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DBMs; Extenders and Synthetics

9th Annual Spine Symposium

Deer Valley

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Orthopaedic Spine Surgery

Orthopaedic Specialty Institute

Director, Hoag Orthopaedic Institute Spine Fellowship

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Disclosures

- Research/Institutional support:
  - Nuvasive
- Consultancies/Scientific Advisory:
  - Nuvasive, Spineart
- Royalties:
  - Nuvasive, Spineart

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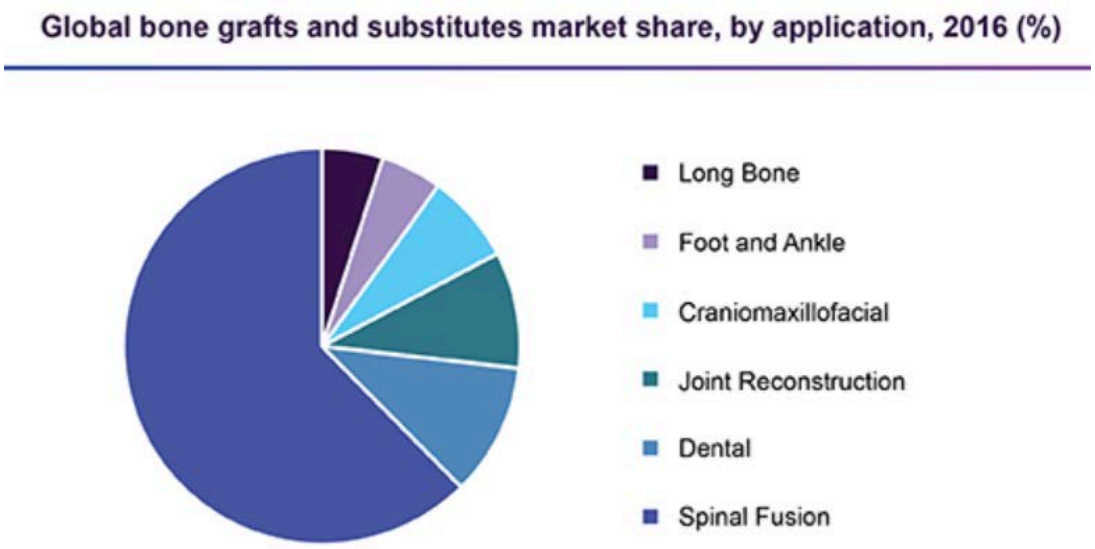
OrthoBiologics

- 5.5 billion in 2019
  - 600,000 per year
    - ½ spine



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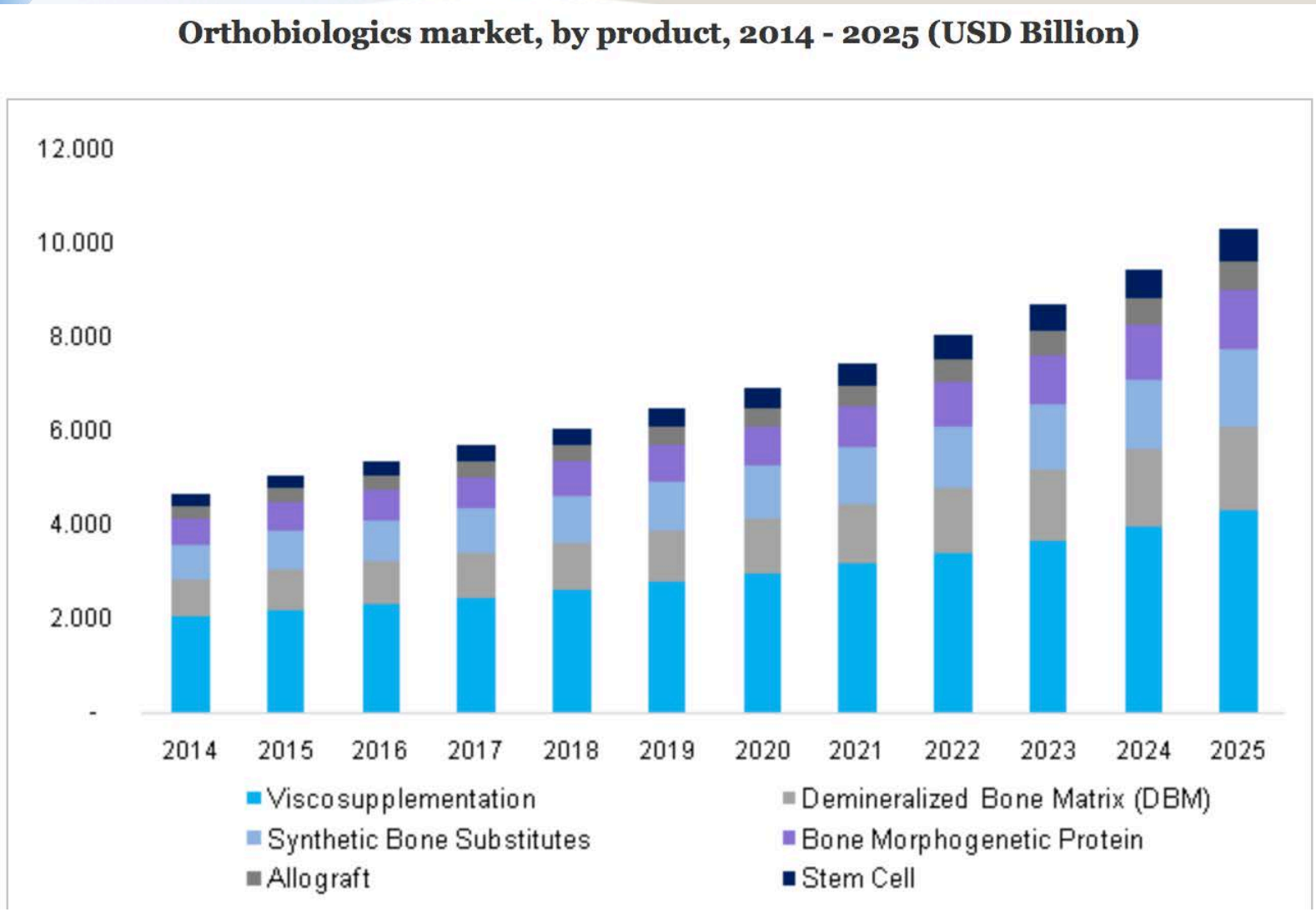
Orthobiologics



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- Autograft
- BMP
- Everything else

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Graft Type	Attributes	Advantages	Disadvantages	Healing Mechanism(s)
Autograft	Cancellous	Cell Rich (Osteoblasts, MSC's)	Donor site morbidity	Osteogenesis
	Cortical	Strength	Donor site morbidity	Osteoconduction
	Marrow aspirate	Live cells Minimal morbidity	Harvest variability Requires a matrix	Osteogenesis
Allograft				
Mineralized	Availability of shapes, sizes	Bone quality Avoid morbidity	Incorporates by creeping substitution	Osteoconduction
Demineralized Bone Matrix (DBM)	Powder or chips	Rapid incorporation and remodeling, Osteoinductive	Non-structural Generally requires excipient for handling	Osteoinduction
Demineralized Bone Fibers (DBF)	Fiber geometry enhances osteoconductivity	Rapid incorporation and remodeling, Osteoinductive and Osteoconductive	Non-structural	Osteoinduction and Osteoconduction
Cell Based Matrix products	Allograft bone with viable cells	Theoretical benefit of osteogenic cells	Cost, limited data supporting efficacy, sterility, immunogenicity	Osteoconduction, osteogenisis, osteoinduction
Synthetics	HA/TCP, collagen	Standardized, Safety	HA remodels slowly	Osteoconduction
Bone Growth Factors	Proteins, need carrier	Potent bone stimulation	Cost, ectopic bone, others?	Osteoinduction

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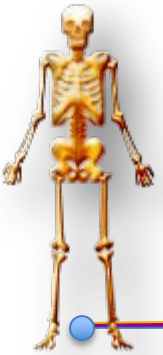
History of Bone Grafting



1688
Autograft
First described

1892
Calcium
Sulfate

1970
Allograft
Chips

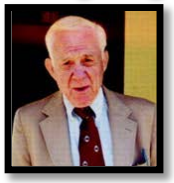
1980s
BMA &
Pro Osteon

2001
DBX DBM
Vitoss
OP-1 (HDE)

2004
Actifuse
Vitoss Foam

2009
Biogennix
OsteoSpain

2012
AttraX



1965
Marshall Urist
Discovers BMP

1979
Calcium
Carbonate

1990's
Grafton
Crunch, flex,
Gel & Putty

2002
Infuse
Cellect
MasterGraft

2005
Osteocel

2013
AttraX Putty
Osteocel Flow

Improving the Clinical Evidence of Bone Graft Substitute Technology in Lumbar Spine Surgery

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Global Spine J 2012;2:239–248.

Global Spine J 2012;2:239–248.

Table 1 Fusion Rates for Various Bone Graft Substitutes in Posterolateral Fusion

	Number of Studies	Number of Patients	Number of Patients Fused	Fusion Rate (%)	Range (%)
Autologous iliac crest bone graft	23	1389	1103	79	40–100
Local autograft alone	8	714	637	89	65–95
Allograft alone	4	269	141	52	0–92
Bone marrow aspirate (concentrated)	2	40	34	85	78–91
Bone morphogenetic protein-2	3	213	201	94	90–100
Ceramics[a]	16	697	603	87	5–100
Demineralized bone matrices[1]	3	192	171	89	63–97
Autologous growth factors[1]	4	209	154	74	54–100

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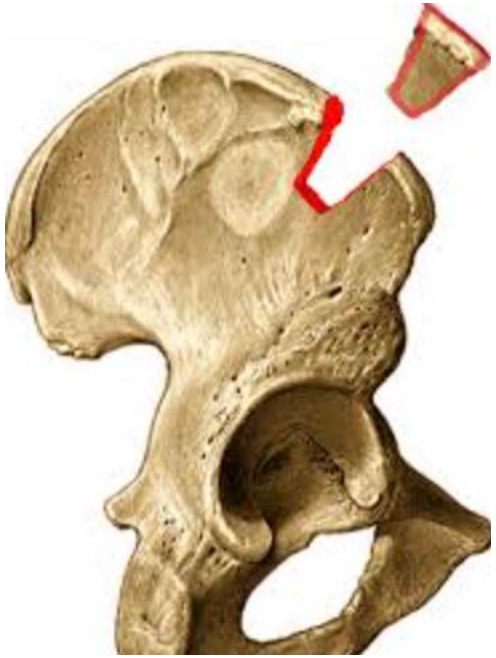
Autograft

- Gold standard
  - Donor site morbidity
  - Increased operative time
  - Blood loss
  - Limited supply



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Bone Healing

- Osteogenesis
  - New bone from live cells (Autograft, BMA)
- Osteoconduction
  - Scaffold allows ingrowth from host cells
- Osteoinduction
  - New bone formed by active recruitment of cells
  - Induced cell differentiation (needs a growth factor)

- Graft extenders
  - Added to lesser amount of autogenous graft to maximize healing efficiency
- Graft enhancers
  - Added to usual or lesser amount of autogenous bone results in higher fusion rates than autogenous bone alone
- Graft substitutes
  - Can replace autogenous bone graft and yield comparable fusion rates

- Ideal bone graft substitute
  - Mimic properties of autogenous
    - Osteoinductive
    - Osteoconductive

- Osteoconductive
  - Ceramics
    - Scaffolds facilitate cellular adhesion, vascular ingrowth, bone formation
  - Calcium Sulfate
    - Osteoblasts attach, osteoclasts can resorb
  - Collagen
    - Type I-conductive for mineral deposition, vascular ingrowth, growth factor binding

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- Osteoconductive
  - Degradable polymers, bioactive glass, metals
    - avoid immune reaction, excellent biocompatibility
- Osteoinductive
  - DBM
  - BMPs

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DBM

- Demineralized Bone Matrix
  - Acid treated bone remove mineralized portions
  - ~93% collagen, 5% BMPs

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DBM

- Acid decalcification of cortical bone
  - BMPs
    - BMPs have little to no osteogenic capability
    - Variability in content
  - Noncollagenous proteins
  - Type I collagen
- Less allogenic

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DBM

- Extender, enhancer or substitute
- Not a good structural graft
  - Amorphous consistency
- Osteoinductive potential

Company	DBM-based product	Formulation	Product composition	Peer-reviewed clinical evidence/ongoing study	Regulatory clearance/approval FDA 510(k), CFR 1270, CFR 1271
Allosource	Allostem Cellular Bone Autograft	Strips, blocks, cubes, morselized	partially demineralized allograft bone combined with adipose derived mesenchymal stem cells (MSC)	n/a	Regulated under CFR 1270, 1271 as a human tissue
	AlloFuse® Gel	Injectable gel and putty	DBM, reverse phase medium (RPM) carrier	n/a	510(k) cleared
	AlloFuse® Putty (identical to Stimublast Putty and Gel manufactured for Arthrex)		Carrier comprised of polyethylene oxide polypropylene oxide block copolymer dissolved in water exhibiting reverse phase characteristics (i.e., an increase in viscosity as temperature increases)		K071849, 2008 Dec
	Allofuse Plus	Paste, putty	DBM, RPM, cancellous chips	n/a	510(k) cleared K103036, 2011 Jan
	Alloflex	Strips, blocks, fillers	Cancellous bone allograft, DBM, strip form, no carriers added	n/a	marketed as human tissue
Bacterin International Inc.	Osetoselect DBM	putty	74% DBM dry weight	n/a	510(k) cleared K091321, 2009 Sept K130498, 2013 May
	Osetoselect Plus DBM			n/a	510(k) cleared K150621, 2015 Aug
Biomet Osteobiologics	Intergro	Putty (40% DBM), paste (35% DBM)	DBM, Lethicin carrier (resorbable, biocompatible, semi-viscous lipid)	Prospective case series	510(k) cleared K082793, 2009 Apr K031399, 2005 Feb
ETEX	CaP Plus	CaP Plus	synthetic calcium phosphate, an inert carrier, carboxymethyl cellulose (CMC) and DBM	n/a	510(k) cleared K063050, 2007 Nov K080329, 2008 Apr
Exactech	Optecure	Injectable paste	DBM (81% by dry weight), hydrogel carrier	Prospective RCT	510(k) cleared K121989, 2012 Nov K061668, 2006 Sept K050806 2006 Feb
	Optecure™ +CCC	Injectable paste	Polymer powder, DBM, cortical cancellous chips (1–3 mm)	n/a	510(k) cleared K121989; 2012 Nov
	Optefill (OSTEOFIL® DBM Paste, OSTEOFIL® RT DBM Paste)	DBM paste or dry powder—hydrated to become injectable paste	DBM in gelatin carrier	n/a	510(k) cleared K043420, 2005 Feb
	Opteform	Putty or dry powder—hydrated to become paste	gelatin, DBM and cortical cancellous bone chips	n/a	510(k) cleared K043421, 2005 Feb
Integra Orthobiologics/ (Isotis OrthoBiologic), Inc., Irvine, CA	Accell Connexus	Injectable putty	DBM (70% by weight), RPM	Retrospective comparative	510(k) cleared K060306, 2006 Mar K061880, 2007
	Accell Evo3™	Injectable putty	DBM (Accell Bone Matrix), RPM	Clinical trial: ClinicalTrials.gov Identifier: NCT02018445 ("Efficacy and Safety of Integra Accell Evo3™ Demineralized Bone Matrix in Instrumented Lumbar Spine Fusion")	510(k) cleared K103742, 2011 Mar

Company	DBM-based product	Formulation	Product composition	Peer-reviewed clinical evidence/ongoing study	Regulatory clearance/approval FDA 510(k), CFR 1270, CFR 1271
	Accell TBM	Preformed Matrix (strip, square, round)	100% DBM (accell bone matrix)	n/a	510(k) cleared K081817
	Dynagraft II	Injectable gel, putty	DBM (accell bone matrix), RPM, cancellous bone chips	n/a	510(k) cleared K040419
	Orthoblast II	Injectable paste, putty	DBM (accell bone matrix), RPM, cancellous bone chips from same donor	n/a	510(k) cleared K050642, 2005 Dec
Lifenet Health	IC Graft Chamber	Freeze-dried in injectable delivery chamber, can be mixed with whole blood, PRP, or BMA	DBM, cancellous chips	n/a	Regulated under CFR 1270, 1271 as a human tissue
	Optium DBM Putty	Putty	DBM, glycerol carrier	n/a	510(k) cleared K053098, 2005 Nov
Medtronic Spinal and Biologics	Magnifuse Bone Graft	Resorbable mesh bag	DBM mixed with autograft in 1:1 ratio packed into polyglycolic acid (PGA) resorbable mesh bag	n/a	510(k) cleared K123691 2013 Jan K082615 2008 Oct
	Osteofil DBM	Injectable paste, moldable strips	DBM (24% by weight) in porcine gelatin	Prospective case series	510(k) cleared K043420, 2005 Feb
	Progenix™ Plus	Putty with demineralized cortical chips	DBM in type-1 bovine collagen and sodium alginate	n/a	510(k) cleared K081950,2008 Jul
	Progenix Putty	Injectable putty	DBM in type-1 bovine collagen and sodium alginate	Retrospective comparative study	510(k) cleared K080462 2008 May
MTF Orthofix	Trinity Evolution™	Moldable allograft fibers, varying sizes	DBM, osteoprogenitor cells (OPC), MSC (minimum of 500,000 cells/cc; 100,000 of which are MSC and/or OPC)	n/a	Regulated under CFR 1270, 1271 as a human tissue
	Trinity Elite	Moldable allograft fibers, varying sizes	DBM, osteoprogenitor cells, MSC (minimum of 500,000 cells/cc; 100,000 of which are MSC and/or OPC)	n/a	Regulated under CRF 1270, 1271 as a human tissue
MTF/Synthes	DBX	Paste, putty mix, strip	DBM (32% by weight,), sodium hylauronate carrier (mix vary for paste, putty, mix)	n/a	510(k) cleared K040262, 2005 Mar (putty, paste,matrix mix) K040501 2005 Mar (putty, paste, matrix mix) K053218, 2006 Dec (putty, paste, matrix mix) K063676, 2007 Mar (putty, paste, matrix mix) K080399, 2008 Oct (paste) K091217, 2009 Oct (putty)

					K091218, 2009 Sep (putty) K103795, 2011 Apr (putty K103784, 2011 Apr (putty) K042829, 2006 Jan (strip)
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)	Prospective case series, Retrospective comparative study, Retrospective case series, clinical trial: ClinicalTrials.gov Identifier: NCT00948532 (Osteocel® Plus in eXtreme Lateral Interbody Fusion (XLIF®): Evaluation of Radiographic and Patient Outcomes)	Regulated under CFR 1270, 1271 as a human tissue
Osteotech/Medtronic	GRAFTON A-Flex	Round flexible sheet	DBM	n/a	510(k) cleared K051188, 2006 Jan
	GRAFTON Crunch	Packable graft	DBM, demineralized cortical cubes	n/a	510(k) cleared K051188, 2006 Jan
	GRAFTON Flex	Flexible sheets, varying sizes	DBM	Retrospective comparative study	510(k) cleared K051195, 2005 Dec
	GRAFTON Gel	Injectable syringe	DBM	RCT, Prospective case series	510(k) cleared K051195, 2005 Dec
	GRAFTON Matrix PLF	troughs	DBM	RCT	510(k) cleared K051195, 2005 Dec
	GRAFTON Matrix Scoliosis Strips	Strips, various sizes	DBM	Retrospective case series	510(k) cleared
	GRAFTON Orthoblend Large Defect	Packable graft	DBM, crushed cancellous chips	n/a	510(k) cleared
	GRAFTON Orthoblend Small Defect	Packable, moldable graft	DBM, crushed cancellous chips	n/a	510(k) cleared
	GRAFTON PLUS® DBM Paste	Paste	Human bone allograft demineralized bone matrix (DBM) + inert starch-based carrier has been added	n/a	510(k) cleared K043048, Nov 2005 (Osteotech)-Traditional K042707, Nov 2005 (Osteotech)
	Grafton Putty	Packable, moldable graft	DBM (17% by weight), glycerol	Prospective case series, Retrospective case series, Prospective comparative study, Retrospective comparative study	510(k) cleared K051195, 2005 Dec
Regeneration Technologies	BioSet™	Injectable paste, putty, strips and blocks with cortical cancellous chips	DBM, gelatin carrier	n/a	510(k) cleared K060180 2006 Dec
Smith & Nephew	VIAGRAF	Putty, paste, gel, crunch and flex	DBM, glycerol	n/a	510(k) cleared K043209–2005 Dec
Spinal Elements	Hero DBM	Putty, paste, gel	DBM, RPM	n/a	Regulated under CFR 1270, 1271 as human tissue
	Hero DBM Powder		DBM	n/a	Regulated under CFR 1270, 1271 as human tissue

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Company	DBM-based product	Formulation	Product composition	Peer-reviewed clinical evidence/ongoing study	Regulatory clearance/approval FDA 510(k), CFR 1270, CFR 1271
Wright Medical	ALLOMATRIX	Various volumes, consistency varies depending on proportion of cancellous chips utilized	DBM (86% by volume) ± cancellous bone matrix (CBM) in surgical grade calcium sulfate powder	Retrospective comparative study	510(k) cleared K041663, 2004 Sept
	ALLOMATRIX RCS	Formable putty	DBM, synthetic resorbable conductive scaffold (RCS), calcium sulfate and hydroxypropylmethylcellulose (HPMC)	n/a	510(k) cleared K041663, 2004 Sept
	IGNITE	Percutaneous graft for fracture mal/ nonunion	DBM in surgical grade calcium sulfate powder to be mixed with bone marrow aspirate	n/a	510(k) cleared K052913
	Osteoset DBM Pellets	Packable pellets	3.0-mm or 4.8-mm pellets surgical grade calcium sulfate, DBM (53% by volume), stearic acid	n/a	510(k) cleared K022828, 2004 K053642, 2006 Jan
	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
Zimmer	Puros DBM with RPM Gel and Paste	Gel, paste	DBM, RPM, ground cancellous bone (<500 μm)	n/a	Regulated under CFR 1270, 1271 as human tissue
	Puros DBM with RPM Putty & Putty with chips	Putty	DBM, RPM, ± cortical bone chips (850 μm 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

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BMP content

- Difference between and within products
  - Osteoinductive ability variable
    - Storage
    - Demineralization process
    - Washing/sterilization
    - Source of bone

SPINE Volume 31, Number 12, pp 1299–1306

Intervariability and Intravariability of Bone Morphogenetic Proteins in Commercially Available Demineralized Bone Matrix Products

Hyun W. Bae, MD, Li Zhao, MD, PhD, Linda E. A. Kanim, MA, Pamela Wong, BS, Rick B. Delamarter, MD, and Edgar G. Dawson, MD*

Table 4. Concentrations of BMP-2 and BMP-7 Assayed From Extracts From Various DBM Formulations

	Lot No. 1 ng/g DBM	Lot No. 2 ng/g DBM	Lot No. 3 ng/g DBM	CV
ELISA analysis of BMP-2 ng/g DBM				
Allomatrix® C bone graft putty[7]	97.5	30.1	28.2	76.01%
DBX® DBM putty[8]	51.4	40.9	36.6	17.72%
DynaGraft® II osteoinductive gel[9]	49.2	38.8	25.4	31.56%
DynaGraft® II osteoinductive putty[11]	39.5	30.8	29.5	16.34%
Grafton® gel[12]	85.6	33.6	20.2	74.35%
Grafton® putty[13]	61.3	51.9	29.0	35.05%
Grafton® crunch (written communication, February 2004)	40.8	30.5	29.0	19.21%
InterGro® DBM putty (written communication, November 2003)[14]	89.7	50.5	33.0	50.29%
Osteofil® allograft paste[15]	120.6	48.4	28.4	73.71%
BMP-2, lots: $F = 15.12$, $P < 0.0002$; products: $F = 1.29$, NS	70.6	39.5	28.8	
ELISA analysis of BMP-7 ng/g DBM				
Allomatrix® C bone graft putty[7]	118.8	67.8	66.3	35.45%
DBX® DBM putty[8]	179.7	94.1	90.9	41.43%
DynaGraft® II osteoinductive gel[9]	188.9	95.6	54.2	61.11%
DynaGraft® II osteoinductive putty[11]	226.8	67.9	55.0	82.08%
Grafton® gel[12]	70.5	69.9	60.3	8.56%
Grafton® putty[13]	84.7	80.0	78.6	3.95%
Grafton® crunch (written communication, February 2004)	73.5	68.1	66.9	5.06%
InterGro® DBM putty (written communication, November 2003)[14]	77.5	72.7	72.7	3.71%
Osteofil® allograft paste[15]	81.6	68.1	66.5	11.51%
BMP-7, lots: $F = 6.43$, $P < 0.01$; products: $F = 1.19$ NS	122.4	76.0	67.9	

NS indicates not significant, CV, coefficient of variation.

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DBM in Cervical Fusion

- An et al- Level II
  - Allograft with DBM (Grafton) vs autograft
    - Higher nonunion and graft collapse in allograft
      - 33% vs. 22% (statistically insignificant

SPINE Volume 20, Number 20, pp 2211–2216

Comparison Between Allograft Plus Demineralized Bone Matrix Versus Autograft in Anterior Cervical Fusion

A Prospective Multicenter Study

Howard S. An, MD,* J. Michael Simpson, MD,† J. Michael Glover, MD,* and Jeffrey Stephany, BS*

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DBM in Cervical Fusion

- Level IV data

Topuz et al[50]	Retrospective, case series study	Patients underwent 2-level contiguousanterior cervical discectomy and fusion	PEEK cages and DBM (Grafton®) and autologous blood, $n = 79$	87.3% "excellent" and "good" clinical outcomes, final fusion rate 91.7% (145/158 levels)	IV
Moon et al[51]	Retrospective case series	Patients undergone 2-level, non-instrumented cervical fusion for degenerative disk disease, $n = 27$ (54 levels)	PEEK cages and DBM	Fusion rate was 88.9% of levels. All patients showed improvements in clinical outcomes (VAS score, neurologic pain and JOA myelopathy score)	IV
Demircan et al[53]	Prospective case series	Patients undergone non-instrumented anterior cervical fusion for degenerative disk disease, $n = 16$ (42 levels)	Polyetheretherketone cages packed with autologous blood, curettage microchip material, and DBM (Grafton®)	Fusion rate was 90.5% of levels, at 18 mo after surgery with improved clinical outcomes using JOA score ($P = 0.004$)	IV

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DBM in Lumbar Fusion

Grafton and Local Bone Have Comparable Outcomes to Iliac Crest Bone in Instrumented Single-Level Lumbar Fusions

James Kang, MD,* Howard An, MD,† Alan Hilibrand, MD,‡ S. Tim Yoon, MD, PhD,§ Eoin Kavanagh, MD,‖ and Scott Boden, MD¶

- PMRCT- single level posterior lumbar fusion
  - DBM (Grafton+local bone vs autologous ICB
    - DBM- 86% vs ICBG 92%
    - DBM- higher physical function at 2 years
    - Greater blood loss in ICBG group

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sion

SPINE Volume 29, Number 6, pp 660-666
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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

Frank P. Cammisa, Jr, MD,* Gary Lowery, MD, PhD,† Steven R. Garfin, MD,‡
Fred H. Geisler, MD, PhD,§ Peter M. Klara, MD, PhD,¶ Robert A. McGuire, MD,‖
Walter R. Sassard, MD,** Harrison Stubbs, PhD,†† and Jon E. Block, PhD‡‡

- Cammisa et al- level II
  - Prospective multicenter control-
    - 120 patients
    - Lateral gutter ICBG side vs. Grafton+local bone
      - 2 year- Grafton side 52% ICBG side 54%
      - 75% overall fusion rate
    - Grafton +local similar to autograft alone

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- Level III and IV data

Vaccaro et al[55]	Prospective, comparative study	Patients undergone instrumented posterolateral lumbosacral spinal fusion	DBM (Grafton®) + Bone Marrow, *n* = 19, DBM + Iliac crest autograft, *n* = 27 Autograft, *n* = 27	Fusion rates were 63% with DBM + Bone Marrow, 70% DBM + autograft and 67% with autograft	III
Sassard et al[56]	Retrospective comparative study	Instrumented posterolateral lumbar spinal fusion with rigid pedicle screw fixation (*n* = 108)	Iliac crest bone graft (*n* = 52). Local autograft-Grafton® (*n* = 56)	Fusion rates at 24 mo after surgery: In Iliac crest bone graft group: 56% and in local autograft-Grafton group: 60%	III
Schizas et al[57]	Retrospective case control study	Patients undergone posterolateral, one or two-level, instrumented, lumbar fusion, *n* = 59 (78 levels)	DBM (Accell Connexus® putty) with Iliac crest autograft or local decompression material, *n* = 33. Iliac crest autograft or local decompression material, *n* = 26	Fusion rate was 69.7% with DBM *vs* 76.9% without DBM. There were no differences in complication rates, ODI or VAS pain score	III
Epstein et al[58]	Prospective, clinical study	Patients undergone multilevel lumbar laminectomies, 1-level (*n* = 95) and 2-levels (*n* = 45)	Lamina autograft + DBM (Osteofil), *n* = 140	1-level fusion rates: 98%, 2-levels fusion rates: 96%. Revealed essentially comparable outcomes on 6 of 8 Health Scales of SF-36	IV

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- Level III and IV data contd'

Thalgott et al[61]	Prospective case series study	Patients undergone lumbar interbody fusion ($n = 50$)	Titanium mesh cages filled with coralline hydroxyapatite (ProOsteon™ 500R) and DBM (Grafton®)	96% fusion rate, decrease in mean pain scores by 60% from baseline	IV
Girardi et al[60]	Retrospective case series study	Instrumented lumbar spinal fusion for various diagnoses ($n = 65$)	Combination of autologous bone graft and allograft DBM (AlloMatrix® Injectable Putty)	Gradual and constant improvement based on radiographic measurements taken 1, 3, 6 and 12 mo after surgery	IV
Thalgott et al[62]	Retrospective case series	Patients undergone instrumented posterolateral lumbar fusion, $n = 40$	Coralline hydroxyapatite (Pro Osteon™ 500) + DBM (Grafton®), $n = 28$ Pro Osteon™ 500 alone, $n = 12$	Radiographic fusion rates was 100% with coralline hydroxyapatite alone, than 89.3% with Grafton added.	IV
Epstein[59]	Prospective case series	Geriatric patients undergone posterolateral non-instrumented lumbar fusion, $n = 75$	Lamina autograft mixed with DBM (Osteofil) in 1:1 ratio	Fusion rate was 82.7% of levels. Improved clinical outcomes using SF-36 score.	IV

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INNOVASIS
INNOVATE / INVOLVE / INVENT

- Physio
  - mix of processed cortical bone tissue allograft blended mineralized cancellous particulate
    - No carrier
  - naturally occurring levels of BMP 2, 4 and 7 as wells as VEGF

No Extrinsic Carrier

Wet Field Integrity

Growth Factor Rich Allograft

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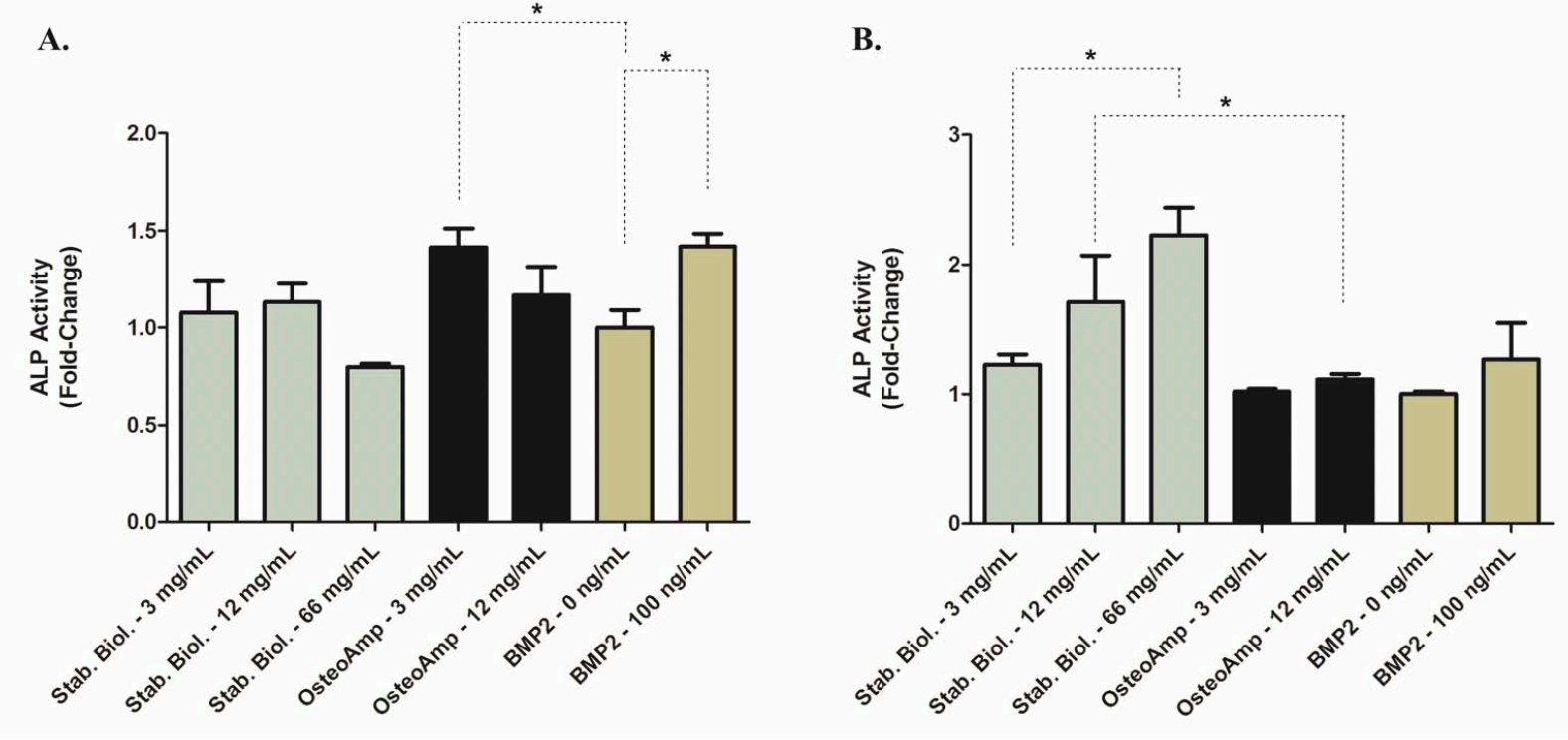
INNOVASIS
INNOVATE / INVOLVE / INVENT

- Physio-
  - Alk Phos activity day 6 and 13



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Synthetics

- Ceramics
  - Scaffolds facilitate cellular adhesion, vascular ingrowth, bone formation
- Calcium Sulfate
  - Osteoblasts attach, osteoclasts can resorb
- Collagen
  - Type I-conductive for mineral deposition, vascular ingrowth, growth factor binding

JNS SPINE
LITERATURE REVIEW
J Neurosurg Spine 25:509–516, 2016

Synthetic bone graft versus autograft or allograft for spinal fusion: a systematic review

Zorica Buser, PhD,[1] Darrel S. Brodke, MD,[2] Jim A. Youssef, MD,[3] Hans-Joerg Meisel, MD, PhD,[4] Sue Lynn Myhre, PhD,[3] Robin Hashimoto, PhD,[5] Jong-Beom Park, MD,[6] S. Tim Yoon, MD, PhD,[7] and Jeffrey C. Wang, MD[1]

- Synthetics
  - Low regulatory barrier
    - Proliferation of products available
  - Analysis of 27 studies
    - Bias very high in almost all studies
    - No RCT or Level I evidence
    - Preventing synthetic grafts from being deemed beneficial

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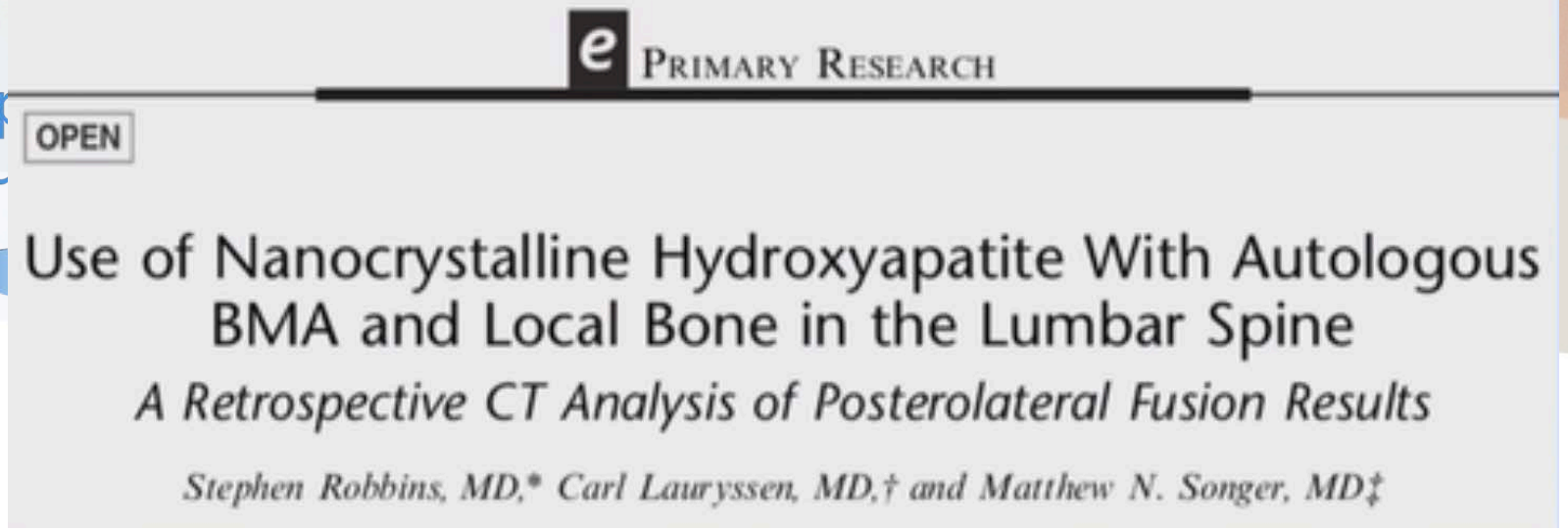

- Nano crystalline HA with porcine collagen carrier used as bone graft extender with BMA and local bone
  - Radiographically 91% patients treated exhibited bilateral or unilateral posterolateral bridging bone

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Bone Morphogenetic Protein

- Member of TGF-β family of growth factors
  - In high concentrations results in direct intramembranous ossification
- Recombinant technology allows for mass production of multiple BMPs
- rhBMP-2 FDA approved in 2002 for single level ALIF in grade I spondy with LT cage
  - 08 posterolateral lumbar pseudo, open tibia
- rhBMP-7- HDE exemption only

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- 2002- .7% of fusions

- 2006- 30% of fusions

- 2007- 16% used in ALIF
  - The rest off label

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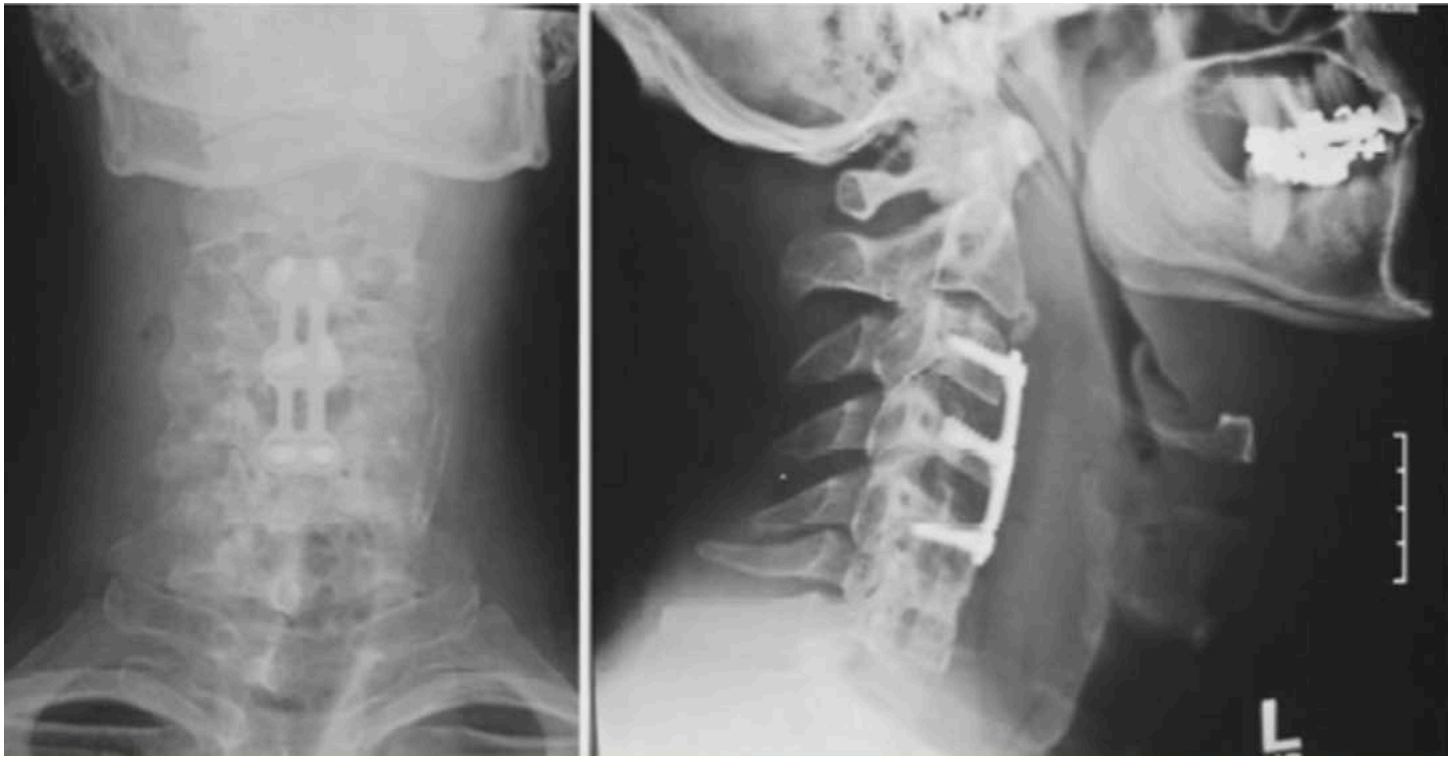
BMP

- 2008- FDA Black-box warning for cervical
  - Likely dose phenomenon



ELSEVIER

The Spine Journal 11 (2011) 471–491

THE SPINE JOURNAL

Review Article

A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: emerging safety concerns and lessons learned

Eugene J. Carragee, MD[a,*], Eric L. Hurwitz, DC, PhD[b], Bradley K. Weiner, MD[c]

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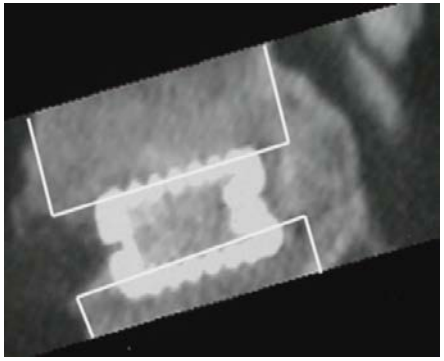
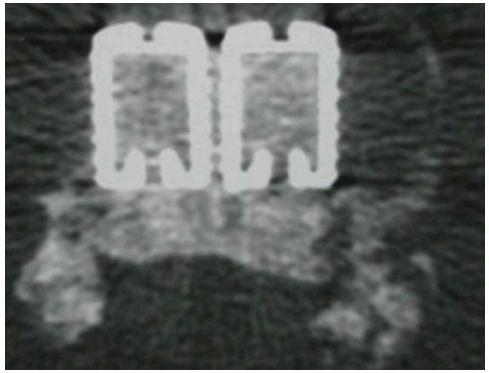
Received 18 February 2011; revised 5 April 2011 and 25 April 2011; accepted 27 April 2011

- Publication bias
  - Complications underreported?
- Safety concerns
  - 10-50% worse than original estimate





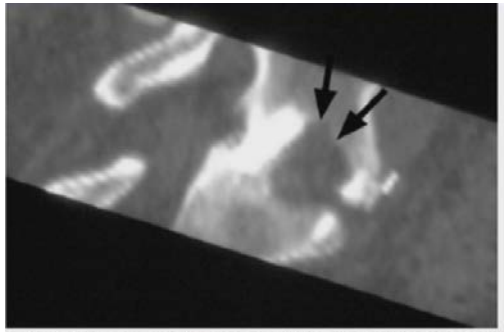


Figure 7. Bone remodeling zone at 6 months. A lucent area of active bone remodeling within the cancellous portion of the vertebral body (arrows) is seen adjacent to the cortical margins of the bone dowel.

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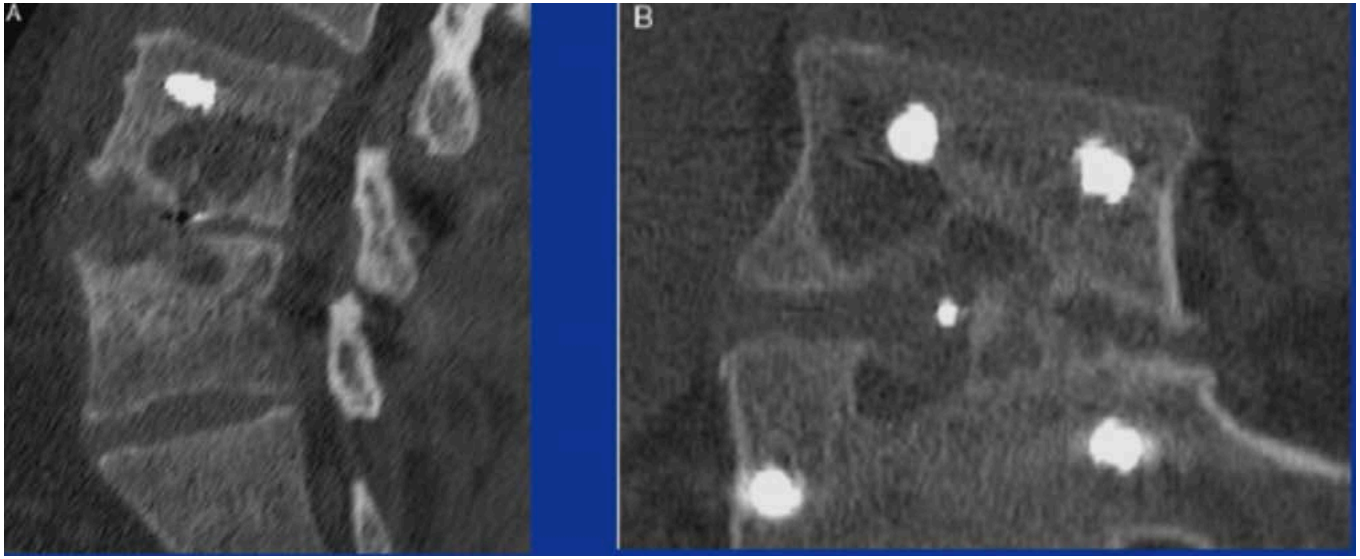
Vertebral Bone Resorption After Transforaminal Lumbar Interbody Fusion With Bone Morphogenetic Protein (rhBMP-2)

John W. McClellan, MD. Daniel S. Mulconrey, MD.† Robert J. Forbes, MD.‡ and Nancy Fullmer, BS, RN**



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Yale Open Data Access

- YODA
  - Controversy re: promotion indication and ethics of use of InFuse
  - Allegations of improper complication reporting
    - Medtronic 2.5 million funding
  - 2 independent research groups to evaluate rhBMP-2 clinical studies
  - 2 meta-analysis papers

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Safety and Effectiveness of Recombinant Human Bone Morphogenetic Protein-2 for Spinal Fusion: A Meta-analysis of Individual-Participant Data

FREE

Mark C. Simmonds, PhD, MA; Jennifer V.E. Brown, MSc, BA; Morag K. Heirs, MSc, MA; Julian P.T. Higgins, PhD, BA; Richard J. Mannion PhD; Mark A. Rodgers, MSc, BSc; Lesley A. Stewart, PhD, MSc, BSc

Article, Author, and Disclosure Information

BJR

SPINE

Effectiveness and safety of recombinant human bone morphogenetic protein-2 for adults with lumbar spine pseudarthrosis following spinal fusion surgery

A SYSTEMATIC REVIEW

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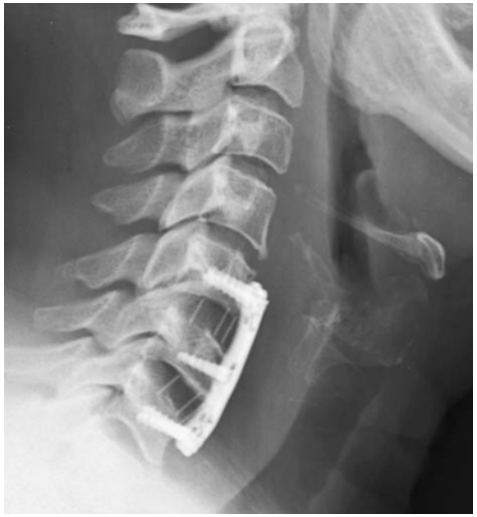
BMP

- Bottom line
  - Reasonably safe per FDA indications
  - As effective as ICBG
  - Unsafe when used off label
    - Cervical spine surgery
    - TLIF



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Cellular Bone Matrices

- Several products now filling "space" left in controversy surrounding Infuse
- Multiple sponsored trials underway
- Variants of quiescent stem cells adhered to a carrier, usually DBM
  - Variance in donor age, cell concentration

- Fast growing segment of market ($400M in 2018)
  - Higher price than DBM and synthetics
- Processed by tissue bank and licensed by spine company
  - Tissue donor-
    - Cancellous bone processed-immunodepletion to preserve cells
    - Cortical bone- DBM

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Cellular Bone Matrices

- Clinical evidence?
  - Been on market for 13 years
  - Pubmed search
    - 9 studies, 5 osteocel, 3 Trinity evolution
  - Limited data-conclusions are weak
  - Acceptable fusion rates but
    - No observed clinical benefits to justify price premium
  - In general, insufficient evidence
    - Studies ongoing

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The End