and ankle<br>Pre-shaped bicortical allografts | n/a | FDA Establishment Registration and Listing for Human Cells (FDA-HCT/Ps) |
| | Cross-Fuse® Advantage Lateral Allograft | All cortical bone implant designed for a lateral approach to provide maximum potential for fusion<br>Produced from femoral or tibial tissue | n/a | FDA Establishment Registration and Listing for Human Cells (FDA-HCT/Ps) |
| | Bigfoot® ALIF Allograft | All cortical bone implant designed for use as an intervertebral spacer in anterior lumbar interbody fusion (ALIF) approach | n/a | FDA Establishment Registration and Listing for Human Cells (FDA-HCT/Ps) |

| | | | | | |
|---|---|---|---|---|---|
| | | | Freeze-dried: rehydrate for a minimum of 30 s<br>Frozen: thaw for a minimum of 15 min | | |
| | Traditional cortical and/or cancellous strut allobone | | Femoral head, hemi femoral shaft, humeral head, ilium tricortical block, ilium tricortical strip, proximal and distal femur, proximal and distal humerus, proximal and distal tibia, unicortical block, whole femur, fibula and humerus, and bicortical block | n/a | FDA Establishment Registration and Listing for Human Cells (FDA-HCT/Ps) |
| SeaSpine, Carlsbad, CA, USA | Capistrano™ System | | Cervical allograft spacer system is precision machined from cortical and cancellous allograft bone | n/a | 361-HCT/P US FDA 21 CFR 1271 Restricted to homologous use for the repair, replacement, or reconstruction of bony defects by a qualified healthcare professional (e.g., physician) |
| Stryker | AlloCraft™ CA, CL, CP, CS | | Machined from femoral/tibial allograft ➔ ACDF<br>Freeze dried<br>Chamfered edge | n/a | AATB<br>US FDA regulations for tissue management. US FDA 21 CFR 1271 |
| Xtant, USA | Ilium tricortical blocks, unicortical blocks, fibula segments, and femoral struts | | Traditional allografts | n/a | Processed by tissue banks that are members of the American Association of Tissue Banks (AATB) |
| X-spine Systems, Inc./Xtant, USA | Atrix-C™ Cervical Allograft Spacer | | Precision-milled cortical bone w/ teeth like keel surfaces | n/a | Processed by tissue banks that are members of the American Association of Tissue Banks (AATB) |
| Zimmer Biomet | OsteoStim® Cervical Allograft System<br>OsteoStim® PLIF<br>OsteoStim® ALIF/[a] | | Fully machined cortical spacer bone for cervical and lumbar w/ teeth like keel surfaces | n/a | Processed by tissue banks that are members of the American Association of Tissue Banks (AATB) |

AATB (American Association of Tissue Banks) Policies (2018)
*FDBA* Freeze-dried bone allograft
n/a not available on ClinicalTrials.org/no clinical data found or clinical trial registered
[a]Indicates cancellous chips "crunch" available

**Table 4** Commercially available DBM-based products

| Company | DBM-based product (human) | Formulation | Product composition | Peer-reviewed clinical evidence/ongoing study ClinicalTrials.gov identifier | Regulatory clearance/ approval FDA 510(k), CFR 1270, CFR 1271 |
|---|---|---|---|---|---|
| AlloSource®, Centennial, Co, USA, 1995 Allosource.org | AlloFuse® Gel AlloFuse® Putty (identical to StimuBlast Putty and Gel manufactured for Arthrex) | Injectable gel and putty | DBM, reverse phase medium (RPM) carrier Carrier comprised polyethylene oxide-polypropylene oxide block copolymer dissolved in water exhibiting reverse phase characteristics (i.e., an increase in viscosity as temperature increases) | n/a | 510(k) cleared K071849, 2008 Dec |
| | AlloFuse Plus | Paste, putty | DBM, RPM, cancellous chips | n/a | 510(k) cleared K103036, 2011 Jan |
| | AlloFlex | Strips, blocks, fillers | Cancellous bone allograft, DBM, strip form, no carriers added | n/a | Marketed as human tissue |
| Amend Surgical, Inc | NanoFUSE® Bioactive Matrix | Putty | DBM + 45S5 bioactive glass: bond void filler | n/a | 510(k) cleared K161996 2017 Feb |
| | NanoFUSE® DBM | Putty 2 cc to 10 cc | 45S5 bioactive glass + porcine gelatin + demineralized bone matrix (DBM) 45S5 bioactive glass: osteoconductive scaffold, DBM: osteoinductive potential | Kirk et al. 2013 Xynos et al. 2000a Xynos et al. 2000b | Regulated under CFR 1270, 1271 as a human tissue K110976, 2011 May www.accessdata.fda.gov/cdrh_docs/pdf11/K110976.pdf accessdata.fda.gov/cdrh_docs/pdf16/K161996.pdf 510(k) |
| ATEC, Carlsbad, CA | AlphaGRAFT®DBM AlphaGRAFT ProFuse DBM | Putty or gel | A reverse phase medium sponge-like DBM, superior handling characteristics, and ready-to-use application (thickens at body temp.) | n/a | unk |
| Aziyo Biologics | OsteoGro | | Cancellous bone and partially demineralized bone | | |

| | | | | | |
|---|---|---|---|---|---|
| Bacterin International, Inc. ➔ Changed to Xtant Medical | OsteoSelect DBM | Putty | 74% DBM dry weight | n/a | 510(k) cleared<br>K091321, 2009 Sept<br>K130498, 2013 May |
| | OsteoSelect Plus DBM | Putty | 74% DBM dry weight + demineralized cortical chips (1–4 mm) | n/a | 510(k) cleared<br>K150621, 2015 Aug<br>HCT/P (FEI 3005168462) |
| | OsteoSponge® | The malleable sponge | DBM (100% human demineralized cancellous bone) | Shehadi and Elzein 2017 | 510(k) cleared<br>HCT/P (FEI 3005168462), 2017 Nov |
| | OsteoSponge® SC | The malleable sponge | Demineralized cancellous bone intended to treat the pathology of damaged subchondral bone of the articulating joints | Galli et al. 2015 | 510(k) cleared<br>HCT/P (FEI 3005168462), 2017 Nov |
| | OsteoWrap® | Flexible handling characteristics with a scalpel or scissors | 100% human demineralized cortical bone | n/a | 510(k) cleared<br>HCT/P (FEI 3005168462), 2017 Nov |
| | 3Demin® | Various shapes (fiber, boat shape, strip) | 100% human demineralized cortical bone fiber<br>Contain BMPs and other growth factor<br>3Demin allografts are also available as loose cortical fibers in three volume options | n/a | Compliance with FDA guidelines regarding human cells, tissues, and cellular tissue-based products<br>HCT/P 361 regulated viable allogeneic bone scaffold<br>American Association of Tissue Banks guidelines |
| Berkeley Advanced Biomaterials, CA, USA | H-GENIN™ | Putty matrix sponge powder | 100% demineralized bone matrix putty and crush mix | n/a | 510(k) cleared (as B-GENIN, R-GENIN)<br>K092046, 2010 Mar |
| Biomet Osteobiologics ➔ Merged into Zimmer Biomet. | InterGro® DBM | Putty (40% DBM), paste (35% DBM) | DBM, lecithin carrier (resorbable, biocompatible, semi-viscous lipid) | Prospective case series | 510(k) cleared<br>K082793, 2009 Apr<br>K031399, 2005 Feb |

(continued)

**Table 4** (continued)

| Company | DBM-based product (human) | Formulation | Product composition | Peer-reviewed clinical evidence/ongoing study ClinicalTrials.gov identifier | Regulatory clearance/ approval FDA 510(k), CFR 1270, CFR 1271 |
|---|---|---|---|---|---|
| Bioventus® Surgical | Exponent™ | Putty form | Demineralized bone matrix is composed of human demineralized bone (DBM) mixed with resorbable carrier, carboxymethylcellulose (CMC) | n/a | AATB<br>US FDA 21 CFR 1271. (HCT/P) |
| | PUREBONE | Sponge shape (available in block or strip format) | 100% demineralized cancellous bone (osteoconductive matrix with osteoinductive potential that provides a natural scaffold for cellular ingrowth and revascularization)<br>Sterilized by gamma irradiation | n/a | FDA 510(k) cleared<br>AATB<br>US FDA 21 CFR 1271. (HCT/P) |
| Bone Bank™ Allografts 2017/ Texas Human Biologics | SteriFuse™ DBM Putty | Flowable, formable putty | 100% demineralized bone matrix from human bone | n/a | Regulated under 21 CFR Part 1271 (h FDA requirements for human cellular and tissue-based products (HCT/P)) |
| | SteriFuse™ Crunch | Flowable, formable crunch | SteriFuse™ DBM putty with cortical cancellous bone chips | n/a | Regulated under 21 CFR Part 1271 (h FDA requirements for human cellular and tissue-based products (HCT/P)) |
| DePuy Synthes | DBX® | Putty type | DBM + sodium hyaluronate | ClinicalTrials.gov Identifier: NCT02005081: RCT, results are not reported | 510(k) cleared<br>K103795, 2011 Apr |

| | | | | | |
|---|---|---|---|---|---|
| | Synthes® Dento | Powder type<br>Granule type<br>Putty type | Powder type: demineralized cortical powder, mineralized cancellous powder, mineralized cortical powder<br>Granule type: demineralized cortical (80%)/cancellous granules, mineralized cortical (80%)/cancellous granules<br>DBM putty type: 93% DBM | n/a | unk |
| ETEX (Zimmer Biomet, 2014 October) | CaP Plus | CaP Plus | Synthetic calcium phosphate, an inert carrier, carboxymethyl cellulose (CMC), and DBM | n/a | 510(k) cleared<br>K063050, 2007 Nov<br>K080329, 2008 Apr |
| | EquivaBone Osteoinductive Bone Graft | Powder and hydration solution | Synthetic calcium phosphate, an inert carrier, carboxymethyl cellulose (CMC) and DBM | | 510(k) cleared<br>K090855, 2009 Sep<br>K090310, 2009 Mar |
| Exactech | Optecure | Injectable paste | DBM (81% by dry weight), hydrogel carrier | Prospective RCT: ClinicalTrials.gov Identifier: NCT00254852 | 510(k) cleared<br>K121989, 2012 Nov<br>K061668, 2006 Sept<br>K050806, 2006 Feb |
| | Optecure® + CCC | Injectable paste | Polymer powder, DBM, cortical cancellous chips (1–3 mm) | Comparative study allograft vs Optecure® + CCC: ClinicalTrials.gov Identifier: NCT02127112 | 510(k) cleared<br>K061668, 2006 Sep<br>K121989, 2012 Nov |
| | Optefil (OSTEOFIL® DBM Paste, OSTEOFIL® RT DBM Paste) | DBM paste or dry powder – hydrated to become injectable paste | DBM in gelatin carrier | n/a | 510(k) cleared<br>K043420, 2005 Feb |
| | Opteform | Putty or dry powder – hydrated to become paste | Gelatin, DBM, and cortical-cancellous bone chips | n/a | 510(k) cleared<br>K043421, 2005 Feb |

(continued)

**Table 4** (continued)

| Company | DBM-based product (human) | Formulation | Product composition | Peer-reviewed clinical evidence/ongoing study ClinicalTrials.gov identifier | Regulatory clearance/ approval FDA 510(k), CFR 1270, CFR 1271 |
|---|---|---|---|---|---|
| Integra OrthoBiologics (IsoTis OrthoBiologics), Inc., Irvine, CA/SeaSpine 2018 | Accell Connexus | Injectable putty | DBM (70% by weight), RPM | Retrospective comparative: Schizas et al. 2008 | 510(k) cleared K060306, 2006 Mar K061880, 2007 Aug |
| | Accell Evo3™ | Injectable putty | DBM (Accell Bone Matrix), RPM | NCT02018445 ("Efficacy and Safety of Integra Accell Evo3™ Demineralized Bone Matrix in Instrumented Lumbar Spine Fusion") NCT01714804 (Integra Accell Evo3 Demineralized Bone Matrix) NCT01430299 | 510(k) cleared K103742, 2011 Mar |
| | Accell TBM | Preformed matrix (strip, square, round) | 100% DBM (Accell Bone Matrix) | n/a | 510(k) cleared K081817, 2008 Sep |
| | Dynagraft II | Injectable gel, putty | DBM (Accell Bone Matrix), RPM, cancellous bone chips | n/a | 510(k) cleared K040419, 2005 Mar |
| | Orthoblast II | Injectable paste, putty | DBM (Accell Bone Matrix), RPM, cancellous bone chips from same donor | n/a | 510(k) cleared K050642, 2005 Dec |
| LifeNet Health | IC Graft Chamber | Freeze dried in injectable delivery chamber, can be mixed with whole blood, PRP, or BMA | DBM, cancellous chips | n/a | Regulated under CFR 1270, 1271 as a human tissue |
| | Optium DBM Putty | Putty | DBM, glycerol carrier | n/a | 510(k) cleared K053098, 2005 Nov |
| | Optium® DBM Gel | Gel | Particulate DBM & Glycerol | n/a | 510(k) cleared K053098, 2005 Nov |
| | Cellect DBM® | Provided in a specialized cartridge | DBM fibers + cancellous chips | Case reports: Lee and Goodman 2009 | 510(k) cleared Regulated under CFR 1270 and 1271 |

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|---|---|---|---|---|---|
| Medtronic Spinal and Biologics | OSTEOFIL DBM | Injectable paste, moldable strips | DBM (24% by weight) in porcine gelatin | Prospective case series: Epstein and Epstein 2007 | 510(k) cleared K043420, 2005 Feb |
| | Progenix TM Plus | Putty with demineralized cortical chips | DBM in type I bovine collagen and sodium alginate | n/a | 510(k) cleared K081950, 2008 Jul |
| | Progenix Putty | Injectable putty | DBM in type 1 bovine collagen and sodium alginate | n/a (human) Blinded observations/ assessment of study in rabbit (Smucker and Fredericks 2012) | 510(k) cleared K080462, 2008 May |
| | Magnifuse™ Family 1) Magnifuse Bone Graft substitute/bone void filler 2) Magnifuse II Bone Graft | | DBM mixed with autograft in 1:1 ratio packed into polyglycolic acid (PGA) resorbable mesh bag 1) DBM + surface-demineralized chips 2) Combination of surface demineralized cortical chips and allograft fibers that have been processed removing the mineral component leaving only the organic portion | ClinicalTrials.gov Identifier: NCT02684045: retrospective case series study, results are not posted | 510(k) cleared K123691, 2013 Jan K082615, 2008 Oct |
| MTF/Synthes | DBX | Paste, putty mix, strip | DBM (32% by weight), sodium hyaluronate carrier (mix vary for paste, putty, mix) | n/a | 510(k) cleared K040262, 2005 Mar (putty, paste, matrix mix) K040501, 2005 Apr – (putty, paste, matrix mix) K053218, 2006 Dec (putty, paste, matrix mix) K063676, 2007 Mar (putty, paste, matrix mix) K080399, 2008 Oct (paste) K091217, 2009 Oct (putty) K091218, 2009 Sep (putty) K103795, 2011 Apr (putty K103784, 2011 Apr (putty) K042829, 2006 Jan (strip) |

(continued)

**Table 4** (continued)

| Company | DBM-based product (human) | Formulation | Product composition | Peer-reviewed clinical evidence/ongoing study ClinicalTrials.gov identifier | Regulatory clearance/ approval FDA 510(k), CFR 1270, CFR 1271 |
|---|---|---|---|---|---|
| Nanotherapeutics, Inc. | Origen™ DBM with Bioactive Glass (NanoFUSE® DBM) | A malleable, putty-like, bone void filler | Human demineralized bone matrix (DBM) and synthetic calcium-phospho-silicate particulate material particles (45S5 bioactive glass), both coated with gelatin derived from porcine skin | n/a | 510(k) cleared K120279, 2012 Apr K110976, 2011 May |
| NuTech Medical, Inc. | Matrix: Osteoconductive Matrix Plus | Putty type | Allograft cancellous and demineralized cortical mixture Freeze-dried for convenient ambient temperature storage | n/a | |
| | Matrix: FiberOS | Putty type | Demineralized cortical fibers, mineralized cortical powder, and demineralized cortical powder Gamma sterilized for patient safety Freeze-dried for convenient ambient temperature storage | | Nutec |
| Osteotech/ Medtronic | GRAFTON A-Flex | Round flexible sheet | DBM | n/a | 510(k) cleared K051188, 2006 Jan |
| | GRAFTON Crunch | Packable graft | DBM, demineralized cortical cubes | n/a | 510(k) cleared K051188, 2006 Jan |
| | GRAFTON Flex | Flexible sheets, varying sizes | DBM | Retrospective comparative study | 510(k) cleared K051195, 2005 Dec |
| | GRAFTON Gel | Injectable syringe | DBM | RCT, prospective case series | 510(k) cleared K051195, 2005 Dec |
| | GRAFTON Matrix PLF | Troughs | DBM | RCT | 510(k) cleared K051195, 2005 Dec |

| | | | | | |
|---|---|---|---|---|---|
| | GRAFTON Matrix Scoliosis Strips | Strips, various sizes | DBM | Retrospective case series | 510(k) cleared (Recalled 10/18/2012) |
| | GRAFTON Orthoblend Large Defect | Packable graft | DBM, crushed cancellous chips | n/a | 510(k) cleared |
| | GRAFTON Orthoblend Small Defect | Packable, moldable graft | DBM, crushed cancellous chips | n/a | 510(k) cleared |
| | GRAFTON PLUS® DBM Paste | Paste | Human bone allograft demineralized bone matrix (DBM) + inert starch-based carrier has been added | n/a | 510(k) cleared K043048, Nov 2005 (Osteotech)-traditional K042707, Nov 2005 (Osteotech) |
| | Grafton Putty 22076647 | Packable, moldable graft | DBM (17% by weight), glycerol | Kang et al. 2012 | 510(k) cleared K051195, 2005 Dec |
| Pioneer® Surgical Technology and Regeneration Technologies ➔ All companies merged into RTI Surgical® | BioSet TM | Injectable paste, putty, strips, and blocks with cortical cancellous chips | DBM, inert porcine, gelatin carrier | n/a | 510(k) cleared K080418, 2008 Apr Regulated under 21 CFR Part 1271 (h FDA requirements for human cellular and tissue-based products (HCT/P)) 12.07.2016 (validated by FDA) |
| | BioAdapt® DBM | Powder form | Dried granular powder form (70% of DBM by weight) from 100% human bone matrix | n/a | Regulated under 21 CFR Part 1271 (h FDA requirements for Human Cellular and Tissue-based Products (HCT/P)) 12.07.2016 (validated by FDA) |

(continued)

**Table 4** (continued)

| Company | DBM-based product (human) | Formulation | Product composition | Peer-reviewed clinical evidence/ongoing study ClinicalTrials.gov identifier | Regulatory clearance/ approval FDA 510(k), CFR 1270, CFR 1271 |
|---|---|---|---|---|---|
| | BioReady® DBM Putty and Putty with Chips | Putty/putty with bone chip | Putty: 56% DBM by weight<br>Putty with chips: 42% DBM by weight + small or large mineralized cortical cancellous chip<br>➔ 100% allograft DBM | n/a | Regulated under 21 CFR Part 1271 (h FDA requirements for human cellular and tissue-based products (HCT/P))<br>12.07.2016 (validated by FDA) |
| SeaSpine, Carlsbad, CA | OsteoBallast™ Demineralized Bone Matrix | DBM in resorbable mesh | 100% DBM | n/a | FDA 510(k) cleared |
| | OsteoSurge® 300 Demineralized Bone Matrix | The moldable putty form | DBM + Accell® bone matrix (it is an open-structured, dispersed form of DBM) + cancellous bone | NCT01430299 | It is same material to Accell Evo3 |
| | OsteoSurge® 300c Demineralized Bone Matrix | The moldable putty including cancellous chips | DBM + Accell® bone matrix (it is an open-structured, dispersed form of DBM) + cancellous bone + bioresorbable, reverse phase medium carrier. | n/a | It is same material to Accell Evo3c<br>SeaSpine new sponsor, same material |
| | OsteoSparx® Demineralized Bone Matrix | Gel or putty-like consistency | DBM + reverse phase medium carrier | n/a | It is same material to Accell Evo3 (NCT01430299) |
| | OsteoSparx® C Demineralized Bone Matrix | Gel or putty-like consistency. | DBM + reverse phase medium carrier + cancellous bone | n/a | It is same material to Accell Evo3c |
| | Accell Total Bone Matrix® | Pre-formed shape (round or rectangular) | DBM + Accell® bone matrix<br>➔ 100% DBM | NCT01430299 | It is same material to Accell Evo3 |
| | Accell Evo3c™ | Putty | DBM + Accell® bone matrix (it is an open-structured, dispersed form of DBM) + cancellous bone + bioresorbable, reverse phase medium carrier | n/a | FDA510(k) cleared K103742, 2011 Mar |

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|---|---|---|---|---|---|
| | Accell Evo3™ | Putty | DBM + Accell® bone matrix (it is an open-structured, dispersed form of DBM) + bioresorbable, reverse phase medium carrier | 1. Case study on posterolateral fusion (12/2013 ~ 06/2017, ClinicalTrials.gov Identifier: NCT02018445)<br>2. Prospective study on posterolateral fusion (12/2017 ~ 01/2018, ClinicalTrials.gov Identifier: NCT01714804)<br>3. RCT on posterolateral fusion Accell Evo3 Demineralized Bone Matrix (DBM) (93.5% fused) vs. rhBMP-2(100% fused). (ClinicalTrials.gov Identifier: NCT01430299) | FDA 510(k) cleared K103742, 2011 Mar |
| | Capistrano™ | DBM + allobone | DBM (demineralized bone matrix) + machined cortical and cancellous allograft bone | n/a | FDA 510(k) cleared |
| Smith & Nephew | VIAGRAF | Putty, paste, gel, crunch, and flex | DBM, glycerol | n/a | 510(k) cleared K043209 – 2005 Dec |
| Spinal Elements | Hero DBM | Putty, paste, gel | DBM, RPM | n/a | Regulated under CFR 1270, 1271 as human tissue |
| | Hero DBM Powder | Powder | DBM | n/a | Regulated under CFR 1270, 1271 as human tissue |
| Wright Medical technology | ALLOMATRIX® | Various volumes, consistency varies depending on proportion of cancellous chips utilized | DBM (86% by volume) +/− cancellous bone matrix (CBM) in surgical-grade calcium sulfate powder | Retrospective comparative study | 510(k) cleared K041663, 2004 Sept |
| | ALLOMATRIX ®RCS | Formable putty | DBM, synthetic resorbable conductive scaffold (RCS), calcium sulfate, and hydroxypropylmethylcellulose (HPMC) | n/a | 510(k) cleared K041663, 2004 Sept |

(continued)

**Table 4** (continued)

| Company | DBM-based product (human) | Formulation | Product composition | Peer-reviewed clinical evidence/ongoing study ClinicalTrials.gov identifier | Regulatory clearance/ approval FDA 510(k), CFR 1270, CFR 1271 |
|---|---|---|---|---|---|
| | ALLOMATRIX™ C | Putty | ALLOMATRIX™ + small cancellous chips | n/a | 510(k) cleared K040980, 2004 Jul |
| | ALLOMATRIX™ CUSTOM | Putty | ALLOMATRIX™ + large cancellous chips | n/a | 510(k) cleared K040980, 2004 Jul |
| | ALLOMATRIX™ | Injectable | DBM (86% by volume) + OSTEOSET™ (surgical-grade calcium sulfate) | RCT in trauma treatment ClinicalTrials.gov Identifier: NCT00274378 | 510(k) cleared K020895, 2004 Mar |
| | ALLOMATRIX® DR | Putty | Calcium sulfate, DBM, and small cancellous chips | n/a | 510(k) cleared K040980, 2004 Jul |
| | PROSTIM™ | Procedure kits, various volumes of injectable paste/formable putty | 50% calcium sulfate, 10% calcium phosphate, and 40% DBM by weight | n/a | FDA 510(k) cleared K190283, 2019 Feb |
| Zimmer ➔ It merged into Zimmer Biomet company | IGNITE | Percutaneous graft for fracture mal/nonunion | DBM in surgical-grade calcium sulfate powder to be mixed with bone marrow aspirate | n/a | 510(k) cleared K052913, 2005 Nov |
| | OSTEOSET DBM Pellets | Packable pellets | 3.0 mm or 4.8 mm pellets Surgical-grade calcium sulfate, DBM (53% by volume), stearic acid | n/a | 510(k) cleared K022828, 2004 Apr K053642, 2006 Jan |
| | PROSTIM™ Injectable Inductive Graft | Injectable paste/ formable putty | DBM (40% by weight), calcium sulfate (50% by weight), calcium phosphate (10% by weight) | n/a | 510(k) cleared K190283, 2019 Feb |
| | Puros DBM with RPM Gel and Paste | Gel, paste | DBM, RPM, ground cancellous bone (<500 microns) | n/a | Regulated under CFR 1270, 1271 as human tissue |
| | Puros DBM with RPM Putty and Putty with chips | Putty | DBM, RPM, +/− cortical bone chips (850 microns–4 mm) | n/a | Regulated under CFR 1270, 1271 as human tissue |
| | Puros DBM Block and Strip | Blocks, strips in varying sizes | DMB (100%) | n/a | Regulated under CFR 1270, 1271 as human tissue |

| | | | | | |
|---|---|---|---|---|---|
| | Bonus® CC Matrix | Putty type | Demineralized cortical bone (DBM) + mineralized cancellous chips<br>All-inclusive bone grafting kit | n/a | FDA registration number: FEI 1000160576 (till 06.30.2020)<br>AATB and HTC/P |
| | StaGraft™ DBM Putty and Plus | | DBM + natural lecithin carrier + resorbable coralline hydroxyapatite/calcium carbonate granules<br>Available as a 40% DBM Putty, or 35% DBM PLUS | n/a | FDA registration number: FEI 1000160576 (till 06.30.2020) |
| | StaGraft™ Cancellous DBM Sponge and Strips | | Cancellous DBM Sponge and Strips are machined from a single piece of cancellous bone<br>Osteoinductive bone, trabecular structure, sponge-like handling | n/a | FDA registration number: FEI 1000160576 (till 06.30.2020) |
| | FiberStack™ Demineralized Bone Matrix (DBM) | | Manufactured entirely from cortical bone, which has been demonstrated to maintain higher osteoinductivity than cancellous bone after demineralization 100% DBM (without carrier) | n/a | FDA registration number: FEI 1000160576 (till 06.30.2020) |

510(K) is a premarket submission made to FDA to demonstrate that the device to be marketed is at least as safe and effective, that is, substantially equivalent, to a legally marketed device that is not subject to premarket approval. 501(k) documentation for individual products is available via FDA online database (http://www.accessdata.fda.gov)
Code of Federal Regulations (CFR) 1270 (Human tissue intended for transplantation) and 1271 (Human cells, tissues and tissue-based products) are federal regulations relating to the procurement and processing of human-derived tissues
Human Tissues Banks: https://images.magnetmail.net/images/clients/AATB/attach/Bulletin_Links/18_2/AATB_Accreditation_Policies_February_08_2018.pdf (last update 2018 Feb)
TBI/Tissue Banks International National Processing Center (an AATB-accredited tissue bank)
US Human Tissue Bank Lic States: California, Florida, Maryland, and New York

proteins, and inductive growth factors (Gupta et al. 2015). Even after processing, DBM possesses osteoconductivity and osteoinductivity, but as a putty-/paste-like substance, it lacks structural integrity (Gupta et al. 2015). Since DBM base powder is derived from human bone allograft, disease transmission related with implantation is low, yet possible, although still less than structural-type allografts (bacterial infection estimated at 0.7 for non-massive to 11.7% for massive bone) (Zamborsky et al. 2016; Kwong et al. 2005; Lord et al. 1988).

Due to lack of structural integrity and relatively low osteoinduction potential comparing to autograft, DBM mixed with a carrier (DBM-based product, DBMs) is frequently used as a bone graft extender/carrier in interbody fusion. Commonly, DBMs are mixed with morselized autografts and exogenous peptide/differentiation factors along with collagen matrix, bone marrow aspirate, and/or isolated native blood-derived growth factors to stimulate new bone growth. In previous clinical reports on spine surgery, DBMs with autograft, and DBMs with growth factors (bone marrow aspiration), DBMs mixed with peptides (rhBMP-2/ACS) may be substituted for ICBG (Kang et al. 2012; Morris et al. 2018). DBM-based products or DBM powder are rarely used as a stand-alone graft material (Kinney et al. 2010).

There are several limitations to overcome in the clinical use of DBM-based products. The clinical effectiveness of DBM-based products is known to be variable according to manufacturer, form of product, as well as different lot-based batches from the same product form and manufacturer (Bae et al. 2006, 2010). The possible features of DBM-based products that contribute to varied reliability are varying native BMPs, growth/differentiation factors (donor bone), and dosages (Bae et al. 2006, 2010); forms such as putty, gel, flexible sheets, or mixed with cortical chips; compositions of carriers, scaffolds, gels, and other fillers; particle sizes of final bone powder; quality of the donor bone; and manufacturers processing procedures and sterilization method of products (Peterson et al. 2004; Bae et al. 2006, 2010). Amid these limitations, DBM-based products provide a diverse range of DBM-based grafting options that have been commonly employed for specific applications. DBM-based products introduced to the market over the last two decades and currently used are presented in Table 4.

## Exogenous Inductive Differentiation Growth Factors and Other Peptides (Table 5)

### Bone Morphogenetic Protein

Bone morphogenetic proteins (BMPs) are soluble members of the transforming growth factor-β superfamily that are involved in the differentiation, maturation, and proliferation of mesenchymal stem cells (MSCs) into osteogenic cells (Miyazono et al. 2005). To describe the acting mechanism, BMPs act via serine-threonine kinase receptors found on the surface of target cells and often transduce their signal via the SMAD pathway, leading to nuclear translocation and subsequent expression of target genes involved in osteogenesis (Hoffmann and Gross 2001; Sykaras and Opperman 2003). The reaction mechanism of BMP is mainly osteoinduction and reactively much less osteogenic potential (Campana et al. 2014). The graft material includes rhBMP-2 (exogenous protein) along with absorbable collage sponge (ACS, rhBMP-2 carrier). The carrier (ACS) has BMP binding competence in order to decrease diffusion away from the desired site for bone formation and increase controlled continual delivery of protein at the site. Although numerous carriers such as metals, collagen, ceramic such as tricalcium phosphate (TCP) and HCO, bioactive glass (BG), and polymers have been described (Agrawal and Sinha 2017), the most commercially available scaffold is an absorbable type 1 collagen sponge (ACS) bovine derived (Kannan et al. 2015).

For several decades, over 20 BMPs have been identified and described. Among them, BMP-1, BMP-2 (BMP-2A), BMP-3 (osteogenin, less osteoinductive) BMP-4 (BMP-2B), BMP-5, BMP-6, BMP-7, and osteoinductive factor (OIF) have been shown to induce bone formation

**Table 5** Commercially available bone inductive peptides, proteins-based products, recombinant versions

| Company | Peptide, growth factor product | Formulation | Product composition | Peer-reviewed clinical evidence/ongoing study ClinicalTrials.gov identifier | Regulatory clearance/US approval/PMA, FDA 510 (k) |
|---|---|---|---|---|---|
| CeraPedics Inc. | P-15L Bone Graft | Bone graft putty | ABM, lecithin carrier (resorbable, biocompatible, semi-viscous lipid)<br>P-15 synthetic peptide, calcium phosphate particles, porcine derived ABM anorganic bone matrix, along with bovine collagen carrier, P-15L | Ongoing clinical trials NCT03438747 (P-15L Bone Graft in an instrumented TLIF) | PMA |
| | i-FACTOR Bone Graft 'i-FACTOR™ Peptide Enhanced Bone Graft P-15 Putty, or iFACTOR Putty' | Synthetic small peptide (P-15) and peptide bone matrix (PBM) used in an allograft bone ring and with supplemental anterior plate fixation C3–C4 to C6–C7 following single-level discectomy for intractable radiculopathy (arm pain and/or a neurological deficit), with or without neck pain, or myelopathy due to a single-level abnormality localized to the disc space | A composite bone substitute consisting of a synthetic collagen fragment (P-15) bound to calcium phosphate particles<br>As an engineered product, P-15 quantity and viability remain consistent from lot to lot<br>P-15 in anorganic bone mineral (ABM). This unique combination replicates the organic (type I human collagen) and inorganic (calcium phosphate) components of autograft bone | Arnold et al. 2016b, 2018<br>NCT00310440 (P-15 synthetic osteoconductive bone substitute, ACDF)<br>NCT01618435 (i-FACTOR Bone Graft in non-instrumented Posterolateral Spondylodesis in Elderly with LSS)<br>NCT02895555 (5-10 CC i-FACTOR putty mixed with local harvested autograft, fusion lumbar spinal stenosis) | PMA cleared P140019, 2015 Nov www.accessdata.fda.gov/cdrh_docs/pdf14/p140019a.pdf |

(continued)

**Table 5** (continued)

| Company | Peptide, growth factor product | Formulation | Product composition | Peer-reviewed clinical evidence/ongoing study ClinicalTrials.gov identifier | Regulatory clearance/US approval/PMA, FDA 510 (k) |
|---|---|---|---|---|---|
| Medtronic Sofamor Danek, Inc., USA (Medtronic BioPharma B.V., Netherlands) | INFUSE™ Bone Graft/LT-CAGE™ | Recombinant human bone morphogenetic protein and a carrier/scaffold inserted into a hard LT-CAGE™ | rhBMP-2 (derived from a recombinant Chinese Hamster Ovary (CHO) cell line)<br>Bovine absorbable collagen I scaffold (ACS) (filler)<br>Ti metal prosthesis (Ti-6Al-4V) | NCT01491386<br>NCT01491425 | FDA approved, regulated under PMA P000058, 2002 Jul www.accessdata.fda.gov/cdrh_docs/pdf/p000058b.pdf |
| | | | rhBMP-2/ACS/INTERFIX™ | NCT01491451 | |
| | INFUSE® Bone Graft | LT-CAGE® Lumbar Tapered Fusion Device and INFUSE® Bone Graft | rhBMP-2, collagen scaffold (ACS) (filler)<br>Ti metal prosthesis (Ti-6Al-4V) | NCT00635843<br>Litrico et al. 2018 | |
| | INFUSE® Bone Graft | INFUSE® Bone Graft | INFUSE® Bone Graft consists of two components – recombinant human bone morphogenetic protein-2 (rhBMP-2, known as dibotermin alfa)<br>1.5 mg/mL of rhBMP-2; 5.0 mg sucrose, NF; 25 mg glycine, USP; 3. 7 mg L-glutamic acid, FCC; 0.1 mg sodium chloride, USP; 0.1 mg polysorbate 80, NF; and 1.0 mL of sterile water. Reconstituted rhBMP-2 solution has a pH of 4.5 and is clear, colorless, and essentially free from plainly visible particulate matter<br>Placed on an absorbable collagen sponge (ACS): bovine type I collagen obtained from the deep flexor (Achilles) tendon | ClinicalTrials.gov listings | FDA approved, regulated under PMA P000053, 2007 Mar www.accessdata.fda.gov/cdrh_docs/pdf5/p050053b.pdf |

| | | | | | |
|---|---|---|---|---|---|
| | INFUSE/ MASTERGRAFT™ | AMPLIFY™ | Posterolateral Revision Device<br>The INFUSE/ MASTERGRAFTTM Posterolateral Revision Device is indicated for the repair of symptomatic, posterolateral lumbar spine pseudarthrosis. This device is intended to address a small subset of patients for whom autologous bone and/or bone marrow harvest is not feasible or is not expected to promote fusion. These patients are diabetics and smokers. This device is indicated to treat two or more levels of the lumbar spine<br>Orthopedics Adult Oct. 10, 2008 | NCT01491542<br>https://www.accessdata.fda.gov/cdrh_docs/pdf4/h040004c.pdf | INFUSE/ MASTERGRAFTTM This device has been withdrawn at the request of the sponsor effective Mar 2010 |
| | INFUSE® Bone Graft | Polyetheretherketone (PEEK) in oblique lateral interbody fusion (OLIF) | OLIF 51 procedures with Divergence-L Interbody Fusion Device at a single level from L5–S1<br>OLIF 25 procedures with Pivox Oblique Lateral Spine System at a single level from L2–L5<br>ALIF procedures with Divergence-L at a single level from L2–S1 | NCT01415908, NCT04073563 | PMA supplement approval, 2015 Dec |

(continued)

**Table 5** (continued)

| Company | Peptide, growth factor product | Formulation | Product composition | Peer-reviewed clinical evidence/ongoing study ClinicalTrials.gov identifier | Regulatory clearance/US approval/PMA, FDA 510 (k) |
|---|---|---|---|---|---|
| | INFUSE® Bone Graft PEEK ACDF | | | NCT00485173, 2013 Arnold et al 2016a; Zadegan et al. 2017b IDE# G010188/ NCT00642876 and IDE# G000123/NCT00437190 (www.clinicaltrials.gov) Arnold et al. 2016a | Not cleared. |
| | InductOs® (Medtronic Spinal and Biologics) | Dibotermin alfa | Dibotermin alfa (recombinant human bone morphogenetic protein-2; rhBMP-2) is a human protein derived from a recombinant Chinese Hamster Ovary (CHO) cell line Bovine collagen I carrier | NCT02280187, InductOs® in Real World Spine Surgery; A Retrospective, French, Multi-centric, Study (InductOR) | Cleared in EU 1/02/226/ 002 |
| Stryker 2004 (Olympus Biotech 2010–2014, then closed facility) | OP-1 Putty | OP-1 Putty | OP-1/rhBMP-7 produced delivered on a purified type I bovine collagen carrier and Carboxymethylcellulose | For revision posterolateral lumbar spinal fusion spinal fusion Vaccaro et al. 2008 PMID: 17588821 Guerado and Fuerstenberg 2011 | Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) humanitarian device exemption (HDE) (check current 2018, not |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | sold in the USA)<br>OP-1 Implant is approved in 28 additional countries, including Australia, Canada, and the European Union<br>OP-1 no longer marketed in the USA (note, 2019) |
| Stryker 2004<br>Pfizer (Wyeth is now a wholly owned subsidiary of Pfizer) | Op-1 Putty | | OP-1(rhBMP-7) / purified Type I bovine collagen carrier and carboxymethylcellulose | Delawi et al. 2016<br>OP-1 group (54% versus 74% in the autograft group, $p = 0.03$) | FDA Advisory Committee: ("against expanded approval")<br>Not recommended |
| | | rhBMP-2/CPM<br>rhBMP-2/CPM matrix | Recombinant human bone morphogenetic protein-2 (rhBMP-2)/calcium phosphate matrix (CPM) | NCT00752557 (bone mineral density)<br>Closed fractures<br>NCT00161629 (radius)<br>NCT00384852 (humerus) | Not yet approved |
| BioAlpha Inc. | InjectBMP | ExcelOS-Inject ExcelOS 14-01 | Injectable Ceramics Bone Graft (beta-TCP) containing rhBMP-2 | NCT02714829 | Not USA, Korea |

Includes US FDA-tracked products (excludes products controlled exclusively under other regulatory agencies outside of USA)

(Wozney 1989, 2002). However, only two commercial forms of recombinant human BMPs currently are available for clinical use (Kannan et al. 2015). Recombinant human forms of BMP-2 (Infuse®; Medtronic) and BMP-7 (OP-1; Stryker) have been developed and approved both in the USA and Europe for commercial purposes by employing mammalian cells transfected with the corresponding human BMP sequence (Campana et al. 2014). Extensive research (over 30 years) has been conducted in support of the US-FDA approval process of rhBMP-2 and rhBMP-7; translational problems include scaling up, as super physiologic concentrations of rhBMP-2 are needed to meet MEDs in widely applicable orthopaedic indications in humans (Vallejo et al. 2002).

Internationally, in Korea, several products were developed employing various production processes for BMP-2 and different carriers. Its approved by Korea Food and Drug Administration (KFDA); to date its not approved by US-FDA. For spine fusion, the product carrier is granular HA and is based on *Escherichia coli*-derived rhBMP-2 (E.BMP-2, CGBio, Korea; E. BMP-2/HA, Novosis®, Korea) designed to improve the protein yield over the production process of using mammalian origin cell lines, such as Chinese hamster ovary (CHO) cells that incur low yield and high cost. There are several animal and clinical studies demonstrating the effectiveness and safety of Novosis® (Lee et al. 2012; Kong et al. 2014; Kim et al. 2015). According to the study of Cho et al. (2017), a fusion rate of 100% for E.BMP-2/HA (Novosis®) was comparable with that of 94.1% for AIBG demonstrating clinical efficacy and safety in PLF. E.BMP-2 production of rhBMP-2-based products and clinically used or in investigation are a rhBMP-2/Beta-TCP putty type (NCT01764906, Novosis® Korea), another Beta-TCP product containing rhBMP-2 (ExcelOS-inject, ExcelOS 14-01, NCT02714829, BioAlpha Inc., Korea), and a collagen gel +DBM containing rhBMP-2 (50 ug/cc) (rhBMP-2 produced from CHO cells, RafugenTM BMP-2, Cellumed Co Ltd., Seoul, Korea) employed as graft for interbody spinal fusion (pivotal RCT completed, 2017; submitted KFDA 2018, approved for dental application KFDA 2013).

US Regulatory approval by the FDA was initially granted for rhBMP-2/ACS (Infuse, Medtronic) in single-level anterior lumbar interbody fusion procedures in 2002 (Burkus et al. 2002). rhBMP-2 was then approved for tibia nonunion as an alternative to autograft in 2004 and for oral maxillofacial reconstructions in 2007 (Rengachary 2002). During last decade, rhBMP-2 has been commonly used off-label in posterolateral lumbar fusion surgery (Morris et al. 2018).

RhBMP-7, an osteogenic growth factor related to BMP-2, was first approved by the FDA in 2001 for use as an alternative to autograft for long bone fracture repair. In 2004, approval was expanded to cover PLLF (Morris et al. 2018). RhBMP-7 or OP-1 was approved for limited use under humanitarian device exemption (HDE) (no longer marketed in the USA (https://www.transparencymarketresearch.com/bone-morphogenetic-protein-market.html). In the last decade, several types of rhBMPs were developed and commoditized to medical market. RhBMP-based products were introduced to the market over the last two decades. Currently used products are presented in Table 5.

The osteogenic/osteoinductive potential of rhBMPs was strongly investigated in both preclinical and clinical studies, with a reported performance that is comparable to autogenous cancellous bone, with fusion rates between 80% and 99% (Campana et al. 2014). There are approximately 80 clinical studies on rhBMP-2 testing various surgical indications. According to a Level I comparison study of ICBG vs. rhBMP-2 with collagen sponge and ceramic granule by Dawson et al. (2009), at 24 months the rhBMP-2-/CS-/CM-treated patients had significantly higher solid fusion rates than those in the iliac crest autograft group (95% vs. 70%). Additionally, patients in the rhBMP-2/CS/CM group reported significantly greater improvement in clinical outcomes than did those in the iliac crest autograft group. According to the studies of Vaccaro et al. (2004, 2005), the use of rhBMP-7

(as OP-1 putty from) in conjunction with bovine collagen and carboxymethylcellulose (carrier) showed similar or slightly superior clinical result in spine fusion (posterolateral non-instrumented fusion) compared with autograft from the iliac crest.

However, limitations for general use of BMPs and complete substitution for autograft remain. First, rhBMPs have marked species-specific concentration requirements for osteogenesis, and thus results from preclinical studies are not considered as valuable background information for human application. Second, the dose-dependent efficacy in humans of rhBMPs has been observed in previous studies, and various clinical trials are aimed toward elucidating the optimal dosage of rhBMP-2/ACS (Govender et al. 2002). However, the optimal dosage/concentration for various off-label applications has rarely been reported or suggested in spine surgery. Third, during clinical trials, several major and minor adverse effects like ectopic bone formation in the neural canal, dysphagia when used in cervical fusion applications, prevertebral swelling, seroma/hematoma formation, radiculitis, osteolysis, heterotopic ossification, retrograde ejaculation, increased rates of new malignancy, and implant subsidence due to end-plate osteolysis are reported (Shields et al. 2006; James et al. 2016). Because of these limitations, numerous ongoing areas of investigation target alterations in dosage for optimal minimal dosage, scaffold to maintain concentration, and the implementation of supplemental proteins or growth factors to regulate the nonspecific action of rhBMP-2 (Agrawal and Sinha 2017; Burke and Dhall 2017; Poorman et al. 2017). Outside the USA, alternative-type protein products are in development (BoneAlbumin™, plasma protein) used to enhance bone allograft (Gmbh, OrthoSera, Austria).

## Peptide-Based Materials

Although naturally derived extracellular matrix (ECM) has demonstrated some degree of success in selected studies, it is challenging to modify, characterize, and control the presentation of natural ECM biomaterials (Shekaran and Garcia 2011). The limitations of ECM molecules have spurred the use of ECM-derived peptides or recombinant fragments that incorporate the minimal functional sequence of their parent protein to convey bioactivity to implant materials.

### Cerapedics

P-15 is a synthetic 15-amino acid peptide derived from the (766)GTPGPQGIAGQRGVV(780) sequence found in the α1(I) chain of type I collagen. Several preclinical studies have demonstrated that P-15 enhances cell adhesion, osteoblastic gene expression, and mineralization when implanted on anorganic bone matrix (ABM) in vitro and accelerates early bone formation in porcine and rat cranial defects (Shekaran and Garcia 2011). In a head-to-head comparison of DGEA peptide and P-15-coated hydroxyapatite discs implanted into rat tibiae, both peptides improved new bone formation, but P-15 failed to enhance bone implant contact. A recent study in the larger bovine model, ABM/P-15 (ABM an allograft in this application), failed at 4.5 months after uninstrumented posterior lumbar spine surgery; 68% fusion in allograft implanted sheep vs. 0% fusion as determined by bridging between transverse processes was found in ABM/P-15 implanted sheep (Axelsen 2019).

For human applications of a xenograft carrier (a sinterized cancellous bovine bone matrix), the implemented carrier has been employed. P-15 peptide-coated ABM has been used in human periodontal osseous defects resulting in better clinical outcomes than open flap debridement alone and has also been used in a pilot clinical study for long-bone defects (Shekaran and Garcia 2011). In a prospective, randomized, single-blinded trial of single-level ACDF using P-15/CBM in an allograft spacer versus local autograft in an allograft spacer, 89.0% vs. 85.8% fusion rates were reported, respectively, at 1-year follow-up with equivalent clinical outcomes and complications (Hsu et al. 2017).

### B2A

B2A is a bioactive synthetic multi-domain peptide that augments osteogenic differentiation via increasing endogenous cellular BMP-2 by pre-osteoblast receptor modulation at spine fusion

site (Lin et al. 2012). The empirical formula of B2A is C241H418N66O65S2 containing 42 amino acids and 3 lysine analogue residues of 6-aminohexanoic (Glazebrook and Young 2016). This peptide has osteoinductive potential; it is used with a scaffold. The osteoconductive scaffold is a ceramic granule from which B2A elutes in vivo. Two commercialized products PREFIX® (Ferring Pharmaceuticals, Saint-Prex, Switzerland) and AMPLEX® (Ferring Pharmaceuticals, Saint-Prex, Switzerland) are based on this converged technology. After grafting of B2A with ceramic granules, complete absorption of B2A occurs within approximately 6–8 weeks (Glazebrook and Young 2016).

There is great interest in the benefits of conjugation technology for modulating release kinetics in grafting materials. However, there are limited preclinical and clinical studies on the safety and effectiveness of B2A/ceramics. B2A/ceramic granule was tested in two animal studies (rabbit and sheep). B2A/ceramic significantly improved the fusion rate in PLLF and PLIF over simple autograft bone graft (Smucker et al. 2008; Cunningham et al. 2009). In a clinical study, higher fusion rates were observed in B2A-coated ceramic granule (formulated as PREFIX®)-grafted patients than in ICBG-grafted patients after an interbody fusion procedure (Sardar et al. 2015). Studies are limited; Clinicaltrials.gov indicates two registered multicenter studies with "unknown" status. Validating the safety and efficacy of this bone graft material necessitates high-quality clinical studies and/or multicenter studies enrolling large number of patients. To date, there is only one published pilot study (Sardar et al. 2015, Canada) with a small/insufficient sample size.

## Synthetic Materials and Drafts (Table 6)

Synthetic graft materials are typically employed during fusion surgery as bone graft extenders and sometimes substitutes. Traditionally, these materials provide an osteoconductive scaffold with ideally no reactive inflammatory immunogenic response from host tissues. The known advantageous properties of synthetic materials like ceramics include osteoconductive, biodegradable, no risk of infection, no donor site morbidity, unlimited supply, relatively easy sterilization, easiness of molding sized and shape, and lack of immunogenicity and toxicity (Gupta et al. 2015; Kannan et al. 2015). More recently, the emerging novel synthetics involve new technological advances in material science and/or incorporate a menagerie of cross-product materials in order to address the molecular biologic demands for bone induction, consolidation or healing, and fusion mass incorporation. Design innovation may lead to a true potent autograft substitute.

For making an ideal bone graft extender or graft substitute, several characteristics should be considered. The development of products used for bone regeneration has followed the basic criteria of providing a biocompatible three-dimensional scaffold with controlled architecture capable of stimulating or supporting bone growth in the natural in vivo environment (O'Brien 2011). The ability of the material to be used in conjunction with other cellular and signal-based therapies (peptides, growth factors) is a key strategy in maximizing the efficacy and likely success of fusion. The primary characteristics of bone graft substitutes are shown in Table 6.

### Calcium Phosphate Materials

Calcium phosphates are a common base for synthetic graft materials. This is primarily because 70– 90% of inorganic material in the body is a type of calcium phosphate. Calcium phosphate materials have been cleared in the USA for use as "bone void fillers" (FDA MQV, MBP) that can be used for spine fusion and orthopedic applications. The common types of calcium phosphate materials are beta tricalcium phosphate $Ca_3(PO_4)_2$ (TCP) and hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$ (HA).

TCP was one of the earliest synthesized forms of calcium phosphate materials that was used as an osteoconductive bone void filler. TCP in the form of granules or blocks is available as a three-dimensional structure with interconnected pores from 1 to 1,000 microns. However, TCP and all

**Table 6** Commercially available synthetic bone void fillers, extenders, and substitutes products

| Company | Synthetic product | Formulation | Product composition | Peer-reviewed clinical evidence ClinicalTrials.gov/ongoing study | Regulatory clearance/approval FDA 510(k), CFR 1270, CFR 1271 MQV, filler, bone void, calcium compound common name – bone grafting material classification name – bone grafting material, synthetic |
|---|---|---|---|---|---|
| Amend Surgical, Inc., FL, USA | 0.5 cc NanoFUSE® (posterolateral fusion) | Putty-like, malleable | Amend Surgical, Inc., NanoFUSE® comprised synthetic calcium-phospho-silicate particulate material particles (45S5 bioactive glass) coated with gelatin derived from porcine skin. (there is a DBM version of this material) | n/a | 510(k) cleared 21 CFR 888.3045 K161996, 2017 Feb |
| | 45S5 bioactive glass (1–10 cc) | Particulate material | 45 wt% SiO2, 24.5 wt% CaO, 24.5 wt% $Na_2O$, and 6.0 wt% $P_2O_5$ Synthetic binder | | 510(k) cleared K110368, 2017 Jan |
| Aspine USA, Oakland, CA | Osteo-G Bone Void Filler System | Pellets/paste | Bioabsorbable, calcium sulfate dihydrate (prefabricated or kit to form into various shape implants), radiopaque | n/a | FDA 510(k) cleared K031319, 2003 Jul |
| APATECH LTD, United Kingdom ➔ Merged into Baxter Healthcare | **ACTIFUSE** synthetic bone graft | | Phase-pure silicon-substituted calcium phosphate Osteoconductive bone graft substitutes, comprising a single-phase calcium phosphate scaffold, either granules or granules delivered in a matrix of resorbable polymer | NCT01833962, no results posted | 510(k) cleared K090850 {K040082, K071206, K080736, K082073, K081979, K082575} |
| | **ACTIFUSE** Shape | Flexible shape | Distinctive moldability and versatility allowing the unique contours of each defect to be addressed Silicon-substituted calcium phosphate | NCT02005081 Anterior cervical corpectomy (ACC), no results posted | FDA 510(k) cleared K082575, 2008 Nov |

(continued)

**Table 6** (continued)

| Company | Synthetic product | Formulation | Product composition | Peer-reviewed clinical evidence ClinicalTrials.gov/ongoing study | Regulatory clearance/approval FDA 510(k), CFR 1270, CFR 1271 MQV, filler, bone void, calcium compound common name – bone grafting material classification name – bone grafting material, synthetic |
|---|---|---|---|---|---|
| | **ACTIFUSE** ABX | | A sculptable synthetic bone graft substitute<br>Silicon-substituted calcium phosphate | ClinicalTrials.gov Identifier: NCT01852747 (fusion rate for multilevel fusion in spine)<br>ClinicalTrials.gov Identifier: NCT01013389 (RCT, interbody fusion, comparative study with infuse)<br>ClinicalTrials.gov Identifier: NCT01018771 (RCT, PLF fusion, comparative study with infuse) | FDA 510(k) cleared<br>K082575, 2008 Nov |
| | **ACTIFUSE** Microgranules | Granules | Synthetic bone graft substitute designed for smaller defects<br>Silicon-substituted calcium phosphate | n/a | FDA 510(k) cleared<br>K082575, 2008 Nov |
| | **ACTIFUSE** Granules | Granules | Synthetic bone graft substitute, designed for larger defects<br>Silicon-substituted calcium phosphate | n/a | FDA 510(k) cleared<br>K082575, 2008 Nov |
| | **ACTIFUSE** MIS System | Injectable type | A ready-to-use applicator and cartridge designed for controlled delivery during minimally invasive procedures<br>It contains ACTIFUSE ABX | NCT02845141, revision ACL | FDA 510(k) cleared<br>K082575, 2008 Nov |
| | **ACTIFUSE** E-Z-Prep Syringe | Putty Matrix | A preloaded syringe containing ACTIFUSE Microgranules | n/a | FDA 510(k) cleared<br>K082575, 2008 Nov |
| | Inductigraft | | MAUDE adverse event report<br>Active bone graft substitute 45S5 bioactive glass (M-45 granules, | NCT01452022, Inductigraft in posterolateral fusion | Not registered in the USA |

| | | | | | |
|---|---|---|---|---|---|
| | | | MS-45 microspheres) and bovine type I collagen (hydration with saline or blood). For use in posterolateral fusion | | |
| Berkeley Advanced Biomaterials, Berkeley, CA, USA, 1996 | Cem-Ostetic®, Bi-Ostetic™, GenerOs™ | Granule, block Injectable putty | Bone void fillers are based on nanocrystalline hydroxyapatite (HAP) and tricalcium phosphate (TCP) | Bi-Ostetic Bioactive Glass Foam | FDA 510(k) cleared K170917, 2017 Oct ISO 13485 certified and CGMP |
| Biomatlante, France | MBC PTM | Various shapes and sizes | Microporous and macroporous biphasic calcium phosphate ceramic consisting of 60% hydroxyapatite (HA) and 40% beta-Tricalcium Phosphate (β-TCP) | NCT00206791 | K043005, 2015 May |
| BioAlpha Inc., Korea | Novomax | Intervertebral spacer | Bioactive glass-ceramic spacer | NCT03532945 | unk |
| | Bongros®-HA | | Hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$) highly pure with trabecular structure, 3-dimensional interconnected pores | | K090793, 2009 May |
| Biomet Osteobiologies ➔Merge into Zimmer-Biomet | Calcigen™-S | Paste granules | Calcium sulfate dihydrate, isothermic | n/a | FDA 510(k) cleared K013790, 2002 Jun |
| | BonePlast® | Powder | Calcium sulfate with or without HA/CC | n/a | FDA 510(k) cleared K070864, 2007 Jun |
| | BonePlast®Quick Set | Quick setting paste | Calcium sulfate (mixed setting solution, QS) (limited to be used in posterolateral fusion) | n/a | FDA 510(k) cleared K070864, 2007 Jun |
| Biomimetic Therapeutics, Inc., Franklin, TN | Augment Bone Graft | | β-Tricalcium phosphate-containing matrices + recombinant human platelet-derived growth factor-BB | Solchaga 2012 (ovine) rhPDGF-BB solution (0.3 mg/mL) was mixed with the β-TCP (1:1, v:v), allowed to incubate at room temperature for 10–15 min and then transferred to a 3 mL syringe with the end removed | |

(continued)

**Table 6** (continued)

| Company | Synthetic product | Formulation | Product composition | Peer-reviewed clinical evidence ClinicalTrials.gov/ongoing study | Regulatory clearance/approval FDA 510(k), CFR 1270, CFR 1271 MQV, filler, bone void, calcium compound common name – bone grafting material classification name – bone grafting material, synthetic |
|---|---|---|---|---|---|
| | Augment Injectable | | β-Tricalcium phosphate-containing matrices + recombinant human platelet-derived growth factor-BB | Solchaga 2012 (ovine) rhPDGF-BB solution (0.3 mg/mL) was mixed with the β-TCP/collagen (3:1, v:w), allowed to incubate at room temperature for 5–15 min and then transferred to a 3 mL syringe with the end removed. The syringe was used to dispense 0.4 mL of Augment Injectable to the interior of the PEEK spacer | |
| Bioventus® Surgical | Signafuse™ | Putty type | Microporous and macroporous biphasic calcium phosphate + bioactive glass Multidirectional interconnected porosity structure similar to that of human cancellous bone (20–30% microporous (pore size <10 μm) and 50–55% macroporous) | n/a in clinical study Comparative study in rabbit (Fredericks et al. 2016) | FDA 510(k) cleared K132071, 2014 Jan (permitted as Biostructures, LLC) |
| | INTERFACE | Powder type | 45S5 bioactive glass Particle size of 200–420 microns is designed for a faster speed of bone fill | n/a | FDA 510(k) cleared K112857, 2011 Dec (permitted as Biostructures, LLC) |
| | OsteoMatrix™ | Strip type | 60% hydroxyapatite (HA) + 40% beta-tricalcium phosphate (β-TCP) + type 1 collagen A synthetic two-phase calcium phosphate embedded in a cross-linked collagen carrier | n/a | FDA 510(k) cleared K051774, 2006 Jan (as a product name of MBCP™) |

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|---|---|---|---|---|---|
| | Osteo Plus™ | Granules in delivery syringe | Biphasic calcium phosphate (BCP): 60% hydroxyapatite (HA) + 40% beta-tricalcium phosphate (β-TCP)<br>Synthetic two-phase calcium phosphate granules with interconnected macro and 3D micropores | n/a | FDA 510(k) cleared<br>K051774 (01.20.2006) (as a product name of MBCP™) |
| Bone Bank Allografts, Texas, USA | Confirm™ Bioactive:<br>Confirm™ Gel:<br>Confirm™ Crunch | Gel and crunch type | Gel type<br>Composition: Bioglass + hyaluronic acid + glycerol<br>Sterile-packed in a syringe<br>Available in three sizes: 2, 5, and 10 cc<br>Uniform Bioglass particle sizes<br>Crunch type<br>Composition: Bioglass + hyaluronic acid + glycerol<br>Sterile-packed in a syringe<br>Available in three sizes: 2, 5, and 10 cc<br>Mixture of Bioglass particle sizes | n/a | FDA 510(k) cleared<br>K133678, 2014 Aug |
| BonAlive Biomaterials, Biolinja 12, 20750 Turku, Finland | BonAlive® | Granule and putty type<br>Various sizes | S53P4 bioactive glass (53% SiO2, 23% Na2 O, 20% CaO, 4% P2 O) | Long bone defect treatment, Aurégan and Bégué 2015<br>Osteomyelitis treatment, Malat et al. 2018 | BonAlive® products are not sold in the USA. (05.22.2018) |
| BONESUPPORT AB, Scheelevägen 19, SE-223 70, Lund, Sweden | CERAMENT® BONE VOID FILLER | Injectable type | Combination of two natural materials – hydroxyapatite and calcium sulfate – with a radiopacity enhancing agent 40% hydroxyapatite +60% calcium sulfate + iohexol (as a radio-opacity enhancer) | Ongoing RCT<br>NCT01828905 (active status)<br>BONESUPPORT AB:<br>NCT02820363<br>Other Study ID Numbers:<br>CLIN001 – FORTIFY<br>US Food and Drug Administration (FDA) ongoing Investigational Device Exemption (IDE) study of its product | FDA 510(k) cleared<br>K073316, 2008 Jun |

(continued)

**Table 6** (continued)

| Company | Synthetic product | Formulation | Product composition | Peer-reviewed clinical evidence ClinicalTrials.gov/ongoing study | Regulatory clearance/approval FDA 510(k), CFR 1270, CFR 1271 MQV, filler, bone void, calcium compound common name – bone grafting material classification name – bone grafting material, synthetic |
|---|---|---|---|---|---|
| CAM Bioceramics BV/CAM implants BV (University of Leiden)/ 1993 Osteotech Inc. | Camceram TCP | Granules (1–4 mm) or block | Beta-tricalcium phosphate with 90% porous (Available specialty compound form; β –TCP, Milled β-TCP, α –TCP Cement Powder) | n/a | FDA 510(k) cleared K050357, 2005 Apr |
| DePuy Synthes, West Chester, Pennsylvania | HEALOS® Bone Graft Substitute | Putty type | Type 1 collagen + HA scaffold | Yousef MAA, 2017 (MSCs)<br>Villa et al. 2015<br>Kunakornsawat et al. 2013<br>Ploumis et al. 2010<br>Carter et al. 2009<br>Birch and D'Souza 2009 (Implant Removal)<br>Magit et al. 2006 (w/rhBMP2)<br>Neen et al. 2006<br>Kraiwattanapong et al. 2005<br>Jahng et al. 2004<br>Furstenberg et al. 2010 | HEALOS® Bone Graft Substitute (K012751, 2001 Nov and K043308, 2005 Feb) |
| | HEALOS Fx Injectable Bone Graft Replacement | Injectable type | Type I bovine collagen + hydroxyapatite<br>HEALOS Fx is approximately 20–30% mineral by weight | *Same material of HEALOS® Bone Graft Substitute* | HEALOS® Fx Bone Graft Substitute (K062495)<br>Mixing Device K081758, 2008 Sep |
| | Conduit | Putty type | Pure β-tricalcium phosphate (β-TCP) + a non-animal-derived sodium hyaluronate | ClinicalTrials.gov Identifier: NCT02056834 (tibia plateau fracture) (observatory case series study)<br>ClinicalTrials.gov Identifier: NCT01615328 (cervical spine fusion) | 510(k) cleared K041350, 2004 Jul |

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|---|---|---|---|---|---|
| | Synthes chronOS™ chronOS™ inject | Granules, blocks, wedges, and cylinders | β-Tricalcium phosphate (β-TCP) | NCT02803177 (vs. cells)<br>NCT02056834 (chronOS Inject, fractures)<br>NCT00943384 (strip +BMA+ local bone) (posterolateral fusion)<br>NCT00841152 (b-TCP vs. bioactive glass) filling defects (tumor) | FDA 510(k) cleared<br>K0430453, 2005 Jan |
| | CONDUIT® TCP | Granules type | 100% β-TCP<br>TCP Granules obtained after high-temperature ceramicization of tribasic calcium phosphate. Interconnected pores 70% of volume (1 and 600 μm) | n/a (MAUD report) | FDA 510(k) cleared<br>K014053, 2002 Mar |
| ETEX (Zimmer Biomet 2014 October) | CaP Plus | CaP Plus | Synthetic calcium phosphate, an inert carrier, carboxymethyl cellulose (CMC), and DBM | n/a | 510(k) cleared<br>K063050, 2007 Nov<br>K080329, 2008 Apr |
| Globus Medical, Inc. | MicroFuse® Putty and MicroFuse® ST MIS | | Resorbable calcium salt bone void filler | Is a bone graft extender | K102392, 2010 Dec<br>MicroFuse® Bone Void Filler (K071187, K082442) |
| | MicroFuse™ Bone Void Filler<br>MicroFuse™ granules<br>MicroFuse™ blocks | Granules, sheets, and pre-formed blocks | Porous bone graft scaffold composed of bonded poly(lactide-co-glycolide) or poly(lactic acid) microspheres with and without barium sulfate and calcium sulfate form of granules, sheets, and pre-formed blocks. MicroFuse™ implants are available in short-term (ST), mid-term (MT), or long-term (LT) compositions | n/a | K083232, 2008 Dec |
| Isto Biologics, USA | InQu® | Past Mix, Matrix Granules | Synthetic PLGA (poly(lactide-co-glycolide)) with HyA (hyaluronic acid) | NCT01746212<br>Bone graft extender | K063359, 2007 Apr |
| Inion Oy, Lääkärinkatu 2, FIN-33520 Tampere, Finland | Bioactive glass (S53P4) | Variable shape: cylinders, blocks, and morsels | Different size degradable bioactive glass (S53P4) | NCT01304121, no results posted | K070998,<br>2007 Oct |

(continued)

**Table 6** (continued)

| Company | Synthetic product | Formulation | Product composition | Peer-reviewed clinical evidence ClinicalTrials.gov/ongoing study | Regulatory clearance/approval FDA 510(k), CFR 1270, CFR 1271 MQV, filler, bone void, calcium compound common name – bone grafting material classification name – bone grafting material, synthetic |
|---|---|---|---|---|---|
| Medtronic Spinal and Biologics | MASTERGRAFT® | Granule form Putty type (combined with a type I collagen) Strip type | Biphasic, resorbable ceramics composed of hydroxyapatite (HA) and β-TCP | ClinicalTrials.gov Identifier: NCT01491542 (PLF as Pilot study) ClinicalTrials.gov Identifier: NCT00549913 (PLF, clinical study to evaluate the feasibility, safety, and tolerability of 3 different doses of immunoselected, culture-expanded, nucleated, allogeneic MPCs (NeoFuse)) | FDA 510(k) cleared, K081784, 2008 Sep: putty form FDA 510(k) cleared, K082166, 2008 Sep: strip form |
| Molecular Matrix | Osteo-P bone graft substitute | | Osteo-P is a non-mineralized, synthetic bone void filler made of a hyper-crosslinked carbohydrate polymer. It is highly porous, biocompatible, and biodegradable | n/a | 510(k) cleared K170165, 2017 Dec |
| NovaBone Jacksonville, FL, USA ➔ Osteogenics Biomedical | NovaBone Putty – Bioactive Synthetic Bone Graft | Soft malleable putty | Bimodal particle distribution of calcium-phospho-silicate (CPS, Bioglass) + polyethylene glycol (PEG) as additive + glycerin as binder Volume of active ingredient is 70% | n/a | 510(k) cleared K082672, 2008 Dec CE approval |
| | NovaBone-AR | Packable graft | Synthetic calcium-phospho-silicate (Bioglass) particulate, fused into a bulk porous form having a multidirectional interconnected porosity | n/a | 510(k) cleared K041613 |

| | | | | | |
|---|---|---|---|---|---|
| | NovaBone IRM™ | Flexible sheets, varying sizes | IRM (irrigation resistant matrix) Bioactive calcium-phospho-silicate particulate and a synthetic, absorbable binder | Retrospective comparative study | 510(k) cleared KO4 16 13, 2005 Dec November 19, 2016 (21 CFR 888.3045) |
| | NovaBone Bioactive Strip | Strip type | Purified fibrillar collagen and resorbable bioactive synthetic granules (Bioglass) | n/a | K141207, 2014 May |
| | NovaBone MacroFORM | Moldable type | Open porous structure to facilitate the absorption of bone marrow aspirate<br>Purified collagen and resorbable bioactive synthetic granules (Bioglass) | n/a | 510(k) cleared K0140946, 2014 Aug |
| | NovaBone porous | Powder | Synthetic calcium-phospho-silicate (Bioglass) | n/a | 510(k) cleared K090731, 2009 Apr |
| ORTHOReBIRTH Co., Ltd. | ReBOSSIS | Cottony type: glass wool-like physical form | A synthetic, resorbable bone void filler<br>40% beta-tricalcium phosphate (β-TCP), 30% siloxane-containing vaterite (a form of calcium carbonate, CaCO3), and 30% poly(L-lactide-co-glycolide)<br>The electrospinning process used in manufacturing ReBOSSIS results in a cotton like form, which had a merit like easier-to-handle, good elasticity and resilient capability | n/a | K142090 ReBOSSIS ORTHOReBIRTH CO., LTD. 2014 Oct<br>K172573/K170620 ReBOSSIS85, 2017 Dec<br>Primary Predicate K140375 scaffold is type I bovine collagen scaffold |
| Orthovita Inc. ➔ Merged into Stryker | Vitoss | Various types (original, foam pack, foam strip, Morsel, and block) | Highly porous beta-tricalcium phosphate (>90% porous) + type I bovine collagen (may be combined with saline, autogenous blood, and/or bone marrow) | ClinicalTrials.gov Identifier: NCT00147823: RCT (comparative study) | 510(k) cleared STRIP and PACK – K081439, 2008 Nov<br>K032288 – Vitoss Scaffold Foam Bone Graft Material |
| | Vitoss BA (Bioactive Bone Graft Substitute) | Various types (original, foam pack, foam strip) | Highly porous β-TCP + bioactive glass | n/a | 510(k) cleared K083033, 2008 Nov |
| | Vitoss® Bone Graft Substitute-Bioactive Foam Strip | Strip type | Highly porous β-TCP + bioactive glass | n/a | 510(k) cleared K072184, 2007 Sept |

(continued)

**Table 6** (continued)

| Company | Synthetic product | Formulation | Product composition | Peer-reviewed clinical evidence ClinicalTrials.gov/ongoing study | Regulatory clearance/approval FDA 510(k), CFR 1270, CFR 1271 MQV, filler, bone void, calcium compound common name – bone grafting material classification name – bone grafting material, synthetic |
|---|---|---|---|---|---|
| | Vitoss BBTrauma | Putty type (foam pack) | Highly porous β-TCP + bioactive glass<br>A broader range of bioactive glass particle size distribution and has a unique porosity, structure, and chemistry to help drive 3D regeneration of bone | n/a | 510(k) cleared |
| | Vitoss BA2X (Bioactive Bone Graft Substitute) | Putty type (foam pack) | Highly porous β-TCP + bioactive glass<br>Increased levels of bioactive glass compared to Vitoss BA and has a unique porosity, structure, and chemistry to help drive 3D regeneration of bone | n/a | 510(k) cleared K103173, 2011 Feb; K16321, (2017 Mar (BA Injectable) |
| | HydroSet<br>HydroSet XT | Injectable type | Tetracalcium phosphate that is formulated to convert to hydroxyapatite, the principal mineral component of bone<br>HydroSet XT is simple and easy form of HydroSet | n/a | 510(k) cleared<br>K161447, 2016 Oct |
| Pioneer Surgical Technology, MI USA ➔ Merged into RTI Surgical | Pioneer FortrOss Bone Void Filler | Putty type | Porous calcium phosphate material mixed with a porcine gelatin carrier | n/a | 510(k) cleared<br>K091031, 2009 Nov |
| | Pioneer E-Matrix Bone Void Filler | Granular gelatin-based | Porous calcium phosphate material mixed with a porcine gelatin carrier | n/a | 510(k) cleared<br>K083449, 2009 Jun |
| Progentix Orthobiology BV, The Netherlands | CuriOS™ | | Micro-structured calcium phosphate resorbable bone void filler for the repair of bony | | K090641, 2009 Oct |

| | | | | | |
|---|---|---|---|---|---|
| | | | defects. The product comprises a beta-tricalcium phosphate and hydroxyapatite | | |
| Progentix Orthobiology BV, The Netherlands/ NuVasive | AttraX Putty | AttraX Putty cylinders, strips, and blocks | AttraX Putty is a synthetic ceramic granule premixed with a polymeric binder that provides cohesion between the granules<br>Beta-tricalcium phosphate (β-TCP > 90%) and hydroxyapatite (HA <10%)<br>The granule size range: 500–1000 μm<br>The premixed binder is alkylene oxide copolymer (AOC) | NCT02250248, XLIF, Brazil RCT<br>NCT01982045, Netherlands<br>Sponsors: UMC Utrecht NuVasive | K151584, 2015 Jun |
| Prosidyan Inc., USA | FIBERGRAFT® BG | Morsels | FIBERGRAFT® BG Morsels is an ultraporous synthetic bone graft substitute made entirely from crystalline 45S5 bioactive glass | (Fortier et al. 2017) | Class II (Special Controls)<br>K151154, K141956, K132805, 2017 May (posterolateral fusion) |
| | FIBERGRAFT® BG Putty Bone Graft Substitute | Putty | FIBERGRAFT™ 45S5 bioactive glass (M-45 granules, MS-45 microspheres) and bovine type I collagen (hydration with saline or blood). For use in posterolateral fusion | | K143533, K170306, K180080, 2018 Mar<br>The technological characteristics of the FIBERGRAFT™ BG Putty are similar to FIBERGRAFT™ BG Morsels Bone Graft Substitute |
| Regeneration Technologies, Inc., FL, USA<br>➔ Merges with Tutogen to form RTI Biologics® (2008)<br>➔ Change to RTI Surgical | nanOss® Loaded Advanced Bone Graft Substitute | Prefilled mixing syringe | Nano-structured hydroxyapatite (HA) has extremely high surface area | NCT02586116, ongoing<br>Cervical Spine<br>Belgium<br>Ahn and Webster 2009 | K081558 – NanOss Bone Void Filler, 2008 Aug |
| | nanOss® 3D Advanced Bone Graft Substitute | Strip type | Nano-structured hydroxyapatite granules suspended in a porous gelatin-based foam matrix | ClinicalTrials.gov Identifier: NCT01829997: case series study (active status) | 510(k) cleared<br>K132050, 2013 Jun |
| | nanOss® Advanced Bone Graft Substitute | Putty type | Nano-structured hydroxyapatite granules and an open structured engineered collagen carrier | ClinicalTrials.gov Identifier: NCT01968993: A Prospective, Nonrandomized Study (PLF) | 510(k) cleared<br>K141600, 2014 Oct |
| Science for Biomaterials, France | BIOSORB RESORBABLE BONE VOID FILLER | Variable shape | Resorbable calcium salt bone void filler 9 shapes: stick, granule, cube, block (6 shapes) | n/a | K130953, 2013 Jul<br>K(021963 and K(071155) |

(continued)

**Table 6** (continued)

| Company | Synthetic product | Formulation | Product composition | Peer-reviewed clinical evidence ClinicalTrials.gov/ongoing study | Regulatory clearance/approval FDA 510(k), CFR 1270, CFR 1271 MQV, filler, bone void, calcium compound common name – bone grafting material classification name – bone grafting material, synthetic |
|---|---|---|---|---|---|
| SeaSpine, Carlsbad, CA | Accell Connexus® | | | NCT01873586<br>1: Schizas et al. 2008 | |
| SeaSpine, Carlsbad, CA | OsteoStrux® Putty | | Moldable, osteoconductive scaffold composed of purified collagen and β-TCP<br>20% type I bovine collagen and 80% highly purified β-TCP<br>The matrix was developed to resemble the composition and pore structure of natural human bone | NCT01873586: Case series study; results are not posted. | K073316 2008 Jun |
| | OsteoStrux® Strip | | Strip is a compression-resistant, osteoconductive scaffold composed of purified collagen and β-TCP | NCT01873586 | K073316 2008 Jun |
| Synergy Biomedical, LLC | BioSphere® Putty | Putty type | 80% bioactive glass spheres; 20% phospholipid carrier | n/a | K122868, 2013 Apr |
| | BioSphere MIS Putty (BioSphere MIS) | Prefilled type | Medical-grade 45S5 bioactive glass particles + carrier (same composition of BioSphere® Putty) | n/a | K173301, 2018 Jan |
| THERICS, LLC | TheriGraft™ TCP Putty Bone Void Filler | Putty type | Synthetic f3-tricalcium phosphate granules<br>(0.1–0.4 mm diameter) in a poloxamer based carrier<br>Approximately 0.1–0.4 mm granules | n/a | 510(k) cleared<br>K053228, 2006 Jan |

| | | | | | |
|---|---|---|---|---|---|
| Vivoxid Ltd.: Turku, Finland | Bioactive Glass (S53P4) as granules (BonAlive™) | Granules<br>Plates | By weight, $SiO_2$ 53%, $Na_2O$ 23%, CaO 20%, and $P_2O_5$ 4% (synthetic, osteoconductive, and bacterial growth-inhibiting material) | ***NCT00935870***<br>Sponsor<br>Turku, Finland<br>NCT00841152<br>Bonalive (Vivoxid Ltd., Turku, Finland) | K071937 2007 Oct |
| Wright Medical Technology | OSTEOSET® | Pellet type<br>➔ Moldable in operation room | Engineered calcium sulfate hemihydrate | n/a | K053642, 2006 Jan |
| | PRO-DENSE™ | Injectable type (4, 10, 15, 20 cc) | 75% calcium sulfate and 25% tricalcium phosphate | n/a | K113871, 2013 Mar |
| Zimmer Biomet/ BONESUPPORT AB, Sweden | CERAMENT™ | Injectable type | Biphasic ceramic bone substitute: 60% synthetic calcium sulfate (CaS) (calcium sulfate hemihydrate and sintered hydroxyapatite) + 40% hydroxyapatite (HA) pellet + radio-contrast agent iohexol (180 mg/ml) | NCT01828905 ongoing trial | K073316, 2008 Jun |
| | Pro Osteon® 200R | Powder type | Hydroxyapatite and calcium carbonate diameter of 190–230 microns<br>Calcium carbonate matrix covered by a very thin outer layer of calcium phosphate, approximately 2–10 microns in thickness. The calcium phosphate is located on the outer surface of the porosity throughout the entire structure of the implant | Walsh et al. 2003: A resorbable porous ceramic composite bone graft substitute in a rabbit metaphyseal defect model. Journal of Orthopaedic Research, 2003 | 510(k) cleared<br>K000515, 2000 Sep |
| Zimmer Biomet Spine, Inc. (Interpore Cross International, Irvine, CA) | Pro Osteon® 500R (Chapman and Madison 1993) | Powder type | Thin, 2–10 micron layer of hydroxyapatite over a calcium carbonate core<br>Provides a natural scaffold for new bone growth when placed in contact with viable bone | NCT00858598<br>Thalgott et al. 2001<br>Harris et al. 1995 | 510(k) cleared<br>K031336, 2002 Jul |

Materials in this class are most always used with BMA, whole blood, serum, and physiological saline and/or also mixed with autograft
BMA, bone marrow aspirate. BMA is typically added at the time of surgery to these synthetic materials for grafting into the spinal fusion surgical bed/site
Whole blood or serum (patient's own) may be used
https://510k.directory/clearances/MQV/1. Accessed April–June 2018

calcium phosphate materials are brittle, as they do not possess the tensile properties of bone. Therefore, TCPs and calcium phosphates have been used in areas of relatively low tensile stress or non-load-bearing applications. Thus, the calcium phosphate-based materials are not recommended alone for use in load-bearing applications (Park et al. 2013). It is important to recognize that most osteoconductive products have been approved for use only in posterolateral spine fusion applications and not in interbody fusion applications. Since TCP has only osteoconductive effects, these TCP-type products may be used in conjunction with biologic osteoinductive or osteogenic supplements of autograft, BMPs, growth factors, mesenchymal stem cell (MSC) derivatives, etc. (see combined products, Table 7) (Gupta et al. 2015; Duarte et al. 2017).

The most widely recognized TCP product is Vitoss® Bone Graft Substitute (Stryker, Allendale, NJ). This material was first commercialized in 2004, and its application in different formats has established it as the preferred TCP material. Another TCP-based material that has been reported is the Augment® Bone Graft from Wright medical. Augment® Bone Graft combines recombinant human platelet-derived growth factor B homodimer (rhPDGF-BB) with a bio-resorbable synthetic bone matrix (β-TCP). This product has been developed for use in bone repair. It is reported that the use of this product eliminates the need for using autograft, proposed as a "substitute." However, Augment® Bone Graft is only indicated for use as an alternative to autograft in the ankle or hindfoot (Augment® bone graft – FDA. https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100006d.pdf). There are several TCP-based products combined with different carriers to provide improved handling characteristics (see combined products, Table 7).

HA is another calcium phosphate material of significance, since x-ray diffraction and chemical studies have demonstrated that the primary mineral phase in bone is HA. HA is a biomaterial for medical devices and is available in the form of nanocrystalline powders, porous granules, and dense blocks. It can be manufactured from natural coral, bovine cortical bone, or synthesized by chemical reactions. HA is stronger (less brit tle) than TCP providing high compression strength but is still somewhat brittle. Due to its brittle quality, HA use is limited in load-bearing applications (Zdeblick et al. 1994; Park et al. 2013). Unlike autograft, allograft, and TCP, the absorption rate of HA is very slow (with incomplete absorption/resorption), and HA remains at the site of implantation for years (Zadegan et al. 2017a). In most circumstances, this prolonged resorption may not be advantageous. Grafting materials are ideally completely resorbed and replaced by new bone eventually. If the material does not resorb, it can act as an obstacle or inhibit new bone formation. Historically, coralline HA has been used effectively as a bone graft extender in patients as an adjunct to autologous bone for PLLF (Morris et al. 2018). The critical amount of graft volume per area of functional level (spine) has not been reported. Yoo et al. suggest that an amount of at least 12 mL of bone graft is needed to achieve a satisfactory bone fusion in minimal invasive TLIF surgery regardless of mixture ratio of HA with autograft bone (Yoo et al. 2015). There are several HA-based products combined with different carriers to provide improved handling characteristics (Tables 6 and 7).

According to study of Nickoli MS et al., ceramic-based bone grafts (TCP) with an osteoinductive stimulus represent a promising bone graft extender in lumbar spine fusion (Nickoli and Hsu 2014). In a meta-analysis review of 1,332 patients in 30 studies, from 1980 to 2013, ceramics used in combination with local autograft resulted in significantly higher fusion rates compared with all other adjuncts and bone marrow aspirate and platelet concentrates (Nickoli and Hsu 2014). Previous clinical studies on HA-based bone graft such as HA when used alone, or in combination with BAG (bioactive glass), BMA (bone marrow aspirate), or rhBMP-2 have been shown to improve function to the and reduce preoperative pain same extent as ICBG, yet have been associated with suboptimal radiographic fusion rates in lumbar spine (Singh et al. 2006; Acharya et al. 2008; Ploumis et al. 2010).

**Table 7** Commercially available combination grafting products, naturally occurring peptides, growth differentiating factors, cellularized grafts, cellular bone matrices (CBMs)

| Company | Combination product | Formulation | Product composition | Peer-reviewed clinical evidence/ongoing study | Regulatory clearance/approval<br>FDA 510(k),<br>FDA 361, 21 CFR Part 1271<br>CFR 1270, CFR 1271<br>21 CFR 3.2(e)<br>HCT/P 361, Human allografts (No Clinical Studies)<br>Biologic Drugs and Devices 351 (Clinical Trials) |
|---|---|---|---|---|---|
| Advanced Biologics, Carlsbad, CA., 2009 (marketed OsteoAMP in the USA since 2009) | OsteoAMP | Granules or sponge | OsteoAMP, an allogeneic growth factor implant, exploits the angiogenic, mitogenic, and osteoinductive growth factors that are within marrow cells | Field et al. 2014<br>Cervical Spine-Fusion | Bioventus manages orders and sales of HCT/Ps (not a distributor, FDA) |
| Bioventus' Surgical, Durham, NC, USA (original developer) | | | Growth factor-rich naturally occurring growth factors including BMP-2, BMP-7, aFGF, and TGF-β1 bone graft substitute: intended for homologous use repair, replacement, or reconstruction of musculoskeletal defects | ClinicalTrials.gov Identifier: NCT02225444<br>Lumbar Spine-PLF<br>Roh et al. 2013 | Regulated under CFR 1270, 1271 as a human tissue, registration held by Tissue Bank Permit: Millstone Medical Outsourcing, LLC, Olive Branch, MS (Bone, Demineralized Bone Matrix, Ligament, Musculoskeletal Tissues, Tendon.) Maryland, New York State<br>Tissue Bank Permit: Advanced Biologics, LLC (Bone Demineralized Bone Matrix) |
| AlloSource®, Centennial, Co, USA, 1995 Allosource.org | AlloStem Cellular Bone Autograft | Strips, blocks, cubes, morselized | Partially demineralized allograft bone combined with adipose-derived mesenchymal stem cells (MSC) | n/a | Regulated under CFR 1270, 1271 as a human tissue |

(continued)

**Table 7** (continued)

| Company | Combination product | Formulation | Product composition | Peer-reviewed clinical evidence/ongoing study | Regulatory clearance/approval<br>FDA 510(k),<br>FDA 361, 21 CFR Part 1271<br>CFR 1270, CFR 1271<br>21 CFR 3.2(e)<br>HCT/P 361, Human allografts (No Clinical Studies)<br>Biologic Drugs and Devices 351 (Clinical Trials) |
|---|---|---|---|---|---|
| Aziyo Biologics, Inc. MD, Ga, CA | OsteoGro™ | Cancellous Bone | Partially demineralized cortical bone | NCT03425682 | Regulated under CFR 1270, 1271 as a human tissue |
| | VBone | Structural allografts<br>Package<br>Bone matrix | Preserve natural components of the matrix<br>Viable bone matrix | | |
| BBS-Bioactive Bone Substitutes Oyj (Finland) | ARTEBONE® | | Tricalcium phosphate (TCP) + natural cocktail of bone proteins (growth factors) | ClinicalTrials.gov Identifier: NCT02480868: case series study for ankle fusion | FDA 510(k)<br>~2020 |
| Bioventus® Surgical | OsteoAMP | Granule, putty, and sponge form | Cervical and lumbar spine fusion procedures<br>Allograft with growth factors (such as BMP-2, BMP-7, TGF-β1, aFGF, VEGF, and ANG1, within bone marrow cells) | Active but no results posted: Posterolateral Lumbar Fusions (PLF) With OsteoAMP® (ClinicalTrials.gov Identifier: NCT02225444)<br>Comparative study with rhBMP-2 with OsteoAMP (Roh et al. 2013) | AATB<br>US FDA 21 CFR 1271 (HCT/P) |
| BONESUPPORT AB, Scheelevägen 19<br>SE-223 70, Lund, Sweden | CERAMENT® G | Injectable type | Injectable antibiotic-eluting bone graft substitute that provides local sustained bactericidal effect and scaffold for fusion<br>CERAMENT (40% hydroxyapatite +60% calcium sulfate) + 17.5 mg gentamicin/mL paste | ClinicalTrials.gov Identifier: NCT02820363: Clinical Trial (RCT) for open tibial fracture (recruiting status)<br>ClinicalTrials.gov Identifier: NCT02128256: Case series study (unknown status) | Combination product, HCT/P GS1, HIBCC, ICCBBA<br>FDA-PMA approval underway (communication from BoneSupport 2020 Feb |

| | | | | | |
|---|---|---|---|---|---|
| | CERAMENT® V | Injectable type | Injectable antibiotic-eluting bone graft substitute that provides local sustained bactericidal effect and scaffold for fusion<br>CERAMENT (40% hydroxyapatite +60% calcium sulfate) + iohexol (as a radio-opacity enhancer) + 66 mg vancomycin/mL paste | US-NCT03389646 trial of Cerament TM V, G for hip or knee prosthesis infection | CE Mark approval<br>FDA-PMA approval underway (communication from BoneSupport 2020 Feb |
| DePuy Synthes | ViviGen Cellular Bone Matrix Vertigraft® | Cryo Cortical Cortical cancellous bone matrix and demineralized bone | ViviGen® Cellular Bone Matrix comprised cryopreserved viable cortical cancellous bone matrix and demineralized bone.<br>ViviGen Cellular Bone Matrix is a human cells, tissues, and cellular and tissue-based product (HCT/P). ViviGen Cellular Bone Matrix is processed from donated human tissue, resulting from the generous gift of an individual or his/her family | NCT02814825<br>HCT/P (Divi and Mikhael 2017) | (HCT/P) as defined by the US Food and Drug Administration in 21 CFR 1271.3(d). 21CFR 1271 |
| | CONFORM CUBE® | Cube shape | Demineralized cancellous bone, organic matrix (osteoinductive, promotes cellular ingrowth and vascularization)<br>General bone void filler and use with lumens of allograft spinal spacers | n/a | (HCT/P) as defined by the US Food and Drug Administration in 21 CFR 1271.3(d). 21CFR 1271 |
| | CONFORM SHEET® | Sheet shape | Demineralized cancellous bone, organic matrix (osteoinductive, promotes cellular ingrowth and vascularization)<br>For PLF (posterolateral gutters of the spine) | n/a | (HCT/P) as defined by the US Food and Drug Administration in 21 CFR 1271.3(d). 21CFR 1271 |

(continued)

**Table 7** (continued)

| Company | Combination product | Formulation | Product composition | Peer-reviewed clinical evidence/ongoing study | Regulatory clearance/approval<br>FDA 510(k),<br>FDA 361, 21 CFR Part 1271<br>CFR 1270, CFR 1271<br>21 CFR 3.2(e)<br>HCT/P 361, Human allografts (No Clinical Studies)<br>Biologic Drugs and Devices 351 (Clinical Trials) |
|---|---|---|---|---|---|
| Mesoblast Ltd., Australia | NeoFuse(TM) | Cells + Granules | Allogenic mesenchymal precursor cells (MPCs) combined w/ MasterGraft in PEEK cage | NCT00549913 (Lumbar PLF) | FDA 510(k) cleared, K153615 2016 Jun (HA Enhanced PLIF/TLIF) |
| Angioblast Systems Inc., USA | NeoFuse(TM) | Cells + Granules | Allogenic mesenchymal precursor cells (MPCs) combined w/ MasterGraft in anterior cervical discectomy and fusion (ACDF)<br>Anterior cervical plate fixation | NCT01106417 (Cervical fusion) | FDA 510(k) cleared, K170318 2017 Jun |
| MTF Orthofix | Trinity Evolution TM | Moldable allograft fibers, varying sizes | Allogenic DBM, osteoprogenitor cells (OPC), MSC (minimum of 500,000 cells/cc; 100,000 of which are MSC and/or OPC) | NCT00951938 (Anterior cervical)<br>Peppers et al. 2017<br>Vanichkachorn et al. 2016 | Regulated under CFR 1270, 1271 as a human tissue |
| | Trinity Elite | Moldable allograft fibers, varying sizes | DBM, osteoprogenitor cells, MSC (minimum of 500,000 cells/cc; 100,000 of which are MSC and/or OPC)<br>Trinity Elite and/or local bone | NCT02969616 (PLF, TLIF,ALIF, XLIF, etc., lumbar fusion)<br>NCT00965380 | Regulated under CRF 1270, 1271 as a human tissue |

| | | | | | |
|---|---|---|---|---|---|
| | | | with supplemental pedicle screw fixation allogeneic cancellous bone matrix containing viable osteoprogenitor cells, mesenchymal stem cells, and a demineralized cortical bone (DCB) | | |
| NuVasive | Osteocel | Moldable bone matrix | DBM, OPC, MSC (<50,000 cells/cc, >70% viability) | Retrospective case series | Regulated under CFR 1270, 1271 as a human tissue |
| | Osteocel Plus | Moldable bone matrix | DBM, OPC, MSC (<50,000 cells/cc, >70% viability) | McAnany et al. 2016, Retrospective comparative study; NCT00948532 (Osteocel® Plus in extreme lateral interbody fusion (XLIF®): Kerr et al. 2011; Tohmeh et al. 2012 Extreme lateral interbody fusion (XLIF) Ammerman et al. 2013 Eastlack et al. 2014: (Osteocel Plus in a polyetheretherketone cage and anterior plating at 1 or 2 consecutive levels) Prospective case series Retrospective case series, clinical trial: ClinicalTrials.gov Identifier: Evaluation of Radiographic and Patient Outcomes Hollawell 2012 | Regulated under CFR 1270, 1271 as a human tissue |
| Organogenesis 2017 Mar/NuTech Medical, Inc. | NuCel® | Putty type | Cryopreserved, bioactive amniotic suspension allograft Cellular, growth factor, and | ClinicalTrials.gov Identifier: NCT02023372: A Prospective, Efficacy Study (RCT) for PLF | unk |

(continued)

**Table 7** (continued)

| Company | Combination product | Formulation | Product composition | Peer-reviewed clinical evidence/ongoing study | Regulatory clearance/approval<br>FDA 510(k),<br>FDA 361, 21 CFR Part 1271<br>CFR 1270, CFR 1271<br>21 CFR 3.2(e)<br>HCT/P 361, Human allografts (No Clinical Studies)<br>Biologic Drugs and Devices 351 (Clinical Trials) |
|---|---|---|---|---|---|
| | | | extracellular matrix components | NCT02070484: NuCel vs. DBM | |
| Osteotech's<br>➔ Merged into Medtronic | Plexur M(TM) | Moldable type (putty like) | Human allograft bone tissue + resorbable polymer<br>Processed human bone particles that are mixed with resorbable/ biodegradable non-tissue components | MAUDE Adverse Event Report | FDA 510(k) cleared<br>K073405 2008 Mar |
| RTI Surgical Inc.<br>Allendale, NJ, USA | map3® Cellular Allogeneic Bone Graft | Putty type<br>Strip type | Cortical cancellous bone chip (or strip shape bone) + DBM + cryogenically preserved, viable multipotent adult progenitor (MAPC®)-class cells | ClinicalTrials.gov Identifier: NCT02161016: case series study in foot and ankle. Results posted<br>ClinicalTrials.gov Identifier: NCT02628210: A Prospective, Multi-Center, Non-Randomized Study for lumbar interbody fusion (active status) | Unk status (Regulated under 361 PHS Act<br>42 U.S.C. 264 and reg. 21CFR Part 1271.1O(s)(4)(ii)<br>(b) + FDA Act {21 U.S. C. 321 (g)++) |

| | | | | | |
|---|---|---|---|---|---|
| Stryker | BIO (Hollawell 2012) | Putty type<br>(1, 2.5, 5, 10 cc) | Allograft bone (cortical and cancellous) + periosteum<br>A viable bone matrix containing endogenous bone forming cells (including mesenchymal stem cells, osteoprogenitor cells, and osteoblasts) as well as osteoinductive and angiogenic growth factors | ClinicalTrials.gov Identifier: NCT03077204: Clinical case series study (cervical spine), recruiting status | AATB<br>US FDA regulations for tissue management. US FDA 21 CFR 1271 |
| Vericel Corporation | | Bone repair cells | Bone repair cells (BRCs) with allogeneic, demineralized bone matrix | NCT00797550 (posterolateral spinal fusion) terminated no results<br>NCT00424567 repair pseudarthrosis atrophic nonunion | Biologics License Application (BLA) w/ post-marketing commitments (~2017 June), status unknown |
| Xtant | OsteoVive™ | Putty type | A cell population that includes marrow-isolated adult multilineage-inducible (MIAMI) cells<br>Blend of microparticulate cortical, cancellous, and demineralized cortical allograft bone (particle size range of 100–300 microns) | n/a | FDA 510(k) cleared<br>Compliance with FDA guidelines regarding human cells, tissues, and cellular tissue-based products<br>HCT/P 361 regulated viable allogeneic bone scaffold<br>American Association of Tissue Banks guidelines |

510(K) is a premarket submission made to FDA to demonstrate that the device to be marketed is at least as safe and effective, that is, substantially equivalent, to a legally marketed device that is not subject to premarket approval. 501(k) documentation for individual products is available via FDA online database (http://www.accessdata.fda.gov)
Code of Federal Regulations (CFR) 1270 (Human tissue intended for transplantation) and 1271 (Human cells, tissues, and tissue-based products) are federal regulations relating to the procurement and processing of human-derived tissues
Claims: grafting with component to provide the required osteoconduction, osteogenesis, and osteoinduction necessary for successful bone grafting
GS1: it is an international, not-for-profit association that creates and implements standards to bring efficiency and visibility to supply chains across industries
*HIBCC* Health Industry Business Communications Council
*ICCBBA* International Council for Commonality in Blood Banking Automation
PEEK, a polyetheretherketone material used for cage devices employed as instrumentation in anterior interbody spinal fusion procedures

### Silicate-Substituted Calcium Phosphate

Silicate-substituted calcium phosphate (Si-CaP) constitutes a newer generation of ceramics produced by adding silicate which has been found to play role in bone metabolism to previously developed calcium phosphate ceramics (Gao et al. 2001). This combination provides superior biocompatibility and osteoconductivity. In addition combining Si-CaP with a graft provides negative surface charge that results in enhanced osteoblast activity and neovascularization of the bone which lead to more ideal spine fusion as a substitute of ICBG (Campion et al. 2011; Alimi et al. 2017).

Silicated hydroxyapatite has been prepared by the addition of a small amount of silicon (0.4% to 0.8% by wt.) into the structure of HA. The role of silicate-based materials in improving tissue implant interactions has been reported (Zhou et al. 2017). Silica-substituted HA, such as Actifuse™ from Baxter, is available in the form of granules, pastes, and blocks. The performance of these products has been investigated in preclinical models and clinical study. According to study of Jenis and Banco (2010), a silica-substituted hydroxyapatite (Actifuse™) with BMA has been shown to be effective as a graft substitute as ICBG with significant pain improvement in PLLF. According to study of Licina P et al. (Licina et al. 2015), silicate-substituted calcium phosphate (Actifuse™) and rhBMP-2 with ceramic granule were comparable in view of achieving PLLF.

Clinical data are limited for various types of lumbar surgery and the numbers of enrolled patients in trials. For confirming the efficacy and safety of Si-CaP and/or silicated hydroxyapatite as a bone-grafting substitute, further investigations using greater numbers of subjects will be necessary. And the radio-opaque nature of Si-CaP allows for intra- and post-operative localization, but this radio-dense characteristic immediately after surgery resembling bone and the long residence time exceeding a year has decreased the accurate assessment of the process of bone formation.

### Bioactive Glass (Table 8)

Bioactive glass (BAG) is a class of glass-based graft substitute or extender products having a compositional range that allows the formation of nanocrystalline hydroxyapatite (ncHA) as a surface layer when exposed to an aqueous phosphate-containing solution, such as simulated body fluid. The ncHA layer that forms within an aqueous phosphate-containing solution plays a significant role in forming a strong bond with natural bone.

BAG has an established history of bone bonding that occurs as a result of a rapid sequence of reactions on its surface when implanted into living tissues (Hench and Jones 2015). There are two mechanisms of bioactivity for bioactive glass products. Bone bonding is attributed to the (1) formation of an HA layer, which interacts with collagen fibrils of damaged bone to form a bond (Hench and Jones 2015), while the action of the (2) dissolution products from the bioactive glass is reported to simulate osteogenesis (Hench and Polak 2002). When hydrated, a layer of silica gel forms on the surface of the bioactive glass. The adhesion of amorphous calcium, phosphate, and carbonate ions to the silica surface leads to an eventual crystallization of a bone-like HA as early as 24 hours. Bone-forming cells migrate and colonize the surface of the bioactive glass and promote the production of a new bone-like matrix (Beckham et al. 1971). Gao et al. (2001) observed increased expressed detectable mRNA levels of BMP-2 from Saos-2 osteoblastic cells when cultured on two types of BAG (BAG containing 6% $Na_2O$, 12% $K_2O$, 20% CaO, 4% $P_2O_5$, 5% MgO and *53% $SiO_2$* and biocompatible glass (BCG) containing 6% $Na_2O$, 12% $K_2O$, 15% CaO, 4% $P_2O_5$, 5% MgO and *58% $SiO_2$* (wt.%)) than on control inert glass (Gao et al. 2001).

The mechanism for the formation of the ncHA layer is now quite well understood and well characterized, but the biological interactions at the ncHA–host bone interface are still under intense investigation in view of potential employment with stem cells (Tsigkou et al. 2014).

In addition, the high pH and the subsequent osmotic effect caused by dissolution of the bioactive glass have been suggested as an antibacterial material quality (Stoor et al. 1998; Allan et al. 2001). Recently, Sanchez-Salcedo et al. (2017) introduce the design and synthesis of a new

**Table 8** Composition and properties of bioactive glasses and glass-ceramics used clinically for ontological, musculoskeletal, and dental grafting applications (Baino et al. 2018; Hench and Jones 2015)

| Product | Composition wt % | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $Na_2O$ | $CaO$ | $CaF_2$ | $MgO$ | $P_2O_5$ | $SIO_2$ | $B_2O_3$ | $K_2O$ | $CuO$ | $ZnO$ |
| 45S5 Bioglass<br>Otology: MEP® a, Douek-MED™, Ceravital® a, Bioglass-EPI® a<br>Dental graft: EMRI® a, Biogran®, PerioGlas®, NovaMin®<br>Orthopedics: NovaBone®, GlassBone™, FIBERGRAFT®, BioSphere® Putty | 24.5 | 24.5 | 0 | 0 | 6 | 45 | 0 | 0 | 0 | 0 |
| S53P4<br>Dental graft: AdminDent1<br>Orthopedics: BonAlive® | 23.0 | 20.0 | 0 | 0 | 4 | 53 | 0 | 0 | 0 | 0 |
| A-W glass-ceramic<br>Dental graft: Cerabone® | 0 | 44.7 | 0.5 | 4.6 | 16.2 | 34 | 0 | 0 | 0 | 0 |
| Strontium substituted bioactive glasses: StronBone® | 4 | 17.8 | 0 | 7.5 | 4.5 | 44.5 | 0 | 0 | 0 | 0 |
| 13-93 | 6 | 20 | 0 | 5 | 4 | 53 | 0 | 0 | 0 | 0 |
| Bioactive glass by the sol-gel process<br>TheraGlass® a | 0 | 30 | 0 | 0 | 0 | 70 | 0 | 0 | 0 | 0 |
| Boron bioactive | 6 | 20 | 0 | 5 | 4 | 0 | 51.6 | 12 | 0.4 | 1 |

[a]This product is not commercially available due to side effects, structural problems, lack of clinical effect, etc.

nano-structured zwitterionic mesoporous bioactive glasses (MBGs) with incorporation with amino acid for antibio-fouling capability that inhibits bacterial adhesion (formation of biofilm) wherefrom they report successful results in vitro.

BAG has been used for a variety of clinical applications since it was first created in 1969 (Hench and Jones 2015). There are many types of BAG (Table 6) and glass-based products used (Hench and Jones 2015) in periodontal repair and orthopaedic applications (Table 8).

The originally developed composition was bioactive glass 45S5 (Food and Drug Administration (FDA) approved in 1993 (Jones 2015). 45S5 bioactive glass consists of 45 wt.% $SiO_2$, 24.5 wt.% CaO, 24.5 wt.% $Na_2O$, and 6.0 wt.% $P_2O_5$ which demonstrated effective biological properties. NovaBone®, a product based on this 45S5 technology, has been approved as a bone graft substitute in 1999 (Jones 2013; Hench and Jones 2015). The NovaBone® material is considered an early generation of bioactive glass. This is due to the lack of inherent porosity of the NovaBone® granules or granules in which porosity has been manufactured by the fusion of smaller granules. NovaBone® was compared to autograft in posterior spinal fusion procedures for treatment of adolescent idiopathic scoliosis in 88 patients (Ilharreborde et al. 2008). NovaBone® showed improved clinical results in terms of reduced infection, donor site complication, and fewer mechanical failures in a 4-year follow-up. However, its clinical use for spine fusion applications has not been reported widely.

A commercially available bioactive glass product is BonAlive® (BonAlive Biomaterials, Turku, Finland), which was programmed in Finland based on S53P4 bioactive glass. BonAlive® received European approval for orthopedic use as a bone graft substitute in 2006 (Jones 2015). The S53P4 bioactive glass contains 53 wt.% SiO2, 23 wt.% $Na_2O$, 20 wt.% CaO, and 4 wt.% $P_2O_5$. According to Frantzen et al. (2011) a prospective long-term study (11 years) of Frantzen et al., the fusion rate of all fusion sites for BAG-S53P4 with autograft as a bone substitute was 88% at the L4/L5 level and 88% at the L5/S1

level compared to 100% for autograft in degenerative spondylolisthesis patients. Similar results were seen after surgical treatment of a spondylitis patient (Lindfors et al. 2010). BonAlive® was also compared to autograft in the same patients in PLF procedures for treatment of spine burst fractures. At the 10-year follow-up, 5 out of 10 implants had full fusion compared to all 10 autografts (Rantakokko et al. 2012).

Fibergraft® BG Morsels (Prosidyan Inc., USA) is a 100% BAG material (no additives) specifically FDA cleared for orthopedic and spine grafting applications. Traditional bioactive glass does not allow for ease of handling and has slow resorption due to low porosity. Fibergraft® BG Morsels is the first osteostimulative (or bioactive) material engineered to take advantage of the unique properties of bioactive glass. The morsels are engineered with overlapping and interlocking bioactive glass fibers with pores dispersed throughout. The material structure and ultra-porous, nano-, micro-, and macro-porosity provides direct connectivity for cell in-growth and material resorption, enabling new bone formation.

A 95% radiographic success rate was reported in a retrospective study of Fibergraft® BG Morsels use when mixed with local autograft and bone marrow aspirate in 63 patients at 1 year after 1-, 2-, and 3-level posterolateral fusions (Barcohana et al. 2017). Additionally, a high rate of 88.5% (46/52 levels with complete fusion) together with a 5.8% (3/52, levels partial fusion) in anterior cervical fusion was demonstrated after use of Fibergraft® BG Morsels mixed with BMA, bone dust, and or local bone in 27 patients (51 levels of fusion) at approximately 6 months after anterior cervical discectomy and fusion study (Fortier et al. 2017).

Fibergraft® BG Morsels (Prosidyan Inc., USA) is also provided in a putty form as Fibergraft® BG Putty and in a Matrix form as Fibergraft® BG Matrix. All Fibergraft® products are specifically FDA cleared for orthopedic and spine grafting applications. The BG Putty can be used for Minimally Invasive Surgery (MIS) applications, while the BG Matrix can be combined with bone marrow aspirate and used as a compression-resistant strip that can be molded to the shape of the defect.

Clinical and in vivo studies on commercially available bioactive glass particulates show that BAG can perform better than other bio-ceramic particles and have performed similarly to autograft in multiple in vivo studies (Walsh et al. 2017; Bedi 2017).

## Unmet Challenges for Engineered Bioactive Glass Matrices

The major scientific and technical challenges exist with previously developed bioactive glass. Glass based materials lack osteogenesis, are difficult in clinical handling, not load bearing due to brittleness, and have slow resorption due to low porosity (Hench and Jones 2015; Jones 2015). To overcome these limitations and use BAG as effective substitute for autograft, several experiments were attempted to combat these limitations.

First, to enhance osteogenesis, tissue regeneration through gene activation by controlled release of inorganic ions from BAG is required. However, the role of the dissolution products from implanted BAG on bone marrow-derived mesenchymal stem cells (MSC) is not yet controllable. In some studies dissolution products induced osteogenic differentiation into osteoblast-like cells, and in others, it did not (Reilly et al. 2007; Karpov et al. 2008; Brauer et al. 2010). To control this problem, the fundamental mechanisms involved in ionic stimulation in the stem cell nucleus and the exact mechanism of "how the bioactive glass particles/dissolution products" should be explained (Hench and Jones 2015).

Second, particles and putties containing a variety of BAG particulates are in widespread clinical use, but large interconnected macroporous scaffolds for regeneration of large bone defects were not developed. To overcome and address this, the bottom-up sol–gel process, where gelation of nanoparticles in a sol (polycondensation) forms a glass network by avoiding sintering of crystalized Bioglass 45S5, was initially developed (Li et al. 1991). After, a room temperature gelation process was employed, allowing pores interconnection with a compression strength equivalent to porous bone (Jones et al. 2006). Melt-derived glass scaffolds were introduced to make macroporous scaffolds (Wu et al. 2011). According to a review by

Hench and Jones (2015), none of described techniques are being further developed for use by medical device companies even though sol–gel and melt-derived scaffolds still exist.

Third, tissue-engineered constructs for replacement of large bone defects have been investigated for many years but are still not available as routine clinical products. To achieve this, a stable vasculature is necessary during initial grafting. Tsigkou et al. (2010) demonstrated that it is possible in mice models (Tsigkou et al. 2010). More research is needed to test the possible enhancement of angiogenesis optimal activity duration in humans (Azevedo et al. 2015).

Fourth, load-bearing devices that can be used in orthopedics over the long term, which also regenerate living bone, are still not available clinically. Therefore, the 3D printing technology was adapted to bioactive glass scaffolds to generate interconnected pores similar in diameter to the porous foam scaffolds but with higher compressive strengths (Fu et al. 2011; Kolan et al. 2011). However, BAG scaffolds are still brittle and therefore not suitable for all grafting applications, such as sites that are under cyclic loads.

## Mixed Use Graft Materials with Antibacterial Effects (Table 7)

### Infection Prevention and Treatment of Previous Surgical Site Infection

For improvement of bone graft materials including substitutes, dual-functional graft materials have been designed. Among several possible additional options, prevention or treatment of surgical site infection with/without bone destruction is needed for clinical application (Turner et al. 2005; Anderson et al. 2014). Risk factors associated with surgical conditions (relatively wide soft tissue dissection, muscular damage, long operation time, and limited control of bleeding during operation) and patient characteristics and health status (old age, comorbidities like diabetes mellitus, renal failure and vasculopathy, and smoking, etc.) in spine fusion operations.

For prevention or control of the post-operative infection, systemic and localized bactericide are necessary. However systemic delivery of antibiotics to infected site or vulnerable to infection is limited by abnormal blood supply in operated site, drug toxicity to organs, antimicrobial-resistant form of bacteria, etc. (Shiels et al. 2017). Due to mentioned causes, newly designed graft materials have been developed for local bactericidal carrier, which may increase the safety and satisfaction after treatment (Lentino 2003; Radcliff et al. 2015).

A variety of materials including calcium-based substitutes, synthetic polymers, DBM, and protein-based materials have been proposed as alternative delivery vehicles with bone fusion function (McLaren 2004; Nelson 2004). Because the most common pathogen responsible for spinal infections after surgery is the gram-positive bacteria *Staphylococcus aureus*, the antibiotic candidates for biomaterials for infection-targeted delivery (or prevention) may be limited to vancomycin, aminoglycoside series like tobramycin, gentamicin, amikacin, and quinolone series like ciprofloxacin (Turner et al. 2005; Logoluso et al. 2016; Shiels et al. 2017; Boles et al. 2018; Wells et al. 2018).

Several animal studies have shown that calcium sulfate pellets are substantially resorbed and replaced with new bone formation by 6 weeks and a similar rate of pellet resorption has been reported clinically (Turner et al. 2001; McKee et al. 2002). According to study by Shiels SM.et al., vancomycin continued to be released from the DBM over the course of 6 days while maintaining sufficient eluate concentrations to maintain a zone of inhibition similar or larger than a vancomycin control in spine fusion in rabbit (Shiels et al. 2017).

There are several obstacles to overcome in order to use this newly designed bone graft material in clinical spine fusion. First, the ideal shape, desired materials of bone graft, and release concentrations are not established. McLaren et al. questioned the effect of laboratory sampling methods on characterizing the elution of tobramycin from calcium sulfate and the reliability of in vitro elution data in predicting the in vivo release of antibiotics (McLaren et al. 2002). Second, local site effects by eluted antibiotics are of

concern. Since neither the optimal level of antibiotic nor the duration of its release has been established, the effect of high local levels of antibiotics on the ability of grafted material to enhance bone healing is largely unknown. In a rabbit study, the use of vancomycin-loaded DBM showed a decrease in the fusion rate compared to DBM when used in a sterile wound (Shiels et al. 2017). Furthermore, an in vitro study suggests that vancomycin has toxic effects on hMSCs, a cell population particularly important for bone formation (Chu et al. 2017). Finally, clinical studies on the use of antibiotic-impregnated graft materials for spine fusion in humans are few. Pilot studies focused on the use of antibiotic-impregnated graft material in total joint arthroplasty and osteomyelitis (Logoluso et al. 2016) (Table 7).

## Conclusion

A wide variety of bone graft materials are used in spinal surgery applications. Increasingly, over the past decade, diverse materials and composites are being developed as grafting options for use in spinal surgery. Consideration of the ideal properties of a grafting material and the material's mechanism of action, structural and handling characteristics, FDA classification and related approval or registration, and available clinical and preclinical data will optimize appropriate grafting choice for a certain surgical application for spinal fusion. Moreover, bone grafts do not fuse immediately; instead, they provide a foundation or scaffold for the patient's body to grow new bone in anatomical sites wherein bone did not previously exist such as in a spinal fusion site.

The development of products used for bone regeneration has followed the basic criteria of providing a biocompatible three-dimensional scaffold with controlled architecture capable of stimulating or supporting bone growth in the natural in vivo environment. The ability of the material to be used in conjunction with other cellular and signal (growth factors)-based therapies is a key strategy in maximizing the efficacy and likely success of fusion. However, while many bone graft substitutes perform well as bone graft extenders, only autogenous bone grafts are osteogenic and BMPs are osteoinductive.

Variations in anatomical location, surgical application (meticulous surgical preparation including adequate decortication), instrumentation type, and the patient's risk factors (metabolic and nutritional status, vitamin D, diabetes, smoking, drug and alcohol abuse) are critically important factors to consider in choosing an ideal grafting agent or bone graft to achieve a successful biologic bone union.

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