INTERNATIONAL JOURNAL of SPINE SURGERY

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Int J Spine Surg 2021, 15 (s1) 68-93
doi: https://doi.org/10.14444/8056
https://www.ijssurgery.com/content/15/s1/68

Errata An erratum has been published regarding this article. Please see next page or: /content/17/5/754.full.pdf

The International Journal of Spine Surgery
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International Journal of Spine Surgery, Vol. 15, Supplement 1, 2021, pp. S68–S93
https://doi.org/10.14444/8056

Allografts and Spinal Fusion

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ABSTRACT

Background: Back pain is a common chief complaint within the United States and is caused by a multitude of etiologies. There are many different treatment modalities for back pain, with a frequent option being spinal fusion procedures. The success of spinal fusion greatly depends on instrumentation, construct design, and bone grafts used in surgery. Bone allografts are important for both structural integrity and providing a scaffold for bone fusion to occur.

Method: Searches were performed using terms "allografts" and "bone" as well as product names in peer reviewed literature Pubmed, Google Scholar, FDA-510k approvals, and clinicaltrials.gov.

Results: This study is a review of allografts and focuses on currently available products and their success in both animal and clinical studies.

Conclusion: Bone grafts used in surgery are generally categorized into 3 main types: autogenous (from patient's own body), allograft (from cadaveric or living donor), and synthetic. This paper focuses on allografts and provides an overview on the different subtypes with an emphasis on recent product development and uses in spinal fusion surgery.

Special Issue

Keywords: spine fusion, allograft, bone graft material, bone grafts

INTRODUCTION

Back pain is a common chief complaint within the United States and is caused by a multitude of etiologies. According to the National Center for Health Statistics, more than 650 000 spinal fusion surgeries are performed annually.[1] The success of arthrodesis in spine surgery depends on multiple factors; however, an important component to success depends on the bone graft and graft substitutes used in surgery. 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/or to provide initial structural support.[2] The graft material used in spinal fusion procedures can be categorized generally into 3 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.[3,4] Autograft is considered the "gold standard"; however, the authors believe allograft and synthetics are currently replacing separate surgical site–harvested autografts as the standard because of patient donor site morbidity, advancement in the development of other products, limited quantity available, host limiting bone quality, and lack of training of young surgeons in the technique of autograft harvest.[4] This paper focuses on allografts and recent advancements in product development and uses in spinal fusion surgery.

BONE GRAFT PROPERTIES

Osteogenesis, or bone formation, occurs via 2 mechanisms: endochondral ossification or intramembranous ossification. Intramembranous ossification involves direct conversion of mesenchymal tissue into bone, does not require cartilage as an intermediate, and does require bone morphogenic proteins and CBFA1 transcription factors.[5] Endochondral ossification requires cartilage as an intermediate and can be divided into 5 stages. The stages of endochondral ossification are as follows:—mesenchymal cells differentiate to cartilage cells, formation of chondrocytes, proliferation of chondrocytes to form the model for the bone, formation of hypertrophic chondrocytes, and invasion of blood vessels.[5] Both mechanisms of bone formation rely on complex intracellular signaling events, and each contributes to bone formation after spinal fusion surgeries.

Critical elements that are required for bone formation and are important in bone graft properties include osteoconduction, osteoinduction, osteogenesis, mechanical stability, and vascularization. Osteoconduction relies on a scaffold that supports cell ingrowth, facilitates vascularization, and provides a network for cells to attach.[4] 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.[4] Osteogenesis relies on the immediate provision of viable cells emanating from the host to the defect site differentiating into bone-forming cells.[4] Autologous bone is the only bone graft available that intrinsically contains all 3 properties and is therefore considered the "gold standard." However, with advancements in allograft processing and development, recent products have theoretically been able to acquire all 3 properties of bone development.

ALLOGRAFT

Allograft bone is obtained from either living or deceased donors and then processed for sterility. Common preparation includes freezing or lyophilization (ie, freeze drying), which involves dehydration and vacuum packaging to store at room temperature.[6] In general, allografts are primarily osteoconductive with minimal osteoinductive potential and are traditionally not osteogenic because the donor cells are eradicated during processing.[7,8] Surgeons prefer allografts because they are readily accessible, available in various forms delivering handling properties, facilitate bone formation, and do not require donor site morbidity. However, traditionally available allografts consist of nonviable tissue and cannot stimulate bone formation without the addition of bone-stimulating factors and cells.[9–11] These limitations lead to slower and less complete incorporation with native bone. Additionally, allografts have a potential risk of disease transmission even if the incidence is very low and the risk can be controlled during the procurement and sterilization process.[7] Allogenic bone is traditionally available in many forms: cortico-cancellous, demineralized bone matrix (DBM), morselized and cancellous chips, and osteochondral and whole bone-segments.[12]

Recently, a new class of allograft has emerged called *viable cellular allografts* or *cellular bone matrices* (CBMs), which are designed to have all 3 properties of bone formation: osteoconduction, osteoinduction, and osteogenesis. CBMs are created using osteoconductive cadaveric bone with the retention or addition of allogeneic stem cells (ie, mesenchymal stem cells) to initiate an osteogenic process.[13] The efficacy of mesenchymal stem cells has been shown to be as efficacious as rhBMP and allograft.[12] Overley et al[14] retrospectively examined 78 patients (98 fusion levels) and found no difference in radiographic fusion and rate of revision surgery in patients who underwent MS-TLIF with either rhBMP-2 or CBM as fusion adjuncts.

Table 1 provides a description of the different types of allografts and their corresponding characteristics. For a more thorough description of all classes of bone grafts, please refer to the chapter by Yang et al[4] in the *Handbook of Spine Technology* or the review article by Gruskin et al.[3] A comprehensive review of bone graft characteristics can be found in the chapter by Bae et al[23] in *AAOS Comprehensive Orthopaedic Review 2*.

Cortico-Cancellous Allograft

Cortico-cancellous allografts are the most commonly used allograft today. They are strictly osteoconductive without any osteoinductive or osteogenic properties. These grafts can be prepared as whole pieces, such as rings of femoral head/neck used traditionally for interbody fusion, or prepared as chips to aid in void-filling scenarios or posterolateral fusion.[24] Cortical allograft is most commonly used as a mechanical strut graft, whereas cancellous allograft functions as a osteoconductive scaffold for bone formation.[4] In a study by Park et al,[25] 46 patients underwent ACDF with either a cortico-cancellous allograft or iliac crest autograft, and there was no significant difference in fusion status between the 2 groups. Another study by Suchomel et al[26] evaluated fibular allografts versus autologous iliac crest grafts in 80 patients undergoing ACDF procedures and found in single-level procedures that there was no difference in fusion rates and graft collapse between autograft and allograft. Table 2 provides a list of commercially available cortico-cancellous allografts used for spinal fusions and specifics on each product.

Table 1. Description characteristics of different types of allografts.

Grafting Material	Grafting Material (Typical Abbreviation)	Grafting Material Category and Description	Variability	Osteogenic	Osteoinductive	Osteoconductive	Immunogenicity/ Disease Transmission	Strength (Immediate)	Donor Site Morbidity
Allograft	Fresh[15]	1. Living donor (patient-to-patient transfer) 2. Cadaveric donor (harvested within 12 h and allotransplantation within 72 h) → Femoral head (as osteochodral form)	Lot-to-lot variability donor's bone condition + sterilization processing techniques	? (No data for otsteogenic graft for human)	? (No data for otsteogenic graft for human)	? (No data for otsteogenic graft for human)	+++ (Generally causes an unacceptable host immune reaction as osteogenic graft) → Not used commercially only animal studies.		–
Allograft	Fresh (ostechondral graft)[16]	1. Living donor (patient-to-patient transfer) 2. Cadaveric donor (harvested within 12 h and allotransplantation within 24 h) → Femoral head (as osteochodral form)[17]		+/– (Only chondrocyte viability remains)	–	++	+ (Reduced/mild immune reaction by cartilaginous portion of graft) + (Infection risk due to storage media)	++ (Grafted at articular portion for weight support)	–
Allograft	Fresh-frozen[18]	From 1. living donor 2. cadaveric donor		–	–	++ (Less than autogenous bone)[19]	+ (Reported cases)	++[1]	–
Allograft	Freeze-dried	From 1. living donor 2. cadaveric donor		–	–	++	+/–	+/– (Significantly affected by drying process)[20]	–
Allograft	Gamma sterilization			–	–	++	+/–	+ (By radiation effect)[21]	–
Allograft	Demineralized bone matrix[22]	Mostly cadaveric donors	Demineralization processes + particle sizes	–	+/–	++	+/–	–	–
Selective cell retained allografts	Osteogenic cell		Patient characteristics	+	+/–	–	–	–	–

+++ 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; for demineralized bone matrix osteoinductive depending on the processing and sterilization techniques (product variability).
– None/no effect.

Table 2. Commercially available allograft mineralized products, structural and/or nonstructural.[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, Colorado, 1995 Allosource.org	AlloFuse	Cortical/cancellous spacers Cancellous cervical spacers Cortical cervical spacers	n/a	Regulated human tissue CFR 1270, 1271
	Spinal grafts–freeze-dried	Bicortical blocks Dowel Patella wedge Cervical spacers, parallel spacer/textured lordotic Femoral rings Fibular rings, radial rings, ulna rings	n/a	Regulated human tissue CFR 1270, 1271
	Spinal grafts–freeze-dried/ frozen	Cortical Strut 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
AlloSource	Allofuse cortical fibers Allofuse cortical chips Cancellous	Cortical/cancellous chips Cancellous chips, crushed, cubed, block, unicortical dowels, tricortical ilium, femoral shafts, AlloTrue terminal sterility gamma irradiation	(None in spine) NCT01413061 Subtalar arthrodesis	
ATEC, Carlsbad, California	AlphaGRAFT Structural Allografts	Vacuum-level allograft designed to hydrate	n/a	AATB standards and Good Tissue Practices
Australian Biotechnologies	Cervical spacers Femoral ring	PureCleanse, then chemical soak; low-temperature, high-pressure CO_2		Therapeutic Good Administration (TGA), code of Good Manufacturing Practice for Therapeutic Goods—Human Blood and Blood Components, Human Tissues and Human Cellular Therapy Products, 2013
Beijing Datsing Bio-Tech Co Ltd, Beijing, China	BioCage	Cortical bone (from donor femur) contoured wedge-shaped, end plates large contact area with dentate protrusions (saw-tooth), sagittal convex angle, center open "window" and side hole	Spinal fusion anterior portion with BioCage 2 y (30/33, 90.9% vs 30/ 34, 88.2%) PEEK† (360° posterior rods and screws), 1-level lumbar spine[27]	Tissue banks in China products are now approved by the National Medical Products Administration, China. Previously CFDA/State Food and Drug Administration, China
BoneBank Allografts, Texas	SteriSorb*	Osteoconductive sponge allografts (100% cancellous bone) Characteristics of a sponge by absorbing saline, blood, or bone marrow aspirate	n/a	Bone Bank Allografts Registration—FDA BBA Manufacturing Registration—FDA (previously THB) Bone Bank Allografts—Accreditation AATB CTO Registration Certificate—Bone Bank Allografts (International Registration)
	SteriFlex	Wrappable bone allografts (100% cortical bone) Can be bent, contoured, rolled, trimmed, molded, or sewn, making this flexible bone material	n/a	

Table 2. 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 SteriGraft—ACF cortical-cancellous spacer SteriGraft – ALIF SteriGraft—PLIF SteriGraft—unicortical dense cancellous block SteriGraft—dense cancellous block	Fully machined, constructed of 100% human cortical bone (femur or tibia) Fully machined, constructed of 100% human cortical bone with an internal cancellous plug (femur or tibia) Fully machined, constructed of 100% human cortical bone (femur) Fully machined, constructed of 100% human cortical bone (femur or tibia) Unicortical dense cancellous block (femoral head, patella, distal tibia, talus, or calcaneus) Dense cancellous block (femoral head, patella, distal tibia, talus or calcaneus)	n/a	
	Traditional bone/cancellous bone allografts Traditional bone/cortical-cancellous bone allografts	Traditional-type cancellous bone chip or tricortical alloililac 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 (December 2, 2015) FDA 510(k) cleared
Hospital Innovations	Ilium tricortical strips* Bone blocks* Whole shaft and hemishaft*	Traditional cortical/cancellous bone graft Available freeze-dried (FD) or frozen (FZ) Sterilized SAL 10^{-6}	n/a	
Globus Medical Inc	FORGE* FORGE Oblique*	Fully machined corticocancellous spacer (cervical spine fusion) Fully machined cortical spacer designed to provide a natural option for transforaminal lumbar fusion	n/a	K153203 (December 3, 2015) FDA 510(k) cleared
Life Link Tissue Bank	Cortical cancellous spacer*	Fully machined cortical-cancellous spacer (from femur and tibia) for cervical spine		AATB FDA Florida, California, and New York Holds a permit to provide tissue in Maryland
Maintain States Medical → 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 Cornerstone SR* Cornerstone ASR* Cornerstone-RESERVE*	Fully machined cortical block (from femur or tibia) with capital D shape Fully machined cortical lateral wall with a cancellous center with capital D shape 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 Cornerstone bicortical Cornerstone unicortical Cornerstone dense cancellous block	Freeze-dried cortical/cancellous (iliac crest) Freeze-dried cortical/cancellous (iliac crest) Freeze-dried anterior cortical wall with cancellous center 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

Table 2. 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
Orthofix	AlloQuent-s, Monolithic Cortical* Structural allograft*	Structural allograft (cervical fusion, lumbar fusion) Different sizes and shapes (ALIF, PLIF, TLIF)	NCT00637312, has results posted—cervical disc Trial was stopped; approval not being pursued for device (clinicaltrial.gov)	Unknown
RTI Surgical	Elemax cortical spacer allograft* Elemax cortical spacer allograft* Elemax PLIF allograft*	Precision-machined cortical spacer for anterior cervical discectomy and fusion procedures Fully machined cortical lateral wall with a cancellous center with capital D shape for anterior cervical discectomy and fusion procedures Fully machined cortical spacer designed to provide a natural option for PLIF	n/a	AATB Accreditation Certificate (Florida) FDA Establishment Registration and Listing for Human Cells, FDA-HCT/Ps Florida Tutogen Medical, GmbH (Germany) International Organization of Standards (ISO) Tutogen Medical, GmbH (Germany) CMDCAS—RTI Surgical (Florida) CE certificates Pioneer Surgical Technology (Michigan) International Facility Registrations Canada—CTO Registration State Tissue Banking Licenses California, Florida, Maryland, New York, Oregon, Illinois, Delaware
	AlloWedge bicortical allograft bone	Options for approaching opening wedge osteotomies in the foot and ankle Preshaped 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 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 ALIF approach Freeze-dried: rehydrate for a minimum of 30 s Frozen: thaw for a minimum of 15 min	n/a	FDA Establishment Registration and Listing for Human Cells, FDA-HCT/Ps
	Traditional cortical and/or cancellous strut allobone	Femoral head, hemifemoral 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, California	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 health care professional (eg, physician)
Stryker	AlloCraft CA, CL, CP, CS*	Machined from femoral/tibial allograft → ACDF Freeze-dried Chamfered edge	n/a	AATB US FDA regulations for tissue management. US-FDA 21 CFR 1271

Table 2. 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
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 AATB
X-spine Systems Inc/ Xtant USA	Atrix-C cervical allograft spacer	Precision-milled cortical bone with teeth like keel surfaces	n/a	Processed by tissue banks that are members of the AATB
Zimmer Biomet	OsteoStim cervical allograft system* OsteoStim PLIF* OsteoStim ALIF*	Fully machined cortical spacer bone for cervical and lumbar with teeth like keel surfaces	n/a	Processed by tissue banks that are members of the AATB

Abbreviations: AATB, American Association of Tissue Banks; ALIF, anterior lumbar interbody fusion; FDA, US Food and Drug Administration; n/a, not available on ClinicalTrials.org/no clinical data found or clinical trial registered (December 31, 2020); PLIF, posterior lumbar interbody fusion; THB, xxxx.

[a]AATB policies.[28]

*Indicates cancellous chips "crunch" available.

†PEEK cage made from engineered plastic polyetheretherketone.

Demineralized Bone Matrix

DBM is derived from human allografts and prepared by acid extraction of innate minerals to create an osteoconductive organic matrix with differing quantities of proteins that aid in osteoinduction.[5] DBM is a composite of collagens (mostly type I), noncollagenous proteins and growth factors, residual calcium phosphate mineral (1%–6%), and some cellular debris.[3] The use of DBM was developed in 1965 by Urist,[29] who observed that soluble signals contained within the organic phase of bone were capable of promoting bone formation. After processing, DBM lacks structural integrity but retains osteoconductive and osteoinductive properties.[3] DBM base is available, and when mixed with other substances these DBM-based products come in many forms, including powders, granules, gels, putties, and strips.[30] Importantly, the concentration of native BMP in DBM products differs significantly by manufacturer, donor lot, and batch, making it difficult to study the efficacy of DBM in clinical trials.[30–33] In an athymic rat model, Bae et al[34] observed significant lot-to-lot variability of a single DBM-based product, commercially available "off-the-shelf" with regard to BMP concentrations and associated in vivo bone formation for fusion rates.[35] Therefore, it is important to note the efficacy of DBM's osteoconduction and osteoinduction properties in clinical studies is limited by mainly narrative study designs with limited levels of evidence, small sample size, and lack of appropriate controls.[26]

In current clinical practice, because DBM-based products lack structural integrity, they are exclusively/mostly used in spinal applications as bone graft extenders, typically mixed with surgical site local bone or morselized harvested bone from the iliac crest (ICBG) autografts, and/or exogenous peptide/differentiation factors (rhBMP-2) to promote bone growth.[4] Kang et al[36] completed a 2-year prospective randomized clinical trial comparing outcomes of Grafton DBM with local bone to those of ICBG in a single-level instrumented posterior lumbar fusion. In the study, 46 patients (30 Grafton, 16 ICBG) were evaluated, and primary outcome was solid posterolateral lumbar fusion. Results indicated no significant difference in overall fusion rates between the 2 study groups (86% for Grafton, 92% for ICBG). Lower blood loss was recorded in the patients who received an implant of DBM-base matrix (Grafton DBM-Matrix), but with equal or slightly greater improvement in Oswestry Disability Index scores for the DBM-base matrix patients.

Cammisa et al[37] completed a multicenter, prospective, side-to-side (right versus left) comparison of a DBM-based gel (Grafton DBM gel) combined with iliac crest autograft (2:1 ratio) placed on one side of the fusion construct versus iliac crest autograft alone on the other side in 120 patients who underwent posterolateral spinal fusion (PLF) procedures. At 24 months nearly equivalent fusion rates between the sides implanted with a composite of DBM-based gel (Grafton DBM gel) + one-third iliac autograft were 52% fused (42 of 81 sides) versus contralateral sides at 54% fused (44 of 81 sides) after being implanted with autograft alone. Specifically, radiographically fused rates of 40.7% bilateral (33 of 81 consistently both right and left sides fused) or 24.7% unilateral (only autograft side fused in 14% [11 of 81] versus DBM-based gel + autograft composite fused in 11% [9 of 81]). Although 34.6% (28 of 81) were not radiographically fused, the pseudarthrosis revision surgery rate was <1% (1 of 81). Interestingly, the fusion rate in this study is substantially lower than the accepted solid fusion rate of PLF surgery (90%),[38–40] and the authors ascribe this discrepancy to a difficult patient population, strict radiologic criteria for fusion, and only evaluating bone graft lateral to the instrumentation on anterioposterior film.

These authors conclude that DBM-based allograft products may be used to augment the amount of autograft bone graft needed for successful lumbar fusion. Cammissa et al[37] report that one third the quantity of autograft may be used with this DBM-based gel graft extender to achieve consolidated bony fusion, and Kang et al[36] used 15 to 20 cm^3 of autograft with DBM compared with 25 to 30 cm^3 ICBG for successful fusion. The studies by Kang et al and Cammissa et al provide level 1 evidence that Grafton can be used as a bone graft extender for lumbar spinal fusion.[37]

Interestingly, Grafton is the only bone graft extender to have level 1 evidence and shows different efficacy in the lumbar spine versus the cervical spine. As the above studies showed Grafton to be effective in lumbar spinal fusions, a study by An et al showed level 1 evidence that Grafton DBM is not useful for cervical spinal fusion.[41,42] In a randomized control trial, An et al[42] compared 77 ACDF patients with either Grafton DBM + tricortical bone versus tricortical bone alone. Nonunion developed in 46% of patients in the Grafton group compared with 26% of patients in the standalone tricortical bone group.

Table 3 provides a list of commercially available DBM-based products used for spinal fusion and specifics on each product.

Viable Cellular Allografts (Cellular Bone Matrices)

The advancement in the field of stem cell procurement has generated the development of allogenic bone grafts containing live mesenchymal stem cells (MSCs), also known as cellular bone matrices.[63] Mesenchymal stem cells were identified in 1966 by Fridenstein et al in bone marrow and have been shown to differentiate into chondroblasts and osteoblasts.[63,64] These commercially available bone allografts are composed of osteoconductive partially demineralized cadaveric bone as matrix carriers with components of cryopreserved allogeneic cells (MSCs) that promote osteogenesis and osteoinduction.[6,65] MSCs can be isolated from bone marrow, placenta, umbilical cord blood, connective tissue, skin, synovial fluid, fat, and teeth.[63,66] MSCs are capable of evading the immune system because they uniquely do not express human leukocyte antigen class II molecules, which are essential for activation of the cellular immune response.[63,67–69]

In the United States, the process to manufacture these materials involves the American Association of Tissue Banks (AATB) approval processes for cadaveric human bone recovering (contract with independent US Food and Drug Administration [FDA]–registered tissue recovery groups), processing, storing, and preserving cellular components of the bone, or addition of cells, and removal of noncellular proteins. Marketed under FDA-HCT wherein the regulation of product directive is safety, safety is exercised by restricted donor screening. Unlike other DBM-based allografts approved via 510(k) or premarket approval pathways, CBMs are not required to be terminally sterilized, relying on the donor screening and aseptic processing to ensure safety. The exact procedures vary by manufacturer. The HCT/P classification does not require lot-to-lot cell composition or validation of growth factor production. (Per FDA guidance documents on HCT/P products, to "rely on the metabolic activity of living cells for their primary function" would render a product as a biologic drug [section 360], which would require a biologic license application and clinical trials.)

CBMs are commercially provided as frozen products and must be stored at –80°C, and they require thawing prior to surgical implantation. Neither the reproducibility of cell recovery, after thaw, nor the viability of the cells following implantation has been established for commercially available products or production lots of them. The average number of cells across products is claimed to range from 66 000 to 3 million. Attempting to preserve the viable cells, these products are not terminally sterilized, like 510(k) DBMs or premarket approval products, but rely on aseptic processing to ensure safety. Table 4 provides a list of commercially available CBMs used for spinal fusion and specifics on each product.

The efficacy of viable cellular allografts in spinal fusion is difficult to determine. Given the properties of mesenchymal stem cells, their ability to promote osteogenesis, and their ability to evade the immune system, it is reasonable to think they would be advantageous for bone fusion. Several in vivo studies have demonstrated theoretical benefits of using CBMs. Cui et al[90] compared cloned osteoprogenitor cells to mixed marrow cells and found that cloned cells produced a greater amount of mature osseous tissue at an earlier time point during spine fusion in an athymic rat model. Gupta et al[91] used an ovine posterolateral lumbar fusion model and found similar fusion rates with osteoprogenitor-enriched graft compared with autograft.

To date, there have been very few non–industry-sponsored clinical trials. McAnany et al[92] evaluated 57 patients who underwent a 1- or 2-level ACDF using interbody allograft with Osteocel (NuVasive, San Diego, California). The patients were matched to a control group of 57 patients where only interbody allograft was used. At the 1-year follow-up, 87% in the Osteocel cohort had solid fusion compared with 94.7% in the control group.[81]

There are many factors that can influence the efficacy of CBMs and therefore result in limitations to these products. Hernigou et al[93] showed that bone marrow aspirates containing fewer than 1500 MSC/cc were ineffective for the treatment of tibial nonunion, suggesting that this is the minimal MSC concentration for bony healing.[63] Preparation of MSCs is not standardized, and variation in donor age, donor site, and viability of stem cells after thawing the allograft can all influence the effectiveness of CBM.

Although human clinical data are lacking, the athymic rat model allows for direct testing of CBM bone graft products. In a well-established rat model, fusion is assessed by manual palpation of a bony mass 6 to 8 weeks after implantation of DBM-based or CBM-based graft placed between the transverse processes during a posterolateral fusion procedure.[33,34,76] Using this model, Bhamb et al[33] reported at 8 weeks a 0 of 16 fusion rate in rats implanted with CBM Osteocel Plus Pro (NuVasive) compared with 88% to 100% fusion rate after noncellular human DBM–based products were implanted (Acell Evo3, DBX Mix, DBX Strip, Grafton Crunch, Grafton Flex, and Grafton Matrix), and 13% (2 of 16) were manually fused when implanted with syngeneic bone graft. Lin et al[76] at 6 weeks detected manual palpation fusion in 73% (11 of 15) of Cellentra (Zimmer Biomet, Warsaw, Indiana), 53% (8 of 15) of Trinity Elite (OrthoFix, Lewisville, Texas), 13% (2 of 15) of Vivi-Gen (Dupey Synthes, Raynham, Massachusettes) and 0 of 15 for each of Osteocel Plus Pro, Bio4 (BIO, Stryker, Kalamazoo, Michigan), and Map3 (RTI Surgical, Marquette, Michigan) implanted rats; 33% (5 of 15) were manually fused for syngeneic bone graft–implanted rats. Johnstone et al[80] recently evaluated manual palpation results after posterolateral fusion performed with several commercially available human CBM grafts; the highest manual palpation fusion rates were 71% (10 of 14) for Trinity Evolution and 77% (10 of 13) for Trinity Elite compared with 7% (1 of 14) for Osteocel Plus Pro and 40% (6 of 15) for syngeneic bone–implanted rats.

The findings of these studies highlight the variability among CBM commercial products and potentially among production lots.[32] Yet, interestingly, there are common observations across these studies: Syngeneic bone graft, a proxy for ICBG in this model, containing some live cells yielded low fused rates (13%, 33%, and 40%) across the studies, whereas the Osteocel Plus preparations consistently yielded almost no sites fused (0%, 0%, and 7%). Trinity Elite (53% and 77%) and Trinity Evolution (71%) formulations, along with Cellentra (73%), seem to yield somewhat comparable results. Preparations, sterilization, formulation, manufacturing

Table 3. Commercially available demineralized bone matrix (DBM)–based products.[a]

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 Inc Centennial, Colorado, 1995 Allosource.org	AlloFuse Gel AlloFuse Putty (identical to Stimublast Putty and Gel manufactured for Arthrex)	Injectable gel and putty	DBM, RPM carrier Carrier composed of polyethylene oxide polypropylene oxide block copolymer dissolved in water exhibiting reverse-phase characteristics (ie, an increase in viscosity as temperature increases)	n/a	K071849, December 2008
	Allofuse Plus	Paste, putty	DBM, RPM, cancellous chips	n/a	K103036, January 2011
	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	Kirk et al,[43] 2013 In vivo mouse muscle	K161996, February 2017
	NanoFUSE DBM	Putty 2-10 cc	45S5 bioactive glass + porcine gelatin + DBM 45S5 bioactive glass: osteoconductive scaffold, DBM: osteoinductive potential	Kirk et al,[43] 2013 In vivo mouse muscle	Regulated under CFR 1270, 1271 as a human tissue K110976, May 2011 www.accessdata.fda.gov/cdrh_docs/pdf11/K110976.pdf www.accessdata.fda.gov/cdrh_docs/pdf16/K161996.pdf 510(k)
ATEC, Carlsbad, California/Alphatec Spine Inc	ALPHAGRAFT DBM	Putty or gel	DBM of 100% demineralized fiber, an RPM DBM with superior handling characteristics and ready-to-use application. RPM. Thickens at body temperature	n/a	DCI regulatory classification LIT-84817A, LIT-84806A Linked to K150621, August 2015 (Bacterin International Inc)
Australian Biotechnologies, Sydney, Australia	Allovance Fibre Mat	Demineralized bone fibers	Demineralized bone long fibers cut (low-energy technique) preserving bone collagen alignment and microstructure	Rajadurai et al,[44] 2019 Case report ALIF	Australian Therapeutic Good Administration (TGA), Code of Good Manufacturing Practice for ~2017
Bacterin International Inc → Changed to Xtant Medical	OsetoSelect DBM	Putty	74% DBM dry weight	Yao et al,[45] 2020 MI-TLIF, lumbar spine Yao et al,[46] 2019 MI vs open TLIF	K091321, September 2009 K130498, May 2013
	OsetoSelect Plus DBM	Putty	74% DBM dry weight + demineralized cortical chips (1-4 mm)	n/a	K150621, August 2015 HCT/P (FEI 3005168462)
	OsteoSponge	The malleable sponge	DBM (100% human demineralized cancellous bone)	Shehadi and Elzein,[47] 2017	HCT/P (FEI 3005168462), November 2017
	OsteoSponge SC	The malleable sponge	Demineralized cancellous bone intended to treat the pathology of damaged subchondral bone of the articulating joints	Galli et al,[48] 2015, 717–722, *Journal of Foot & Ankle Surgery*	HCT/P (FEI 3005168462), November 2017
	OsteoWrap	Flexible handling characteristics with a scalpel or scissors	100% Human demineralized cortical bone	n/a	HCT/P (FEI 3005168462), November 2017
	3Demin	Various shape (fiber, boat shape, strip)	100% Human demineralized cortical bone fiber Contain BMPs and other growth factors 3Demin allografts are also available as loose cortical fibers in 3 volume options	n/a	Compliance with FDA guidelines regarding human cells, tissues, and cellular tissue–based products HCT/P 361 regulated viable allogeneic bone scaffold AATB guidelines
Berkeley Advanced Biomaterials, California	H-GENIN	Putty Matrix sponge Powder	100% DBM putty and crush-mix	Shehadi and Elzein,[47] 2017	510(k) cleared (as B-GENIN, R-GENIN) K092046, March 2010
Biomet Osteobiologics → Merged into Zimmer Biomet	InterGro DBM	Putty (40% DBM) Paste (35% DBM)	DBM, lethicin carrier (resorbable, biocompatible, semiviscous lipid)	Prospective case series	510(k) cleared K082793, April 2009 K031399, February 2005

Table 3. 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	n/a	AATB 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) Sterilized by gamma irradiation	n/a	FDA 510(k) Cleared AATB US FDA 21 CFR 1271. (HCT/P)
BoneBank Allografts 2017/ Texas Human Biologics	SteriFuse DBM Putty	Flowable, formable putty	100% DBM from human bone	n/a	Regulated under 21 CFR Part 1271 (h FDA requirements for HCT/P)
	SteriFuse Crunch	Flowable, formable crunch	SteriFuse DBM putty with cortical cancellous bone chips (composition?)	n/a	Regulated under 21 CFR Part 1271 (h FDA requirements for HCT/P)
DePuy Synthes	DBX	Putty type Paste Mix	DBM + sodium hyaluronate	NCT02005081: DBX and Autograft vs Actifuse in ACC Cervical spine (translational PLF, Russell et al,[49] 2020; Bhamb et al,[33] 2019)	K103795, April 2011 K080399, October 2008
	SYNTHES Dento	Powder type Granule type Putty type Paste	Powder type: demineralized cortical powder, mineralized cancellous powder, mineralized cortical powder Granule type: demineralized cortical (80%)/cancellous granules, mineralized cortical (80%)/ cancellous granules DBM putty type: 93% DBM	NCT04635865	
ETEX/Zimmer Biomet	CaP Plus	CaP Plus	Synthetic calcium phosphate, an inert carrier, carboxymethyl cellulose, and DBM	n/a	K063050, November 2007 K080329, April 2008
Exactech	Optecure	Injectable paste	DBM (81% by dry weight), hydrogel carrier	NCT00254852 (terminated)	K121989, November 2012 K061668, September 2006 K050806 February 2006
	Optecure + CCC	Injectable paste	Polymer powder, DBM, cortical cancellous chips (1-3 mm)	NCT02127112 Optecure + CCC vs allograft Adams BD 2016 Wrist Arthrodesis[50]	K061668, September 2006 K121989, November 2012
	OSTEOFIL DBM Paste, OSTEOFIL RT DBM Paste	DBM paste or Dry powder—hydrated to become injectable paste	DBM in gelatin carrier	n/a (translational Wang et al,[32] 2007; Togawa et al,[51] 2003)	K043420, February 2005
	Opteform	Putty or dry powder—hydrated to become paste	Gelatin, DBM, and cortical-cancellous bone chips	n/a	K043421, February 2005

Table 3. 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 OrthoBiologic) Inc, Irvine, California, SeaSpine 2018	Accell Connexus	Injectable putty	DBM (70% by weight), RPM	Retrospective comparative Schizas et al,[52] 2007	K060306, March 2006 K061880, August 2007
	Accell Evo3TM	Injectable putty	DBM (Accell Bone Matrix), RPM	NCT02018445 Instrumented Lumbar PLF DBM (Accell Evo3) + LB NCT01714804 Instrumented Lumbar PLF (Accell Evo3) Orndorff DG 2019, NASS 2019[53] NCT01430299 Prospective cohort, PLF DBM (Accell Evo3) vs rhBMP-2 (Infuse) Klineberg et al,[54] 2020 AOSpine	K103742, March 2011
	Accell TBM	Preformed matrix (strip, square, round)	100% DBM (Accell Bone Matrix)	n/a	K081817, September 2008
	Dynagraft II	Injectable gel, putty	DBM (Accell Bone Matrix), RPM, cancellous bone chips	n/a	K040419, March 2005
	Orthoblast II	Injectable paste, putty	DBM (Accell Bone Matrix), RPM, cancellous bone chips from same donor	Lee et al,[55] 2019 ADCF plate fixation + DBM (Orthoblast II) vs tricortical iliac autograft	K050642, December 2005
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	K053098, November 2005
	Optium DBM Gel	Gel	Particulate DBM and glycerol	n/a	K053098, November 2005
	Cellect DBM	Provided in a specialized cartridge	DBM fibers + cancellous chips	Lee et al,[56] 2009—case reports treat secondary osteonecrosis	Regulated under CFR 1270 and 1271
Medtronic Spinal and Biologics	Osteofil DBM	Injectable paste, moldable strips	DBM (24% by weight) in porcine gelatin	Prospective case series Epstein et al,[57] 2007	K043420, February 2005
	Progenix TM Plus	Putty with demineralized cortical chips	DBM in type 1 bovine collagen and sodium alginate	n/a	K081950, July 2008
	Progenix Putty	Injectable putty	DBM in type 1 bovine collagen and sodium alginate	Muzević et al,[58] 2018 ACDF Blinded observations/ assessment of study in rabbit (Smucker et al,[59] 2008)	K080462, May 2008
	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 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 and leaving only the organic portion	NCT02684045: PLF 1- to 2-level retrospective review cases Spine	K123691, January 2013 K082615, October 2008

Table 3. 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
MTF/Synthes	DBX	Paste, putty mix, strip	DBM (32% by weight), sodium hyaluronate carrier (mix varies for paste, putty, mix), processed human cortical bone	NCT02005081: DBX and Autograft vs Actifuse SHAPE (Baxter) in ACC cervical spine	K040262, March 2005 (putty, paste, matrix mix) K040501, 2005—(putty, paste, matrix mix) April 2005 K053218, December 2006 (putty, paste, matrix mix) K063676, March 2007 (putty, paste, matrix mix) K080399, October 2008 (paste) K091217, October 2009 (putty) K091218, September 2009 (putty) K103795, April 2011 (putty) K103784, April 2011 (putty) K042829, January 2006 (strip) DBX approved in more than 50 countries
Nanotherapeutics Inc NanoFuse Biologics LLC, Malden, Massachusetts	Origen DBM with Biosotive Glass (NanoFUSE DBM)	A malleable, puttylike, bone-void filler	Human DBM and synthetic calcium phosphor-silicate particulate material particles (45s5 bioactive glass), both coated with gelatin derived from porcine skin	NCT03751943 PLF with autograft NCT03762811 (NanoFUSE with autograft in voids fusion)	K120279, April 2012 K110976, May 2011
NuTech Medical Inc	Matrix: Osteoconductive Matrix Plus	Putty type	Allograft cancellous and demineralized cortical mixture Freeze-dried for convenient ambient temperature storage	(See: Table 4 NCT02023372)	
	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		
Osteotech/Medtronic	GRAFTON A-Flex	Round, flexible sheet	DBM	n/a	K051188, January 2006
	GRAFTON Crunch	Packable graft	DBM, demineralized cortical cubes	n/a	K051188, January 2006
	GRAFTON Flex	Flexible sheets, varying sizes	DBM	Retrospective comparative study	K051195, December 2005
	GRAFTON Gel	Injectable syringe	DBM	RCT, prospective case series	K051195, December 2005
	GRAFTON Matrix PLF	Troughs	DBM	RCT	K051195, December 2005
	GRAFTON Matrix Scoliosis Strips	Strips, various sizes	DBM	Retrospective case series	*(Recalled October 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 DBM + inert starch-based carrier has been added	n/a	K043048, November 2005 (Osteotech)—traditional K042707, November 2005 (Osteotech)
	Grafton Putty 22076647	Packable, moldable graft	DBM (17% by weight), glycerol	Kang et al,[36] 2012 PLF RCT Grafton and local bone vs ICBG Park 2013[35] ACDF, prospective case series PEEK cage packed with Grafton Cammisa et al,[37] 2004 PLF Prospective comparative study, side-by-side in same patient: Grafton DBM gel vs ICBG An et al,[42] 1995, cervical ACDF Prospective comparative study DFDBA tricortical graft filled with Grafton vs ICBG	K051195, December 2005

Table 3. 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
Pioneer Surgical Technology and Regeneration Technologies → All companies merged into RTI Surgical	BioSet	Injectable paste, putty, strips, and blocks with cortical cancellous chips	DBM, gelatin carrier	n/a	510(k) cleared Regulated under 21 CFR Part 1271 (h FDA requirements for HCT/P) December 7, 2016 (validated by FDA)
	BioAdapt DBM	Powder form	Dried powder form (70% DBM by weigh) donated from 100% donated human musculoskeletal tissue	n/a	Regulated under 21 CFR Part 1271 (h FDA requirements for HCT/P) December 7, 2016 (validated by FDA)
	BioReady DBM Putty and Putty with Chips	Putty/putty with bone chip	• Putty: 56% DBM by weight • Putty with chips: 42% DBM by weight + small or large mineralized cortical cancellous chip → 100% allograft DBM	n/a	Regulated under 21 CFR Part 1271 (h FDA requirements for HCT/P) December 7, 2016 (validated by FDA)
SeaSpine, Carlsbad, California	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 (Same Accell Evo3)	AccellEvo3, same material
	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, RPM carrier	NCT01430299 (Same Accell Evo3)	AccellEvo3, same material (SeaSpine, new sponsor)
	OsteoSparx Demineralized Bone Matrix	Gel or puttylike consistency	DBM + RPM carrier	NCT01430299 (Same Accell Evo3)	AccellEvo3, same material (SeaSpine, new sponsor)
	OsteoSparx C Demineralized Bone Matrix	Gel or puttylike consistency	DBM + RPM carrier + cancellous bone	NCT01430299 (Same Accell Evo3)	It is the same material as Accell Evo3
	Accell Total Bone Matrix	Preformed shape (round or rectangular)	DBM + Accell bone matrix → 100% DBM	NCT01430299	It is the same material as Accell Evo3
	Accell Evo3c	Putty	DBM + Accell bone matrix (it is an open-structured, dispersed form of DBM) + cancellous bone + bioresorbable, RPM carrier	n/a	K103742, March 2011
	Accell Evo3	Putty	DBM + Accell bone matrix (it is an open-structured, dispersed form of DBM) + bioresorbable, RPM carrier	NCT02018445 Case study PLIF (December 2013 ~ June 2017) DBM (Accell Evo3) + LB NCT01714804 Prospective PLF vs retrospective PLF rhBMP-2 (December 2017 ~ January 2018) NCT01430299 RCT on PLF DBM (Accell Evo3) (93.5% fused) vs rhBMP-2(100% fused). Eleswarapu et al,[60] 2020	K103742, March 2011
	Capistrano	DBM + allobone	DBM + machined cortical and cancellous allograft bone	n/a	FDA 510(k) cleared
SeaSpine Orthopaedics Corp, Irvine, California (IsoTis Orthobiologics)	OsteoStrand Plus OsteoStrand	Bone matrix	100% demineralized bone fibers with (Powered by Accell Bone Matrix)	NCT04629807, ALIF DBM vs DBM NCT04629794 PLF deformity correction: DBM (OsteoStrand [Fibers]) vs rhBMP-2	361 HCT/P

Table 3. 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
SeaSpine Inc	All Products SeaSpine			NCT04364295 (Global Registry Study) Effectiveness of SeaSpine products n = 500	
Smith & Nephew	VIAGRAF	Putty, paste, gel, crunch, and flex	DBM, glycerol	n/a	K043209, December 2005
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
SpineFrontier, Malden, Massachusetts		Included DBM	Interbody fusion device		K193106 (likely a combination product, June 2020)
Wright Medical Technology	ALLOMATRIX	Various volumes, consistency varies depending on proportion of cancellous chips used	DBM (86% by volume) with or without CBM in surgical-grade calcium sulfate powder	Fu et al,[61] 2016, TLIF/PLIF with DBM (Allomatrix) + LB HA/β-TCP vs AIBG + LB + HA/β-TCP; retrospective comparative study	K041663, September 2004
	ALLOMATRIX RCS	Formable putty	DBM, synthetic RCS, calcium sulfate, and hydroxypropylmethylcellulose	n/a	K041663, September 2004
	ALLOMATRIX C	Putty	ALLOMATRIX + small cancellous chips	n/a	510(k) cleared K040980 (July 14, 2004)
	ALLOMATRIX CUSTOM	Putty	ALLOMATRIX + large cancellous chips	n/a	K040980 September 2004
	ALLOMATRIX	Injectable	DBM (86% by volume) + OSTEOSET (surgical-grade calcium sulfate)	NCT00274378 Injectable DBM (Allomatrix) putty in distal radius fracture	510(k) cleared K020895
	ALLOMATRIX DR	Putty	Calcium sulfate, DBM, and small cancellous chips	n/a	K040980, July 2004
	PRO-STIM	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

Table 3. 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
Zimmer → it merged into Zimmer Biomet company	IGNITE	Percutaneous graft for fracture malunion/ nonunion	DBM in surgical-grade calcium sulfate powder to be mixed with BMA	n/a	510(k) cleared K052913, November 2005
	Osteoset DBM Pellets	Packable pellets	3.0- or 4.8-mm pellets Surgical-grade calcium sulfate, DBM (53% by volume), stearic acid	Xie et al,[62] 2014 Cervical fusion (ACDF) PEEK with either Osteoset vs ICBG	510(k) cleared K022828, April 2004 K053642, January 2006
	PRO-STIM 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, February 2019
	Puros DBM with RPM Gel and Paste	Gel, paste	DBM, RPM, ground cancellous bone (<500 microns)	NCT03112772 (Socket Preservation)	Regulated under CFR 1270, 1271 as human tissue
	Puros DBM with RPM Putty & Putty with chips	Putty	DBM, RPM, with or without cortical bone chips (850 microns to 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 (molded, packed)	50% Demineralized cortical bone (DBM) + 50% mineralized cancellous chips All-inclusive bone grafting kit	n/a	FDA registration number: FEI 1000160576 (until June 30, 2020) AATB and HTC/P
	StaGraft DBM Putty and Plus	Putty/granules (molded, packed)	DBM + natural lecithin carrier + resorbable coralline hydroxyapatite/ calcium carbonate granules. Available as a 40% DBM Putty or 35% DBM PLUS	n/a	FDA registration number: FEI 1000160576 (until June 30, 2020)
	StaGraft Cancellous DBM Sponge and Strips	Sponge strips from a single piece cancellous bone	Cancellous DBM sponge and strips are machined from a single piece of cancellous bone. Osteoinductive bone, trabecular structure, spongelike handling	n/a	FDA registration number: FEI 1000160576 (until June 30, 2020)
	FiberStack Demineralized Bone Matrix	Molded, packed	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 (until June 30, 2020)

Abbreviations: AATB, American Association of Tissue Banks guidelines; ACC, anterior cervical corpectomy with fusion; ACDF, anterior cervical discectomy fusion; AIBG, autologous bone chips; ALB, autologous Local bone chips; ALIF anterior lumbar interbody fusion; BMA, bone marrow aspirate; BRC, bone repair cells; CBM, cellular bone matrix, cellular bone allograft; FDA, US Food and Drug Administration; HA/β-TCP, hydroxyapatite β-tricalcium phosphate; ICBG, iliac crest bone graft; LB, local bone; LIF, lumbar interbody fusion; OLIF, oblique lateral lumbar interbody fusion; PEEK, a polyetheretherketone material used for cage devices employed as instrumentation in anterior interbody spinal fusion procedures; PLF, posterolateral lumbar fusion; PLIF, posterior lumbar interbody fusion; RCS, resorbable conductive scaffold; RCT, randomized control trial; RhBMP-2, recombinant human morphogenic protein-2, infuse; RPM, reverse-phase medium; TLIF, transforaminal lumbar interbody fusion; VBM, viable bone matrix; VCBM, viable cell bone matrix; XLIF, extreme lateral interbody fusion.

[a]510(k) is a premarket submission made to the FDA to demonstrate that the device to be marketed is at least as safe and effective as, 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 the FDA online database (http://www.accessdata.fda.gov). CFR Code of Federal Regulations 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 Tissue Banks: https://images.magnetmail.net/images/clients/AATB/attach/Bulletin_Links/18_2/AATB_Accreditation_Policies_February_08_2018.pdf (last update February 2018). TBI: Tissue Banks International National Processing Center (an AATB-accredited tissue bank). US human tissue bank license states: California, Florida, Maryland, and New York.

Table 4. Commercially available combination grafting products, naturally occurring peptides, growth differentiating factors, cellularized grafts, and cellular bone matrices (CBMs).

Company	Combination Product	Formulation	Product Composition	Peer-Reviewed Clinical Evidence/Ongoing Study ClinicalTrials.gov Identifier: NCT	Regulatory Clearance/Approval FDA 510(k), FDA 361, 21 CFR Part 1271 CFR 1270, CFR 1271 21 CFR 3.2(e) HCT/P 361, Human Allografts (No Clinical Studies) Biologic Drugs and Devices 351 (Clinical Trials)
Advanced Biologics, Carlsbad, California, 2009 (marketed OsteoAMP in the USA since 2009/ Bioventus) Bioventus Surgical, Durham, North Carolina (original developer)	OsteoAMP	Granules or sponge	OsteoAMP, an allogeneic growth factor implant, exploits the angiogenic, mitogenic, and osteoinductive growth factors that are within marrow cells 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	Field et al,[70] 2014 Cervical Spine-Fusion NCT02225444 Lumbar Spine-PLF (TLIF, LLIF) Roh et al,[71] 2013 Yeung et al,[72] 2014, evaluation of donor bone, processing aseptically terminal sterilization in cervical/ lumbar	Bioventus manages orders and sales of HCT/Ps (not a distributor, FDA) Regulated under CFR 1270, 1271 as a human tissue, registration held by Tissue Bank Permit: Millstone Medical Outsourcing LLC, Olive Branch, Mississippi (Bone, Demineralized Bone Matrix, Ligament, Musculoskeletal Tissues, Tendons) Maryland, New York State Tissue Bank Permit: Advanced Biologics LLC (Bone Demineralized Bone Matrix)
AlloSource, Centennial, Colorado, 1995 Allosource.org	Allostem Cellular Bone Autograft (ACBM) AlloWrap	Strips, blocks, cubes, morselized Amniotic membrane	Partially demineralized allograft bone combined with adipose-derived MSCs Amniotic membrane dual-sided epithelial layer	NCT01413061 ACBM (69.2%) vs tibia/ICBG (45.6%). Nonunion rate after Subtalar Arthrodesis Myerson et al,[73] 2019 NCT04684901 (Cervical Spine, 2-level, ACDF) Reduction of Soft Tissue Swelling	Regulated under CFR 1270, 1271 as a human tissue
Aziyo Biologics Inc Richmond, California	FiberCel (Medtronics) OsteoGro V OsteoGro V ViBone	Putty	OsteoGro V Fiber Cancellous bone particles with preserved cells combined with demineralized cortical particles Viable Bone Matrix (ViBone, Aziyo gentle VBM processes) OsteoGro Allogaft Bone Matrix sterile bone matrix composed of cancellous particles and demineralized cortical fibers	NCT03896347 (3-level OLIF) NCT03425682 Lumbar (PLIF, TLIF) or Cervical (ACDF) Fusion using ViBone	Regulated under CFR 1270, 1271 as a human tissue
BBS-Bioactive Bone Substitutes Oyj, Finland	ARTEBONE		TCP + natural cocktail of bone proteins (growth factors)	NCT02480868: case series study for ankle fusion	FDA 510(k) cleared
Bioventus Surgical Durham, North Carolina Hoofddorp, Netherlands	OSTEOAMP	Granule, putty, and sponge form	Cervical and lumbar spine fusion procedures Allograft with growth factors (such as BMP-2, BMP-7, TGF-β1, aFGF, VEGF, and ANG1, within bone marrow cells)	PLF with OsteoAMP NCT02225444 (Roh et al,[71] 2013) Comparative study with rhBMP-2 with OsteoAMP (Roh et al,[71] 2013)	FDA 510(k) cleared AATB US FDA 21 CFR 1271. HCT/P

Table 4. Continued.

Company	Combination Product	Formulation	Product Composition	Peer-Reviewed Clinical Evidence/Ongoing Study ClinicalTrials.gov Identifier: NCT	Regulatory Clearance/Approval FDA 510(k), FDA 361, 21 CFR Part 1271 CFR 1270, CFR 1271 21 CFR 3.2(e) HCT/P 361, Human Allografts (No Clinical Studies) Biologic Drugs and Devices 351 (Clinical Trials)
Bone Biologics Corp, Victoria, Australia		Putty (NB1 bone graft)	Demineralized bone, sodium hyaluronate (DBX) + rhNell-1 (osteogenic factor)	NCT03810573 (TLIF) NB1 rhNELL-1/DBX) low vs high dose	Regulated Australia Regulation
BONESUPPORT AB: Lund, Sweden	CERAMENT G With MSCs + cytokines	Injectable type	Injectable antibiotic-eluting bone graft substitute that provides local sustained CERAMENT (40% hydroxyapatite + 60% calcium sulfate) + 17.5 mg gentamicin/mL paste.	NCT02820363 (RCT) for open tibial fracture (recruiting status) NCT02128256: case series study (reinfection prophylaxis) NCT04244942 (Registry Study) Cell study Alfotawi et al,[74] 2013	CE Mark approval FDA Combination Products (CDRH's Division of General Restorative and Neurological Devices)
	CERAMENT V With MSCs + cytokines	Injectable type	Injectable antibiotic-eluting bone graft substitute that provides local sustained CERAMENT (40% hydroxyapatite + 60% calcium sulfate) + iohexol (as a radio-opacity enhancer) + 66 mg vancomycin/mL paste	Cell study Alfotawi et al,[74] 2013	CE Mark approval FDA Approvals Separate for Cerement/Bone Void Filler K090871 September 2009 K073316, June 2008 Iohexol, initial approval 1985
DePuy/Synthes	ViviGen Cellular Bone Matrix Vertigraft	Cryo Cortical cortical cancellous bone matrix and demineralized bone	ViviGen Cellular Bone Matrix is composed of cryopreserved viable cortical cancellous bone matrix and demineralized bone. ViviGen Cellular Bone Matrix is an HCT/P. ViviGen Cellular Bone Matrix is processed from donated human tissue, resulting from the generous gift of an individual or his or her family	NCT02814825 (ACDF cervical) HCT/P Divi SN 2017 Divi SN 2017[75] NCT03733626 (Lumbar) NCT04007094 (PLF lumbar) Translational PLF CBMs (Lin et al,[76] 2020) NCT03527966 (n = 3, V-CBA (ViviGen) vs rhBMP-2, Lumbar Fusion Retrospective study 1- to 2-level study V-CBA vs rhBMP-2, Lumbar Fusion (Wetzell et al,[77] 2020)	(HCT/P) as defined by the FDA in 21 CFR 1271.3(d). 21CFR 1271
	CONFORM CUBE	Cube shape	Demineralized Cancellous Bone, organic matrix (osteoinductive, promotes cellular ingrowth and vascularization) General bone-void filler and use with lumens of allograft spinal spacers	n/a	(HCT/P) as defined by the FDA in 21 CFR 1271.3(d). 21CFR 1271
	CONFORM SHEET	Sheet shape	Demineralized cancellous bone, organic matrix (osteoinductive, promotes cellular ingrowth and vascularization) For PLF (posterolateral gutters of the spine)	n/a	(HCT/P) as defined by the FDA in 21 CFR 1271.3(d). 21CFR 1271

Table 4. Continued.

Company	Combination Product	Formulation	Product Composition	Peer-Reviewed Clinical Evidence/Ongoing Study ClinicalTrials.gov Identifier: NCT	Regulatory Clearance/Approval FDA 510(k), FDA 361, 21 CFR Part 1271 CFR 1270, CFR 1271 21 CFR 3.2(e) HCT/P 361, Human Allografts (No Clinical Studies) Biologic Drugs and Devices 351 (Clinical Trials)
Mesoblast Ltd, Australia	NeoFuse	Cells + granules	Allogenic mesenchymal precursor cells combined with MasterGraft in PEEK cage	NCT00549913 (3 DosesNeoFuse, Lumbar PLF) NCT00996073 (LIF)	FDA 510(k) cleared K153615, May 2016
Angioblast Systems Inc, USA	NeoFuse	Cells + granules	Allogenic mesenchymal precursor cells combined with MasterGraft in ACDF Anterior cervical plate fixation	NCT01106417 (ACDF, cervical) NCT01097486 (ACDF)	FDA 510(k) cleared K170318, July 2017
MTF Orthofix	Trinity Evolution	Moldable allograft fibers, varying sizes	Allogenic DBM, OPC, MSC (minimum of 500 000 cells/cc, 100 000 of which are MSC and/or OPC)	NCT00951938 Anterior Cervical Vanichkachorn et al,[78] 2016 Peppers, 2017 JOSR Lumbar Observational Musante et al,[79] 2016 JOSR NCT00965380 (PLIF/TLIF) Observational (completed) *	Regulated under CFR 1270, 127cer1 as a human tissue
	Trinity Elite	Moldable allograft fibers, varying sizes	DBM, OPC, MSC (minimum of 500 000 cells/cc, 100 000 of which are MSC and/or OPC) Trinity Elite and/or local bone with supplemental pedicle screw fixation Allogeneic cancellous bone matrix containing viable OPCs, MSCs, and a demineralized cortical bone	NCT029696169 (PLF, TLIF, ALIF, XLIF) lumbar fusion Bone graft *Johnstone et al,[80] 2020 (translational PLF, Trinity Elite vs Trinity Evolution)	Regulated under CRF 1270, 1271 as a human tissue

Table 4. Continued.

Company	Combination Product	Formulation	Product Composition	Peer-Reviewed Clinical Evidence/Ongoing Study ClinicalTrials.gov Identifier: NCT	Regulatory Clearance/Approval FDA 510(k), FDA 361, 21 CFR Part 1271 CFR 1270, CFR 1271 21 CFR 3.2(e) HCT/P 361, Human Allografts (No Clinical Studies) Biologic Drugs and Devices 351 (Clinical Trials)
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,[81] 2016, retrospective comparative study; NCT00948532 (Osteocel Plus in eXtreme Lateral Interbody Fusion [XLIF]: Kerr et al,[82] 2011; Tohmeh et al,[65] 2012 Extreme lateral interbody fusion [XLIF] Osteocel Plus in a polyetheretherketone cage and anterior plating at 1 or 2 consecutive levels) Lumbar spine: NCT00948831 (ALIF, observational) NCT00941980 (PLIF, observational) NCT00947583 (TLIF, observational) Ammerman et al,[83] 2013 NCT03649490 (XLIF 1 or 2 levels, comparative: interbody implant [PEEK] with cancellous allograft + BMA vs with cellular allograft [Osteocel]) Attenello et al 2018 LLIF XLIF (open vs percutaneous) IBF with PEEK + DBM (Osteocel Plus cellular bone matrix) Cervical spine: NCT00942045 (ACDF) Eastlack et al,[84] 2014 *Johnstone et al,[80] 2020 (translational PLF, Osteocel Plus)	Prospective case series Retrospective case series, clinical trial: ClinicalTrials.gov identifier: Evaluation of Radiographic and Patient Outcomes Regulated under CFR 1270, 1271 as a human tissue
NuTech Medical Inc	NuCel	Putty type	Cryopreserved, bioactive amniotic suspension allograft Cellular, growth factor, and extracellular matrix components	NCT02023372: LIF NuCel and Autograft NCT02808234: Prospective, DDD Lumbar spine LIF Efficacy NuCel NCT02070484 (RCT) for PLF NuCel vs DBX Other: Nunley et al,[85] 2016 (ALIF, LLIF, TLIF) retrospective	AATB and FDA guidelines for banked human tissues (is a minimally manipulated allograft tissue)

Table 4. Continued.

Company	Combination Product	Formulation	Product Composition	Peer-Reviewed Clinical Evidence/Ongoing Study ClinicalTrials.gov Identifier: NCT	Regulatory Clearance/Approval FDA 510(k), FDA 361, 21 CFR Part 1271 CFR 1270, CFR 1271 21 CFR 3.2(e) HCT/P 361, Human Allografts (No Clinical Studies) Biologic Drugs and Devices 351 (Clinical Trials)
Osteotech Merged into Medtronic	Plexur P Plexur M	Moldable type (puttylike)	Human cortical bone allograft fibers + resorbable polymer Processed human bone particles that are mixed with resorbable/ biodegradable nontissue components.	NCT00837473 (Pilot Study, iliac crest backfill) Note MAUDE Adverse Event Report	FDA 510(k) cleared K073405 (March 3, 2008)
RTI Surgical Inc Alachua, Florida	map3 Cellular Allogeneic Bone Graft	Putty type Strip type	Cortical cancellous bone chips (or strip shape bone) + DBM + cryogenically preserved, viable multipotent adult progenitor–class cells	NCT02161016: case series study in foot and ankle. Results posted Dekker et al,[86] 2016 Dekker et al,[87] 2017 (revisions nonunions) NCT02628210: A Prospective, Multi-Center, Non-Randomized Study for lumbar interbody fusion (active status) Other: Lee,[88] 2017	Unknown Status Cell Components, 2018 (FDA biologics license needed [201(g)FDA 21USC 321(g)351(i) of PHS Act 42 USC262] based product [HCT/P]. Also bone chip DBMs regulated under 361 PHS Act 42 USC 264 and reg. tissues part 21 CFR 1271.3 + 21/CFR 1271.10)
Stryker Spine, Allendale, New Jersey Manufactured by Osiris Therapeutics Inc	BIO[4]	Putty type (1, 2.5, 5, and 10 cc)	Allograft bone (cortical and cancellous) + periosteum A viable bone matrix containing endogenous bone-forming cells (including MSCs, OPCs, and osteoblasts) as well as osteoinductive and angiogenic growth factors	NCT03077204: Clinical case series study (ACDF, cervical spine), completed	AATB US FDA regulations for tissue management. US FDA 21 CFR 1271 (Osiris Therapeutics—data on file)
Vivex Biomedical, Mariettta, Georgia Miami, Florida	Via Graft Via Graft M Via Form Via Form M	"Wet Sand" (matrix + gel) Putty type (matrix + gel)	Allograft bone microparticulate scaffold (cortical and cancellous) + cell mixture (cell population derived from vertebral body that includes MIAMI cells [Vivex]) M = added bone gel component	Tally et al,[89] 2018, MIS-TLIF case review (level of evidence IV, n = 75) Inserted expandable cage prefilled with ViaGraft sponge-soaked BMA (from pedicles) was placed interbody with posterior pedicle screws and packed Beta TCP + BMA[89]	US FDA regulations for tissue management. US FDA 21 CFR 1271
Xtant/distribution agreement with Vivex, Mariettta, Georgia (formerly Bacterin International Holdings Inc)	OsteoVive	Putty type	A cell population derived from vertebral body that includes MIAMI cells (Vivex) Blend of microparticulate cortical, cancellous, and demineralized cortical allograft bone (particle size range of 100-300 microns) DMSO-free cryoprotectant (to protect MIAMI cells)	Application: Spine, Extremity, Foot & Ankle	FDA 510(k) cleared, compliance with FDA guidelines regarding human cells, Tissues, and cellular tissue-based products, HCT/P 361 regulated viable allogeneic bone scaffold AATB guidelines

Table 4. Continued.

Company	Combination Product	Formulation	Product Composition	Peer-Reviewed Clinical Evidence/Ongoing Study ClinicalTrials.gov Identifier: NCT	Regulatory Clearance/Approval FDA 510(k), FDA 361, 21 CFR Part 1271 CFR 1270, CFR 1271 21 CFR 3.2(e) HCT/P 361, Human Allografts (No Clinical Studies) Biologic Drugs and Devices 351 (Clinical Trials)
Zimmer Biomet	Cellentra Viable Cell Bone Matrix		Naturally occurring cells in fresh frozen, cryopreserved allograft comprising cancellous bone mix with cortical bone	NCT02182843, prospective ACDF interventional, results 2018 clinicaltrials.org Lin et al,[76] 2020 (translational)	AATB US FDA regulations for tissue management. US FDA 21 CFR 1271

Abbreviations: AATB, American Association of Tissue Banks guidelines; ACDF, anterior cervical discectomy fusion; ALIF, anterior lumbar interbody fusion; BLA, biologics license application; BMA, bone marrow aspirate; BRC, bone repair cell; DBM, demineralized bone matrix; FDA, US Food and Drug Administration; IBF, XXXX; LB, local bone (from surgical site dissection); LIF, lumbar interbody fusion; MIAMI, marrow-isolated adult multilineage-inducible; MSC, mesenchymal stem cell; OLIF, oblique lateral lumbar interbody fusion; OSC, osteoprogenitor cell; PEEK, a polyetheretherketone material used for cage devices employed as instrumentation in anterior interbody spinal fusion procedures; PLF, posterolateral lumbar fusion; PLIF, posterior lumbar interbody fusion; RCT, randomized control trial; TCP, tricalcium phosphate; TLIF, transforaminal lumbar interbody fusion; VBM, viable bone matrix; VCBM, viable cell bone matrix; XLIF, extreme lateral interbody fusion.

[a]CFR 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

FDA510(k) cleared. 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). FDA premarket approval, typically investigational; HDE, humanitarian device exemption, FDA-approved under an HDE; IND, investigational new drug application.

processes, and the donor bone itself contribute to differences among the products. Unlike for clinical use, for purposes of testing in rats, the products are not mixed with autograft bone. Clinically these allografts are not used in isolation; bone from the surgical dissection is morselized and mixed with allograft bone graft extenders of DBM-based or CBM products. Autograft potentially compensates for allograft products' debility.

In conclusion, there is no definitive clinical evidence that viable cellular allografts promote increased fusion compared with regular allograft DBM-based products. The claimed advantage of osteoinductive and osteogenic properties remains theoretical. The CBM allografts are available at an increased cost compared with other allografts, and more research is needed to justify each product's use instead of standard allografts.

CONCLUSION

Use of bone grafting techniques performed in surgical procedures for spinal fusion have been reported since the beginning of the 20th century.[94] Novel instrumentation and surgical techniques are designed and inspired by advances in grafting technologies. The history of allografts dates back many decades and has greatly evolved since Urist's first observation on how bone demineralization impacts the incorporation at the graft-host interface. The advancements in allograft products have purposely been designed to facilitate surgical procedures for fracture healing and spinal fusion. Allografts vary in size, shape, consistency, strength, viable cellular components, and many other properties. For the past decades, with a clinical history of use of allografts and DBM bases, diverse materials and composites have been continually combined with various materials and allograft forms to improve material properties, and further developed as novel grafting options.[4] Once bone allografts in various forms are approved or cleared by the responsible agency of the intended market country, they are rapidly adopted into specific surgical application. However, graft-contributing complications may still occur, and sometimes systematically with the use of a particular form or product. The target allograft then moves from bedside to "bench" for reevaluation. In the application process for approval, grafts' safety is evaluated, yet the osteoinductive and conductive effectiveness burden may not have been investigated, which likely has unintended consequences.

As discussed in this paper, there is a great unmet need for improvement in allografts. The ideal bone graft provides a biocompatible scaffold that promotes osteoconduction, osteoinduction, and osteogenesis. Allografts predominantly contain osteoconductive and some osteoinductive potential. However, with the advancement of viable cellular allografts, there is the theoretical addition of osteogenesis. Allografts with blood-derived augmentation (either with BMAC or PRP) were not directly discussed in this paper because this subject is the primary focus of another article in submission. With time and technologic advantages in stem cells and differentiation factors, more products will be developed to enrich the bone graft–to–fusion process and increase the rapidity and success rate of bone healing after spinal fusion procedures.

REFERENCES

1. Clough BH, McNeill EP, Palmer D, et al. An allograft generated from adult stem cells and their secreted products efficiently fuses vertebrae in immunocompromised athymic rats and inhibits local immune responses. *Spine J*. 2017;17(3): 418–430.

2. Wang W, Yeung KWK. Bone grafts and biomaterials substitutes for bone defect repair: a review. *Bioact Mater*. 2017;2(4):224–247.

3. Gruskin E, Doll BA, Futrell FW, Schmitz JP, Hollinger JO. Demineralized bone matrix in bone repair: history and use. *Adv Drug Deliv Rev*. 2012;64(12):1063–1077.

4. Yang JH, Glaeser JD, Kanim LEA, Battles CY, Bondre S, Bae HW. Bone grafts and bone graft substitutes. In: Cheng B, ed. *Handbook of Spine Technology*. Cham: Springer International Publishing; 2020:1–77.

5. Gilbert SF. *Developmental Biology*. 6th ed. Sunderland, MA: Sinauer Associates; 2000.

6. Kadam A, Millhouse PW, Kepler CK, et al. Bone substitutes and expanders in spine surgery: a review of their fusion efficacies. *Int J Spine Surg*. 2016;10:33.

7. Campana V, Milano G, Pagano E, et al. Bone substitutes in orthopaedic surgery: from basic science to clinical practice. *J Mater Sci Mater Med*. 2014;25(10):2445–2461.

8. Duarte RM, Varanda P, Reis RL, Duarte ARC, Correia-Pinto J. Biomaterials and bioactive agents in spinal fusion. *Tissue Eng Part B Rev*. 2017;23(6):540–551.

9. Goldberg VM, Stevenson S. The biology of bone grafts. *Semin Arthroplasty*. 1993;4(2):58–63.

10. Garbuz DS, Masri BA, Czitrom AA. Biology of allografting. *Orthop Clin North Am*. 1998;29(2):199–204.

11. Stevenson S, Gertzman AA. Allograft tissue material for filling spinal fusion cages or related surgical spaces. US Patent 5,910,315. June 8, 1999.

12. Zimmermann G, Moghaddam A. Allograft bone matrix versus synthetic bone graft substitutes. *Injury*. 2011;42(suppl 2):S16–S21.

13. D'Souza M, Macdonald NA, Gendreau JL, Duddleston PJ, Feng AY, Ho AL. Graft materials and biologics for spinal interbody fusion. *Biomedicines*. 2019;7(4):75.

14. Overley SC, McAnany SJ, Anwar MA, et al. Predictive factors and rates of fusion in minimally invasive transforaminal lumbar interbody fusion utilizing rhBMP-2 or mesenchymal stem cells. *Int J Spine Surg*. 2019;13(1):46–52.

15. Meyers MH. Resurfacing of the femoral head with fresh osteochondral allografts: long-term results. *Clin Orthop Relat Res*. 1985;(197):111–114.

16. Rauck RC, Wang D, Tao M, Williams RJ. Chondral delamination of fresh osteochondral allografts after implantation in the knee: a matched cohort analysis. *Cartilage*. 2019;10(4):402–407.

17. Torrie AM, Kesler WW, Elkin J, Gallo RA. Osteochondral allograft. *Curr Rev Musculoskelet Med*. 2015;8(4):413–422.

18. Kawaguchi S, Hart RA. The need for structural allograft biomechanical guidelines. *Instr Course Lect*. 2015;64:87–93.

19. Miyazaki M, Tsumura H, Wang JC, Alanay A. An update on bone substitutes for spinal fusion. *Eur Spine J*. 2009;18(6):783–799.

20. Clifford R. Allografts. Wheeless' Textbook of Orthopaedics Web site. 2013. http://www.wheelessonline.com/ortho/allografts.

21. Hamer AJ, Stockley I, Elson RA. Changes in allograft bone irradiated at different temperatures. *J Bone Joint Surg Br*. 1999;81(2):342–344.

22. Morris MT, Tarpada SP, Cho W. Bone graft materials for posterolateral fusion made simple: a systematic review. *Eur Spine J*. 2018.

23. Bae HW KL, Rajaee S, Yang JH. Bone grafts, bone morphogenetic proteins, and bone substitutes. AAOS chapter 59. In: Boyer M, ed. *AAOS Comprehensive Orthopaedic Review 2*. Rosemont, IL: American Academy of Orthopaedic Surgeons; 2019.

24. Urrutia J, Molina M. Fresh-frozen femoral head allograft as lumbar interbody graft material allows high fusion rate without subsidence. *Orthop Traumatol Surg Res*. 2013;99(4):413–418.

25. Park JJ, Hershman SH, Kim YH. Updates in the use of bone grafts in the lumbar spine. *Bull Hosp Jt Dis*. 2013;71(1):39–48.

26. Suchomel P, Barsa P, Buchvald P, Svobodnik A, Vanickova E. Autologous versus allogenic bone grafts in instrumented anterior cervical discectomy and fusion: a prospective study with respect to bone union pattern. *Eur Spine J*. 2004;13(6):510–515.

27. Li Y, Yu Y, Hou TY, et al. Efficacy of Biocage in treating single-segment lumbar degenerative disease in patients with high risk of non-fusion: a prospective controlled study with at least 2 years' follow-up. *J Int Med Res*. 2020;48(9):300060520945500.

28. American Association of Tissue Banks. Accreditation policies. https://images.magnetmail.net/images/clients/AATB/attach/Bulletin_Links/18_2/AATB_Accreditation_Policies_February_08_2018.pdf. Accessed February 8, 2018.

29. Urist MR. Bone: formation by autoinduction. *Science*. 1965;150(3698):893–899.

30. Gupta A, Kukkar N, Sharif K, Main BJ, Albers CE, El-

Amin Iii SF. Bone graft substitutes for spine fusion: a brief review. *World J Orthop*. 2015;6(6):449–456.

31. Peterson B, Whang PG, Iglesias R, Wang JC, Lieberman JR. Osteoinductivity of commercially available demineralized bone matrix: preparations in a spine fusion model. *J Bone Joint Surg Am*. 2004;86A(10):2243–2250.

32. Wang JC, Alanay A, Mark D, et al. A comparison of commercially available demineralized bone matrix for spinal fusion. *Eur Spine J*. 2007;16(8):1233–1240.

33. Bhamb N, Kanim LEA, Drapeau S, et al. Comparative efficacy of commonly available human bone graft substitutes as tested for posterolateral fusion in an athymic rat model. *Int J Spine Surg*. 2019;13(5):437–458.

34. Bae H, Zhao L, Zhu D, Kanim LE, Wang JC, Delamarter RB. Variability across ten production lots of a single demineralized bone matrix product. *J Bone Joint Surg Am*. 2010;92(2):427–435.

35. Aghdasi B, Montgomery SR, Daubs MD, Wang JC. A review of demineralized bone matrices for spinal fusion: the evidence for efficacy. *Surgeon*. 2013;11(1):39–48.

36. Kang J, An H, Hilibrand A, Yoon ST, Kavanagh E, Boden S. Grafton and local bone have comparable outcomes to iliac crest bone in instrumented single-level lumbar fusions. *Spine*. 2012;37(12):1083–1091.

37. Cammisa FP Jr, Lowery G, Garfin SR, et al. Two-year fusion rate equivalency between Grafton DBM gel and autograft in posterolateral spine fusion: a prospective controlled trial employing a side-by-side comparison in the same patient. *Spine*. 2004;29(6):660–666.

38. Yuan HA, Garfin SR, Dickman CA, Mardjetko SM. A historical cohort study of pedicle screw fixation in thoracic, lumbar, and sacral spinal fusions. *Spine*. 1994;19(20 suppl):2279S–2296S.

39. Turner JA, Ersek M, Herron L, et al. Patient outcomes after lumbar spinal fusions. *JAMA*. 1992;268(7):907–911.

40. Yahiro MA. Comprehensive literature review: pedicle screw fixation devices. *Spine*. 1994;19(20 suppl):2274S–2278S.

41. van der Stok J, Hartholt KA, Schoenmakers DAL, Arts JJC. The available evidence on demineralised bone matrix in trauma and orthopaedic surgery: a systematic review. *Bone Joint Res*. 2017;6(7):423–432.

42. An HS, Simpson JM, Glover JM, Stephany J. Comparison between allograft plus demineralized bone matrix versus autograft in anterior cervical fusion: a prospective multicenter study. *Spine*. 1995;20(20):2211–2216.

43. Kirk JF, Ritter G, Waters C, Narisawa S, Millán JL, Talton JD. Osteoconductivity and osteoinductivity of Nano-FUSE(®) DBM. *Cell Tissue Bank*. 2013;14(1):33–44.

44. Rajadurai J, Lovric V, Mobbs RJ, Choy WJ, Walsh WR. The use of demineralised bone fibres (DBF) in conjunction with supercritical carbon dioxide (SCCO 2) treated allograft in anterior lumbar interbody fusion (ALIF). *J Spine Surg*. 2019;5(4):589–595.

45. Yao YC, Chou PH, Lin HH, Wang ST, Liu CL, Chang MC. Risk factors of cage subsidence in patients received minimally invasive transforaminal lumbar interbody fusion. *Spine*. 2020;45(19):E1279–E1285.

46. Yao YC, Lin HH, Chou PH, Wang ST, Chang MC. Differences in the interbody bone graft area and fusion rate between minimally invasive and traditional open transforaminal lumbar interbody fusion: a retrospective short-term image analysis. *Eur Spine J*. 2019;28(9):2095–2102.

47. Shehadi JA, Elzein SM. Review of commercially available demineralized bone matrix products for spinal fusions: a selection paradigm. *Surg Neurol Int*. 2017;8:203.

48. Galli MM, Protzman NM, Bleazey ST, Brigido SA. Role of demineralized allograft subchondral bone in the treatment of shoulder lesions of the talus: clinical results with two-year follow-up. *J Foot Ankle Surg*. 2015;54(4):717–722.

49. Russell N, Walsh WR, Lovric V, et al. In-vivo performance of seven commercially available demineralized bone matrix fiber and putty products in a rat posterolateral fusion model. *Front Surg*. 2020;7:10.

50. Adams BD, Kleinhenz BP, Guan JJ. Wrist arthrodesis for failed total wrist arthroplasty. *J Hand Surg Am*. 2016;41(6):673–679.

51. Togawa D, Bauer TW, Lieberman IH, Takikawa S. Histologic evaluation of human vertebral bodies after vertebral augmentation with polymethyl methacrylate. *Spine*. 2003;28(14):1521–1527.

52. Schizas C, Triantafyllopoulos D, Kosmopoulos V, Tzinieris N, Stafylas K. Posterolateral lumbar spine fusion using a novel demineralized bone matrix: a controlled case pilot study. *Arch Orthop Trauma Surg*. 2008;128(6):621–625.

53. Orndorff DG, Youssef JA, Heiner AD. Efficacy of demineralized bone matrix for instrumented combined posterolateral interbody lumbar fusion. *Spine J*. 2019;19(9 suppl):S162.

54. Klineberg EO, Passias PG, Poorman GW, et al. Classifying complications: assessing adult spinal deformity 2-year surgical outcomes. *Global Spine J*. 2020;10(7):896–907.

55. Lee JC, Jang HD, Ahn J, Choi SW, Kang D, Shin BJ. Comparison of cortical ring allograft and plate fixation with autologous iliac bone graft for anterior cervical discectomy and fusion. *Asian Spine J*. 2019;13(2):258–264.

56. Lee K, Goodman SB. Cell therapy for secondary osteonecrosis of the femoral condyles using the Cellect DBM System: a preliminary report. *J Arthroplasty*. 2009;24(1):43–48.

57. Epstein NE, Epstein JA. SF-36 outcomes and fusion rates after multilevel laminectomies and 1 and 2-level instrumented posterolateral fusions using lamina autograft and demineralized bone matrix. *J Spinal Disord Tech*. 2007;20(2):139–145.

58. Muzević D, Splavski B, Boop FA, Arnautović KI. Anterior cervical discectomy with instrumented allograft fusion: lordosis restoration and comparison of functional outcomes among patients of different age groups. *World Neurosurg*. 2018;109:e233–e243.

59. Smucker JD, Bobst JA, Petersen EB, Nepola JV, Fredericks DC. B2A peptide on ceramic granules enhance posterolateral spinal fusion in rabbits compared with autograft. *Spine*. 2008;33(12):1324–1329.

60. Eleswarapu A, Rowan FA, Le H, et al. Efficacy, cost, and complications of demineralized bone matrix in instrumented lumbar fusion: comparison with rhBMP-2. *Global Spine J*. 2020:2192568220942501.

61. Fu TS, Wang IC, Lu ML, Hsieh MK, Chen LH, Chen WJ. The fusion rate of demineralized bone matrix compared with autogenous iliac bone graft for long multi-segment posterolateral spinal fusion. *BMC Musculoskelet Disord*. 2016;17:3.

62. Xie Y, Li H, Yuan J, Fu L, Yang J, Zhang P. A prospective randomized comparison of PEEK cage containing calcium sulphate or demineralized bone matrix with autograft

in anterior cervical interbody fusion. *Int Orthop*. 2015;39(6):1129–1136.

63. Skovrlj B, Guzman JZ, Al Maaieh M, Cho SK, Iatridis JC, Qureshi SA. Cellular bone matrices: viable stem cell-containing bone graft substitutes. *Spine J*. 2014;14(11):2763–2772.

64. Friedenstein AJ, Chailakhjan RK, Lalykina KS. The development of fibroblast colonies in monolayer cultures of guinea-pig bone marrow and spleen cells. *Cell Tissue Kinet*. 1970;3(4):393–403.

65. Tohmeh AG, Watson B, Tohmeh M, Zielinski XJ. Allograft cellular bone matrix in extreme lateral interbody fusion: preliminary radiographic and clinical outcomes. *Sci World J*. 2012;2012:263637.

66. Sethe S, Scutt A, Stolzing A. Aging of mesenchymal stem cells. *Ageing Res Rev*. 2006;5(1):91–116.

67. Ryan JM, Barry FP, Murphy JM, Mahon BP. Mesenchymal stem cells avoid allogeneic rejection. *J Inflamm (Lond)*. 2005;2:8.

68. Le Blanc K, Ringdén O. Immunomodulation by mesenchymal stem cells and clinical experience. *J Intern Med*. 2007;262(5):509–525.

69. Le Blanc K, Tammik C, Rosendahl K, Zetterberg E, Ringdén O. HLA expression and immunologic properties of differentiated and undifferentiated mesenchymal stem cells. *Exp Hematol*. 2003;31(10):890–896.

70. Field J, Yeung C, Roh J. Clinical evaluation of allogeneic growth factor in cervical spine fusion. *J Spine*. 2014;3(2). doi:10.4172/2165-7939.1000158

71. Roh JS, Yeung CA, Field JS, McClellan RT. Allogeneic morphogenetic protein vs. recombinant human bone morphogenetic protein-2 in lumbar interbody fusion procedures: a radiographic and economic analysis. *J Orthop Surg Res*. 2013;8:49.

72. Yeung C, Field J, Roh J. Clinical validation of allogeneic morphogenetic protein: donor intervariability, terminal irradiation and age of product is not clinically relevant. *J Spine*. 2014;3:173.

73. Myerson CL, Myerson MS, Coetzee JC, Stone McGaver R, Giveans MR. Subtalar arthrodesis with use of adipose-derived cellular bone matrix compared with autologous bone graft: a multicenter, randomized controlled trial. *J Bone Joint Surg Am*. 2019;101(21):1904–1911.

74. Alfotawi R, Naudi K, Dalby MJ, Tanner KE, McMahon JD, Ayoub A. Assessment of cellular viability on calcium sulphate/hydroxyapatite injectable scaffolds. *J Tissue Eng*. 2013;4:2041731413509645.

75. Divi SN, Mikhael MM. Use of allogenic mesenchymal cellular bone matrix in anterior and posterior cervical spinal fusion: a case series of 21 patients. *Asian Spine J*. 2017;11(3):454–462.

76. Lin C, Zhang N, Waldorff EI, et al. Comparing cellular bone matrices for posterolateral spinal fusion in a rat model. *JOR Spine*. 2020;3(2):e1084.

77. Wetzell B, McLean JB, Moore M, Kondragunta V, Dorsch KA. A large database study of hospitalization charges and follow-up re-admissions in US lumbar fusion surgeries using a cellular bone allograft (CBA) versus recombinant human bone morphogenetic protein-2 (rhBMP-2). *J Orthop Surg Res*. 2020;15. doi:10.1186/s13018-020-02078-7

78. Vanichkachorn J, Peppers T, Bullard D, Stanley SK, Linovitz RJ, Ryaby JT. A prospective clinical and radiographic 12-month outcome study of patients undergoing single-level anterior cervical discectomy and fusion for symptomatic cervical degenerative disc disease utilizing a novel viable allogeneic, cancellous, bone matrix (Trinity Evolution™) with a comparison to historical controls. *Eur Spine J*. 2016;25(7):2233–2238.

79. Musante DB, Firtha ME, Atkinson BL, Hahn R, Ryaby JT, Linovitz RJ. Clinical evaluation of an allogeneic bone matrix containing viable osteogenic cells in patients undergoing one- and two-level posterolateral lumbar arthrodesis with decompressive laminectomy. *J Orthop Surg Res*. 2016;11(1):63.

80. Johnstone B, Zhang N, Waldorff EI, et al. A comparative evaluation of commercially available cell-based allografts in a rat spinal fusion model. *Int J Spine Surg*. 2020;14(2):213–221.

81. McAnany SJ, Ahn J, Elboghdady IM, et al. Mesenchymal stem cell allograft as a fusion adjunct in one- and two-level anterior cervical discectomy and fusion: a matched cohort analysis. *Spine J*. 2016;16(2):163–167.

82. Kerr EJ 3rd, Jawahar A, Wooten T, Kay S, Cavanaugh DA, Nunley PD. The use of osteo-conductive stem-cells allograft in lumbar interbody fusion procedures: an alternative to recombinant human bone morphogenetic protein. *J Surg Orthop Adv*. 2011;20(3):193–197.

83. Ammerman JM, Libricz J, Ammerman MD. The role of Osteocel Plus as a fusion substrate in minimally invasive instrumented transforaminal lumbar interbody fusion. *Clin Neurol Neurosurg*. 2013;115(7):991–994.

84. Eastlack RK, Garfin SR, Brown CR, Meyer SC. Osteocel Plus cellular allograft in anterior cervical discectomy and fusion: evaluation of clinical and radiographic outcomes from a prospective multicenter study. *Spine*. 2014;39(22):E1331–E1337.

85. Nunley PD, Kerr EJ 3rd, Utter PA, et al. Preliminary results of bioactive amniotic suspension with allograft for achieving one and two-level lumbar interbody fusion. *Int J Spine Surg*. 2016;10:12.

86. Dekker TJ, White P, Adams SB. Efficacy of a cellular allogeneic bone graft in foot and ankle arthrodesis procedures. *Foot Ankle Clin*. 2016;21(4):855–861.

87. Dekker TJ, White P, Adams SB. Efficacy of a cellular bone allograft for foot and ankle arthrodesis and revision nonunion procedures. *Foot Ankle Int*. 2016;38(3):277–282.

88. Lee DD, Kim JY. A comparison of radiographic and clinical outcomes of anterior lumbar interbody fusion performed with either a cellular bone allograft containing multipotent adult progenitor cells or recombinant human bone morphogenetic protein-2. *J Orthop Surg Res*. 2017;12(1):126.

89. Tally WC, Temple HT, Subhawong TY, Ganey T. Transforaminal lumbar interbody fusion with viable allograft: 75 consecutive cases at 12-month follow-up. *Int J Spine Surg*. 2018;12(1):76–84.

90. Cui Q, Ming Xiao Z, Balian G, Wang GJ. Comparison of lumbar spine fusion using mixed and cloned marrow cells. *Spine*. 2001;26(21). doi:10.1097/00007632-200111010-00003.

91. Gupta M, Theerajunyaporn T, Maitra S, et al. Efficacy of mesenchymal stem cell enriched grafts in an ovine posterolateral lumbar spine model. *Spine*. 2007;32:720–726; discussion 727.

92. McAnany SJ, Ahn J, Elboghdady IM, et al. Mesenchymal stem cell allograft as a fusion adjunct in one- and two-level anterior cervical discectomy and fusion: a matched cohort analysis. *Spine J*. 2016;16(2):163–167.

93. Hernigou P, Mathieu G, Poignard A, Manicom O, Beaujean F, Rouard H. Percutaneous autologous bone-marrow grafting for nonunions: surgical technique. *J Bone Joint Surg Am*. 2006;88(suppl 1, pt 2):322–327.

94. Denaro V, Di Martino A. Cervical spine surgery: an historical perspective. *Clin Orthop Relat Res*. 2011;469(3):639–648.

Disclosures and COI: The authors received no funding for this study and declare no conflicts of interest.

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Published 30 April 2021

International Journal of Spine Surgery, Vol. 17, No. 5, 2023, pp. 754
https://doi.org/10.14444/8056cxx

Corrections

Cohen JD, Kanim LE, Tronits AJ, Bae HW. Allografts and spinal fusion. 2021;15(S1):68-93. https://doi.org/10.14444/8056

In this article, the author's name Andrew J. Tronits was misspelled and should have appeared as Andrew J. Trontis. (doi:10.14444/8056cxx)