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**Use of recombinant human bone morphogenetic protein-2 in spine surgery**

Lykissas M *et al*. Use of rhbmp-2 in spine surgery

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**Abstract**

Bone morphogenetic proteins are osteoinductive factors which have gained popularity in orthopaedic surgery and especially in the spine surgery. The use of recombinant human bone morphogenetic protein-2 (rhBMP-2) has been officially approved by the United States Food and Drug Administration only for single level anterior lumbar interbody fusion (ALIF), nevertheless it is widely used by many surgeons with off-label indications. Despite advantages in bone formation, its use still remains a controversial issue and several complications have been described by authors who oppose their wide use.

**Key words:** Recombinant human bone morphogenetic protein-2; Spine; Fusion; Bone graft; Yale University Open Data project

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**Core tip:** The use of recombinant human bone morphogenetic protein-2 is widely used in spine surgery not only in approved indications but also in off-label indications. Despite its ability to promote infusion there are many reported disadvantages. That's why the Yale University Open Data project aims to serve both the patients but also the companies which fund the vast majority of research in medical products.

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**INTRODUCTION**

During the last 10 years, the use of bone morphogenetic proteins (BMPs) has become very popular in orthopaedic surgery. BMPs are osteoinductive factors which are capable of inhibiting chondrocyte differentiation independently and they are recognized as important regulators of growth, differentiation, and morphogenesis during embryology[[1](#_ENREF_1),[2](#_ENREF_2)]. They are members of the superfamily of transforming growth factor-β (TGF-β) and play an important role in the development and regeneration of various tissues including bone, cartilage, and tendons[[3](#_ENREF_3),[4](#_ENREF_4)]. Marshall Urist[[5](#_ENREF_5)] in 1965 described first these factors with the term “bone autoinduction principle”. During the last two decades BMPs gradually gained popularity in bone healing and especially in spinal fusion enhancement. BMPs are released by platelets and osteogenitor cells and their main role is to stimulate cellular proliferation, angiogenesis, osteoblast differentiation, and direct bone matrix formation[[6](#_ENREF_6)]. More than 20 different types of BMPs have been identified since Marshal Urist[[7](#_ENREF_7)] described their properties and all of them have significant osteogenic properties. From all types of BMPs, BMP-2 has been found to be the most osteoinductive and its efficacy to generate an osseous fusion mass has been well established in several preclinical spine models[[8](#_ENREF_8)].

In spine surgery, autogenous bone grafting is often used to stimulate fusion. Due to the insufficiency of traditional techniques of bone grafting in long spinal fusions or spinal fusions in adverse metabolic conditions, bone grafts substitutes, such as recombinant human bone morphogenetic protein-2 (rhBMP-2), have been introduced in the clinical practice[[9](#_ENREF_9)].

**INDICATIONS**

RhBMP-2 in spinal surgery was first studied clinically in anterior lumbar interbody fusion (ALIF) and was compared with iliac crest bone graft[[10](#_ENREF_10)]. The fusion rate of rhBMP-2 group was 94.5% whereas the fusion rate in the group where iliac crest bone graft was used was 88.7%. More studies supporting the effectiveness of rhBMP-2 in spine fusion followed, which resulted in the approval of rhBMP-2 by the United States Food and Drug Administration (FDA) for single-level ALIF within specific threaded cages in skeletally mature patients. In a meta-analysis in 2014 the authors report that rhBMP-2 in lumbar spine fusion can increase the fusion rate[[11](#_ENREF_11)], while reduce the reoperation rate and operating time. Additionally, it does not increase the complication rate, the amount of blood loss, and the hospital stay.

**OFF-LABEL USE**

Although rhBMP-2 has been approved by the FDA for a single narrow method of spinal fusion, over the last 10 years, numerous articles on BMP-2 have documented its use for a far wider range of spinal applications. Since its approval, rhBMP-2 has gained popularity as an effective bone-graft substitute as it obviates the need for autologous bone graft harvesting and eliminates associated complications and donor site morbidity[[12](#_ENREF_12),[13](#_ENREF_13)]. Many surgeons, began the off-label use of the product in all spinal regions[[14-17](#_ENREF_14)], after which new complications associated with the use of rhBMP-2 emerged, including among others severe soft-tissue swelling following anterior cervical discectomy and fusion, heterotopic bone formation, and vertebral body osteolysis in the thoracic and lumbar spine[[18-20](#_ENREF_18)]. Ong *et al*[[21](#_ENREF_21)] reported that the 85% of all surgeries in which rhBMP-2 was used were for “off-label” applications. These off-label indications included posterior lumbar interbody infusion (PLIF), transforaminal lumbar interbody infusion (TLIF), posterior lumbar fusion (PLF), anterior cervical discectomy and fusion (ACDF), and more recently, lateral lumbar interbody fusion (LLIF)[[22](#_ENREF_22)].

Rihn *et al*[[23](#_ENREF_23)]*,* in 2009 published their study about the use of rhBMP-2 in single-level transforaminal lumbar interbody fusion. They showed high rate of fusion and symptomatic improvement of symptoms. Nevertheless, its use was associated with complications that raise concern including a high rate of postoperative radiculitis. One year later, Oliveira *et al*[[24](#_ENREF_24)] presented their results using rhBMP-2 in standalone lateral lumbar interbody fusion. Following a 24 mo follow-up, the authors concluded that single level disc degenerative disease can be successfully treated with standalone lateral lumbar interbody fusion using rhBMP-2 providing except of pain relief significant cost reduction. Complications included cage subsidence, heterotopic bone formation, persistent stenosis, and adjacent level degeneration.

According to a current retrospective cohort study[[25](#_ENREF_25)], during the last years a decrease in the off-label use of BMP-2 in spinal fusions and particularly in cervical spine fusions was noticed. The authors noted that although there was a tendency of decreased odds from 2009 to 2012, a higher resource utilization and odds for complications remained in patients in whom BMP-2 was used.

**ADVANTAGES**

One of the main advantages of the use of rhBMP-2 in spinal fusion is the elimination of adverse events that have been associated with iliac crest bone graft harvesting despite the improvement of bone-harvesting techniques. These complications include pain, hematoma formation, sacral fracture, and infection[[8](#_ENREF_8)].

In spine surgery, the rhBMP-2 fusion rate is usually compared with the iliac crest bone graft fusion rate. In the first prospective randomized controlled trial in 2000 Boden *et al*[[26](#_ENREF_26)] supported that arthrodesis occurred more reliably in patients treated with rhBMP-2 filled cages than in controls treated with autogenous bone graft. In general, the fusion rate with the use of rhBMP-2 ranges from 94.5% to 100%, whereas with the use of iliac crest bone graft the fusion rate ranges from 88.7% to 100%. The main complaint in the group of patients treated with iliac crest bone graft was the pain at the donor site. It was also suggested that there is more blood loss with the use of iliac crest bone graft, as well as more operating time. Moreover, in some specific cases, such as in women with osteoporosis, it was speculated that the osteoinductive ability of rhBMP-2 was more efficient when compared to iliac crest bone graft[[10](#_ENREF_10),[17](#_ENREF_17)].

In 2009, Dawson *et al*[[27](#_ENREF_27" \o "Dawson, 2009 #624)] combined rhBMP-2 on an absorbable collagen sponge with a ceramic-granule bulking agent in patients undergoing single level posterolateral lumbar fusion. The group of patients who received this combination was compared with a control group of patients who were treated with autogenous iliac crest bone graft. The authors concluded that the combination of the absorbable collagen sponge soaked with rhBMP-2 and ceramic granules provided not only improved clinical results, but also higher radiographic fusion rates when compared to the control group of patients.

The cost should also be taken seriously into consideration. In 2008, Glassmann *et al*[[28](#_ENREF_28" \o "Glassman, 2008 #597)] compared the perioperative costs for patients treated with rhBMP-2 or iliac crest bone graft. Surprisingly, the mean cost for the 3 mo perioperative period was 33860 $ in the rhBMP-2 group and 37227 $ in the iliac crest bone graft group. A decreased physician fee was also noticed in the rhBMP-2 group (5082 $ and 5316 $, respectively).

Taking all these into consideration, someone can assume that there is no difference between the rhBMP-2 and the iliac crest bone graft in terms of obtaining a solid spinal fusion. Nevertheless, it seems that the rhBMP-2 can achieve an “easier” and faster fusion with no donor site morbidity.

**COMPLICATIONS**

The first studies presenting the results of rhBMP-2 in spine surgery, reported no adverse events directly related to BMP-2 usage[[7](#_ENREF_7)]. It has to be mentioned though that all these studies were industry supported.

More recently, authors started to present disadvantages for the use of BMPs especially in its off-label indications. Nancy Epstein[[29](#_ENREF_29)] in 2013 presented several complications associated with the off-label use of rhBMP-2 including heterotopic ossification, postoperative seroma/hematoma formation, increased infection rate, arachnoiditis, dysphagia following ACDF, retrograde ejaculation after ALIF, increased neurologic deficits, and cancer. Neurologic deficits following lateral lumbar interbody fusion with the supplementary use of rhBMP-2 were also recorded in another study where 919 treated levels were reviewed[[30](#_ENREF_30" \o "Lykissas, 2014 #609)]. Immediately after surgery, sensory and motor deficits were identified in 38% of the patients treated with rhBMP-2 and in 23.9% of the patients fused with cancellous allograft or iliac crest bone autograft. At the last follow-up, the percentage of sensory and motor deficits was decreased to 24.1% and 17.3%, respectively. A potential deleterious effect of rhBMP-2 on the lumbosacral plexus was suggested[[22](#_ENREF_22)]. Mitchell *et al*[[31](#_ENREF_31" \o "Mitchell, 2016 #720)] in an experimental study in 2016, modeled the clinical use of BMP-2 for posterior lumbar fusion. They concluded that the implantation of rhBMP-2 on the lumbar spine may trigger neuroinflammatory responses in the dorsal root ganglia.

Certain cancer cell lines have been shown to have BMPs receptors and local administration of these growth factors has led to stimulation of cell growth of cancer lines *in vitro*[[32](#_ENREF_32)]. In a comparative study of 463 patients, Carraggee *et al*[[33](#_ENREF_33)] concluded that a high dose of 40 mg of rhBMP-2 in lumbar spinal arthrodesis is associated with an increased risk of new cancer. On the other hand, in a current study of Beachler *et al*[[34](#_ENREF_34)] in a large population of elderly United States adults who underwent lumbar arthrodesis, rhBMP-2 was not associated with cancer risk or increased mortality.

The mechanism of rhBMP-2 action that may have led to complications described above has been investigated. Hsu *et al*[[35](#_ENREF_35)] in an experimental study of posterolateral intertransverse lumbar spinal fusion demonstrated that the *in vivo* host response to rhBMP-2 may be associated with circulating proinflammatory and osteoclastic cytokines, such as tumor necrosis factor-α, macrophage inflammatory protein 1-alpha, and interleukin1-β. Additionally, angiogenesis was found to be stimulated through the induction of vascular endothelial growth factors secretion[[36](#_ENREF_36" \o "Deckers, 2002 #538)].

**FURTHER RESEARCH**

Increased use of rhBMP-2 in spine surgery has raised several controversial conflicts among investigators. During the last years a new promising project has been established, which aims to cope with the issue of unpublished or selectively published clinical evidence[[37](#_ENREF_37),[38](#_ENREF_38)]. The Yale University Open Data Access (YODA) project aims to serve patients and produce benefits for the companies that fund the vast majority of research in medical products. Lately two systematic reviews on rhBMP-2, which are based on patient-level data were shared through YODA. The agreement between the YODA team and Medtronic (rhBMP-2 company) included two parts. Firstly, two independent research groups were selected through a competitive process to evaluate the quality of the studies and synthesize evidence regarding the effectiveness and safety of rhBMP-2. Secondly, the YODA team made the data available to others for potential scientific questions. In this way all the clinical trial data for this product should have been made available in order to be used by other investigators for further analysis[[39](#_ENREF_39)].

These two studies concluded in the same results after analyzing their data. Despite the higher fusion rate that was observed with the use of rhBMP-2, clinical results showed no significant differences between the use of iliac crest bone graft and rhBMP-2. The authors of both studies agreed that a clear safety risk is posed when rhBMP-2 is used in the anterior aspect of the cervical spine[[8](#_ENREF_8)]. As far as it concerns the carcinogenicity, one study showed significantly higher rate of cancer in patients who were treated with rhBMP-2, while the other presented statistically insignificant higher incidence of cancer in the rhBMP-2 group. Both teams of investigators reached to the same conclusion: despite the higher rate of cancer appearance, the overall absolute risk of carcinogenesis due to the use of rhBMP-2 for spinal fusion is generally low[[40](#_ENREF_40)].

However, Carraggee *et al*[[41](#_ENREF_41)] supported that despite access to Medtronic trial data, the YODA project will not be able to resolve many, if not most, fundamental safety and efficacy issues on various current uses because there are inadequate trials available.

**CONCLUSION**

RhBMP-2, due to its ability to stimulate bone formation may offer an effective alternative method of fusion in spine surgery. The clinical outcomes and fusion rates are comparable with those of iliac crest bone graft. Ιn some challenging situations though, rhBMP-2 may have even better results. Its cost is higher compared with the cost of other bone graft substitutes, but concerning the total cost for a patient who needs multiple surgeries to achieve a solid spinal fusion, it seems that rhBMP-2 may be proved cost effective. RhBMP-2 is very often used in spinal applications that have not been studied and/or approved by the FDA, where their results may be unpredictable. Long-term outcomes from randomized control trials are warranted to further clarify the appropriate dose, carrier, and indications of rhBMP-2.

**REFERENCES**

1. **Gkiatas I**, Lykissas M, Kostas-Agnantis I, Korompilias A, Batistatou A, Beris A. Factors affecting bone growth. *Am J Orthop* (Belle Mead NJ) 2015; **44**: 61-67 [PMID: 25658073]
2. **Reddi AH**. Bone morphogenetic proteins: from basic science to clinical applications. *J Bone Joint Surg Am* 2001; **83-A Suppl 1**: S1-S6 [PMID: 11263660 DOI: 10.2106/00004623-200100001-00001]
3. **Yamada M**, Akeda K, Asanuma K, Thonar EJ, An HS, Uchida A, Masuda K. Effect of osteogenic protein-1 on the matrix metabolism of bovine tendon cells. *J Orthop Res* 2008; **26**: 42-48 [PMID: 17676621 DOI: 10.1002/jor.20474]
4. **Helm GA**, Alden TD, Sheehan JP, Kallmes D. Bone morphogenetic proteins and bone morphogenetic protein gene therapy in neurological surgery: a review. *Neurosurgery* 2000; **46**: 1213-1222 [PMID: 10807254 DOI: 10.1097/00006123-200005000-00038]
5. **Urist MR**. Bone: formation by autoinduction. 1965. *Clin Orthop Relat Res* 2002; **(395)**: 4-10 [PMID: 11937861 DOI: 10.1097/00003086-200202000-00002]
6. **Valdes MA**, Thakur NA, Namdari S, Ciombor DM, Palumbo M. Recombinant bone morphogenic protein-2 in orthopaedic surgery: a review. *Arch Orthop Trauma Surg* 2009; **129**: 1651-1657 [PMID: 19280204 DOI: 10.1007/s00402-009-0850-8]
7. **Even J**, Eskander M, Kang J. Bone morphogenetic protein in spine surgery: current and future uses. *J Am Acad Orthop Surg* 2012; **20**: 547-552 [PMID: 22941797 DOI: 10.5435/JAAOS-20-09-547]
8. **Hsu WK**. Recombinant Human Bone Morphogenetic Protein-2 in Spine Surgery. *JBJS Rev* 2014; **2**: pii: 01874474-201402060-00004 [PMID: 27500718 DOI: 10.2106/JBJS.RVW.M.00107]
9. **Carragee EJ**, Hurwitz EL, Weiner BK. A critical review of recombinant human bone morphogenetic protein-2 trials in spinal surgery: emerging safety concerns and lessons learned. *Spine J* 2011; **11**: 471-491 [PMID: 21729796 DOI: 10.1016/j.spinee.2011.04.023]
10. **Burkus JK**, Gornet MF, Dickman CA, Zdeblick TA. Anterior lumbar interbody fusion using rhBMP-2 with tapered interbody cages. *J Spinal Disord Tech* 2002; **15**: 337-349 [PMID: 12394656 DOI: 10.1097/00024720-200210000-00001]
11. **Zhang H**, Wang F, Ding L, Zhang Z, Sun D, Feng X, An J, Zhu Y. A meta analysis of lumbar spinal fusion surgery using bone morphogenetic proteins and autologous iliac crest bone graft. *PLoS One* 2014; **9**: e97049 [PMID: 24886911 DOI: 10.1371/journal.pone.0097049]
12. **Mummaneni PV**, Pan J, Haid RW, Rodts GE. Contribution of recombinant human bone morphogenetic protein-2 to the rapid creation of interbody fusion when used in transforaminal lumbar interbody fusion: a preliminary report. Invited submission from the Joint Section Meeting on Disorders of the Spine and Peripheral Nerves, March 2004. *J Neurosurg Spine* 2004; **1**: 19-23 [PMID: 15291015 DOI: 10.3171/spi.2004.1.1.0019]
13. **Villavicencio AT**, Burneikiene S, Nelson EL, Bulsara KR, Favors M, Thramann J. Safety of transforaminal lumbar interbody fusion and intervertebral recombinant human bone morphogenetic protein-2. *J Neurosurg Spine* 2005; **3**: 436-443 [PMID: 16381205 DOI: 10.3171/spi.2005.3.6.0436]
14. **Glassman SD**, Carreon L, Djurasovic M, Campbell MJ, Puno RM, Johnson JR, Dimar JR. Posterolateral lumbar spine fusion with INFUSE bone graft. *Spine J* 2007; **7**: 44-49 [PMID: 17197332 DOI: 10.1016/j.spinee.2006.06.381]
15. **Glassman SD**, Dimar JR, Burkus K, Hardacker JW, Pryor PW, Boden SD, Carreon LY. The efficacy of rhBMP-2 for posterolateral lumbar fusion in smokers. *Spine* (Phila Pa 1976) 2007; **32**: 1693-1698 [PMID: 17621221 DOI: 10.1097/BRS.0b013e318074c366]
16. **Boden SD**, Kang J, Sandhu H, Heller JG. Use of recombinant human bone morphogenetic protein-2 to achieve posterolateral lumbar spine fusion in humans: a prospective, randomized clinical pilot trial: 2002 Volvo Award in clinical studies. *Spine* (Phila Pa 1976) 2002; **27**: 2662-2673 [PMID: 12461392 DOI: 10.1097/00007632-200212010-00005]
17. **Baskin DS**, Ryan P, Sonntag V, Westmark R, Widmayer MA. A prospective, randomized, controlled cervical fusion study using recombinant human bone morphogenetic protein-2 with the CORNERSTONE-SR allograft ring and the ATLANTIS anterior cervical plate. *Spine* (Phila Pa 1976) 2003; **28**: 1219-124; discussion 1225 [PMID: 12811263 DOI: 10.1097/01.BRS.0000065486.22141.CA]
18. **Shields LB**, Raque GH, Glassman SD, Campbell M, Vitaz T, Harpring J, Shields CB. Adverse effects associated with high-dose recombinant human bone morphogenetic protein-2 use in anterior cervical spine fusion. *Spine* (Phila Pa 1976) 2006; **31**: 542-547 [PMID: 16508549 DOI: 10.1097/01.brs.0000201424.27509.72]
19. **Smucker JD**, Rhee JM, Singh K, Yoon ST, Heller JG. Increased swelling complications associated with off-label usage of rhBMP-2 in the anterior cervical spine. *Spine* (Phila Pa 1976) 2006; **31**: 2813-2819 [PMID: 17108835 DOI: 10.1097/01.brs.0000245863.52371.c2]
20. **Dmitriev AE**, Castner S, Lehman RA, Ling GS, Symes AJ. Alterations in recovery from spinal cord injury in rats treated with recombinant human bone morphogenetic protein-2 for posterolateral arthrodesis. *J Bone Joint Surg Am* 2011; **93**: 1488-1499 [PMID: 22204004 DOI: 10.2106/JBJS.J.00904]
21. **Ong KL**, Villarraga ML, Lau E, Carreon LY, Kurtz SM, Glassman SD. Off-label use of bone morphogenetic proteins in the United States using administrative data. *Spine* (Phila Pa 1976) 2010; **35**: 1794-1800 [PMID: 20700081 DOI: 10.1097/BRS.0b013e3181ecf6e4]
22. **Lykissas MG**, Aichmair A, Sama AA, Hughes AP, Lebl DR, Cammisa FP, Girardi FP. Nerve injury and recovery after lateral lumbar interbody fusion with and without bone morphogenetic protein-2 augmentation: a cohort-controlled study. *Spine J* 2014; **4**: 217-224 [PMID: 242269858 DOI: 10.1016/j.spinee.2013.06.109]
23. **Rihn JA**, Makda J, Hong J, Patel R, Hilibrand AS, Anderson DG, Vaccaro AR, Albert TJ. The use of RhBMP-2 in single-level transforaminal lumbar interbody fusion: a clinical and radiographic analysis. *Eur Spine J* 2009; **18**: 1629-1636 [PMID: 19475434 DOI: 10.1007/s00586-009-1046-1]
24. **Pimenta** L. The use of rh-bmp2 in standalone extreme lateral interbody fusion (Xlif®): clinical and radiological results after 24 months follow-up. *World Spinal Column J* 2010; **1**: 19-25
25. **Poeran J**, Opperer M, Rasul R, Mazumdar M, Girardi FP, Hughes AP, Memtsoudis SG, Vougioukas V. Change in Off-Label Use of Bone Morphogenetic Protein in Spine Surgery and Associations with Adverse Outcome. *Global Spine J* 2016; **6**: 650-659 [PMID: 27781184 DOI: 10.1055/s-0036-1571284]
26. **Boden SD**, Zdeblick TA, Sandhu HS, Heim SE. The use of rhBMP-2 in interbody fusion cages. Definitive evidence of osteoinduction in humans: a preliminary report. *Spine* (Phila Pa 1976) 2000; **25**: 376-381 [PMID: 10703113 DOI: 10.1097/00007632-200002010-00020]
27. **Dawson E**, Bae HW, Burkus JK, Stambough JL, Glassman SD. Recombinant human bone morphogenetic protein-2 on an absorbable collagen sponge with an osteoconductive bulking agent in posterolateral arthrodesis with instrumentation. A prospective randomized trial. *J Bone Joint Surg Am* 2009; **91**: 1604-1613 [PMID: 19571082 DOI: 10.2106/JBJS.G.01157]
28. **Glassman SD**, Carreon LY, Campbell MJ, Johnson JR, Puno RM, Djurasovic M, Dimar JR. The perioperative cost of Infuse bone graft in posterolateral lumbar spine fusion. *Spine J* 2008; **8**: 443-448 [PMID: 17526436 DOI: 10.1016/j.spinee.2007.03.004]
29. **Epstein NE**. Complications due to the use of BMP/INFUSE in spine surgery: The evidence continues to mount. *Surg Neurol Int* 2013; **4**: S343-S352 [PMID: 23878769 DOI: 10.4103/2152-7806.114813]
30. **Lykissas MG**, Aichmair A, Hughes AP, Sama AA, Lebl DR, Taher F, Du JY, Cammisa FP, Girardi FP. Nerve injury after lateral lumbar interbody fusion: a review of 919 treated levels with identification of risk factors. *Spine J* 2014; **14**: 749-758 [PMID: 24012428 DOI: 10.1016/j/.spinee.2013.06.066]
31. **Mitchell K**, Shah JP, Dalgard CL, Tsytsikova LV, Tipton AC, Dmitriev AE, Symes AJ. Bone morphogenetic protein-2-mediated pain and inflammation in a rat model of posterolateral arthrodesis. *BMC Neurosci* 2016; **17**: 80 [PMID: 27905881 DOI: 10.1186/s12868-016-0314-3]
32. **Feeley BT**, Gamradt SC, Hsu WK, Liu N, Krenek L, Robbins P, Huard J, Lieberman JR. Influence of BMPs on the formation of osteoblastic lesions in metastatic prostate cancer. *J Bone Miner Res* 2005; **20**: 2189-2199 [PMID: 16294272 DOI: 10.1359/JBMR.050802]
33. **Carragee EJ**, Chu G, Rohatgi R, Hurwitz EL, Weiner BK, Yoon ST, Comer G, Kopjar B. Cancer risk after use of recombinant bone morphogenetic protein-2 for spinal arthrodesis. *J Bone Joint Surg Am* 2013; **95**: 1537-1545 [PMID: 24005193 DOI: 10.2106/JBJS.L.01483]
34. **Beachler DC**, Yanik EL, Martin BI, Pfeiffer RM, Mirza SK, Deyo RA, Engels EA. Bone Morphogenetic Protein Use and Cancer Risk Among Patients Undergoing Lumbar Arthrodesis: A Case-Cohort Study Using the SEER-Medicare Database. *J Bone Joint Surg Am* 2016; **98**: 1064-1072 [PMID: 27385679 DOI: 10.2106/JBJS.15.01106]
35. **Hsu WK**, Polavarapu M, Riaz R, Larson AC, Diegmueller JJ, Ghodasra JH, Hsu EL. Characterizing the host response to rhBMP-2 in a rat spinal arthrodesis model. *Spine* (Phila Pa 1976) 2013; **38**: E691-E698 [PMID: 23429681 DOI: 10.1097/BRS.0b013e31828cb977]
36. **Deckers MM**, van Bezooijen RL, van der Horst G, Hoogendam J, van Der Bent C, Papapoulos SE, Löwik CW. Bone morphogenetic proteins stimulate angiogenesis through osteoblast-derived vascular endothelial growth factor A. *Endocrinology* 2002; **143**: 1545-1553 [PMID: 11897714 DOI: 10.1210/endo.143.4.8719]
37. **Krumholz HM**. Open science and data sharing in clinical research: basing informed decisions on the totality of the evidence. *Circ Cardiovasc Qual Outcomes* 2012; **5**: 141-142 [PMID: 22438459 DOI: 10.1161/CIRCOUTCOMES.112.965848]
38. **Ross JS**, Lehman R, Gross CP. The importance of clinical trial data sharing: toward more open science. *Circ Cardiovasc Qual Outcomes* 2012; **5**: 238-240 [PMID: 22438465 DOI: 10.1161/CIRCOUTCOMES.112.965798]
39. **Krumholz HM**, Ross JS, Gross CP, Emanuel EJ, Hodshon B, Ritchie JD, Low JB, Lehman R. A historic moment for open science: the Yale University Open Data Access project and medtronic. *Ann Intern Med* 2013; **158**: 910-911 [PMID: 23778908 DOI: 10.7326/0003-4819-158-12-201306180-00009]
40. **Fu R**, Selph S, McDonagh M, Peterson K, Tiwari A, Chou R, Helfand M. Effectiveness and harms of recombinant human bone morphogenetic protein-2 in spine fusion: a systematic review and meta-analysis. *Ann Intern Med* 2013; **158**: 890-902 [PMID: 23778906 DOI: 10.7326/0003-4819-158-12-201306180-00006]
41. **Carragee EJ**, Baker RM, Benzel EC, Bigos SJ, Cheng I, Corbin TP, Deyo RA, Hurwitz EL, Jarvik JG, Kang JD, Lurie JD, Mroz TE, Oner FC, Peul WC, Rainville J, Ratliff JK, Rihn JA, Rothman DJ, Schoene ML, Spengler DM, Weiner BK. A biologic without guidelines: the YODA project and the future of bone morphogenetic protein-2 research. *Spine J* 2012; **12**: 877-880 [PMID: 23199819 DOI: 10.1016/j.spinee.2012.11.002]

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