Washington State Health Care Authority, HTA Program
Final Key Questions

Bone Morphogenic Proteins for use in Spinal Fusion

Introduction

HTA has selected Bone Morphogenic Proteins (BMP) for use as adjuncts in spinal fusion surgery to undergo a health technology assessment where an independent vendor will systematically review the evidence available on its safety, efficacy, and cost-effectiveness. HTA originally posted the topic as Bone Graft Products (autograft, allograft, and synthetic), now modified, and gathered public input on all available evidence. Recombinant bone morphogenetic proteins (rhBMPs) are currently used in place of or in addition to autograft (e.g., iliac crest bone graft or ICBG) or allograft bone (e.g., cadaver bone) as an adjunct to spinal fusion and other bone fusion procedures. To date, two rhBMPs (rhBMP-2 and rhBMP-7) and associated delivery vehicles have received approval from the Food and Drug Administration (FDA).

Key questions guide the development of the evidence report. HTA seeks to identify the appropriate clinical topics (e.g., population, indications, comparators, outcomes, policy considerations) to address the statutory elements of evidence on safety, efficacy, and cost effectiveness relevant to coverage determinations.

This topic was originally more broadly defined as 'bone graft products' to include BMP and other autograft, allograft or synthetic materials used to aid in bone healing or fusion surgery. The topic was focused on BMP based on: 1) the availability of a comprehensive systematic review from the AHRQ published in December 2010 and, 2) subsequent new published information related to safety concerns focused on BMP.

Key Questions

When used in patients undergoing spinal fusion:

(1). What are the expected treatment outcomes of primary single or multilevel lumbar or cervical spinal fusion for degenerative disc disease (DDD), and of revision posterolateral lumbar spinal fusion in compromised patients (i.e., osteoporosis, smoking, diabetes)? Are there validated instruments related to outcomes in patients undergoing these procedures? Has clinically meaningful improvement in outcomes been defined in these patient populations?

(2). Compared with spinal fusion using ICBG or alternative bone graft substitutes, what is the evidence of efficacy and effectiveness of:

a) rhBMP-2 (InFUSE) for on-label lumbosacral spine fusion in patients with DDD?

b) rhBMP-7 (OP-1) for on-label revision posterolateral lumbar spine fusion in compromised (e.g., osteoporosis, smoking, diabetes) patients?

c) rhBMP-2 (InFUSE) for off-label lumbosacral spine fusion?

d) rhBMP-7 (OP-1) for off-label lumbosacral spine fusion?

e) rhBMP-2 (InFUSE) for off-label cervical spine fusion?

f) rhBMP-7 (OP-1) for off-label cervical spine fusion?

Including consideration of perioperative outcomes (including length of surgery) as well as short term and long term:

- Impact on function, pain, radiographic fusion, patient satisfaction, quality of life, activities of daily living and return to work
- Other reported measures

(3). What is the evidence of the safety of on- or off-label use of rhBMP-2 or rhBMP-7 for spinal fusion compared with spinal fusion using ICBG or alternative bone graft substitutes? Including consideration of:

- Short- and long term adverse events and complications type and frequency (pain, donor site morbidity, resorption/osteolysis, heterotopic bone formation, graft subsidence, graft migration, dysphagia or respiratory difficulties, elevated antibody responses to BMPs or collagen, wound complications (infection, hematoma, seroma, or dehiscence), local or systemic toxicity, mispositioned graft, neurological complications, retrograde ejaculation, urogenital complications, allergic reactions, mortality, other major morbidity).
- Revision/re-operation rates

(4). What is the evidence that on- or off-label use of rhBMP-2 or rhBMP-7 for spinal fusion compared with spinal fusion using ICBG or alternative bone graft substitutes has differential efficacy or safety issues in sub-populations? Including consideration of:

- Gender
- Age
- Baseline functional or pain status
- Comorbidities (including but not limited to tobacco use, alcohol use, psychological or psychological)
- Other patient characteristics or evidence-based patient selection criteria
- Provider type, setting or other provider characteristics
- Payor/ beneficiary type: including worker's compensation, Medicaid, state employees

(5). What evidence of cost implications and cost-effectiveness of on- or off-label use of use of rhBMP-2 or rhBMP-7 exists? Including consideration of:

- Costs (direct and indirect) and cost effectiveness
- Short term and long term

Policy Context:

In addition to other applications, BMPs are applied as adjuncts during spinal fusion surgeries.

Technology Description:

Bone morphogenic proteins are naturally produced cell regulating proteins (TGF-B family) necessary for bone healing and regeneration, but also involved in other tissue configuration processes. Recombinant DNA methods have been used to produce higher quantities of bone morphogenic proteins than could be harvested from cadaver sources (due to minute naturally available amounts) for commercial application. Recombinant BMP products have been used since 2001 in procedures where bone healing or fusion is required; they are used in conjunction with collagen scaffolding materials and/or metallic cages.

BMP products provide the potential to avoid bone harvesting procedures necessary for use of autograft (self donated bone material), or to avoid allograft (use of bone from cadavers). Autograft requires bone harvesting, a separate surgical procedure that itself may result in pain and carries some risk related to the procedure and removal of bone, frequently from the iliac crest (hip). If BMP is a safe and effective alternative to autograft, patients may avoid a procedure and associated risk.

Issues:

There have been recent concerns about safety due to adverse event reports and questions about clinical trial methodology and reporting of potential adverse events. Questions were raised about the safety of BMP based on observed effects including excess bone growth (heterotopic bone formation), and other adverse events including possible increased rates of retrograde ejaculation (RE) in men. Publication in June 2011 of a series of papers addressed these concerns as well as concerns about the methods used to determine rates of adverse effects in the original trials designed to test the safety of the then new products. Therefore, significant questions remain about the safety, efficacy and effectiveness, and cost effectiveness of recombinant bone morphogenic proteins when used in spinal surgery.

Reviewer Name	Affiliation	Question	Comment	Response
Dena Scearce	Medtronic	KQ1	**It is our opinion that the focus of this question exceeds the scope of the subject intended for review. The purpose of the review is to assess the evidence on BMP's safety, efficacy, and cost-effectiveness for fusion, and not to evaluate fusion per se. The absence of any mention of BMP will lead to an evidence review that misses this objective.**	No change. Will provide the information relevant to outcome measures for assessing the efficacy/effectiveness of BMP for this application.
		KQ2	**We recommend that the descriptor contained in Key Question # 3 - "compared with spinal fusion using ICBG or alternative bone graft substitutes" also be incorporated into Key Question # 2. Thus, the question would be: "What is the evidence of efficacy and effectiveness of the items listed below compared with spinal fusion using ICBG or alternative bone graft substitutes?" This would provide consistency, as well as better focus, on the comparative outcomes of BMP versus ICBG or alternative bone graft substitutes.**	We have modified KQ2 based on this recommendation.
		KQ3	**"Heterotopic bone formation" is listed as a possible adverse event. In the *Issues* discussion "hypertrophic" ossification is referenced. We recommend using consistent terms, and "heterotopic" or "ectopic" are more consistently utilized and understood in the clinical community.** **For comments on retrograde ejaculation (RE), please see the *Issues* section below.**	We have modified the *Issues* discussion to be consistent within the document.
		KQ4	**We question the relevancy of the final two items on the above list for Key Question # 4. We find it unlikely that there would be clinical evidence with provider and/or payors' data and believe that information would have no bearing on the efficacy or safety of BMP. We recommend elimination of the final two items. If the HTA determines that these items should remain, we would request an explanation of the data expected to be found by including these factors.**	Payor/beneficiary type may be relevant if available.
		Issues section	**Comment on *Issues*:** In reference to the opening sentence in the above paragraph, we think it worth noting that publications may differ in their definition of what constitutes a safety event reported in clinical studies. There may be possible specific protocol differences in premarket trials versus those observed and reported in post-market use. For the latter, there may be no a priori standardized definitions or	Terms modified for consistency and accuracy.

			consistency in data collection of specific safety events, and post-market information may inform risk in ways that were unavailable during pre-market studies. Conclusions made relative to specific events should address strengths and weaknesses with the evidence. We also believe the adverse event **highlighted** above would be more appropriately referenced as retrograde ejaculation (RE). RE is a known potential complication after **anterior** lumbar surgery and thought to be due to injury to the superior hypogastric plexus during the anterior approach. While RE can theoretically lead to infertility or sterility, RE may also resolve spontaneously after its onset. It is also important to note that RE is a known potential complication of anterior lumbar interbody fusion with or without rhBMP-2. In any analysis of RE, the evidence may be best differentiated in terms of approach (e.g., laparoscopic, transperitoneal and retroperitoneal), as well as whether the lumbar fusion included BMP. We thank you for your consideration of the above information. We hope you find this information helpful and we stand ready to be a resource to you during this process. If you have any questions, please feel free to contact me at 901.428.3516.	

SPECTRUM RESEARCH

Clinical Research Consulting

Statement of Financial Interests of Spectrum Research Staff, Consultants, and Subcontractors

Please list below each corporation, company, firm, research organization, educational institution or other organization (proprietary and non-for-profit, domestic and foreign) in which (a) you, (b) your spouse, and (c) your dependent children, have financial interests of $10,000 or more (including research funded by private entities on which you are principal investigator), in the manufacture and distribution of a device, pharmaceutical, dietary supplement or other over-the-counter product, screening/assessment tool, or procedure, or their competitors, which are related to the subject matter reports, publications or other products that will be developed with your participation. Dollar amounts of such interests are not required to be disclosed.

NONE

Statement of Business and Professional Interests of Spectrum Research Staff, Consultants, and Subcontractors

Please list below the name of any professional society or association, company, firm, research organization, educational institution, or other organization or institution (proprietary and not-for-profit, domestic and foreign) in which your services will be provided, with or without compensation, including on a part-time or seasonal basis, as an (a) officer; (b) medical staff; (c) board member; (d) trustee; (e) director; (f) expert advisor; or (g) consultant, that is related to the subject matter reports, publications or other products that will be developed with your participation.

UNIVERSITY OF WASHINGTON MEDICAL CENTER

I certify that the information provided on my and my family's financial interests, and my business and professional interests, is true and complete.

Print Name MICHAEL J. LEE M.D.

Signature MD

Date 2/28/12

705 S. 9th Street, Suite 203 • Tacoma, WA 98402
OFFICE: 253-722-5475 • FAX: 253-722-2810
www.specri.com

Curriculum Vitae

Michael Jihoon Lee M.D.
Assistant Professor of Spine
Department of Orthopaedics and Sports Medicine
University of Washington Medical Center
206-543-3690
Box 356500
1959 NE Pacific ST
Seattle WA 98195-6500
mjl3000@u.washington.edu

PERSONAL DATA

Born April 3rd, 1975. Cincinnati OH

EDUCATION

Cincinnati Country Day School, Cincinnati OH 1989-1993
Northwestern University, Evanston IL, B.S. Biomedical Engineering, 1993-1996
Northwestern University School of Medicine, Chicago IL, M.D. 1996-2000

POST GRADUATE EDUCATION

Case Western Reserve University, Internship, Department of General Surgery, 2000-2001
Allen Orthopaedic Research Fellow 2001-2002
Case Western Reserve University,
Dept of Orthopaedic Surgery, Cleveland Ohio
Case Western Reserve University, Residency, Department of Orthopaedics, 2002-2006

FELLOWSHIP

Rush Presbyterian St Luke's Hospital – Spine 2006-2007
Fellowship director – Howard An M.D.

FACULTY POSITIONS

Assistant Professor of Spine, The University of Washington Medical Center –
Department of Orthopaedics and Sports Medicine
September 2007 to present
AO Spine North America Faculty
April 2011 to present

HOSPITAL POSITIONS

Attending, Harborview Medical Center
September 2007 to present
Attending, University of Washington Medical Center

September 2007 to present
Attending, Seattle Cancer Care Alliance
September 2007 to present

HONORS

Alvin Freehafer Outstanding Junior Resident Award – CWRU 2003
Ohio Orthopaedic Society 2003 1st Place
Ohio Orthopaedic Society 2005 4th Place
Cleveland Orthopaedic Society 2005 2nd place
Cleveland Orthopaedic Society 2005 3rd place
Barry Friedman Orthopedic Award 2005 3rd place
Barry Friedman Orthopedic Award 2006 3rd place
Barry Friedman Orthopedic Award 2006 2nd place
Cervical Spine Research Society 2005 1st Place – J. William Fielding Award
Cervical Spine Research Society 2005 2nd Place – J. William Fielding Award

BOARD CERTIFICATION

American Board of Orthopaedic Surgery	Part I (written)	passed 7/2006
	Part II (oral)	passed 9/2009

LICENSE TO PRACTICE

State of WA	MD 00047891	04/03/2010	Active

PROFESSIONAL ORGANIZATIONS

American Academy of Orthpaedic Surgeons
Washington State Medical Association
Washington State Orthopaedic Association
AO Spine North America

COURSES CHAIRED

1) Advanced Techniques of Spine Tumor Treatment. June 3-4 2011, Seattle WA

TEACHING RESPONSIBILITIES

A. Invited Lecture / Courses Taught

1. **Lee MJ**. Management of Vertebral Artery Injuries. 6th Annual Harborview Forum: Arthritic Disorders of the Spine. Oct 6, 2007. Seattle WA
2. **Lee MJ.** Osteoporosis. Korean American Health Professionals Association Health Fair Symposium. Nov 3, 2007. Tacoma WA.
3. **Lee MJ**. Spinal Stenosis: Cervical and Tandem. Harborview Medical Center Neurosurgery Grand Rounds. Feb 20, 2008. Seattle WA.
4. **Lee MJ**. Emerging Technologies in Spine Surgery. UWMC Rehabilitation and Physiatry symposium. March 27th, 2008. Seattle WA.

5. **Lee MJ**. Imaging the Lumbar Spine: Low Back Pain. UWMC Rehabilitation and Physiatry symposium. March 27th, 2008. Seattle WA.
6. **Lee MJ**. Insights in Measuring Cervical Stenosis. Harborview Spine Symposium. Oct 4, 2008. Seattle WA.
7. **Lee MJ**. Spine Stenosis. Washington State Orthopaedic Association. Nov 15-16, 2008. Seattle WA.
8. **Lee MJ**. Variation in Decompressive Techniques of the Lumbar Spine. Harborview Medical Center/UW. Neurosurgery Grand Rounds. Feb 18, 2008. Seattle WA.
9. **Lee MJ**. Cervical Surgery: Fusion vs. Disc Replacement. The Cervical Spine and Upper Limb Neural Tension: From Different Diagnosis to Rehabilitation, Neurodynamics, and Interventional Treatments. April 26th, 2009. Seattle WA.
10. **Lee MJ**. Office Orthopaedics for the Neurologist. American Academy of Neurology. April 30th, 2009. Seattle WA.
11. **Lee MJ**. Cervical Decompression and Fusion: the argument in favor. Harborview Spine Symposium. Oct 3, 2009. Seattle WA.
12. **Lee MJ**. Degenerative spondylolisthesis and stenosis: laminectomy or laminotomy? Harborview Spine Symposium. Oct 3, 2009. Seattle WA.
13. **Lee MJ**. Structure Around the Spine (vertebral artery, dysphonia, dysphagia etc…) American Academy of Orthopaedic Surgerons. New Orleans, LA. March 13th, 2010. *30 CME credits.*
14. **Lee MJ**. Innovations in Spine Surgery. Principles of Spinal Disorders for Operating Room Personnel: a team approach. AO North America. Seattle, WA. July 17-18, 2010.
15. **Lee MJ**. Complications in Vertebral Augmentation. Harborview Spine Symposium. Oct 2, 2010. Seattle WA.
16. **Lee MJ**. Literature Based Evidence for Treatment of Adult Degenerative Scoliosis. Current & Emerging Issues in Complex Lumbar Spine Surgery. Practical Anatomy and Surgical Education. St Louis School of Medicine Oct 28th, 2010. St Louis MO.
17. **Lee MJ**. Implant Subsidence/ Migration. Current & Emerging Issues in Complex Lumbar Spine Surgery. Practical Anatomy and Surgical Education. St Louis School of Medicine Oct 29th, 2010. St Louis MO. *8.75 CME credits.*
18. **Lee MJ.** Facet Kinematics in Limited vs. Subtotal Microdiscectomy. AO Spine Fellows Forum. April 2nd, 2011. Banff, Alberta Canada.
19. **Lee MJ.** Review of Metastatic Spine Disease. Advanced Techniques of Spine Tumor Treatment. June 3-4 2011, Seattle WA
20. **Lee MJ.** Pathologic Spine Fracture. Advanced Techniques of Spine Tumor Treatment. June 3-4 2011, Seattle WA
21. **Lee MJ.** MIS vs Open Lumbar Spine Surgery: Style vs. Substance. Puget Sound Spine Interest Group. September 15th, 2011, Bellevue WA.
22. **Lee MJ.** Does MIS reduce complications? Spine Summit in Seattle: Enhancing Patient Safety in Spine Surgery. Harborview Medical Center, October 1, 2011, Seattle WA.

23. **Lee MJ.** Adjacent Segment Disease Reoperations: What are the risk factors? Spine Summit in Seattle: Enhancing Patient Safety in Spine Surgery. Harborview Medical Center, October 1, 2011, Seattle WA.
24. **Lee MJ.** Systematic Review: Infections in Spine Surgery. Spine Summit in Seattle: Enhancing Patient Safety in Spine Surgery. Harborview Medical Center, October 1, 2011, Seattle WA.
25. **Lee MJ**. Literature Based Evidence for Treatment of Adult Degenerative Scoliosis. Innovative Technologies in Complex Lumbar Surgery. Practical Anatomy and Surgical Education. St Louis School of Medicine Nov 18th, 2011. St Louis MO.
26. **Lee MJ**. Direct Decompression. Innovative Technologies in Complex Lumbar Surgery. Practical Anatomy and Surgical Education. St Louis School of Medicine Nov 18th, 2011. St Louis MO.
27. **Lee MJ**. Indirect Decompression and New Technologies. Innovative Technologies in Complex Lumbar Surgery. Practical Anatomy and Surgical Education. St Louis School of Medicine Nov 18th, 2011. St Louis MO.

B. Intra- UW lectures (Resident/Nursing/ Fellowship lectures)

1. **Lee MJ.** Metastatic Disease to the Spine. Margo Johnsen Pathology Review. University of Washington Medical Center. Oct 11, 2008. Seattle WA.
2. **Lee MJ.** Metastatic Disease to the Spine. Margo Johnsen Pathology Review. University of Washington Medical Center. Oct 10, 2009. Seattle WA.
3. **Lee MJ.** Metastatic Disease to the Spine. Margo Johnsen Pathology Review. University of Washington Medical Center. Oct 23, 2010. Seattle WA.
4. **Lee MJ**. Lumbar Spine Anatomy, Terminology and Radiographic Imaging. Nursing Continuing Education Spine Bio skills Workshop, University of Washington. August 18, 2010.
5. **Lee MJ**. Lumbar Spine Part 2 (Clinical Management - Surgical Approach). Nursing Continuing Education Spine Bio skills Workshop, University of Washington. August 18, 2010.
6. **Lee MJ.** Spine fusion. 6SE Education Day. University of Washington Medical Center. October 6, 13, 20 2011. Seattle WA
7. **Lee MJ.** Spine Surgery. Lecture to Rehabilitation Medicine Residents. University of Washington Medical Center. October 18, 2011. Seattle WA
8. **Lee MJ.** Metastatic Disease to the Spine. Margo Johnsen Pathology Review. University of Washington Medical Center. Oct 22, 2011. Seattle WA.
9.

POST MEDICAL SCHOOL ACTIVITIES

Case Orthopaedic Journal Editor in Chief 2005-2006
Case Orthopaedic Journal Resident Editor 2003-2005
Orthopaedic Education Committee Member 2004-2006
Resident Representative to the American Academy of Orthopaedic Surgery, 2004-2006
Skeletal Anatomy Instructor

- Teaching musculoskeletal anatomy to 1st year medical students at Case Western Reserve University Medical School Oct 2001. (Part of Orthopaedic Residency Curriculum)

Cleveland Heights High School Team Physician, 2001-2006

BASIC SCIENCE RESEARCH EXPERIENCE

Allen Orthopaedic Research Fellow, Case Western Reserve University, Dept of Orthopaedic Surgery, Cleveland Ohio, 2001-2002

Research Technician Northwestern, Alzheimer's Research, Evanston Illinois; University May-August 2000

SPECIAL NATIONAL RESPONSIBILITIES

Reviewer: Journal of American Academy of Orthopaedic Surgery. 2008 to present.

Reviewer: Evidence Based Spine Journal. 2010 to present

Reviewer: Spine. 2012 to present

Reviewer: Spine Across the Sea 2012 Abstract review

Reviewer: North American Spine Society 2012 Abstract review

SPECIAL LOCAL RESPONSIBILITIES

Naloxone Review Committee, UWMC, 2008 to present

Medical Director 6SE (Orthopaedic ward) of UWMC – April 2010 to present

University of Washington Faculty Senate – 9/2010 – 9/2012

UWMC Dept Orthopaedic Search Committee – Orthopaedic Oncology Faculty 2011

UWMC Dept Orthopaedic Advancement and Promotions Committee 2011

University of Washington Committee for Edwin Laurnen Award – 2011 to present

University of Washington Medical Center founding member of Spine SCOAP- a Washington State registry for spine surgery with the goal of improving quality and safety across all of WA state. 2009-present

University of Washington Medical Center InPatient Clinical Performance Committee. 2011- present

GRANTS / FUNDING

University of Washington Orthopaedic Department Initiative Funding. The Effect of Bilateral Laminotomy and Laminectomy on the motion of the Human Lumbar Spine. **Lee MJ (Principle Investigator)**, Howe C. Bransford R, Chapman J, Ching R. - $32,000. 2008

DePuy Spine. Kyphosis Correction from combined Smith Peterson Osteotomy and an Interbody Strut. **Lee MJ (Principle Investigator),** Ching R. $19,500, 2008-2009.

AO Spine North America Young Investigator Award. **Lee MJ (Principle Investigator)**, Ching RC. $30,000. 2010-2011

AHRQ. Shared Decision-making in Surgery to Improve Patient Safety and Reduce Liability. Domino K, **Lee MJ (Co-Investigator),** Bransford RJ. $300,000. 2010-2011

AO Spine CPP-FFOB. Enhancing pedicle screw fixation in the lumbar spine utilizing allograft bone plug interference fixation. **Lee MJ (Principle Investigator),** Ching R, Chapman JR. $40,000, 2011

BIBLIOGRAPHY

A. PEER REVIEWED/REFEREED PUBLICATION

1) Sarwahi V, Sarwark JF, Schafer MF, Backer C, **Lee M**, King EC, Aminian A, Grayhack JJ. Standards in anterior spine surgery in pediatric patients with neuromuscular scoliosis. J Pediatr Orthop. 2001 Nov-Dec;21(6):756-60.
2) Bazaz R, **Lee MJ**, Yoo JU. Incidence of Dysphagia after Anterior Cervical Spine Surgery – A Prospective Study. Spine 2002. 27(22):2453-2458.
3) **Lee MJ**, Bazaz R, Furey CG, Yoo JU. The Influence of Anterior Cervical Plate Design on Dysphagia: A Two Year Prospective Study. J Spinal Disord Tech. 2005 Oct;18(5):406-409.
4) **Lee MJ**, Bazaz, Furey CG, Yoo JU. Risk Factors for Dysphagia after Anterior Cervical Spine Surgery: A Two Year Prospective Study. Spine J. 2007 Mar-Apr;7(2):141-7.
5) Cassinelli EH, **Lee M**, Skalak AF, Ahn N, Wright N. Anatomic Considerations for the Placement of C2 Intra-laminar Screws. Spine. 2006 Nov 15;31(24):2767-71
6) Nalepka JL, **Lee MJ**, Kraay MJ, Marcus RE, Goldberg VM, Chen X, & Greenfield EM. Lipopolysaccharide Found in Aseptic Loosening of Patients with Inflammatory Arthritis. Clin Orthop Relat Res. 2006 Oct;451:229-35
7) **Lee MJ**, Cassinelli E, Riew KD. The Feasibility of Inserting Atlas Lateral Mass Screws via the Posterior Arch. Spine. 2006 Nov 15;31(24):2798-801).
8) **Lee MJ**, Cassinelli E, Riew KD. The Prevalence of Cervical Stenosis: an anatomic study in cadavers. J Bone Joint Surg Am. 2007 Feb;89(2):376-80.
9) Smith MV, **Lee MJ**, Islam AS, Rohrer JL, Goldberg VM, Biedelschies MA, Greenfield EM. The PI3K/Akt pathway mediates the biological response to titanium particles. J Bone Joint Surg Am. 2007 May;89(5):1019-27.
10) Eubanks JD, **Lee MJ**, Ahn N. Does Lumbar Facet Arthrosis Precede Disc Degeneration? A Postmortem Study. Clin Orthop Relat Res. 2007 Nov;464:184-9.
11) Eubanks JD, **Lee MJ**, Ahn N. Prevalence of lumbar facet arthrosis and its relationship to age, sex and race: an anatomic study of 647 cadaveric specimens. Spine. 2007 Sep 1;32(19):2058-62.
12) **Lee MJ**, Dumonski M, Cahill P, Stanley T, Park D, Singh K. Percutaneous Treatment of Vertebral Compression Fractures: A Meta-Analysis of Complications. Spine 2009 May 15;34(11):1228-32.
13) **Lee MJ**, Garcia R, Cassinelli EH, Furey CG, Riew KD. Tandem Stenosis: A Cadaveric Study in Osseous Morphology. Spine J. 2008 Nov-Dec;8(6):1003-6
14) Dean CL, **Lee MJ**, Robbin M, Cassinelli EH**.** Correlation between Computed Tomography Measurements and Direct Anatomic Measurements of the Axis for Consideration of C2 Laminar Screws. Spine J. 2008 Aug 29.
15) Hong JT, Park D, **Lee MJ**, Kim SW, An HA. Anatomical variations of the V2 segment of the vertebral artery - Analysis by Three-Dimensional Computed Tomography Angiography. Spine. 2008 Oct 15;33(22):2422-6.
16) Yang JY, Song HS, **Lee M**, Bohlman HH, Riew KD. Adjacent Level Ossification Development after Anterior Cervical Fusion without plate fixation. Spine. 2009 Jan 1;34(1):30-3.

17) Park DK, **Lee MJ**, Lin EL, An HS, Phillips FM. The relationship of Intra-Psoas Nerves during a Trans-Psoas Approach to the Lumbar Spine: Anatomical Study. Journal of Spinal Disorders and Techniques 2010 Jun;23(4):223-8.
18) Martin BI, Turner JA, Mirza SK, **Lee MJ**, Comstock BA, Deyo RA. Trends in Health Care Expenditures, Utilization and Health Status among U.S. Adults with Spine Problems: 1997-2006. Spine 2009 Sep 1;34(19):2077-84.
19) **Lee MJ**, Riew KD. The Prevalence Cervical Facet Arthrosis: an Osseous Study in a Cadaveric Population. Spine J 2009 Sep;9(9):711-4.
20) **Lee MJ,** Bransford RJ, Bellabarba C, Chapman JR, Cohen A, Harrington R, Ching RP. The Effect of Bilateral Laminotomy vs. Laminectomy on the Motion and Stiffness of the Human Lumbar Spine. Spine 2010 Sep 1;35(19):1789-93.
21) **Lee MJ**, Lin EL. The use of the Three Pronged Mayfield Head Clamp resulting in an Intra-Cranial Epidural Hematoma in an Adult Patient: a Case Report. European Spine Journal 2010 Jul;19 Suppl 2:S187-9.
22) Bransford RJ, Bellabarba C, **Lee MJ**. Comparison of Anterior Transthoracic versus Modified Transfacet Pedicle-sparing Decompression and Fusion in the Management of Thoracic Disc Herniations. Evidence Based Spine Journal. 2010 1(1) 21-28.
23) **Lee MJ**, Lindsey J, Bransford RJ. Posterior Dynamic Lumbar Stabilization. Journal of American Academy of Orthopaedic Surgery J Am Acad Orthop Surg. 2010 Oct;18(10):581-8.
24) Bransford RJ, **Lee MJ**, Reis A**.** Posterior fixation of the upper cervical spine: contemporary techniques. Journal of American Academy of Orthopaedic Surgery J Am Acad Orthop Surg. 2011 Feb;19(2):63-71..
25) Cahill PJ, Warnick DE, **Lee MJ**, Gaughan J, Vogel LE, Hammerberg KW, Sturm PF. Infection after spinal fusion for pediatric spinal deformity: thirty years of experience at a single institution. Spine 2010 May 20;35(12):1211-7.
26) **Lee MJ,** Wiater B, Bransford RJ, Bellabarba C, Chapman JR. Lordosis Restoration after Smith Petersen Osteotomies and interbody strut placement: a radiographic study in cadavers. Spine (Phila Pa 1976). 2010 Dec 1;35(25):E1487-91.
27) Guyot JP, Cizik AM, Bransford RJ, Bellabarba C, **Lee MJ**. Risk Factors for Cardiac Complications after Spine Surgery. Evidence Based Spine Journal 2010 1(2) 18-25.
28) Imposti F, Cizik AM, Bransford RJ, Bellabarba C, **Lee MJ**. Risk Factors for Pulmonary Complications after Spine Surgery. Evidence Based Spine Journal 2010 1(2) 27-33.
29) Howe C, Agel J, Bransford RJ, **Lee MJ**, Bellabarba C, Wagner TA, Chapman JR. The Morbidity and Mortality of Fusions from the Thoracic Spine to the Pelvis in the Adult Population. Spine (Phila Pa 1976). 2011 Jun 15;36(14):E936-43.
30) Bransford RJ, Russo A, Freeborn M, Nguyen Q, **Lee MJ**, Bellabarba C, Chapman J. Posterior C2 Instrumentation: Accuracy and Complications Associated with Four Techniques. Spine (Phila Pa 1976). 2011 Jun 15;36(14):E936-43.
31) **Lee MJ,** Dumonski M, Phillips FP, Voronov L, Carandang G, Renner S, Havey B, Patwardhan A**.** Disc Replacement adjacent to previous cervical fusion: A Biomechanical Comparison of Hybrid Construct vs. Two-Level Fusion. Spine (Phila Pa 1976). 2011 Feb 1.

32) Stone AT, Bransford RJ, **Lee MJ**, Vilela MD, Bellabarba C, Anderson PA, Agel J, Chapman JR. Reliability of Classification Systems For Subaxial Cervical Injuries. Evidence Based Spine-Care Journal 2011. 1(3): 19-26, December
33) **Lee MJ**, Hacquebord J, Varshney A, Cizik AM, Bransford RJ, Bellabarba C, Konodi MA, Chapman JR. Risk Factors for Medical Complication after Lumbar Spine Surgery: a multivariate analysis of 767 patients. Spine (Phila Pa 1976). 2011 Oct 1;36(21):1801-6.
34) Cizik AM, **Lee MJ,** Martin BI, Bransford RJ, Bellabarba C, Chapman JR, Mirza S. Using the Spine Surgical Invasiveness Index to Identify Risk of Surgical Site Infection: A Multivariate Analysis. JBJS (accepted for publication).
35) Reinhold M, Bransford RJ, Wagner TA, **Lee MJ**, Krengel W, Bellabarba C, Chapman JR. Your manuscript entitled Radiographic analysis of type II odontoid fractures in a geriatric patient population. Description and pathomechanism of the "Geier"-deformity. European Spine Journal. 2011 Jul 28
36) Standaert CJ, Friedly J, Rechtine G, Erwin WM, **Lee MJ**, Hendrickson N, Norvell DC. Comparative effectiveness of exercise, acupuncture, and spinal manipulation for low back pain. Spine (Phila Pa 1976). 2011 Oct 1;36(21 Suppl):S120-30.
37) Cheng J, Skelly AC, Wallace LE, **Lee MJ**, Massicotte E, Ashman B, Gruenberg M. Clinical guidelines and payer policies on treatment of chronic, nonradicular low back pain with fusion: Pilot study of an approach to critical review of quality and evidence. Spine (Phila Pa 1976). 2011 Oct 1;36(21 Suppl):S144-63.
38) Chapman JR, Norvell DC, Hermsmeyer BS, Bransford RJ, Devine J, McGirt M, **Lee MJ**. Evaluating Common Outcomes for Measuring Treatment Success for Chronic LBP. Spine (Phila Pa 1976). 2011 Oct 1;36(21 Suppl):S54-68.
39) Lohse GR, Leopold SS, Theiler S, Sayer C, Cizik AM, **Lee MJ.** Systems-Based Safety Intervention: Reducing falls with Injury and Total Falls on an Orthopaedic Ward. JBJS (accepted for publication)
40) Baker G, Cizik AM, Bransford RJ, Bellabarba C, Konodi MA, Chapman JR, **Lee MJ**. Risk Factors for Unintended Durotomy During Spine Surgery: a Multivariate Analysis. The Spine Journal (accepted for publication).
41) **Lee MJ**, Konodi MA, Cizik AM, Bransford RJ, Bellabarba C, Chapman JR. Risk Factors for Medical Complication after Spine Surgery: a multivariate analysis of 1591 patients. The Spine Journal. (accepted for publication)
42) Bransford RJ, Freeborn MA, Russo AT, **Lee MJ**, Chapman JR, Bellabarba C. Accuracy & Complications Associated with Posterior C1 Screw Fixation Techniques: A Radiographic and Clinical Assessment. The Spine Journal. (accepted for publication)

BOOKS AUTHORED/ EDITED

1) Chapman JR, **Lee MJ**, Dettori JR, Norvell DC (2011) *Measurements in Spine Care*. Stuttgart New York: Thieme Verlag. Pending Publication.
2) **Lee MJ**, Chapman JR, Dettori JR, Norvell DC *AO SPINE SMART-B Handbook*. Stuttgart New York: Thieme Verlag. In progress.
3)

B. BOOK CHAPTERS, REVIEW ARTICLES, & OTHER PUBLICATIONS

1) **Lee MJ**, Chin KR, Yoo JU, Bohlman HH. Vertebral Artery Injury During Cervical Spine Surgery. Contemporary Spine Surgery 2003. 4(5) 37-41.
2) Dean CL, **Lee MJ**, Cassinelli EH. Incidence of Cervical Stenosis: Radiographic and Anatomic. Seminars in Spine Surgery Volume 19, Issue 1 (March 2007): 12-17.
3) Cahill P, **Lee MJ**, Singh K. Degenerative Disc Disease. Orthopaedic Knowledge Update 9 (in press).
4) **Lee MJ,** Stanley T, Dumonski M, Cahill P, Singh K. Iliac Crest Bone Graft. Operative Techniques in Orthopaedic Surgery (in press).
5) Dumonski M, Stanley T, **Lee MJ**, Singh K. Posterolateral Thoracolumbar Fusion with Instrumentation. Operative Techniques in Orthopaedic Surgery (in press).
6) Stanley T , Dumonski M, **Lee MJ**, Singh K. Thoracolumbar Approach. Operative Techniques in Orthopaedic Surgery (in press).
7) Dumonski M, **Lee M**, An H. Clinical Applications: Arthrodesis & Arthroplasty: Spine. In Lindsey R, Gugala Z (Eds.), *Orthopedic implants: Applications, Complications, and Management*. Marcel Dekker, Inc. (in press).
8) **Lee MJ**, Park D, Phillips FM. XLIF Clinical Application: Degenerative Scoliosis. Extreme Lateral Interbody Fusion. Quality Medical Publishing, Inc
9) **Lee MJ,** Phillips FM**.** Kyphoplasty for the treatment of vertebral body fractures. Arthritis and Arthroplasty: The Spine. Elsevier (in press).
10) Phillips FM, **Lee MJ.** Treatment for Osteoporotic Compression Fractures. 2008 Interactive Educational Program (IEP) for Spine Fellows (www.spinefellows.com)
11) Russo A, Bransford R, Wagner T, **Lee M**, Chapman J. Adult Degenerative Scoliosis Insights – challenges – treatment outlook. *Current Orthopaedic Practice*. 19(4):357-365, August 2008.
12) **Lee MJ**, Bransford R. Spinal Manifestations of Rheumatoid Arthritis. Contemporary Spine Surgery.
13) **Lee MJ.** Introduction for Degenerative Measures: Cervical Myelopathy – AO Spine Manual: Spine Classifications and Severity Measures, AO Spine, Switzerland, 2009.
14) **Lee MJ.** Introduction for Stenosis severity measures – AO Spine Manual: Spine Classifications and Severity Measures, AO Spine, Switzerland, 2009.
15) Bransford RJ, **Lee MJ**. Contemporary Fixation Techniques in Posterior Cervical Spine Surgery Part I. Contemporary Spine Surgery.
16) Bransford RJ, **Lee MJ**. Contemporary Fixation Techniques in Posterior Cervical Spine Surgery Part II. Contemporary Spine Surgery.

17) Phillips FM, **Lee MJ**. Osteoporosis: Surgical Strategies. Rothman Simeone: The Spine 6th edition.
18) **Lee MJ**. Commentary: Dropped head syndrome: diagnosis and management. Evidence Based Spine-Care Journal. 2(2): 46, May 2011.
19) Hacquebord J, **Lee MJ**. Osteoporosis and the Aging Spine. Spine Surgery Basics. Springer (in press).
20) **Lee MJ**. Commentary: Risk Factors for Medical Complication after Lumbar Spine Surgery: a multivariate analysis of 767 patients. Spine Blog 2011 (need reference)
21)

C. SUBMITTED FOR PUBLICATION/IN PROGRESS

1. Skalak A, **Lee MJ**, Kraay MJ, Goldberg VM, Cooperman DR. Variations in Acetabular and Femoral Neck Version: Predictive of Osteoarthritis?
2. Dahl MC, Tsantrizos A, **Lee M**, Myint K, Ching RP. Hybrid, Multilevel Lumbar Spine Arthroplasty Using an *In Situ* Cured, Polyurethane Nucleus Replacement Device in Conjunction with Total Disc Replacement (submitted to Spine)
3. Dailey ES, Cizik AM, Kasten J, Chapman JR, Lee MJ. Risk Factors for Readmission of Orthopaedic Surgical Patients. Submitted to JBJS.

D. INTERNATIONAL PRESENTATION & ABSTRACTS

1) Bazaz R, **Lee MJ**, Yoo JU. Risk factors for the Development of Dysphagia after Anterior Cervical Spine Surgery. North American Spine Society 2002, Montreal, Canada
2) Goldberg VM, **Lee MJ**, Skalak A, Kraay MJ, Cooperman DR. The Spectrum of Acetabular and Femoral Version in a Population 18-35 Years of Age. International Hip Society 2005, Vienna Austria
3) Yang JY, **Lee MJ**, Park JB, Bohlman HH, Riew KD. Adjacent Level Ossification Development after Anterior Cervical Fusion without plate fixation. North American Spine Society 2005, Philadelphia PA.
4) **Lee MJ**, Bazaz R, Furey CG, Yoo JU. The Influence of Plate Design on Dysphagia in Anterior Cervical Spine Surgery: A Prospective Study. North American Spine Society 2005, Philadelphia PA
5) Eubanks JD, **Lee MJ**, Ahn N. Prevalence of lumbar facet arthrosis and its relationship to age, sex and race: an anatomic study of 647 cadaveric specimens. International Society for the Study of the Lumbar Spine, Norway 2006.
6) Eubanks JD, **Lee MJ**, Ahn N. The natural history of lumbar disc degeneration and facet arthrosis: a postmortem specimen study. International Society for the Study of the Lumbar Spine, Norway 2006.

7) **Lee MJ**, Dumonski M, Cahill P, Park D, Stanley T, Singh K. A Comparison of Complications from Vertebroplasty and Kyphoplasty: a Meta-Analysis of 124 Studies. North American Spine Society, Austin TX 2007.
8) **Lee MJ**, Garcia R, Cassinelli EH, Furey C, Riew KD. Tandem Stenosis in a Cadaveric Population. North American Spine Society, Austin TX 2007.
9) Phillips FP **, Lee MJ,** Dumonski M, Voronov L, Carandang G, Renner S, Havey B, Patwardhan A**.** Disc Replacement adjacent to previous cervical fusion: A Biomechanical Comparison of Hybrid Construct vs. Two-Level Fusion. Euro Spine Week, Geneva Switzerland 2008
10) **Lee MJ,** Bransford RJ, Bellabarba C, Chapman JR, Cohen A, Harrington R, Ching RP. The Effect of Bilateral Laminotomy vs. Laminectomy on the Motion and Stiffness of the Human Lumbar Spine. Global Spine Congress. San Francisco, 2009.
11) **Lee MJ,** Bransford RJ, Bellabarba C, Chapman JR, Cohen A, Harrington R, Ching RP. The Effect of Bilateral Laminotomy vs. Laminectomy on the Motion and Stiffness of the Human Lumbar Spine. IMAST Vienna, Austria 2009.
    a. **Nominated for Whitecloud Basic Science Award**
12) **Lee MJ**, Dahl M, Tsantrizos A, Ching RP. Hybrid, Multilevel Lumbar Spine Arthroplasty Using an In Situ Cured, Polyurethane Nucleus Replacement Device in Conjunction with Total Disc Replacement. North American Spine Society, San Francisco 2009.
13) Bransford RJ, Russo A, Freeborn M, Nguyen Q, **Lee MJ**, Chapman JR, Bellabarba C. Posterior C2 Instrumentation: Risks and Accuracy associated with 4 techniques. North American Spine Society, San Francisco 2009.
14) Russo A, Freeborn M, Nguyen Q, **Lee MJ**, Bellabarba C, Chapman J, Bransford R. Posterior C2 Instrumentation: Risks and Complications. Global Spine Congress. San Francisco 2009.
15) **Lee MJ,** Bransford RJ, Bellabarba C, Chapman JR, Cohem A, Harrington R, Ching RP. The Effect of Bilateral Laminotomy vs. Laminectomy on the Motion and Stiffness of the Human Lumbar Spine. Global Spine Congress. San Francisco 2009.
16) **Lee MJ,** Bransford RJ, Bellabarba C, Chapmah JR, Cohem A, Harrington R, Ching RP. The Effect of Bilateral Laminotomy vs. Laminectomy on the Motion and Stiffness of the Human Lumbar Spine. EuroSpine. Warsaw Poland, 2009.
17) **Lee MJ,** Varshney A, Cizik AM, Bransford, RJ, Bellabarba C, Chapman JR. Medical Complications after cervical spine surgery: A multivariate analysis of a prospective cohort. Global Spine Congress. Barcelona, Spain 2011.
18) Bellabarba C, Ries A, Bransford RJ, **Lee MJ,** Agel J, Vilela M, Chesnut R, Chapman JR. Diagnosis and treatment of craniocervical dissociation in 48 consecutive survivors. Global Spine Congress. Barcelona, Spain 2011.
19) Bransford RJ, Freeborn MA, **Lee M**J, Russo AJ, Nguyen QT, Bellabarba C, Chapman JR. Accuracy and complications associated with posterior C1 screw fixation techniques: A radiographic and clinical assessment. Global Spine Congress. Barcelona, Spain 2011.

20) **Lee MJ,** Varshney A, Cizik AM, Bransford, RJ, Bellabarba C, Chapman JR. Medical Complications after lumbar spine surgery: A multivariate analysis of a prospective cohort. Global Spine Congress. Barcelona, Spain 2011.
21) **Lee MJ,** Baker G, Cizik AM, Bransford, RJ, Bellabarba C, Chapman JR. Risk factors for dural tear during spine surgery: a mutlrivariate analysis of a prospective cohort of 1591 patients. Global Spine Congress. Barcelona, Spain 2011.
22) Bellabarba C, Kent R, Bransford RJ, **Lee MJ**, Agel J, Chapman JR. Continued experiences with decompression and lumbopelvic fixation for sacral facture dislocation with spino-pelvic dissociation. Global Spine Congress. Barcelona, Spain 2011.

E. NATIONAL PRESENTATIONS & ABSTRACTS

1) Nalepka JL, **Lee MJ**, Kraay MJ, Marcus RE, Goldberg VM,Greenfield EM: Detection of bacterial lipopolysaccharide in periprosthetic tissue from patients with aseptic loosening. *Trans*. ORS 29: 1514, 2004.
2) **Lee MJ**, Bazaz, Furey CG, Yoo JU. The Incidence of Dysphagia in Anterior Cervical Surgery as a Function of Plate Design: A Prospective Study. Cervical Spine Research Society 2004, Boston MA.
    a. **Nominated for J. William Fielding Award**
3) Smith MV, Innocenti MA, **Lee MJ**, Rohrer JL, Sobieraj MC, Greenfield EM. The PI3K/AKT Pathway Mediates the Biological Activity of Titanium Particles. Orthopaedic Research Society 2005, Washington DC
4) Nalepka JL, **Lee MJ**, Marcus RE, Goldberg VM, Chen X, Greenfield EM. Lipopolysaccharide Exists in Periprosthetic Tissue from a Subset of Patients with Aseptic Loosening. Orthopaedic Research Society 2005, Washington DC
5) **Lee MJ**, Cassinelli E, Riew KD. The Feasibility of Inserting Atlas Lateral Mass Screws via the Posterior Arch. Cervical Spine Research Society 2005, San Diego CA.
6) Cassinelli EH, **Lee MJ**, Skalak AF, Bohlman HH, Ahn N. Anatomic Considerations for the Placement of C2 Intra-laminar Screws. Cervical Spine Research Society 2005, San Diego CA.
7) Skalak, AF; **Lee, MJ**; Goldberg, VM; Haille-Sallase, J, Cooperman. Quantifying Acetabular Version Using a Three-Dimensional Digitizer. Orthopaedic Research Society 2006, Chicago IL.
8) **Lee MJ**, Cassinelli E, Riew KD. The incidence of cervical stenosis: a skeletal study of 469 cadaveric specimens. Cervical Spine Research Society, Florida 2006
9) Cassinelli EH, **Lee MJ**, Ahn N, Robbins M. Pre-operative planning using Computed Tomography for Placement of C2 Laminar Screws. Cervical Spine Research Society, Florida 2006.
10) **Lee MJ**, Cassinelli E, Riew KD. The incidence of cervical stenosis: a skeletal study of 469 cadaveric specimens. American Academy of Orthopaedic Surgeons, San Diego 2007.

11) Skalak A, **Lee MJ**, Cooperman DR. Relationships Between Proximal Femoral and Acetabular Anatomy in a Nonarthritic Population. Orthopaedic Research Society, San Diego 2007.
12) **Lee MJ,** Dumonski M, Phillips FP, Voronov L, Carandang G, Renner S, Havey B, Patwardhan A**.** Disc Replacement adjacent to previous cervical fusion: A Biomechanical Comparison of Hybrid Construct vs. Two-Level Fusion. Combined Meeting for Orthopaedic Research Societies. Honolulu HI 2007
13) **Lee MJ**, Garcia R, Cassinelli EH, Furey C, Riew KD. Tandem Stenosis in a Cadaveric Population. Cervical Spine Research Society, San Francisco 2007.
    a. **Nominated for J. William Fielding Award**
14) **Lee MJ,** Dumonski M, Phillips FP, Voronov L, Carandang G, Renner S, Havey B, Patwardhan A**.** Disc Replacement adjacent to previous cervical fusion: A Biomechanical Comparison of Hybrid Construct vs. Two-Level Fusion. Cervical Spine Research Society, San Francisco 2007.
15) Garcia R, **Lee MJ**, Cassinelli EH, Furey C, Riew KD. Tandem Stenosis in a Cadaveric Population. American Academy of Orthopaedic Surgeons, San Francisco 2008.
16) **Lee MJ,** Dumonski M, Phillips FP, Voronov L, Carandang G, Renner S, Havey B, Patwardhan A**.** Disc Replacement adjacent to previous cervical fusion: A Biomechanical Comparison of Hybrid Construct vs. Two-Level Fusion. Orthopaedic Research Society, San Francisco 2008.
17) **Lee MJ,** Dumonski M, Phillips FP, Voronov L, Carandang G, Renner S, Havey B, Patwardhan A**.** Disc Replacement adjacent to previous cervical fusion: A Biomechanical Comparison of Hybrid Construct vs. Two-Level Fusion. Spinal Arthroplasty Society, Miami FL 2008.
18) Cahill PJ, Warnick DR, **Lee MJ**, Vogel LC, Hammerberg KW, Sturm PF. 30 Years of Experience of Infections in Pediatric Neuromuscular Spinal Deformity Surgery. Scoliosis Research Society, Salt Lake City, Utah 2008.
19) Russo A, Freeborn M, Nguyen Q, **Lee MJ**, Bellabarba C, Chapman J, Bransford R. Posterior C2 Instrumentation: Risks and Complications. Cervical Spine Research Society. Austin TX 2008.
20) **Lee MJ,** Bransford RJ, Bellabarba C, Chapmah JR, Cohem A, Harrington R, Ching RP. The Effect of Bilateral Laminotomy vs. Laminectomy on the Motion and Stiffness of the Human Lumbar Spine. Lumbar Spine Research Society. Chicago 2009.
21) Park DK, **Lee MJ**, Lin EL, Braaksma B, An HS, Phillips FM. The relationship of Intra-Psoas Nerves during a Trans-Psoas Approach to the Lumbar Spine: Anatomical Study. Lumbar Spine Research Society. Chicago, 2009.
22) Chen MR, **Lee MJ**, Cooperman DR, Moore TA. Anatomic variability of 120 L5 spondylolytic defects. Lumbar Spine Research Society. Chicago, 2009.

F. LOCAL PRESENTATIONS & ABSTRACTS

1. Sontich JK, **Lee MJ**, Cannada L, Patterson BM. Infected Nonunions with Bone Loss Treated With Ilizarov Bone Transport Technique. Ohio Orthopaedic Society 2003, Cincinnati OH

2. **Lee MJ**, Bazaz R, Furey CG, Yoo JU. The Influence of Plate Design on Dysphagia in Anterior Cervical Spine Surgery: A Prospective Study. Cleveland Orthopaedic Society 2005, Cleveland OH
3. Smith MV, Innocent MA, **Lee MJ**, Rohrer JL, Sobieraj MC, Greenfield EM. The PI3K/AKT Pathway Mediates the Biological Activity of Titanium Particles. Cleveland Orthopaedic Society 2005, Cleveland OH
4. **Lee MJ**, Bazaz R, Furey CG, Yoo JU. The Influence of Plate Design on Dysphagia in Anterior Cervical Spine Surgery: A Prospective Study. Ohio Orthopaedic Society 2005, Columbus OH
5. **Lee MJ**, Skalak A, Kraay MJ, Goldberg VM, Cooperman DR. Decreased Acetabular Version is a Condition of Young Men. Cleveland Orthopaedic Society 2006, Cleveland OH.
6. Eubanks JD, **Lee MJ**, Ahn N. The natural history of lumbar disc degeneration and facet arthrosis: a postmortem specimen study. Reich Lectureship 2006. Lutheran Hospital, Cleveland OH
7. **Lee MJ**, Skalak A, Kraay MJ, Goldberg VM, Cooperman DR. Decreased Acetabular Version is a Condition of Young Men. Reich Lectureship 2006. Lutheran Hospital, Cleveland OH
8. **Lee MJ,** Bransford RJ, Bellabarba C, Chapman JR, Cohem A, Harrington R, Ching RP. The Effect of Bilateral Laminotomy vs. Laminectomy on the Motion and Stiffness of the Human Lumbar Spine. Western Orthopaedic Society, Seattle WA. 2009
9. Lohse GR, Leopold SS, Theiler S, Sayer C, Cizik AM, **Lee MJ.** Systems-Based Safety Intervention: Reducing falls with Injury and Total Falls on an Orthopaedic Ward. JBJS (accepted for publication) – ***2nd place Washington State Orthopaedic Association Competition 2010***
10. Dailey ES, Cizik AM, Kasten J, Chapman JR, **Lee MJ**. Risk Factors for Readmission of Orthopaedic Surgical Patients. Submitted to JBJS. ***2nd place Washington State Orthopaedic Association Competition 2011***
11.

Washington State
Health Care Authority

Participant Conflict Disclosure

Introduction

The HTCC Workgroup is a public service workgroup established to safeguard the public interest by identifying medical tests and treatments where evidence shows they are safe, effective, and cost-effective. Balance, independence, objectivity and scientific rigor are a basis for public trust and crucial to the credibility and integrity of decisions.

Guiding Principle

Conflict of Interest decisions must be disclosed and balanced to ensure the integrity of decisions while acknowledging the reality that interests, and sometimes even conflicting interests, do exist. Individuals that stand to gain or lose financially or professionally, or have a strong intellectual bias need to disclose such conflicts.

> *For example*, the fact that a member or stakeholder is a health care provider that may use a service under review creates a potential conflict. However, clinical and practical knowledge about a service is also useful, and may be needed in the decision making.

Procedure

Declaration of real or potential conflicts of interest, professional, intellectual, or financial is required prior to membership or provision of written or verbal commentary. Participants must sign a conflict of interest form; stakeholders providing comment must disclose conflicts.

The HTCC Chair or HCA Administrator shall make a decision, in his/her sole discretion, as to whether a conflict of interest rises to the level that participation by the conflicted participant could result in a loss of public trust or would significantly damage the integrity of the decision.

HCA defines conflict of interest as any situation in which a voting member or anyone who provides written or verbal testimony regarding products, services, or technologies discussed or voted on during the workgroup meeting, has a relationship with a manufacturer of any commercial products and / or provider of services discussed or voted on during the meeting. Relationship extends to include immediate family member(s) and / or any entity in which the member or person testifying may have an interest.

A relationship is considered as:

1. Receipt or potential receipt of anything of monetary value, including but not limited to, salary or other payments for services such as consulting fees or honoraria in excess of $10,000.
2. Equity interests such as stocks, stock options or other ownership interests in excess of $10,000 or 5% ownership, excluding mutual funds and blinded trusts.
3. Status of position as an officer, board member, trustee, owner or employee of a company or organization representing a company, association or interest group.
4. Loan or debt interest; or intellectual property rights such as patents, copyrights and royalties from such rights.
5. Manufacturer or industry support of research in which you are participating.
6. Any other relationship that could reasonably be considered a financial, intellectual, or professional conflict of interest.
7. Representation: if representing a person or organization, include the organization's name, purpose, and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).
8. Travel: if an organization or company has financially paid your travel accommodations (e.g. airfare, hotel, meals, private vehicle mileage, etc).

Washington State Health Care Authority

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000	X	
2.	Equity interests such as stocks, stock options or other ownership interests		X
3.	Status or position as an officer, board member, trustee, owner		X
4.	Loan or intellectual property rights		X
5.	Research funding		X
6.	Any other relationship, including travel arrangements		X

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

I am a consultant for Zimmer Holdings.

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).		X

7. If yes, Provide Name and Funding Sources: _____

If you believe that you do not have a conflict but are concerned that it may appear that you do, you may ***attach additional sheets*** explaining why you believe that you should not be excluded.

I certify that I have read and understand this Conflict of Interest Form and that the information I have provided is true, complete, and correct as of this date.

X _____ 27 FEB 12 Richard Rooney

Signature *Date* *Print Name*

FOR QUESTIONS: Denise Santoyo, Health Care Authority, 360-923-2742,

Washington State Health Care Authority

Participant Conflict Disclosure

Introduction

The HTCC Workgroup is a public service workgroup established to safeguard the public interest by identifying medical tests and treatments where evidence shows they are safe, effective, and cost-effective. Balance, independence, objectivity and scientific rigor are a basis for public trust and crucial to the credibility and integrity of decisions.

Guiding Principle

Conflict of Interest decisions must be disclosed and balanced to ensure the integrity of decisions while acknowledging the reality that interests, and sometimes even conflicting interests, do exist. Individuals that stand to gain or lose financially or professionally, or have a strong intellectual bias need to disclose such conflicts.

> *For example,* the fact that a member or stakeholder is a health care provider that may use a service under review creates a potential conflict. However, clinical and practical knowledge about a service is also useful, and may be needed in the decision making.

Procedure

Declaration of real or potential conflicts of interest, professional, intellectual, or financial is required prior to membership or provision of written or verbal commentary. Participants must sign a conflict of interest form; stakeholders providing comment must disclose conflicts.

The HTCC Chair or HCA Administrator shall make a decision, in his/her sole discretion, as to whether a conflict of interest rises to the level that participation by the conflicted participant could result in a loss of public trust or would significantly damage the integrity of the decision.

HCA defines conflict of interest as any situation in which a voting member or anyone who provides written or verbal testimony regarding products, services, or technologies discussed or voted on during the workgroup meeting, has a relationship with a manufacturer of any commercial products and / or provider of services discussed or voted on during the meeting. Relationship extends to include immediate family member(s) and / or any entity in which the member or person testifying may have an interest.

A relationship is considered as:

1. Receipt or potential receipt of anything of monetary value, including but not limited to, salary or other payments for services such as consulting fees or honoraria in excess of $10,000.
2. Equity interests such as stocks, stock options or other ownership interests in excess of $10,000 or 5% ownership, excluding mutual funds and blinded trusts.
3. Status of position as an officer, board member, trustee, owner or employee of a company or organization representing a company, association or interest group.
4. Loan or debt interest; or intellectual property rights such as patents, copyrights and royalties from such rights.
5. Manufacturer or industry support of research in which you are participating.
6. Any other relationship that could reasonably be considered a financial, intellectual, or professional conflict of interest.
7. Representation: if representing a person or organization, include the organization's name, purpose, and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).
8. Travel: if an organization or company has financially paid your travel accommodations (e.g. airfare, hotel, meals, private vehicle mileage, etc).

Washington State Health Care Authority

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000		XX
2.	Equity interests such as stocks, stock options or other ownership interests		XX
3.	Status or position as an officer, board member, trustee, owner		XX
4.	Loan or intellectual property rights		XX
5.	Research funding		XX
6.	Any other relationship, including travel arrangements		XX

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

_____

_____

_____

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).		XX

7. If yes, Provide Name and Funding Sources: _____

_____

_____

_____

If you believe that you do not have a conflict but are concerned that it may appear that you do, you may ***attach additional sheets*** explaining why you believe that you should not be excluded.

I certify that I have read and understand this Conflict of Interest Form and that the information I have provided is true, complete, and correct as of this date.

X John Ratliff Digitally signed by John Ratliff DN: cn=John Ratliff, o=Stanford University, ou, email=jratliff@stanford.edu, c=US Date: 2012.02.23 22:04:31 -08'00' 2-23-12 John Ratliff, MD

Signature *Date* *Print Name*

FOR QUESTIONS: Denise Santoyo, Health Care Authority, 360-923-2742,
PO Box 42712, Olympia, WA 98504-2712

Washington State Health Care Authority

Health Technology Assessment

Bone Morphogenetic Proteins for Spinal Fusion

Clinical Committee Meeting
March 16, 2012

Representing

- American Association of Neurological Surgeons
  - Founded in 1931 as the Harvey Cushing Society, the AANS is a scientific and educational association with over 8,000 members worldwide.
  - The AANS is dedicated to advancing the specialty of neurological surgery in order to provide the highest quality of neurosurgical care to the public.
- Congress of Neurological Surgeons
  - The CNS, with nearly 8,000 members across the globe, is a leader in education and innovation and is dedicated to advancing neurosurgery by providing members with the educational and career development opportunities they need to become leaders and innovators in the field.

Outline

- Limit our discussion to the Health Technology Assessment
- Respond to the 5 “Key Questions” provided by the HTA in order

Position

- rhBMPs are a comparably safe and effective bone graft alternative appropriate in patients with medical indications as determined by their treating surgeon
- FDA approval of on-label BMP use evidenced equivalent or superior fusion rates, shorter operative times, and decreased bone donor site complications

Position

- The literature supports use of rhBMPs for single level anterior lumbar interbody fusions and posterior lumbar interbody fusions
- rhBMPs may be considered an appropriate bone graft substitute for single-level posterolateral fusions

Question 1: Expected Outcomes and Validated Instruments

- The HTA notes 3 outcome measures are commonly used in the literature
  - Short form 36 (SF-36)
  - Oswestry disability index (ODI)
  - Visual analogue pain scale (VAS)
- Only the SF-36 has been validated in assessment of spine patients

Question 1: Expected Outcomes and Validated Instruments

- Prospective registry of spine surgery patients is under development
  - National Neurosurgery Quality and Outcomes Database (N2QOD)
  - Foundation for N2QOD outcomes reporting:
    - VAS, ODI, Euro-Qol 5D (EQ-5D), and the North American Spine Society Patient Satisfaction Index
- Ongoing research into optimal capture of patient outcomes

Question 2: Efficacy and Effectiveness of BMP

- HTA thoroughly reviews the literature on the use of rhBMP-2 and rhBMP-7 in the cervical and lumbar spine, reviewing both on-label and off-label reports
- The HTA concludes there is evidence in the literature to support both efficacy and effectiveness of on-label and off-label rhBMP-2 in the lumbar and cervical spine
  - There is literature support as well for off-label use of rhBMP-7 in the lumbar spine
- These conclusions echo the positions held by the AANS and CNS

Question 2: Efficacy and Effectiveness of BMP

- Initial studies assessing rhBMP were designed to demonstrate non-inferiority
- Spine have, and continue, to develop greater clinical proficiency in use of rhBMPs
- The level of evidence supporting use of rhBMPs likely will increase as our experience in using these agents matures

Question 3: Safety

- The HTA notes significant complications associated with rhBMP use in the anterior cervical spine
  - Adjunct use of steroids and decreased use of rhBMP in anterior cervical procedures have decreased the incidence of this complication
- There are significant potential complications with autograft bone harvest

Question 3: Safety

- With the exception of anterior cervical procedures, the literature does not support that complication rates in patients undergoing spine fusions with rhBMP, either on label or off label, are significantly higher than in those patients undergoing autograft harvest
- Beyond case reports and editorial opinions, there is no literature that provides a causal relationship between rhBMP and increased complication risk

Question 4: Differential Efficacy

- The HTA notes there is limited evidence of the differential effectiveness of spinal fusion in subpopulations
  - Smokers
  - Multiple comorbidities
  - Other medical conditions impairing fusion
- Exclusion criteria for many initial studies would have eliminated these patients
- Hence only more recent reports will provide this data

Question 4: Differential Efficacy

- Reports have noted significantly higher fusion rates in smokers undergoing fusion with rhBMP in comparison to autograft harvest
- Extensive reconstructions and multilevel surgeries may also benefit from rhBMP use

Question 4: Differential Efficacy

- Poor evidence may represent spine surgeons developing proficiencies and greater understanding of the appropriate use of rhBMP
- Lack of level 1 evidence should not discount the potential benefit of rhBMP in these patients, especially in patients with challenging medical conditions

Question 5: Cost effectiveness

- Costs of rhBMP are greater than the costs of autograft
- Cost analysis studies in the US and Europe have shown that rhBMP overall produces a cost savings
  - Decreased complications from autograft harvest
  - Quicker rehab
  - Decreased hospital length of stay
  - Decreased narcotic use after surgery
  - Fewer revision surgeries

Conclusion

- We appreciate the opportunity to review the Washington State HTA
- The AANS and CNS believe, based upon review of the literature, that rhBMP is a viable alternative to autograft in clinically appropriate cases, as chosen by treating surgeons

Conclusions

- The full potential of rhBMP has yet to be determined
- There are many patients where rhBMP will maximize potential for successful clinical outcomes and restore greater quality of life

Contributors

- John Ratliff, MD, FACS, *Associate Professor, Stanford University*
- Joseph Cheng, MD, FACS, *Associate Professor, Vanderbilt University*
- Karin R. Swartz, MD, *Associate Professor, University of Kentucky*
- Daniel Hoh, MD, FACS, *Assistant Professor, University of Florida Gainesville*
- D. Kojo Hamilton, MD, *Assistant Professor, University of Maryland School of Medicine*
- Charles Sansur, MD, *Assistant Professor, University of Maryland*
- Luis Tumialan, MD, *Assistant Professor, Barrow Neurological Institute*
- Cathy Hill, *Senior Manager for Regulatory Affairs, AANS/CNS*
- Paul McCormick, MD, MPH, *President, American Association of Neurological Surgeons*
- Christopher Wolfla, MD, *President, Congress of Neurological Surgeons*

Thank you

John Ratliff, MD, FACS
Associate Professor
Stanford University Department of Neurosurgery
Stanford, CA

Washington State Health Care Authority

Participant Conflict Disclosure

Introduction

The HTCC Workgroup is a public service workgroup established to safeguard the public interest by identifying medical tests and treatments where evidence shows they are safe, effective, and cost-effective. Balance, independence, objectivity and scientific rigor are a basis for public trust and crucial to the credibility and integrity of decisions.

Guiding Principle

Conflict of Interest decisions must be disclosed and balanced to ensure the integrity of decisions while acknowledging the reality that interests, and sometimes even conflicting interests, do exist. Individuals that stand to gain or lose financially or professionally, or have a strong intellectual bias need to disclose such conflicts.

> *For example,* the fact that a member or stakeholder is a health care provider that may use a service under review creates a potential conflict. However, clinical and practical knowledge about a service is also useful, and may be needed in the decision making.

Procedure

Declaration of real or potential conflicts of interest, professional, intellectual, or financial is required prior to membership or provision of written or verbal commentary. Participants must sign a conflict of interest form; stakeholders providing comment must disclose conflicts.

The HTCC Chair or HCA Administrator shall make a decision, in his/her sole discretion, as to whether a conflict of interest rises to the level that participation by the conflicted participant could result in a loss of public trust or would significantly damage the integrity of the decision.

HCA defines conflict of interest as any situation in which a voting member or anyone who provides written or verbal testimony regarding products, services, or technologies discussed or voted on during the workgroup meeting, has a relationship with a manufacturer of any commercial products and / or provider of services discussed or voted on during the meeting. Relationship extends to include immediate family member(s) and / or any entity in which the member or person testifying may have an interest.

A relationship is considered as:

1. Receipt or potential receipt of anything of monetary value, including but not limited to, salary or other payments for services such as consulting fees or honoraria in excess of $10,000.
2. Equity interests such as stocks, stock options or other ownership interests in excess of $10,000 or 5% ownership, excluding mutual funds and blinded trusts.
3. Status of position as an officer, board member, trustee, owner or employee of a company or organization representing a company, association or interest group.
4. Loan or debt interest; or intellectual property rights such as patents, copyrights and royalties from such rights.
5. Manufacturer or industry support of research in which you are participating.
6. Any other relationship that could reasonably be considered a financial, intellectual, or professional conflict of interest.
7. Representation: if representing a person or organization, include the organization's name, purpose, and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).
8. Travel: if an organization or company has financially paid your travel accommodations (e.g. airfare, hotel, meals, private vehicle mileage, etc).

Washington State Health Care Authority

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000	XX	
2.	Equity interests such as stocks, stock options or other ownership interests		XX
3.	Status or position as an officer, board member, trustee, owner		XX
4.	Loan or intellectual property rights		XX
5.	Research funding		XX
6.	Any other relationship, including travel arrangements		XX

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

_____Synthes-Teaching Honorarium_____

_____Medtronic-Teaching Honorarium _____

_____

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).		XX

7. If yes, Provide Name and Funding Sources: _____

_____

_____

_____

If you believe that you do not have a conflict but are concerned that it may appear that you do, you may ***attach additional sheets*** explaining why you believe that you should not be excluded.

I certify that I have read and understand this Conflict of Interest Form and that the information I have provided is true, complete, and correct as of this date.

X Trent L. Tredway 2/28/2012 Trent L, Tredway, MD

Signature *Date* *Print Name*

FOR QUESTIONS: Denise Santoyo, Health Care Authority, 360-923-2742,

Washington State Health Care Authority

PO Box 42712, Olympia, WA 98504-2712

Washington State Health Care Authority

Participant Conflict Disclosure

Introduction

The HTCC Workgroup is a public service workgroup established to safeguard the public interest by identifying medical tests and treatments where evidence shows they are safe, effective, and cost-effective. Balance, independence, objectivity and scientific rigor are a basis for public trust and crucial to the credibility and integrity of decisions.

Guiding Principle

Conflict of Interest decisions must be disclosed and balanced to ensure the integrity of decisions while acknowledging the reality that interests, and sometimes even conflicting interests, do exist. Individuals that stand to gain or lose financially or professionally, or have a strong intellectual bias need to disclose such conflicts.

> *For example,* the fact that a member or stakeholder is a health care provider that may use a service under review creates a potential conflict. However, clinical and practical knowledge about a service is also useful, and may be needed in the decision making.

Procedure

Declaration of real or potential conflicts of interest, professional, intellectual, or financial is required prior to membership or provision of written or verbal commentary. Participants must sign a conflict of interest form; stakeholders providing comment must disclose conflicts.

The HTCC Chair or HCA Administrator shall make a decision, in his/her sole discretion, as to whether a conflict of interest rises to the level that participation by the conflicted participant could result in a loss of public trust or would significantly damage the integrity of the decision.

HCA defines conflict of interest as any situation in which a voting member or anyone who provides written or verbal testimony regarding products, services, or technologies discussed or voted on during the workgroup meeting, has a relationship with a manufacturer of any commercial products and / or provider of services discussed or voted on during the meeting. Relationship extends to include immediate family member(s) and / or any entity in which the member or person testifying may have an interest.

A relationship is considered as:

1. Receipt or potential receipt of anything of monetary value, including but not limited to, salary or other payments for services such as consulting fees or honoraria in excess of $10,000.
2. Equity interests such as stocks, stock options or other ownership interests in excess of $10,000 or 5% ownership, excluding mutual funds and blinded trusts.
3. Status of position as an officer, board member, trustee, owner or employee of a company or organization representing a company, association or interest group.
4. Loan or debt interest; or intellectual property rights such as patents, copyrights and royalties from such rights.
5. Manufacturer or industry support of research in which you are participating.
6. Any other relationship that could reasonably be considered a financial, intellectual, or professional conflict of interest.
7. Representation: if representing a person or organization, include the organization's name, purpose, and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).
8. Travel: if an organization or company has financially paid your travel accommodations (e.g. airfare, hotel, meals, private vehicle mileage, etc).

Washington State Health Care Authority

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000		X
2.	Equity interests such as stocks, stock options or other ownership interests		X
3.	Status or position as an officer, board member, trustee, owner		X
4.	Loan or intellectual property rights		X
5.	Research funding		X
6.	Any other relationship, including travel arrangements		X

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).		X

7. If yes, Provide Name and Funding Sources: _____

If you believe that you do not have a conflict but are concerned that it may appear that you do, you may ***attach additional sheets*** explaining why you believe that you should not be excluded.

I certify that I have read and understand this Conflict of Interest Form and that the information I have provided is true, complete, and correct as of this date.

X _____ 2/21/12

Signature *Date*

JOHN K SHUSTER MD
NPI 1710955307
PH(509)343-3915
FAX232-8456 LIC36590

Print Name

FOR QUESTIONS: Denise Santoyo, Health Care Authority, 360-923-2742,

Washington State
Health Care Authority

PO Box 42712, Olympia, WA 98504-2712

Role of BMP in Spinal Fusion

John K. Shuster MD
Northwest Orthopedic Specialists
Spokane, Washington
(that's on the east side of the state)

1

Disclosure

- I have no financial relationship with any orthopedic implant company
- I only use BMP in the anterior or lateral approach, placed in a confined cage in the disc space I wish to fuse

2

My Background

- Northwestern University, Evanston, IL
  - B.S. Biomedical Engineering, 1987
- University of Chicago, Pritzker School of Medicine
  - M.D. 1991
- Loyola University, Maywood, IL
  - Orthopedic Residency, 1996
- Emory University Spine Center
  - Spine fellowship, 1997
- University of South Carolina
  - Director of Spine Service 1997-98
- Northwest Orthopedic Specialists
  - 1998-Present

3

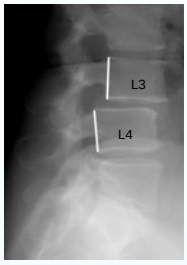
Key Points

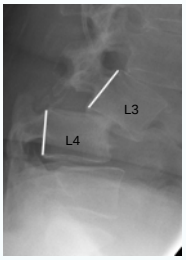
- Safety
- Efficacy
- Cost

4

Why do we do spine fusion?

- At it's most basic, to stop abnormal motion



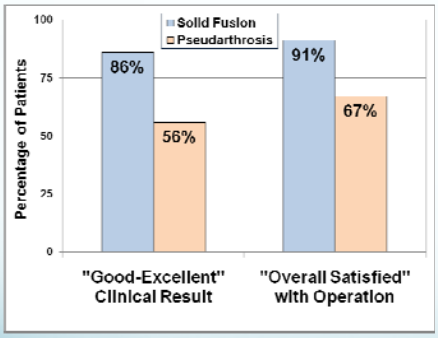


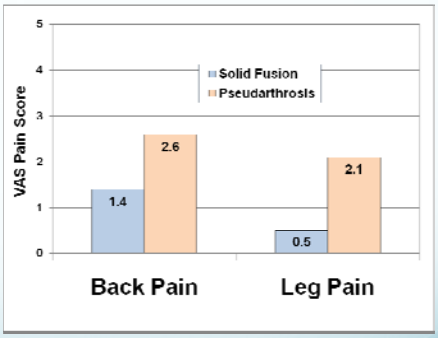
- In some patients, abnormal motion causes pain
- Some have pain without abnormal motion
- Some have abnormal motion without pain

5

Achieving a solid fusion is critical

Long term clinical follow-up (7.7 years post-surgery) of degenerative spondylolisthesis patients who ended up with a solid fusion vs a pseudarthrosis



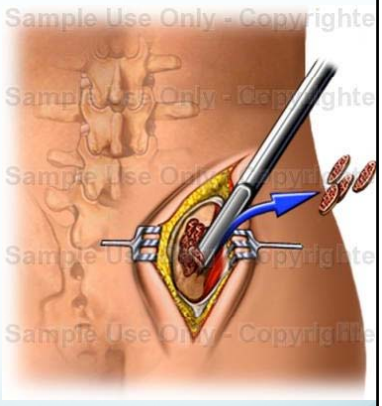


Kornblum, Spine 2004

6

Previous sources of bone for fusion

- Autograft “Self” graft
  - Tibial Autograft (1911, Albee)
  - Iliac crest (8-15% donor site, limited volume)
    - Morbidity, time for harvest
  - Recycle the bone that was removed while taking pressure off the nerves
- Cadaveric Allograft
  - Cost
  - Unlimited supply
  - Disease transmission (rare)
  - Variable effectiveness
- Xenograft “Strange” graft
  - Porcine, bovine, Pachyderm (yes, ivory)



7

rhBMP-2

- Approved 2002
- On label is in a specific device at the lower two lumbar levels, L4-5 and l5-S1
- Anterior fusion
- Away from the nerves
- Confined space
- “Osteoinductive”
- Induces stem cells

8

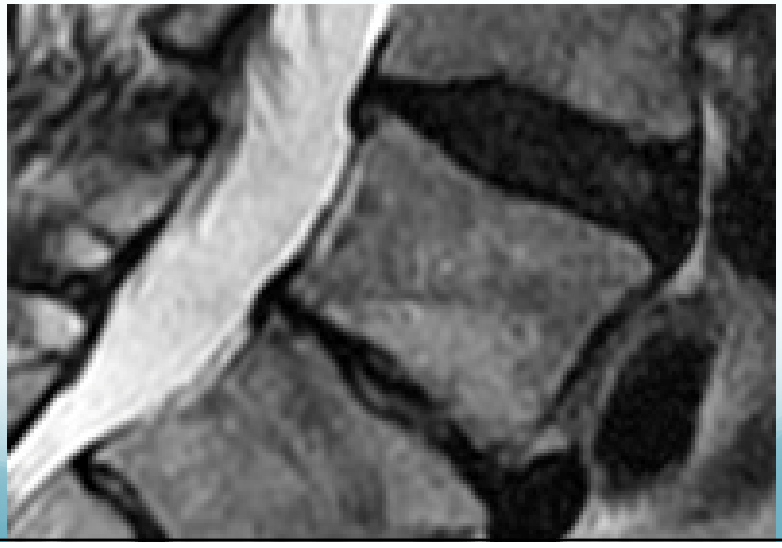
What do we do with it?

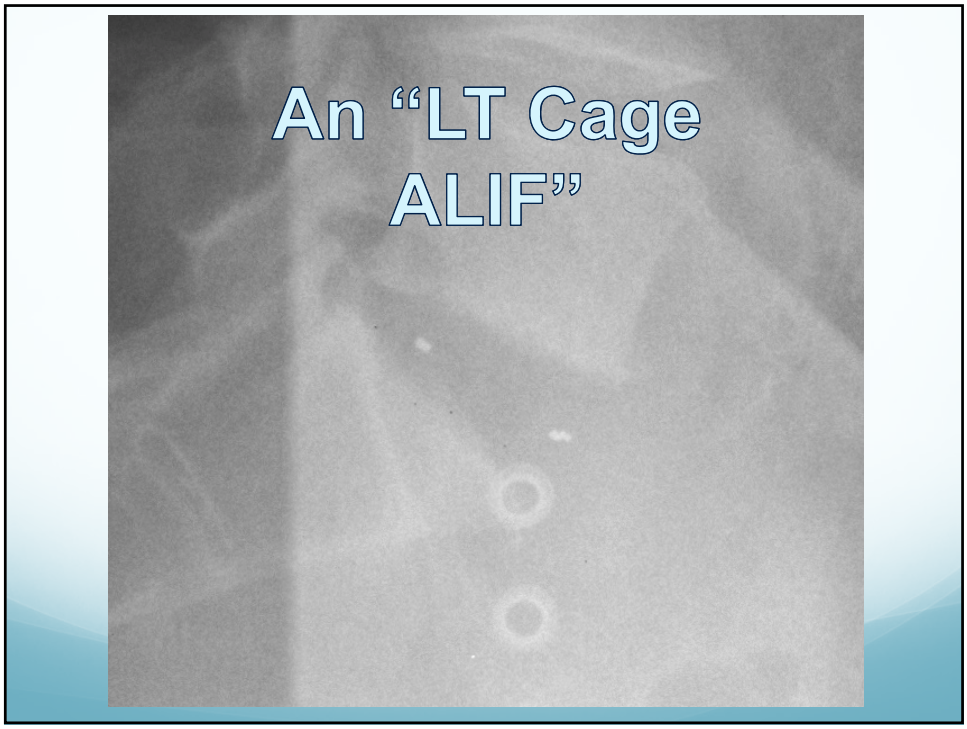
- We solve problems that previously had a lower healing rate and greater cost and morbidity
- We eliminate:
  - Donor site morbidity
  - Infected graft sites and cost to clean them up ($100K)
  - Chronic donor site pain
  - Uncosmetic divots in one's low back
  - 30-60" of operating room time (at $1500 per hour for the room, anesthesia, nurses, CRNAs,)
- I only use BMP in the anterior or lateral approach, placed in a confined cage in the disc space I wish to fuse

9

What do we do with it?

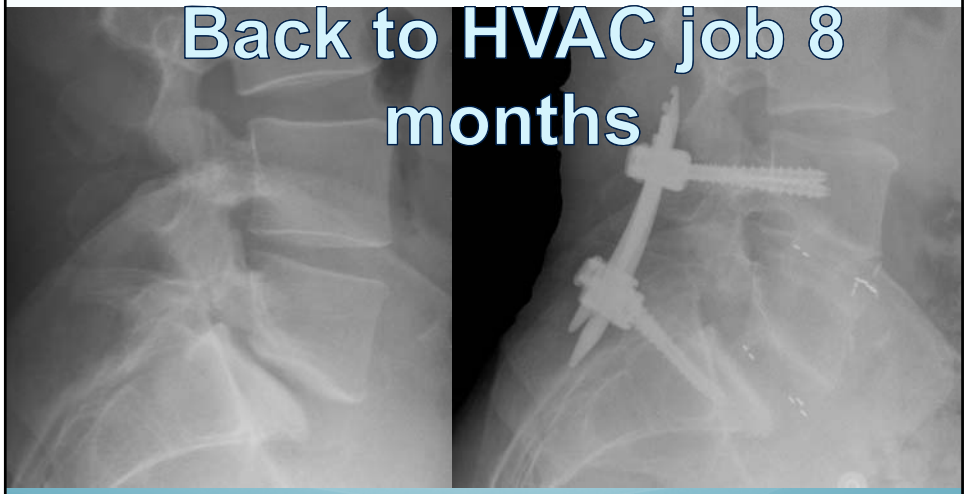
- 60 yr old Male, can't sit, drive or sleep due to back and leg pain




An “LT Cage ALIF”


Remarkable Pain Reduction

45 yr old laborer



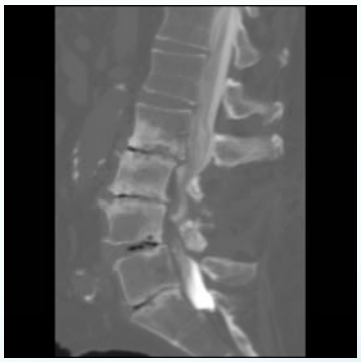
BMP is the most effective alternative for growing bone that we have

- When a patient has had a prior laminectomy, we can't use the patients bone that we normally would have
- Scarring from prior posterior surgery often dictates we must use an anterior surgery to achieve fusion safely

14

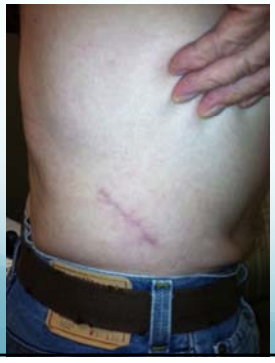
A Scarred Laminectomy

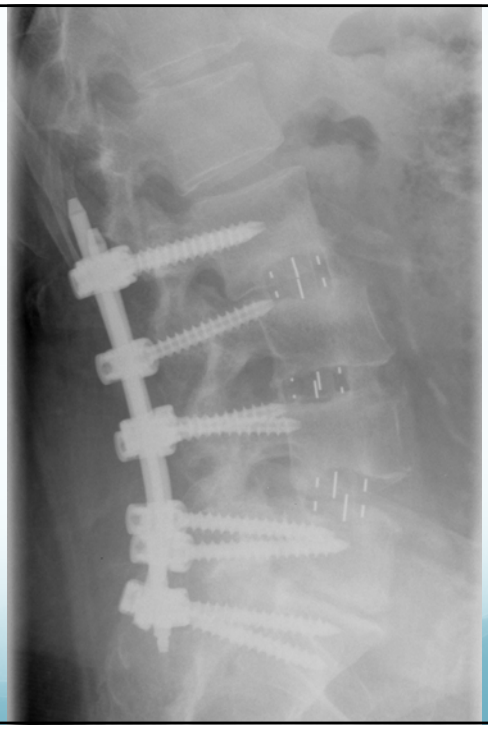
- 65 year old with 4 prior laminectomies
- 4 levels collapsed and scarred
  - Couldn't walk one block
  - Couldn't stand at the sink to brush his teeth



15

- He walked the U.S. Open 2 months after fusion with BMP





BMP-2 is safe and effective

Burkus 2002

- 279 patients fused with cages anteriorly
  - BMP: 94.5%
  - Autograft: 88.7%
- This study led to FDA approval in 2002

Results are Durable

Burkus 2009

- At six years 98% of the patients had a solid fusion
- Significant improvements in ODI and SF-36 were seen at 6 weeks and were present at 6 years
- At the time of the surgery, 52% of the patients were working
  - At 6 months, 63%
  - At 6 years, 68%

17

Is it safe?

- Packaging recommends against use in nursing mothers and osteosarcoma patients
- Every spine surgeon I know:
  - Does not believe that it results in a higher incidence of retrograde ejaculation
  - Does not think that it "causes" de Novo tumors of any sort
  - Understands that it has greater risks when used in an anterior cervical or posterior lumbar application due to it's ability to form bone in an unconfined space

18

What do most spine surgeons think?

- When used in a confined space, BMP allows us to achieve a solid fusion in a better way than we have had before and for ultimately a lower cost
- The intangibles are hard to measure, but the “feeling” among surgeons, and informed patients, is that BMP improves spine care
- Technologies such as this, with track records as good as this should be supported
- The loss of BMP as a option will lead to a giant step backward in spine care in Washington State

19

Thank you

- Questions?

20

Washington State Health Care Authority

Participant Conflict Disclosure

Introduction

The HTCC Workgroup is a public service workgroup established to safeguard the public interest by identifying medical tests and treatments where evidence shows they are safe, effective, and cost-effective. Balance, independence, objectivity and scientific rigor are a basis for public trust and crucial to the credibility and integrity of decisions.

Guiding Principle

Conflict of Interest decisions must be disclosed and balanced to ensure the integrity of decisions while acknowledging the reality that interests, and sometimes even conflicting interests, do exist. Individuals that stand to gain or lose financially or professionally, or have a strong intellectual bias need to disclose such conflicts.

> *For example,* the fact that a member or stakeholder is a health care provider that may use a service under review creates a potential conflict. However, clinical and practical knowledge about a service is also useful, and may be needed in the decision making.

Procedure

Declaration of real or potential conflicts of interest, professional, intellectual, or financial is required prior to membership or provision of written or verbal commentary. Participants must sign a conflict of interest form; stakeholders providing comment must disclose conflicts.

The HTCC Chair or HCA Administrator shall make a decision, in his/her sole discretion, as to whether a conflict of interest rises to the level that participation by the conflicted participant could result in a loss of public trust or would significantly damage the integrity of the decision.

HCA defines conflict of interest as any situation in which a voting member or anyone who provides written or verbal testimony regarding products, services, or technologies discussed or voted on during the workgroup meeting, has a relationship with a manufacturer of any commercial products and / or provider of services discussed or voted on during the meeting. Relationship extends to include immediate family member(s) and / or any entity in which the member or person testifying may have an interest.

A relationship is considered as:

1. Receipt or potential receipt of anything of monetary value, including but not limited to, salary or other payments for services such as consulting fees or honoraria in excess of $10,000.
2. Equity interests such as stocks, stock options or other ownership interests in excess of $10,000 or 5% ownership, excluding mutual funds and blinded trusts.
3. Status of position as an officer, board member, trustee, owner or employee of a company or organization representing a company, association or interest group.
4. Loan or debt interest; or intellectual property rights such as patents, copyrights and royalties from such rights.
5. Manufacturer or industry support of research in which you are participating.
6. Any other relationship that could reasonably be considered a financial, intellectual, or professional conflict of interest.
7. Representation: if representing a person or organization, include the organization's name, purpose, and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).
8. Travel: if an organization or company has financially paid your travel accommodations (e.g. airfare, hotel, meals, private vehicle mileage, etc).

Washington State Health Care Authority

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000	X	
2.	Equity interests such as stocks, stock options or other ownership interests	X	
3.	Status or position as an officer, board member, trustee, owner		X
4.	Loan or intellectual property rights		X
5.	Research funding		X
6.	Any other relationship, including travel arrangements	X	

If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

I am employed by Medtronic Spine and Biologics.

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).	X	

7. If yes, Provide Name and Funding Sources: I am employed by Medtronic Spine and Biologics.

If you believe that you do not have a conflict but are concerned that it may appear that you do, you may ***attach additional sheets*** explaining why you believe that you should not be excluded.

I certify that I have read and understand this Conflict of Interest Form and that the information I have provided is true, complete, and correct as of this date.

X Julie Bearcroft — 2/21/12 — Julie Bearcroft

Signature *Date* *Print Name*

FOR QUESTIONS: Denise Santoyo, Health Care Authority, 360-923-2742,
PO Box 42712, Olympia, WA 98504-2712

Washington State Health Care Authority

Agency Medical Director's Group Comments
Health Technology Clinical Committee
Bone Morphogenetic Protein (BMP) in Spinal Fusion

Dr. Bob Mootz
Office of the Medical Director
Department of Labor & Industries
March 16, 2012

BMP in Spinal Fusion Background

Bone Morphogenic Protein:

- Alternative to autologous bone graft aimed at eliminating bone graft morbidity, considered as high by proponents
- rhBMP-2: FDA premarket approval for single level level anterior lumbar fusion for DDD when conservative care has failed
- rhBMP-7: FDA humanitarian exemption for revision posterolateral lumbar fusion in compromised patients
- During scoping, topic was focused to BMP due concerns regarding safety & efficacy

Original 2010 Concerns Bone Graft Products

- Safety = Medium
- Efficacy = Medium
- Cost = High

BMP in Spinal Fusion
Current State Agency Coverage Policy

Medicaid:
- No specific policy on BMP
- Spinal fusion requires pre-authorization after April 1, 2012

L&I:
- BMP covered under product-specific criteria and UR
  - OP-1: autograft unfeasible, alternatives have failed
  - BMP-2: single level anterior lumbar fusion with prior authorization
- Spinal fusion requires pre-authorization

UMP:
- No specific policy on BMP
- Spinal fusion requires pre-authorization

Washington State Health Care Authority

BMP in Spinal Fusion Background

Agency Perspective

- **Spent $140 Million for spinal fusion surgery over 4 years**
  - ~70% of workers who had fusions are disabled 2 years post surgery compared to < 35% of (matched) workers who avoided surgery are disabled at 2 years. (Maghout, et al. Spine 2006; 31(23):2715-23.)
  - BMP may be associated with serious & life threatening complications (severe dysphagia, airway obstruction) with use in cervical spine (FDA Notice 7/1/08)
  - BMP use may involve a higher complication rate in lumbar fusion than initially reported in industry sponsored trials (eg, overgrowth and uncontrolled bone formation, infertility issues) (Carragee, et al. Spine J 2011;11(6):471-91.
  - May learn from long term safety data and better designed trials that safety and efficacy are comparable to available alternatives, eg fusion for spinal stenosis in Medicare population, however quality and design issues bring significant doubt on industry sponsored trials (Deyo, et al. Spine 2012:37(3):222-230), (Carragee, et al. Spine J 2011;11(6):463-468.

4

Washington State Health Care Authority

BMP in Spinal Fusion
Current State Agency Utilization

From limited agency data:

- ~ 15% of spinal fusions report using BMP
- ~ 10% of BMP use reported in cervical spine (all off-label)
- Off-label use in lumbar spine undetermined
- Specific billing for BMP:
  - Not required (likely underestimate; ~ 50% in literature*)
  - Fusion typically reimbursed via bundled hospital methodology (Diagnostic Related Groupings-DRG)
- Unable to determine how BMP is used in lumbar fusion cases (e.g., multi-level fusions)

* Mitka JAMA 2011; 306(12):1311-12.

5

Washington State Health Care Authority

BMP in Spinal Fusion: Agency Utilization

Agency/Year	2007	2008	2009	2010	4 years overall
PEB Spinal Fusions	$5,283,336	$7,388,972	$13,250,116	$13,894,609	$39,817,033
Procedure Count	247	309	434	414	1404
Average Age	57.7	58.8	58.7	58.8	58.5
% Male	45.3%	37.9%	40.3%	41.8%	41.1%
Avg length of stay	3.5	3.2	3.1	3.1	3.2
All spine fusions	14.6%	10.0%	11.5%	10.4%	11.3%
Cervical fusions	13.9%	12.9%	12.0%	7.0%	11.3%
Avg Length of Stay	3.6	3.5	3.9	4.0	3.8
L&I Spinal Fusions	$16,602,621	$19,419,086	$21,386,792	$22,203,502	$79,612,001
Procedure Count	593	647	708	739	2687
Average Age	57.7	58.8	58.7	58.8	58.5
% Male	71.6%	70.8%	70.1%	69.3%	70.5%
Avg length of stay	4.0	3.7	3.5	3.5	3.6
All spine fusions	16.4%	16.8%	14.0%	14.9%	15.4%
Cervical fusions	8.2%	10.1%	10.1%	11.8%	10.1%
Avg Length of Stay	4.3	4.2	4.1	4.2	4.2
Medicaid Fusions	$6,555,328	$7,497,656	$8,007,877	$2,193,720*	$24,254,581
Procedure Count	381	407	435	216*	1439
Average Age	46.1	45.0	46.5	46.0	45.8
% Male	51.2%	47.5%	45.7%	49.0%	48.1%
Avg length of stay	3.1	3.2	2.8	2.5	3.0

6

* Artifact due to new data processing method

Washington State Health Care Authority

BMP in Spinal Fusion

State Agencies Concerns: Safety

- **Serious side effects** (Carragee Spine J 2011; 11:471-491)
  - Uncontrolled & ectopic bone formation.
  - Severe dysphagia and airway obstruction, death.
  - Concerns of cancer risk – basic science and secondary analysis of Amplify trial, higher dose-more risk; 20 cancer events in BMP-2 vs. 5 in control (FDA2010 P050036, Dimar JBSAm 2009 91:1377-86)
  - Local effects (wound related complications, inflammation, infections).
- **Recent issues raised in literature**
  - Funding bias and controversy (Mitka JAMA 2011; 306(12) ;1311-12)
    - Researcher financial conflict of interest – payments in $ millions
  - Over-reporting of complications in control treatment group for illiac crest graft donor site. (Carragee Spine 2011; 11(6):58-66)
  - Under-reporting of adverse events: No adverse events reported in off-label rhBMP-2 trials supported by industry, but retrospective review showed a near doubling of complication rates. (Carragee Spine 2011; 11(6):58-66)
- **Statistical confidence**
  - Need for high confidence that there is no adverse event
  - ***NOT*** high confidence that there ***IS*** a specific adverse event

Washington State Health Care Authority

BMP in Spinal Fusion

State Agencies Concerns: Efficacy

- Trial Design Concerns - (Mirza 2011 Spine J 11(6):471-491)
  - Blinding – open label design
  - Non-inferiority trial design – no expectation to show better efficacy. May be appropriate when withholding treatment is unethical, not the case with chronic back pain in DDD
  - Primary outcome of ICBG morbidity was grossly over-estimated: All pain in gluteal region was attributed to ICBG harvesting, yet its common in all LBP. (Carragee Spine J 2011; 11:471-491)
  - FDA - less stringent device classification (PMA) – even though BMP is biologically active. Longer device time-frame dilutes early adverse pharmacologic events (eg, edema, radiculitis, urinary and sexual dysfunction)
  - Compromised efficacy in control treatment (wasted local bone, no decortication, or facet arthorodesis)
- Inadequate information for off label use, especially in the cervical spine

Washington State Health Care Authority

State Agencies Concerns

Cost

- Direct cost for BMP per se is not determinable in agency data, but appears in line with higher costs in other reports
- Direct cost to hospitals appears to be more than alternatives (Deyo, et al. Spine 2012:37(3):222-230), (Carragee, et al. Spine J 2011;11(6):463-468.
- Cost-effectiveness cannot be assessed given lack of high-quality, reliable efficacy, effectiveness, and harms data
- Might be worth equivalent cost if demonstrated to be safe over the long term and at least equally effective to autograft (eg, Illiac Crest Bone Graft)

AHRQ (2010)*

- *On-label lumbosacral:* rhBMP-2 comparable to autograft; rhBMP-7 insufficient evidence for safety or effectiveness
- *Off-label cervical:* rhBMP-2 insufficient for fusion/disability; moderate evidence for complications
- *Off-label lumbosacral:* rhBMP-2; sufficient for radiographic fusion, insufficient for efficacy or complications; rhBMP-7 insufficient for safety & effectiveness

*Uses trials where underlying data not available and subsequent analysis of FDA reporting indicates inaccuracies and potential fatal trial design concerns.

Centers for Medicare & Medicaid Services (CMS)

- MEDCAC review and voting followed AHRQ findings
- However, no national coverage decision

Uncertainty regarding BMP

Safety
- Under reporting of severe safety issues
- Over reporting of control complications
- Financial conflicts of researchers

Efficacy
- Control treatment may have been compromised
- Inadequate blinding
- Non-inferiority design controversy

11

BMP in Spinal Fusion Summary

State Agencies Summary View
- Serious safety concerns (Carragee 2011 Spine J 11:471-491)
- Off label use has no reliable data
- Unclear efficacy due to study design & quality concerns
  - Unblinded trials, non-inferiority design, low rigor pre-market approval studies (Mirza 2011 Spine J 11:495-499)
  - Efficacy & safety appears to be similar to autograft in fusion for stenosis in Medicare patients (Deyo 2012 Spine 37(3):222-230)
- Value (cost effectiveness) of BMP depends on efficacy - which is in doubt

12

State Agencies Recommendation

Off-label

- Non-coverage in light of:
  - Serious safety concerns, lack of evidence on efficacy or effectiveness, and increased cost

On-label

- If safety concerns are valid - non-coverage:
  - Safety concerns - known under-reported events, uncontrolled bone growth, osteoclast activity, wound problems, neurologic events, retrograde ejaculation/persistent bladder retention [with ALIF], early back and leg pain, radiculitis, functional loss, potential cancer risk
  - Efficacy concerns – premise of high ICBG morbidity unproven; uncertainty of trial quality (eg, bias, design, compromised comparisons, financial conflict)
- If safety is determined acceptable:
  - Consider only FDA approved indications

Questions?

More Information:
http://www.hca.hta.wa.gov

Robert D. Mootz, DC
Associate Medical Director
Department of Labor & Industries
moot235@lni.wa.gov
Tel: 360-902-4998

BMP in Spinal Fusion Billing Codes

Code Type	Codes	Short Description
ICD9 Procedures		
	84.52	Insertion of recombinant bone morphogenetic rhBMP via collagen sponge, coral, ceramic and other carriers
	84.55	Insertion of bone void filler, insertion of acrylic cement (PMMA) bone void cement calcium based bone void filler polymethylmethacrylate (excepting vertebroplasty and vertebral augmentation)
APDRG	MSDRG	
	M453	Combined anterior/posterior spinal fusion w MCC
806	M454	Combined anterior/posterior spinal fusion w CC
807	M455	Combined anterior/posterior spinal fusion w/o CC/MCC
	M456	Spinal fus exc cerv w spinal curv/malig/infec or 9+ fus w MCC
	M457	Spinal fus exc cerv w spinal curv/malig/infec or 9+ fus w CC
884	M458	Spinal fus exc cerv w spinal curv/malig/infec or 9+ fus w/o CC/MCC
755	M459	Spinal fusion except cervical w MCC
756	M460	Spinal fusion except cervical w/o MCC
	M471	Cervical spinal fusion w MCC
864	M472	Cervical spinal fusion w CC
865	M473	Cervical spinal fusion w/o CC/MCC
836		Spinal procedures w/CC
837		Spinal procedures wo CC

On- and off-label uses of rhBMP-2 or rhBMP-7 for spinal fusion

MARCH 16, 2012

HEALTH TECHNOLOGY ASSESSMENT

prepared by:

Robin Hashimoto, PhD
Annie Raich, MPH
Emily Yoder, BA
Kara McMullen, MPH
Joseph Dettori, PhD, MPH

Spectrum Research, Inc., Tacoma, WA

Background

- Bone augmentation dependent on three properties:
  - Osteoproduction
  - Osteoinduction
  - Osteoconduction
- Commonly used bone graft materials
  - Autologous bone grafts
  - Allografts
    - Demineralized bone grafts
  - Synthetic bone graft substitutes
    - Hydroxyapaptite, tricalcium phosphate
  - Growth factors
    - **Bone morphogenetic proteins (BMPs)**

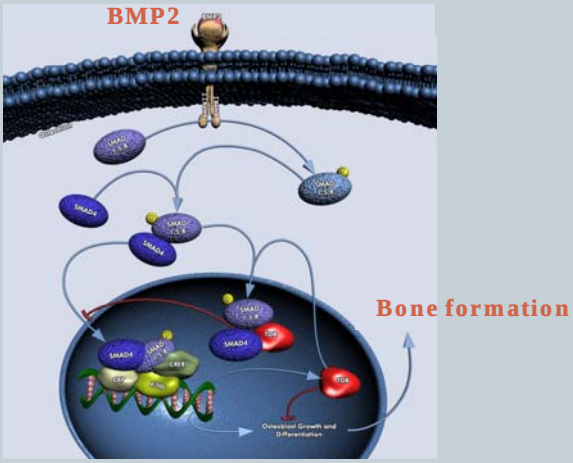
Technology and comparators

- **Autogenous iliac crest bone graft (ICBG)**
  - **Gold standard**
    - Osteogenic, osteoconductive, and osteoinductive
    - Complete histocompatability; non-immunogenic
  - Graft taken at same time as fusion surgery
  - **Limitations**:
    - Donor site morbidity (persistent pain; infection; nerve injury; avulsion fractures)
    - Volume-limited quantity
    - Blood loss
    - Surgical time required
    - Patient dissatisfaction with appearance of harvest site

Bone morphogenetic proteins

- Stimulate new bone formation
- TGF-β superfamily
  - 18 types of BMPs
  - BMP-2, -4, -6, -7, and -9 are osteoinductive
  - BMP-2 and BMP-7 are the two forms available for clinical use
- Use as a bone graft substitute circumvents need for autograft harvesting and associated morbidity

BMP2 stimulates osteogenesis



FDA-approved BMP products

Product	BMP	FDA approval
InFUSE/LT-CAGE (Medtronic)	rhBMP-2	PMA (P000058) (2002)
OP-1 Putty (Stryker)	rhBMP-7	HDE (H020008) (2004)

InFUSE
(Medtronic)

rhBMP-2/ACS

LT-CAGE
Lumbar Tapered
Fusion Device

rhBMP-2/ACS mechanism of action
(Medtronic)

1 Implantation

2 Chemotaxis
mesenchymal stem cells + other cells migrate to site

3 Proliferation
of stem cells

4 Differentiation
rhBMP-2 binds to stem cells;
induces differentiation into osteoblasts

5 Bone formation and angiogenesis

6 Remodeling
in response to local environment

7 Formation of trabecular bone

Adapted from www.medtronic.com

On- and off-label uses

- **FDA-approved (on-label) uses of BMPs:**

Product	BMP	FDA approval	Indications
InFUSE/LT-CAGE (Medtronic)	rhBMP-2	PMA (P000058) (2002)	• Primary anterior open or laproscopic fusion at one level between L4 and S1 • Patients: DDD + ≤ grade 1 spondylolisthesis Failed ≥ 6 months of non-operative care Skeletally mature
OP-1 Putty (Stryker)	rhBMP-7	HDE (H020008) (2004)	• Revision posterolateral lumbar fusion (PLF) • Patients: Compromised patients for whom autologous bone and bone marrow harvest are not feasible or not expected to result in fusion

- **All other uses are considered to be off-label**

Use of BMPs in the US

- Nationwide Inpatient Sample (2003-2007):
  - **340,251 procedures with BMP usage**
- Prevalence of use increased 4.3-fold between 2003 and 2007
- ≥ 85% of procedures were for off-label uses
  - **Primary fusion: 84.5%**
    - PLIF/TLIF: 30.0%
    - Primary PLF: 20.4%
    - Primary ALIF: 16.6%
    - Primary cervical fusions: 13.6%
    - Primary thoracolumbar fusions: 3.9%
  - **Revision fusion: 6.9%**
  - **Other (nonspine fusion): 8.6%**

Ong, KL et al. Spine 35:1794 (2010)

Key Questions

- **KQ1.** Expected treatment outcomes; outcomes measures; clinically meaningful improvement
- **KQ2.** Efficacy and effectiveness
- **KQ3.** Safety
- **KQ4.** Differential efficacy or safety issues in subpopulations
- **KQ5.** Cost effectiveness

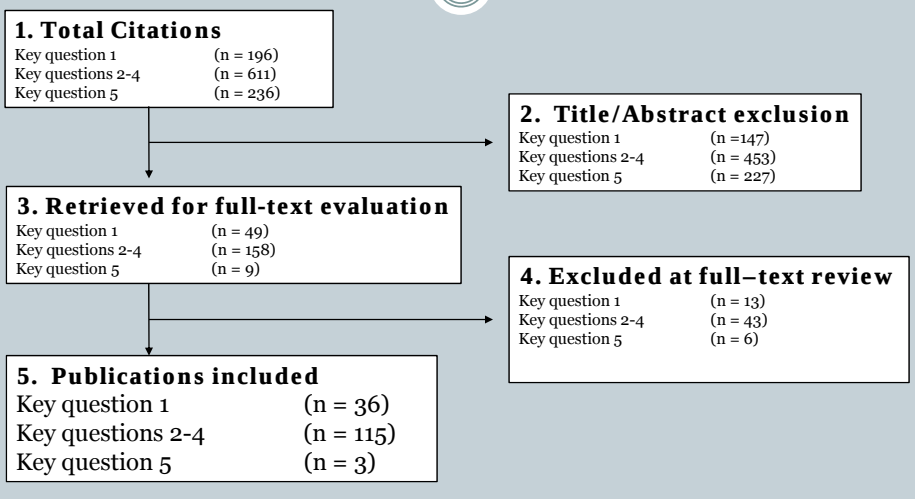
Inclusion criteria (PICO)

- **Participants.** Patients with back and/or leg or neck pain
- **Intervention.** FDA-approved ("on-label") and unapproved ("off-label) implantation of rhBMP-2 or rhBMP-7 in the lumbar or cervical spine
- **Comparators.** Placebo; standard care; physical therapy; fusion with autograft or allograft bone and/or other bone substitutes

Inclusion criteria (PICO)

- **Outcomes.**
  - **Efficacy and effectiveness:**
    - Primary outcomes: pain, function, radiographic fusion
    - Secondary outcomes: perioperative outcomes, patient satisfaction, return to work, medication usage, mental health
  - **Safety:**
    - Complications/adverse events
    - Second surgeries (ie., revision, hardware removal, supplemental fixation, reoperation, fusion at different spinal level, others)

Literature search



Quality of literature available

- KQ1. Validity, reliability, MCID.
  - 36 studies
- KQ2. Efficacy and Effectiveness.
  - 14 RCTs
  - 15 cohort studies
- KQ3. Safety.
  - 14 RCTs
  - 27 cohort studies
  - 33 case series + 16 case reports
- KQ4. Differential efficacy and safety.
  - 8 cohort studies
- KQ5. Cost-effectiveness.
  - 3 economic analyses

Results: KQ1

KQ1.

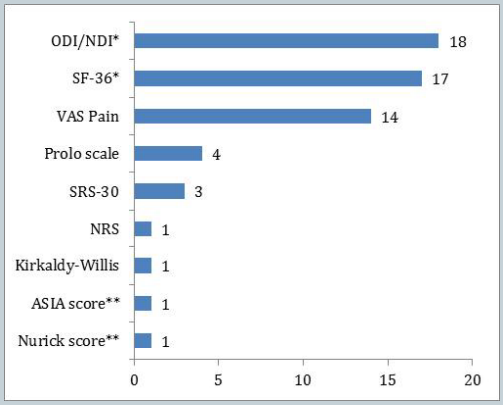
a. What are the expected treatment outcomes of lumbar or cervical spinal fusion?

b. Are there validated instruments related to outcomes in patients undergoing these procedures?

c. Has clinically meaningful improvement in outcomes been defined in these patient populations?

KQ1: Expected treatment outcomes

- Frequency of outcome measures used in comparative studies using rhBMP-2 or rhBMP-7 for lumbar or cervical spinal fusion:



KQ1: Validity, reliability, and MCID

	Valid	Reliable	Responsive	MCID
ODI (0-100 pts)	Spine pain patients	Spine pain patients	Spine pain patients	**15 pts** Range: 10-22.9 pts; or 15% change
NDI (0-100 pts)	Neck pain patients	Neck/arm pain patients	Neck/arm pain patients	**15 pts** Range: 7-19 pts*
Pain (VAS) (0-100 mm)	Spine pain patients	Spine pain patients	Spine pain patients	**20 mm** Range: 2-29 mm
SF-36 (0-100 pts)	**Fusion patients**	Spine pain patients	Spine pain patients	NR

*as reported for neck pain patients

Results: KQ2

KQ2. What is the evidence of efficacy and effectiveness of:

a. **rhBMP-2 for on-label lumbarsacral spine fusion?**
b. **rhBMP-7 for on-label lumbarsacral spine fusion?**
c. **rhBMP-2 for off-label lumbarsacral spine fusion?**
d. **rhBMP-7 for off-label lumbarsacral spine fusion?**
e. **rhBMP-2 for off-label cervical spine fusion?**
f. **rhBMP-7 for off-label cervical spine fusion?**

KQ2: Efficacy
(rhBMP-2 on-label use in lumbar spine)

- **Evidence base: 2 RCTs**
  - **N = 14 – 279 patients**
  - **Intervention:**
    - primary single-level open anterior fusion with InFUSE vs. ICBG
    - BMP dose: 4.2 – 8.4 mg/patient
  - **Follow-up: 24 months**
  - **Studies served as pilot and pivotal trials for FDA SSED on InFuse (2002) (Medtronic)**

	PRIMARY OUTCOMES					SECONDARY OUTCOMES					
	ODI	Back pain	Leg pain	SF-36 fxn	Fusion	LOS	Blood loss	OR time	Pt satisf	Work	Neuro
Result	=	=	=	=	=	=	+	=	=	=	=
SoE	*low*	*low*	*low*	*low*	*low*	*low*	*low*	*low*	*low*	*low*	*low*
# studies	2	1	1	1	2	2	2	2	2	2	1

"=" similar between treatment groups; "+" improved with BMP use; "-" worse with BMP use

KQ2: Efficacy
(rhBMP-2 off-label use in lumbar spine)

- **Evidence base: 6 RCTs**
  - N = 27 – 463 patients
  - Intervention:
    - Primary; single- or multi-level; various approaches; rhBMP-2 vs. ICBG
    - BMP dose: 4.2 – 40 mg/patient
  - Follow-up: 17 (mean) – 24 months

	PRIMARY OUTCOMES					SECONDARY OUTCOMES						
	ODI	Back pain	Leg pain	Fusion	SF-36	LOS	Blood loss	OR time	Pt satisf	Work	Neuro	Overall success
Result	=	=/+	=	=/+	=	=	=/+	=/+	=	=	=	=
SoE	*high*	*mod.*	*high*	*mod.*	*high*	*high*	*mod.*	*mod.*	*low*	*high*	*low*	*low*
# studies	3 - 6	5/1	6	3/3	6	5	4/2	3/3	2	4	1	1

"=" similar between treatment groups; "+" improved with BMP use; "-" worse with BMP use

KQ2: Effectiveness
(rhBMP-2 off-label use in lumbar spine)

- **Evidence base: 8 cohort studies**
  - Prospective: 2 cohort studies + 1 case-control study
  - Retrospective: 3 cohort studies + 2 cohort studies with historical controls
  - N = 36– 126 patients
  - Intervention:
    - Primary or revision; single- or multi-level; various approaches; rhBMP-2 vs. various
    - BMP dose: 3 – 36 mg/patient
  - Follow-up: mean 9 – 39 months

	PRIMARY OUTCOMES				SECONDARY OUTCOMES					
	ODI	Pain	Function	Fusion	Blood loss	OR time	Pt satisf	Mental health	Med use	Overall outcome
Result	=	=	=	=	+	=	=	=	=	=
SoE	*insuff.*	*low*	*insuff.*	*low*	*insuff.*	*insuff.*	*insuff.*	*insuff.*	*insuff.*	*insuff.*
# studies	2	5	2	7/ 1 (+)	1	1	2	1	1	1

"=" similar between treatment groups; "+" improved with BMP use; "-" worse with BMP use

KQ2: Efficacy
(rhBMP-7 off-label use in lumbar spine)

- **Evidence base: 5 RCTs**
  - N = 20 – 293 patients
  - Intervention:
    - Primary single-level PLIF (4) or PLF (1); OP-1 vs. ICBG or autograft
    - BMP dose: 7 mg/patient
  - Follow-up: mean 12 – 54 months

	PRIMARY OUTCOMES					SECONDARY OUTCOMES				
	ODI	Back pain	Leg pain	Fusion	SF-36 phys.	LOS	Blood loss	OR time	Neuro	Overall success
Result	=	=	=	=	=	=	=/+	=/+	=	=
SoE	*high*	*low*	*low*	*high*	*low*	*high*	*low*	*low*	*low*	*low*
# studies	4	1	1	5	1	3	1/1	2/1	1	1

"=" similar between treatment groups; "+" improved with BMP use; "-" worse with BMP use

KQ2: Efficacy
(rhBMP-2 off-label use in cervical spine)

- **Evidence base: 1 RCT**
  - N = 33 patients
  - Intervention:
    - Primary 1- or 2-level ACDF; InFUSE vs. ICBG
    - BMP dose: 0.6 – 1.2 mg/patient
  - Follow-up: 24 months

	PRIMARY OUTCOMES					SECONDARY OUTCOMES				
	NDI	Neck pain	Arm pain	Fusion	SF-36	LOS	Blood loss	OR time	Neuro	Pt satisf.
Result	+	=	+	=	=	=	=	=	=	=
SoE	*low*	*low*	*low*	*low*	*low*	*low*	*low*	*low*	*low*	*low*
# studies	1	1	1	1	1	1	1	1	1	1

"=" similar between treatment groups; "+" improved with BMP use; "-" worse with BMP use

KQ2: Effectiveness
(rhBMP-2 off-label use in cervical spine)

- **Evidence base: 5 cohort studies**
  - Prospective: 1 cohort study
  - Retrospective: 3 cohort studies + 1 case-control database study
  - N = 58 – 775 patients
  - Intervention:
    - Primary or revision; single- or multi-level; various approaches; rhBMP-2 vs. various
    - BMP dose: 0.9 – 12 mg/patient
  - Follow-up: 1 – 36 months

	PRIMARY OUTCOMES				SECONDARY OUTCOMES		
	ODI	Arm pain	Neck pain	Fusion	Blood loss	OR time	LOS
Result	=	=	=/-	=/+	=	=	=/-
SoE	*insuff.*	*insuff.*	*insuff.*	*insuff.*	*low*	*insuff.*	*insuff.*
# studies	2	2	2/1	1/1	3	2	4/1

"=" similar between treatment groups; "+" improved with BMP use; "-" worse with BMP use

Results: KQ3

KQ3. Safety

What is the evidence of the safety of on- or off-label use of rhBMP-2 or rhBMP-7 for spinal fusion compare with spinal fusion using ICBG or alternative bone graft substitutes?

KQ3: Safety

- **Evidence base:**
  - 14 RCTs
  - 27 cohort studies
  - 33 case series
- **Organization of results:**
  - Local safety
  - Neurologic events
  - Other complications
  - Second surgical procedures
  - Graft site morbidity

KQ3: Local safety

	Deep infections/ surgery		Inflammation/ neck swelling
	On-label	Off-label	Off-label cervical
Result		=	-
SoE		*low*	*moderate*
# RCTs	0	1	0
# cohort studies	0	4	6

"=" similar between treatment groups; "+" improved with BMP use; "-" worse with BMP use

Safety: Inflammation and swelling

- **Anterior cervical inflammation/ swelling**
  - Higher risk following off-label use of rhBMP-2 in the cervical spine (SoE *moderate*)
  - Data from 4 cohort studies:
    - **rhBMP-2: 34.9%** (59/169) (range, 11 – 91%)
    - **Control: 9.2%** (35/381) (range, 3.6 – 75%)
  - Data from 2 database studies:
    - **BMP: 5.04%** (128/2537) (range, 3.96 – 6.9%)
    - **Control: 3.06%** (847/27,674) (range, 0.6 – 3.11%)
  - Data from 7 case series:
    - **rhBMP-2: 12.8 – 15.6%** (65 – 79 /506)

KQ3: Neurologic events

	Retrograde ejaculation		Dural injury/ CSF leak	
	On-label	Off-label	On-label	Off-label
Result	-	-	=	=
SoE	*low*	*low*	*insuff*	*high*
# RCTs	0	0	0	3
# cohort studies	1	1	1	7

"=" similar between treatment groups; "+" improved with BMP use; "-" worse with BMP use

Safety: Retrograde ejaculation

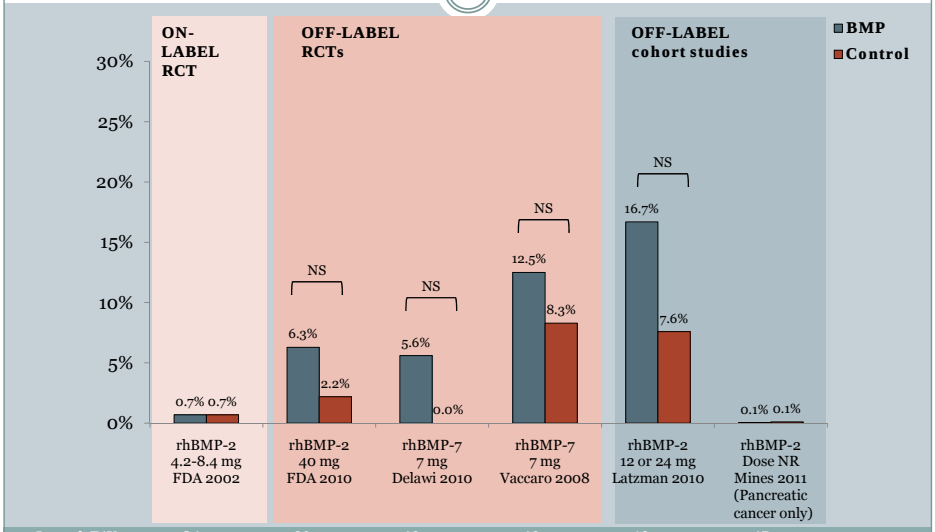
- **Retrograde ejaculation**
  - **Higher risk following use of rhBMP-2 in the lumbar spine (SoE *low*)**
  - **FDA SSED for InFUSE:**
    - **rhBMP-2: 7.9%** (11/140)
    - **Control: 1.4%** (1/70)
    - No cases reported by the 24 month follow-up (range, 19 – 30 months)
  - **Retrospective cohort study:**
    - **1 – 2 level ALIF at L5/S1**
    - **BMP: 7%** (5/69)
    - **Control: 0.06%** (1/174)
    - Same effect for 1 – level fusions
    - No difference between groups for 2 – level fusions
    - 60% (3/5) BMP and 0% (0/1) control patients remained affected at 12 months follow-up.

KQ3: Other

	Cancer		Cardio/vascular		Deep vein thrombosis		Death		
	On-label	Off-label	On-label	Off-label	On-label	Off-label	On-label	Off-label lumbar	Off-label cervical
Result	=	-	=	=	=	=	=	=	-
SoE	*low*	*moderate*	*low*	*high*	*low*	*low*	*low*	*high*	*insuff.*
# RCTs	1	3	1	4	1	1	1	4	0
# cohort studies	0	1	1	3	0	2	1	2	1

"=" similar between treatment groups; "+" improved with BMP use; "-" worse with BMP use

Safety: Cancer



KQ3: Second surgeries

	Revision		Hardware removal		Supplemental fixation		Reoperation	
	On-label	Off-label	On-label	Off-label	BMP-2	BMP-7	On-label	Off-label
Result	=	=/+	=	+/=	+	-	+	=
SoE	*insuff*	*high*	*low*	*mod*	*mod*	*low*	*insuff*	*high*
# RCTs	0	7/0	1	4/0	4	2	0	3
# cohort studies	1	0/3	1	0/2	5	0	1	3

"=" similar between treatment groups; "+" improved with BMP use; "-" worse with BMP use

KQ3: Graft site morbidity

- **In patients who underwent ICBG harvesting:**
  - **Hip pain VAS**
    - Perioperative period: range of 5.7 – 8.0 (scale of 0 – 10) (4 studies)
    - Last follow-up (12 – 24 months): 0.2 – 2.8 (6 studies)
  - **% of patients with pain**
    - Last follow-up (6 – 36 months): 10 – 66% (9 studies)
  - **Additional complications:**
    - Injury to lateral femoral cutaneous nerve
    - ASIS fractures
    - Deep infection requiring surgery
    - Superficial infection
    - Hematoma

Results: KQ4

KQ4. Differential efficacy and safety

What is the evidence of the differential efficacy or safety in subpopulations undergoing spinal fusion with rhBMP-2 or rhBMP-7 compared with ICBG or alternative bone grafts?

KQ4: Differential efficacy and safety in subpopulations

- **Evidence base: 8 cohort studies**
- **Insufficient evidence on differential effectiveness for the following subpopulations:**
  - Age
  - Sex
  - Smoking status
  - Number of levels
  - Complexity of fusions
  - Surgical approach
  - Previous surgeries

Results: KQ5

KQ5. Cost-effectiveness

What is the evidence of cost implications and cost-effectiveness of on- or off-label use of rhBMP-2 or rhBMP-7?

Including consideration of:

- Direct and indirect costs; and
- Short- and long-term cost effectiveness.

KQ5: Cost-effectiveness
(rhBMP-2 on-label use in lumbar spine)

- **Evidence base: 2 studies**

1. **AHRQ cost-effectiveness analysis (2010)**
   - **Study characteristics:**
     - Data from one RCT (N = 279) (rhBMP-2 versus ICBG)
     - CMS payer perspective; Medicare-reported costs
   - **Results:**
     - Base case (both treatments cost same): BMP more cost-effective
     - One- and two-way sensitivity analyses (BMP incurs additional cost ($3000)): ICBG more cost effective
   - **rhBMP-2 only cost effective when initial costs same as ICBG (bundled cost)**

KQ5: Cost-effectiveness
(rhBMP-2 on-label use in lumbar spine)

2. **NHS (UK) cost utility analysis (2007)**
   - **Study characteristics:**
     - Data from same RCT (N = 279) (rhBMP-2 versus ICBG)
     - Used modified ABACUS model for all spinal fusions performed annually in England
   - **Results:**
     - Similar outcomes in both groups
   - **rhBMP-2 unlikely to be more cost-effective than ICBG**
     - Cost per QALY gained: £120,390
   - **Strength of evidence: *low***

KQ5: Cost-effectiveness
(rhBMP-2 off-label use in lumbar spine)

- **Evidence base: one study**

1. **Carreon (2009) cost utility study**
   - **Study characteristics:**
     - Based on actual costs and results from patients enrolled in one RCT (N = 102)
     - Patients aged 60+
     - Single- or multilevel (mean 2 levels/patient) PLF with rhBMP-2 versus ICBG
   - **Initial costs** $2295 higher for rhBMP-2 patients
   - **Results**
     - Similar efficacy
     - Lower risks of complications
   - **Final costs (including initial treatment AND treatment for complications** $2319 lower for rhBMP-2 patients
   - **Strength of evidence:** ***low***

KQ5: Cost-effectiveness

- **On- or off-label use of rhBMP-7 in the lumbar spine**
- **Off-label use of rhBMP-2 or rhBMP-7 in the cervical spine**
  - **No evidence**

Summary and implications

Summary: Efficacy and Effectiveness

- **Lumbar spine**
  - In general, outcomes were similar for both treatment groups
  - There is some evidence that fusion rates are higher with off-label use of rhBMP-2.
    - However, fusion is a surrogate outcome measure.
    - No differences between treatment groups in terms of pain and function outcomes.
  - SoE varied from *insufficient* to *high*
- **Cervical spine**
  - Some outcomes had possible benefit with BMP use (arm pain, NDI, fusion)
  - Other outcomes had possible worse outcome with BMP use (hospital LOS, neck pain)
  - SoE was *insufficient* or *low*

Summary: Safety

- **Retrograde ejaculation**
  - Higher risk following on- and off-label use of rhBMP-2 in the lumbar spine (SoE *low*)
  - RE is a concern with any anterior approach in the lumbar spine
  - Generally thought of as transitory
    - However, one cohort study reported that at one year following ALIF involving L5/S1, 3/5 rhBMP-2 and 0/1 ICBG patients who developed postoperative RE still had RE.

Summary: Safety

- **Cancer**
  - Similar risk following on-label use of rhBMP-2 in lumbar spine (SoE *low*)
  - Higher risk following off-label use of rhBMP-2 or rhBMP-7 in the lumbar spine (SoE *moderate*)
  - Data from one RCT (N = 463) using AMPLIFY (higher dose of rhBMP-2 (40 mg)) reported higher cancer risks with rhBMP-2 compared with ICBG:
    - 24 months: 3.8% vs. 0.9%
    - 60 months: 6.3% vs. 2.2%
  - Various types of cancers reported
  - Some presented relatively soon after surgery so likely were already present
  - Difficult to make a direct connection between BMP and the formation of cancer

Summary: Safety

- **Anterior cervical inflammation/swelling**
  - **Higher risk following off-label use of rhBMP-2 in the cervical spine (SoE *moderate*)**
  - **Range of means (4 cohort studies + 2 database studies):**
    - BMP: 5.04 – 34.9%
    - Control: 3.06 – 9.2%
  - **Occurs perioperatively**
  - **The inflammatory and swelling response may lead to:**
    - Intravenous steriods
    - Dysphagia with possible:
      - PEG placement
      - Reintubation
      - Tracheostomy
      - Surgical exploration and drainage
      - Increased length of hospital stay
      - Readmission

Summary: Safety

- **Second surgeries**
  - **Supplemental fixation:**
    - **Lower risk** following on- or off-label use of rhBMP-2 in the lumbar or cervical spine (SoE *moderate*)
    - **Higher risk** following off-label use of rhBMP-7 in the lumbar spine (SoE *low*)
  - **Revision, hardware removal**
    - Similar risks between groups
    - *Possible* benefit with off-label BMP use
  - **Reoperation**
    - Similar risks between groups
    - *Possible* benefit with on-label rhBMP-2 use

Thank you.

Questions?

HTCC Coverage and Reimbursement Determination Analytic Tool

HTA's goal is to achieve *better health care outcomes* for enrollees and beneficiaries of state programs by paying for proven health *technologies that work*.

To find best outcomes and value for the state and the patient, the HTA program focuses on these questions:

1. Is it safe?
2. Is it effective?
3. Does it provide value (improve health outcome)?

The principles HTCC uses to review evidence and make determinations are:

Principle One: Determinations are Evidence based

HTCC requires scientific evidence that a health technology is safe, effective and cost-effective[1] as expressed by the following standards. [2]

- Persons will experience better health outcomes than if the health technology was not covered and that the benefits outweigh the harms.
- The HTCC emphasizes evidence that directly links the technology with health outcomes. Indirect evidence may be sufficient if it supports the principal links in the analytic framework.
- Although the HTCC acknowledges that subjective judgments do enter into the evaluation of evidence and the weighing of benefits and harms, its recommendations are not based largely on opinion.
- The HTCC is explicit about the scientific evidence relied upon for its determinations.

Principle Two: Determinations result in health benefit

The outcomes critical to HTCC in making coverage and reimbursement determinations are health benefits and harms.[3]

- In considering potential benefits, the HTCC focuses on absolute reductions in the risk of outcomes that people can feel or care about.
- In considering potential harms, the HTCC examines harms of all types, including physical, psychological, and non-medical harms that may occur sooner or later as a result of the use of the technology.
- Where possible, the HTCC considers the feasibility of future widespread implementation of the technology in making recommendations.
- The HTCC generally takes a population perspective in weighing the magnitude of benefits against the magnitude of harms. In some situations, it may make a determination for a technology with a large potential benefit for a small proportion of the population.
- In assessing net benefits, the HTCC subjectively estimates the indicated population's value for each benefit and harm. When the HTCC judges that the balance of benefits and harms is likely to vary substantially within the population, coverage or reimbursement determinations may be more selective based on the variation.
- The HTCC considers the economic costs of the health technology in making determinations, but costs are the lowest priority.

[1] Based on Legislative mandate: See RCW 70.14.100(2).

[2] The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

[3] The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

Using Evidence as the basis for a Coverage Decision

Arrive at the coverage decision by identifying for Safety, Effectiveness, and Cost whether (1) evidence is available, (2) the confidence in the evidence, and (3) applicability to decision.

1. Availability of Evidence:

Committee members identify the factors, often referred to as outcomes of interest, that are at issue around safety, effectiveness, and cost. Those deemed key factors are ones that impact the question of whether the particular technology improves health outcomes. Committee members then identify whether and what evidence is available related to each of the key factors.

2. Sufficiency of the Evidence:

Committee members discuss and assess the evidence available and its relevance to the key factors by discussion of the type, quality, and relevance of the evidence[4] using characteristics such as:

- Type of evidence as reported in the technology assessment or other evidence presented to committee (randomized trials, observational studies, case series, expert opinion);
- the amount of evidence (sparse to many number of evidence or events or individuals studied);
- consistency of evidence (results vary or largely similar);
- recency (timeliness of information);
- directness of evidence (link between technology and outcome);
- relevance of evidence (applicability to agency program and clients);
- bias (likelihood of conflict of interest or lack of safeguards).

Sufficiency or insufficiency of the evidence is a judgment of each clinical committee member and correlates closely to the GRADE confidence decision.

Not Confident	Confident
Appreciable uncertainty exists. Further information is needed or further information is likely to change confidence.	Very certain of evidentiary support. Further information is unlikely to change confidence

3. Factors for Consideration - Importance

At the end of discussion at vote is taken on whether sufficient evidence exists regarding the technology's safety, effectiveness, and cost. The committee must weigh the degree of importance that each particular key factor and the evidence that supports it has to the policy and coverage decision. Valuing the level of importance is factor or outcome specific but most often include, for areas of safety, effectiveness, and cost:

- risk of event occurring;
- the degree of harm associated with risk;
- the number of risks; the burden of the condition;
- burden untreated or treated with alternatives;
- the importance of the outcome (e.g. treatment prevents death vs. relief of symptom);
- the degree of effect (e.g. relief of all, none, or some symptom, duration, etc.);
- value variation based on patient preference.

[4] Based on GRADE recommendation: http://www.gradeworkinggroup.org/FAQ/index.htm

Medicare Coverage and Guidelines

Organization	Date	Outcome	Evidence Base	Grade / Rating
CMS National Policy Decisions – WA HTA Centers for Medicare and Medicaid Services Page: 90		The Centers for Medicare and Medicaid Services have no published National coverage determinations (NCD) for bone morphogenetic proteins.	N/A	N/A
Guidelines – WA HTA Page: 76 Work Loss Data Institute (2011)[71] *Guideline Summary NGC-8517: Low back – lumbar & thoracic (acute & chronic)*	1993-present	*Low back – lumbar & thoracic (acute & chronic)* A summary provided by the NGC indicates that rhBMP was considered as a treatment for workers with low back pain and was not recommended.	NR	
Guidelines – WA HTA Page: 76 Work Loss Data Institute (2011)[72] *Guideline Summary NGC-8518: Neck and Upper back (acute & chronic)*	1993-present	*Neck and Upper back (acute & chronic)* A summary provided by the NGC indicates that rhBMP was considered as treatment for workers with occupational disorders of the neck and upper back. rhBMP was considered and not recommended.	NR	
Guidelines – WA HTA Page: 76 Resnick (2005)[73] *Guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 16: bone graft extenders and substitutes*	1966-November, 2003	Primary conclusions: While evidence for a treatment guideline is insufficient, rhBMP-2 in combination with HA and tricalcium phosphate may be used as a substitute for autograft bone in some cases of PLF. rhBMP-2 is a viable alternative to autografts for interbody fusion procedures.	% f/u, f/u period NR unless specified • 1 RCT (> 90% f/u, ≥ 48 months); N = 279 • 1 RCT; N = 35 • 1 pilot study (17 months); N = 25 1 combined analysis; N = NR	Large RCT: Class I All other studies: LOE III
Guidelines – WA HTA Page: 76 *National Institute for Health and Clinical Excellence (NICE)*		The National Institute for Health and Clinical Excellence (NICE) provides guidance on health technologies and clinical practice for the National Health Service in England and Wales. A variety of keyword searches were performed, including "*BMP*" and "*bone morphogenetic protein.*" No guidelines were found.		

HEALTH TECHNOLOGY EVIDENCE IDENTIFICATION

Discussion Document: What are the key factors and health outcomes and what evidence is there?

	Bone Morphogenetic Proteins
Safety Outcomes	**Safety Evidence**
Mortality	
Overgrowth/uncontrolled bone formation	
Surgical Complications	
Re-operations	
Wound infections	
Infections, seroma, hematoma	
Dysphagia	
Retrograde ejaculation	
Bowel obstruction	
Urinary retention	
Radiculitis	
Dural injury	
Neurological events	
Antibody response	
Cancer	
Cardiovascular	
Reoperation/revision	
Graft site morbidity	

Efficacy – Effectiveness Outcomes	Efficacy / Effectiveness Evidence
Operative Time	
Blood loss	
Length of Stay	
Fusion	
ODI/NDI	
SF-36- Function	
Patient Satisfaction	
Neurological status	
Work status	
Overall success	
Medication use	
SF-36- Mental health	
Special Population / Considerations Outcomes	**Special Population Evidence**
Gender	
Age	
Functional status, baseline	
Comorbidities (including smoking, alcohol use, psychological)	
Other characteristics	
Provider type, setting, other	
Payer or Beneficiary Type	
Cost	**Cost Evidence**
Total Health Care Costs / Societal Costs	
Direct and indirect - Short terms - Over expected duration of use	
Cost Effectiveness	

Clinical Committee Evidence Votes

First voting question
The HTCC has reviewed and considered the technology assessment and information provided by the administrator, reports and/or testimony from an advisory group, and submissions or comments from the public. The committee has given greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

Is there sufficient evidence under some or all situations that the technology is:

	Unproven (no)	**Equivalent** (yes)	**Less** (yes)	**More** (yes)
Effective				
Safe				
Cost-effective				

Discussion
Based on the evidence vote, the committee may be ready to take a vote on coverage or further discussion may be warranted to understand the differences of opinions or to discuss the implications of the vote on a final coverage decision.

- Evidence is insufficient to make a conclusion about whether the health technology is safe, efficacious, and cost-effective;
- Evidence is sufficient to conclude that the health technology is unsafe, ineffectual, or not cost-effective
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for all indicated conditions;
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for some conditions or in some situations

A straw vote may be taken to determine whether, and in what area, further discussion is necessary.

Second vote
Based on the evidence about the technologies' safety, efficacy, and cost-effectiveness, it is

_____Not Covered. _____ Covered Unconditionally. _____ Covered Under Certain Conditions.

Discussion Item

Is the determination consistent with identified Medicare decisions and expert guidelines, and if not, what evidence is relied upon.

Clinical Committee Findings and Decisions

Next Step: Cover or No Cover
If not covered, or covered unconditionally, the Chair will instruct staff to write a proposed findings and decision document for review and final adoption at the following meeting.

Next Step: Cover with Conditions
If covered with conditions, the Committee will continue discussion.

1) Does the committee have enough information to identify conditions or criteria?
   - Refer to evidence identification document and discussion.
   - Chair will facilitate discussion, and if enough members agree, conditions and/or criteria will be identified and listed.
   - Chair will instruct staff to write a proposed findings and decision document for review and final adoption at next meeting.

2) If not enough or appropriate information, then Chair will facilitate a discussion on the following:
   - What are the known conditions/criteria and evidence state
   - What issues need to be addressed and evidence state

The chair will delegate investigation and return to group based on information and issues identified. Information known but not available or assembled can be gathered by staff ; additional clinical questions may need further research by evidence center or may need ad hoc advisory group; information on agency utilization, similar coverage decisions may need agency or other health plan input; information on current practice in community or beneficiary preference may need further public input. Delegation should include specific instructions on the task, assignment or issue; include a time frame; provide direction on membership or input if a group is to be convened.

Efficacy Considerations:

- What is the evidence that use of the technology results in more beneficial, important health outcomes? Consider:
  - Direct outcome or surrogate measure
  - Short term or long term effect
  - Magnitude of effect
  - Impact on pain, functional restoration, quality of life
  - Disease management
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to no treatment or placebo treatment?
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to alternative treatment?
- What is the evidence of the magnitude of the benefit or the incremental value
- Does the scientific evidence confirm that use of the technology can effectively replace other technologies or is this additive?
- For diagnostic tests, what is the evidence of a diagnostic tests' accuracy
  - Does the use of the technology more accurately identify both those with the condition being evaluated and those without the condition being evaluated?
- Does the use of the technology result in better sensitivity and better specificity?
- Is there a tradeoff in sensitivity and specificity that on balance the diagnostic technology is thought to be more accurate than current diagnostic testing?
- Does use of the test change treatment choices

Safety

- What is the evidence of the effect of using the technology on significant morbidity?
    - Frequent adverse effect on health, but unlikely to result in lasting harm or be life-threatening, or;
    - Adverse effect on health that can result in lasting harm or can be life-threatening.
- Other morbidity concerns
- Short term or direct complication versus long term complications
- What is the evidence of using the technology on mortality – does it result in fewer adverse non-fatal outcomes?

Cost Impact

- Do the cost analyses show that use of the new technology will result in costs that are greater, equivalent or lower than management without use of the technology?

Overall

- What is the evidence about alternatives and comparisons to the alternatives
- Does scientific evidence confirm that use of the technology results in better health outcomes than management without use of the technology?