Recombinant Human Bone Morphogenetic Protein (rhBMP-2)

NASS® NORTH AMERICAN SPINE SOCIETY

DEFINING APPROPRIATE COVERAGE POSITIONS

COVERAGE TASKFORCE

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Introduction

North American Spine Society (NASS) coverage policy recommendations are intended to assist payers and members by proactively defining appropriate coverage positions. Historically, NASS has provided comment on payer coverage policy upon request. However, in considering coverage policies received by the organization, NASS believes proactively examining medical evidence and recommending credible and reasonable positions may be to the benefit of both payers and members in helping achieve consensus on coverage before it becomes a matter of controversy.

Methodology

The coverage policies put forth by NASS use an evidence-based approach to spinal care when possible. In the absence of strict evidence-based criteria, policies reflect the multidisciplinary and non-conflicted experience and expertise of the authors in order to reflect reasonable standard practice indications in the United States.

To prepare this coverage policy, an extensive literature search of the PubMed, EMBASE, Web of Science, and Cochrane databases were reviewed.

NASS Coverage Policy Methodology

Scope and Clinical Indications

This coverage policy document addresses the scope and clinical indications for Recombinant human bone morphogenetic protein-2 (rhBMP-2) in spinal fusion surgeries only. There are other indications for its use in the appendicular skeleton (e.g. tibial fracture nonunion repair surgery). Those indications are not addressed in this document.

Based on the available evidence, rhBMP is indicated as an adjunct to spinal fusion in cases in which other alternatives are either not available or are not likely to lead to successful fusion.

As a clearer picture of the risks and potential for adverse events after rhBMP implantation emerges, a reassessment of the risk-benefit calculus is required. This will likely be an ongoing process in the future. For the purpose of determining coverage at the current time, this calculation can be generalized in several anatomic areas and clinical scenarios in which rhBMP should NOT be used. These include patients very likely to fuse without rhBMP, most pediatric patients, healthy patients undergoing one level lumbar fusion procedures, and routine anterior and posterior cervical fusions.

On the other hand, as detailed below, the evidence for continued utilization of rhBMP for spinal fusion surgery in well-selected patients is supportive. The strength of this evidence varies from level I to level IV. Specific patient groups likely to benefit from the availability of rhBMP include: patients undergoing revision fusion for pseudarthrosis; fusion surgery in a compromised graft bed (e.g. prior radiation therapy); multilevel thoracolumbar fusions, especially long fusions to the sacrum in adult patients undergoing correction or stabilization of spinal deformity; patients with metabolic or other conditions increasing their risk for failure with traditional, autogenous bone grafting (e.g. smokers, diabetics, hypertensive patients, and the elderly); patients in whom autogenous bone is either not available or simply of too poor quality to be useful (e.g. rheumatoid arthritis patients).

Coverage Recommendation(s)

rhBMP-2 may be considered as an adjunct to spinal fusion for the following diagnoses with qualifying criteria, when appropriate.

1. Stand-Alone Anterior Lumbar Interbody Fusion (ALIF): in all patient groups except males with a strong reproductive priority.
2. Posterolateral Lumbar Fusion: in patients at high risk for nonunion with autogenous bone graft or in those with inadequate or poor quality autogenous bone available. This group includes:
    - Revision Posterior Fusion
    - Patients with poor quality or unavailable iliac crest autograft (trauma patients with concomitant pelvic injury, rheumatoid patients, etc.)
    - Multilevel surgeries (> 3 levels), particularly those extending to the sacrum or pelvis
    - Elderly patients with osteoporosis
    - Previous radiation or other insult to the fusion bed
    - Metabolic factors that are likely to interfere with proper autograft incorporation, such as: smokers, diabetics, patients with hypertension
3. Posterior Lumbar Interbody Fusion (PLIF and TLIF): in patients at high risk for nonunion with autogenous bone graft or in those with inadequate or poor quality autogenous bone available. This group includes:
    - Revision Posterior Fusion
    - Patients with poor quality or unavailable iliac crest autograft (trauma patients with concomitant pelvic injury, rheumatoid patients, etc.)
    - Multilevel surgeries (> 3 levels), particularly those extending to the sacrum or pelvis
    - Elderly patients with osteoporosis

- Previous radiation or other insult to the fusion bed
- Metabolic factors that are likely to interfere with proper autograft incorporation, such as: smokers, diabetics, patients with hypertension

4. Posterior Cervical or Thoracic Fusions
    - in pediatric patients at very high risk for fusion failure (e.g. neuromuscular scoliosis, occipitocervical pathology
    - in adult patients at high risk for nonunion, for example, revision surgery
5. Anterior cervical fusion: in patients at high risk for nonunion, for example revision surgery

rhBMP-2 should **NOT** be considered in cases that do not fulfill the above criteria. Of note, rhBMP-2 is not indicated in the following scenarios:

- Routine anterior and posterior cervical fusion procedures
- Single level posterior/posterolateral fusions in healthy adults
- Routine pediatric spine fusion procedures (e.g. adolescent idiopathic scoliosis)

Rationale

Background of rhBMP and other Graft Sources: Recombinant human bone morphogenic protein-2 (rhBMP-2) was first identified in 1965 by Marshall Urist and colleagues at UCLA.[1] As part of the transforming growth factor-β (TGF-beta) superfamily of proteins, rhBMPs bind to cell-surface receptors where they initiate signals that control cell growth, differentiation, and migration. These effects can powerful induce bone formation.

It took 30 years of careful work with rhBMP dosing and carriers before rhBMP-2 was FDA approved for use in ALIF surgery. In 2008, it received FDA approval for use in posterolateral spine fusion surgery to repair pseudarthrosis. That same year, the FDA issued a Public Health notification regarding life threatening complications associated with anterior cervical implantation of rhBMP. During that time, competing products such as rhBMP-7 (at one time marketed by Stryker Biotech as OP-1) were also studied. These agents are no longer commonly available in North America.

The initial studies, now roughly 10 year old, suggested that rhBMP-2 could reliably induce bone formation with few, if any, device-related adverse events. More recently, a series of potential rhBMP-related complications have been reported. These complications, in turn, led to a reassessment of the original data from the Medtronic-sponsored, prospective, randomized FDA Clinical trials.

The June, 2011 special issue of *The Spine Journal* and the more recent, June 2013, publication of the YODA studies in the *Annals of Internal Medicine* have prompted surgeons to reassess their use of rhBMP-2 in spine fusion procedures. Certainly, the data reveal a number of potential complications and adverse effects possibly related to rhBMP implantation. On the other hand, in the words of Professors Eugene Carragee and Daniel Riew, rhBMP is "the most powerful inducer of bone formation available commercially." They went on to say that rhBMP "should remain an option for surgeons and well-informed patients."[2] The real question that remains is in which clinical situations do the potential benefits of rhBMP outweigh its risks?

To answer this question, a few words about comparable options are required. As a substrate for fusion, autogenous bone from the iliac crest (ICBG) remains the gold standard. However, while the morbidity of bone graft harvest continues to be debated, this procedure carries its own risks and post-operative morbidity.[3,4] In their review, Carragee and coworkers concluded that study design features in the industry sponsored rhBMP trials may have biased results against iliac crest and favored rhBMP.[5] In the YODA trials, this issue is addressed in detail by Fu et al[6] and less so by Simmonds et al.[7]

Sasso and others studied the impact of bone graft harvest in the control patients of the 208 control patients from the FDA rhBMP ALIF trials.[8] These grafts were typically obtained from separate incisions. At 24 months, 31% of patients still had donor site pain. A fair or poor appearance to the graft site was noted in 16%. On the other hand, Radcliff and others recently analyzed data from the SPORT Trial comparing 108 patients fused with ICBG and 246 fused without as part of management of degenerative spondylolisthesis with stenosis.[9] While OR time was higher in the ICBG group, this group also included more multilevel and lumbosacral fusions. Blood loss, post-operative complications and re-operation rates were statistically similar. No significant differences in SF-36, ODI, Stenosis Bothersomeness Index, Low Back Pain Bothersomeness Scale or patient satisfaction were recorded. The authors concluded "our results are consistent with previous studies that have found no long-term morbidity or worsening in outcome after iliac crest bone-graft harvest."

Additionally, there are large patient populations, typically excluded from prospective, randomized clinical trials, in which autograft volumes are inadequate or are associated with unacceptable healing rates.[10-13] Examples of high risk cases and those cases in which no other, reasonable options exist are:

- No or inadequate volume or poor quality of iliac crest
- Patients at high risk for post-harvest iliac crest fracture
- High pseudarthrosis risk
    - Current surgery to treat pseudarthrosis
    - Smokers

- Elderly
- Multilevel surgery
- Previous radiation
- Metabolic disturbance

Aside from autologous bone and rhBMP-2, other materials are commercially available as fusion substrates. These include allograft bone, demineralized bone matrix (DBM), silicates, and bone marrow aspirate. Unfortunately, the evidence base for these materials remains limited.[14] Currently, there is endorsed as ICBG or rhBMP extenders rather than as primary fusion substrates.

For example, demineralized bone matrix (DBM) is produced by acid extraction of the mineral component allograft bone. With the mineral component removed, Type I collagen, non-collagenous proteins, and rhBMPs are left. This material is thought to be both osteoconductive and, varyingly, osteoinductive.[15,16] While this material is widely available and avoids donor site morbidity, significant variation in rhBMP concentrations and osteoinduction potential have been demonstrated between products and various lots of the same product.[17-19] At the current time, there is little data supporting DBM as a stand-alone graft material.[20] More typically, the material is used as a graft extender.

In 2011, Abdullah and others performed a review of the literature on the available lumbar fusion extenders.[21] They found that calcium phosphate was most supported and that other adjuncts are either "supported by smaller bodies of evidence" (e.g. DBM and rhBMP) or "not conclusively or consistently supported by available clinical studies" (e.g. most others). Previous reviews have found similar, poor levels of evidence to support graft alternatives and extenders other than rhBMP.[22]

Below, we review the rhBMP literature by first focusing on the recent YODA studies. Reasonable people can reach, and have reached, different conclusions. Even the YODA teams from Oregon Health Sciences University and the University of York reached somewhat different conclusions while examining the same data sets. Nonetheless, the YODA process has been quite helpful, but is not definitive. These authors could only analyze the data they had. The initial FDA trial data are also, on average, 10 years old. A number of more recent studies have reported results of large groups of rhBMP patients with very different results.

At this point though, the thoughtful surgeon is rebalancing his or her risk benefit calculus in making recommendations to patients regarding bone graft options in general, and rhBMP implantation in particular. However, it is the general message of the current coverage recommendation that the most

powerful inducer of bone formation, rhBMP-2, should remain available to surgeons for appropriate cases.

The YODA Studies: Increasing reports of complications associated with rhBMP utilization in spine led Eugene Carragee and coworkers to dedicate an entire issue of **The Spine Journal** to the question about the relative risks and benefits of this molecule. A "critical review" paper excited a great deal of attention and debate.[5] These questions spurred rhBMP-2's manufacturer, Medtronic, and it's COO Omar Ishrak, to commission Harlan Krumholz, MD and colleagues at the Yale Open Data Access Project to independently reassess the individual patient data from the original FDA rhBMP trials. YODA, in turn, commissioned two independent groups of researchers from the University of York in the UK and the Oregon Health Sciences University to examine the data. Reports from the YODA process were published in the summer of 2013 in the Annals of Internal Medicine along with a number of editorials to assist readers in interpreting the data.[6,7] Later, North American Spine Society executive committee members Christopher Bono and Todd Wetzel provided an excellent, neutral review of the YODA studies.[23] This "meta-meta-analysis" has been endorsed by the Board of Directors of the North American Spine Society.

In comparing methodology, both YODA Groups[6,7] utilized individual patient data (IPD) from the Medtronic sponsored clinical trials. Each also performed a comprehensive systematic review of published literature using recognized sources (e.g. MEDLINE, EMBASE, Cochrane Library). Their meta-analyses combined data from multiple studies, when statistically appropriate to analyze a larger group of data than reported in any original single study. The goal of this meta-analysis was to increase the probability of finding significant differences not apparent in smaller studies. This approach could also "wash out" erroneous differences, created by small, heterogeneous patient cohorts detected in smaller studies. Fu et al[6] also incorporated internal reports from Medtronic and data from the FDA website. This group, from Oregon Health Sciences University performed separate meta-analyses for the different surgical approaches. Simmonds and colleagues combined the data for a single meta-analysis.

These and other data have been reviewed extensively in order to form reasonable conclusions about the prudent use of and indications for rhBMP-2 for a variety of different spinal procedures. These are discussed per procedure below. Numbering corresponds to those listed in the "Coverage Recommendations" section above.

Item 1: Anterior Lumbar Interbody Fusion

Carragee and colleagues[5] described a number of adverse events associated with the use of rhBMP-2 in anterior lumbar interbody fusion (ALIF) surgeries. Specific concerns included osteolysis, device

subsidence, reoperation rates, incidence of retrograde ejaculation and urinary retention, and infections. As noted in the posterolateral fusion section, the meta-analysis performed by Simmonds et al[7] did not separately analyze adverse events by surgical approach. They concluded that the risk for implant-related events, retrograde ejaculation, and wound complications were increased by at least 50% in rhBMP group at or shortly after surgery. Infections, urogenital events, and implant-related adverse events were also higher in rhBMP group. By 2-years post-operatively, these same adverse events remained somewhat higher in the rhBMP group. They reported that the risk of retrograde ejaculation was substantially higher in rhBMP group (odds ratio 4.76).

Fu et al[6] did analyze ALIF data independently and noted that, by 4 weeks, the overall risk of adverse events was *lower* in the rhBMP group versus ICBG (38% and 45%, respectively). They did find that retrograde ejaculation, subsidence, and urogenital problems were more common with rhBMP (both at 4 weeks and 24 month follow-up), but the differences were not statistically different (with wide and overlapping confidence intervals). Fu's group calculated the relative risk for retrograde ejaculation to be 4.36 at 2 years, a value similar to that reported by Simmonds et al.[7]

Bono and Wetzel concluded that Simmonds et al[7] agree with Carragee et al[5] regarding concerns of retrograde ejaculation, urogenital complications, subsidence, infections, and implant-related adverse events (if this can be used as a proxy for osteolysis). Fu et al[6], though not statistically significant, seem to corroborate these concerns. Both reviews reported similar relative risks for retrograde ejaculation. They could offer no resolution on the issue of reoperation rates, as these were not reported in the YODA reviews.[23]

While YODA and Carragee analyzed the initial FDA trial data, longer follow-up was reported later from the same patient cohorts. In 2009, Burkus and others published their 6 year experience with rhBMP-2 in ALIF surgery.[42] As part of an FDA multicenter RCT, 277 patients were enrolled and received either rhBMP-2 or ICBG. At 6 years, fusion rates were 98% in the rhBMP group. Significant improvements in ODI and SF-26 scores were achieved by 6 weeks and were sustained at 6 years. A similar author group had reported good results using rhBMP-2 and allograft bone dowels in ALIF surgery in 79 investigational patients when compared with 52 patients receiving ICBG.[43] That same year, Pradhan and others warned that the osteolysis associated with allograft interbody grafts was associated with graft resorption, instability and eventual nonunion.[44]

When specifically studying the risk of retrograde ejaculation (RE), disparate results have been reported. Some groups report identical RE rates between stand-alone ALIF with rhBMP and their control groups, such as artificial disc replacement. For example, one group compared RE rates in 54 patients

undergoing ALIF with rhBMP and 41 patients undergoing ADR.[45] The rate was high, but statistically similar in both groups at 7.4% and 9.8%, respectively. Recently, Lubelski et al examined the rate of urogenital complications in 110 male patients undergoing ALIF with or without use of rhBMP.[46] The overall rate of complications was similar (22% vs. 20%, p = 1.0) as was the risk of retrograde ejaculation (8% vs. 8%, respectively; p = 1.0).

In a prospective study evaluating the incidence of RE after ALIF, Tepper and others compared 21 patients treated with rhBMP to 20 patients treated without.[47] In the first study of its kind, the authors utilized not only a standardized questionnaire, but also pre- and post-operative semen and urine analysis. The rate of RE was not significantly different between groups.

Risks were compared between 207 males undergoing stand-alone ALIF with rhBMP2 versus 301 undergoing the same procedure with iliac crest autograft or a disc arthroplasty.[48] Patients had been enrolled in one of five FDA approved RCTs with a minimum of 2 years of follow-up. RE rates dropped as trials progressed. In the RE earliest trial, the RE rate was 4.1% versus 0 to 2.1% in the latest trials. Overall, the RE rate in patients receiving rhBMP was 3.4% versus 1.7% in the non-BMP group. This difference was not significant (p = 0.242). RE rate was far lower in patients undergoing a retroperitoneal approach versus those undergoing the transperitoneal approach. This difference was significant (p = 0.007).

The risk of RE was studied retrospectively using a 10 year prospectively gathered outcomes database from a busy university spine practice.[49] All male patients without baseline sexual incapacity and having ALIF for lumbar spondylosis or spondylolisthesis of the lowest one or two lumbar levels with and without rhBMP-2, from 2002 through 2011 were divided into one of 4 cohorts based on the use of rhBMP. Of 239 patients with exposure to rhBMP-2, RE was diagnosed in 15 subjects (6.3%), compared with an RE diagnosis rate of two of 233 control patients without rhBMP-2 exposure (0.9%; p=.0012). Urinary retention after bladder catheter removal was also more frequently observed in patients exposed to rhBMP-2 (9.7%) compared with control patients (4.6%; p=.043). Patients with previous treatment for prostatic hypertrophy were found to be at increased risk of RE after ALIF with rhBMP. Some studies reported no RE among their male patients undergoing ALIF with rhBMP.[38]

At this point, ALIF remains the single, FDA-approved indication for rhBMP-2. While the YODA and other recent data must be considered when weighing the risks and benefits of this material in a given patient, rhBMP should remain available to physicians and well-informed patients.

Item 2: Posterolateral Fusion

In their review paper, Carragee et al[5] reported a paradoxical effect toward increased leg pain in the rhBMP-2 group in the early postoperative period. In a small pilot study, when compared to patients fused with ICBG, the rhBMP groups exhibited higher percentages of ODI failures and leg pain scores. A higher, 10%, rate of wound complications was also "associated with rhBMP-2 use." In one of the larger RCTs, Carragee et al concluded that there were "three times as many back and leg pain adverse events...during the first 3 months."

In their meta-analysis, which was not specific to the posterolateral approach, Simmonds et al[7] reported a mean improvement in leg pain at all-time points. They demonstrate overlapping confidence intervals for leg pain scores between rhBMP and iliac crest groups. They found that mean back pain scores were worse in rhBMP group than the iliac crest group in the early postoperative period, with a slightly overlapping confidence interval. By 3 months, however, back pain was on average better in the rhBMP-2 group.

Simmonds et al[7] reported that back and leg pain adverse events at or shortly after surgery were significantly more common with rhBMP than ICBG, with no apparent overlap of the confidence intervals. Bono and Wetzel note this data seemed “somewhat incongruous” with clinical outcomes data presented above.[23] In their analysis of four key adverse events (implant-related, infection, neurologic, and pain), over all time periods for all patients, Simmonds and coworkers’ only clear finding increased pain at or shortly after surgery.

When Fu and coworkers[6] reviewed this data, they found no significant difference in overall incidence of adverse events between rhBMP and iliac crest groups, except in the early postoperative period. Early after surgery (4 weeks), back and leg pain scores were higher in rhBMP group.
Bono and Wetzel resolved these conclusions by noting that Carragee et al’s concern about leg pain in the early postop period were substantiated by both YODA reviews.[23] The impact of rhBMP on wound complication rates (which might include infections as reported by Simmonds et al.) remains unclear.[7]

A number of other studies have examined the role of rhBMP-2 in posterolateral spinal fusion. The quality of the data varies, but the data is important in that critical patient populations not included in the Medtronic-sponsored, FDA trials are included.

In a recent, very large study, Glassman and colleagues reported the complication rates from 1037 pts who underwent posterolateral spine fusion using rhBMP-2.[24] Medical and surgical complications were observed in 190 of the 1037 patients (18.3%). Of those, 81 were major complications (7.8%) and 110 minor complications (10.2%). Of those complications, using a worst case analysis, a 0.6% complication

rate was attributed to rhBMP. Previously, a similar author group reported that rhBMP-2 was a "viable ICBG replacement" when they compared 52 patients over the age of 60 undergoing posterolateral lumbar fusion with ICBG with 50 patients undergoing surgery with rhBMP.[25] In this series, 16 ICBG and 10 rhBMP patients required revision procedures for persistent symptoms.

Other recent studies have concluded that rhBMP-2 can offer higher fusion rates than autogenous bone with no or few implant related complications. For example, Park and colleagues compared fusion rates using ICBG with rhBMP versus rhBMP and local bone in 1 or 2 level posterolateral fusions in 16 and 35 patients, respectively.[26] Combining ICBG with rhBMP-2 was associated with a 96.7% fusion rate by 24 months. The fusion rate from local bone with rhBMP was statistically similar. In 2006, Singh and others compared ICBG alone vs. ICBG with rhBMP in a prospective, case-matched cohort study.[27] In their 52 patient study, there were 11 control patients, rhBMP-2 was associated with 30% higher (77 vs. 97%) fusion rate. No patients exhibited soft tissue ossification, dural ossification or laminar bone regrowth. A 2010 study found that rhBMP2 with allograft and local autograft achieved a 97.2% fusion rate in a consecutive cohort of 36 patients.[9] Acosta and others reported 90% good and excellent satisfaction and 97% fusion rates in a series of 200 consecutive patients undergoing primary lumbar fusion at a mean 2.5 levels.[28] The authors concluded that the high patient satisfactions "might be because the morbidity associated with harvesting ICBG was avoided…"

Dawson and others reported the results of a 56 patient randomized prospective trial comparing ICBG and rhBMP-2 in single level instrumented posterolateral fusions.[29] In this multicenter pilot project, more than 86% of the enrolled patients completed 24 month follow-up. Significant improvements in ODI, SF-36 and back and leg VAS pain scores were reported in both groups. There was a trend toward greater improvement and a higher fusion rate in the rhBMP group. In 2009, Dimar and colleagues reported the 2 year outcomes of their randomized, prospective study comparing ICBG with rhBMP-2 for single level posterolateral instrumented lumbar fusions.[30] The failure and second surgery rates were significantly higher ($p = 0.011$) in the ICBG group because there were 18 nonunions in that group (compared with 6 in the rhBMP group). In these 463 patients, both groups should similar improvements in pain and functional outcomes. Use of rhBMP was also associated with shorter OR times and less blood loss. A subset of these patients had previously been reported with similar results.[31]

Independent of the merits of rhBMP in one or two level posterolateral fusions in otherwise healthy patients is the utility of this material in patients at high risk of fusion failure with autogenous bone graft. Recently, Hoffman et al compared the complications of associated with use of rhBMP2 for posterolateral spine fusion in younger vs. older patients.[32] While older patients had a longer hospital stay, other complications were similar. Overall, reasonable complication rates were reported: acute seroma

formation requiring decompression, 3.1%, bone overgrowth, 0.8%, infection requiring debridement, 2.3%, and revision fusion for symptomatic nonunion, 3.7%. These same authors had previously compared rhBMP-2(67.7%), DBM (21.9%) and autograft(10.4%) in 1,398 patients treated over a 7-year period (2003-2009).[33] They reported a statistically similar, but higher incidence of seroma formation in the rhBMP group (3.2%) than in the DBM or autograft group (2.0 and 1.4%, respectively). Revision surgery for "clinically significant nonunion" was required in 103 patients (7.4%). These non-unions were significantly less likely to occur in the rhBMP-2 group, 4.3%, ($p<0.001$) compared to the DBM or autograft group (13.1 and 15.2%, respectively).

Lee and colleagues compared fusion rates and time to fusion in patients receiving ICBG versus rhBMP in posterolateral lumbar fusions.[34] They divided their cohort of 195 patients into four groups: ICBG with or without risk factors for pseudarthrosis and rhBMP2 with or without risk factors. Risk factors included smoking, hypertension, diabetes, osteoporosis, multilevel surgery, revision surgery and other comorbidities. With the relatively low per level dose used, rhBMP was associated with more rapid progression to fusion in all groups. In the no risk factor group, fusion rates were higher in the rhBMP group while the fusion rate was higher with ICBG in the high risk group. The authors concluded that "When compared with patients with fusion-related risk factors, the use of rhBMP-2 was comparable with autograft but was not sufficient to overcome all aspects of the weakened osteoinductive capacity encountered in patients with these risk factors."

Glassman and others compared the fusion rates of smokers and non-smokers in single level posterolateral instrumented fusions.[35] Retrospectively analyzing data extracted from the prospective FDA rhBMP trials, the author reported a fusion rate of 100% in the non-smokers and 95.2% (20 of 21 smokers) using rhBMP-2. They concluded that rhBMP-2 may enhance the fusion rate in smokers. Clinical outcomes were still adversely affected by smoking, however.

In a group of 55 moderately disabled to bedridden, elderly patients, lumbar decompression and fusion with rhBMP produced an 85% rate of improved functional and pain scores at a mean 6 months post-operative.[36] In this fragile population, no metallic implants were employed, yet an 80% fusion rate was reported. The initial, pilot study describing the outcomes of rhBMP-2 use for posterolateral fusion included both instrumented and uninstrumented cases.[37] A 100% fusion rate and "Statistically greater and quicker improvement in patient-derived clinical outcome(s)" were reported.

Another special subgroup of rhBMP fusion cases represents long thoracolumbar fusions, typically performed for spinal deformity. While a large percentage of these cases are performed as anterior-posterior surgeries, the rhBMP-2 is used posteriorly when adequate volumes of ICBG are not available or

when the presumptive fusion rate with ICBG alone is considered suboptimal. In a group of 502 long thoracolumbar deformity procedures in which large doses of rhBMP were used, no major radiculopathy (1%) or seroma (0.6%) problems were noted.[38]

In 2009, Maeda and colleagues reported compared 32 patients undergoing long thoracolumbar fusion with ICBG with 23 patients undergoing the same procedure with rhBMP-2 and no ICBG.[39] The ICBG group had a 28.1% pseudarthrosis rate while rhBMP use was associated with a 4.3% pseudarthrosis rate. Other outcomes were similar between the groups. In 2013, Kim and coworkers compared outcomes and complications associated with rhBMP2 and ICBG in long thoracolumbar fusions for deformity.[12] The two groups were well matched in terms of age, comorbidities and technical details and included 31 patients received rhBMP while 32 received ICBG. Of note, 8 of the patients in the rhBMP group underwent posterior only surgery, while all of the patients in the ICBG group underwent formal anterior-posterior surgery. Oswestry Disability Indexes were similar between groups. However, the rhBMP group demonstrated superior sum composite Scoliosis Research Society scores in pain, self-image and function domains (P = 0.02). The fusion rates for rhBMP group were 93.5% and 71.9% for the ICBG group.

Previously, Mulconrey and coworkers described a minimum 2 year follow-up of anterior, posterior and anterior-posterior spine fusions performed with rhBMP-2. They prospectively followed 98 patients who underwent fusion at a total of 308 levels. The patients were divided into three groups. Their rhBMP doses ranged from 10mg/level (placed in an anterior titanium mesh cage) to 40mg/level (posterolateral fusion patients in whom no autologous bone was available. Fusion rates averaged 95% across the groups with a 100% fusion rate achieved in the posterolateral fusions performed with 40mg rhBMP/level and no autologous bone.[40] Earlier studies from the same center had also shown high fusion rates with rhBMP-2 in long thoracolumbar deformity surgeries.[41]

While the YODA and other recent data must be considered when weighing the risks and benefits of this material in a given patient, rhBMP should remain available to physicians and well-informed patients. Especially in patients at risk for fusion failure or without adequate volume or quality of autogenous bone in the iliac crest, rhBMP remains a viable alternative.

Item 3: TLIF and PLIF

In their review, Carragee et al[5] cited concerns regarding bone overgrowth into the canal with rhBMP causing new radiculitis. They reported that, as with ALIF, posterior interbody implantation of rhBMP could lead to osteolysis with implant subsidence and loss of spinal alignment. Together, these issues were reported to generate more "clinical failures" when compared to iliac crest bone graft both at 6 weeks and 2 years after surgery. These failures, in turn, led to higher rates of reoperation**.**

In their assessment of data derived only from published studies and presumably were not specifically recorded in the IPD or government databases, Simmonds et al[7] found limited data concerning other specific adverse events. In their literature review, on the other hand, heterotopic bone formation and osteolysis were more common in rhBMP-2 groups in comparative studies.

Fu and colleagues[6] did not include a specific meta-analysis of posterior interbody fusion techniques. They found that no "trial defined radiculitis, and adverse events consistent with possible radiculitis were variously classified as back and leg pain, neurologic events, or spinal events. Therefore, they were unable to perform a critical analysis of these complications. In Bono and Wetzel's assessment, they noted that, in apparent absence of IPD, Carragee et al[5], Simmonds et al[7], and Fu et al[6] all relied on limited published data regarding PLIF. The common conclusion, however, was that ectopic bone formation was much more common when rhBMP is implanted in the disc space from a posterior or transforaminal approach.[23]

Other, more recent studies emphasize the evolution in technique and dosing when performing PLIF and TLIF procedures with rhBMP. Most conclude that complications such as osteolysis and ectopic bone formation can be minimized by providing a barrier between the rhBMP and the dura, lowering the dose used and carefully protecting the vertebral endplates. Others have reported excellent results using rhBMP for MIS and open TLIF/PLIF surgeries.[50-52]

For example, Crandall and others reviewed their experience using rhBMP-2 in TLIF procedures at 872 levels in 509 consecutive patients.[53,54] In a series that include one through four level surgery in patients with degenerative disease (179), spondylolisthesis (207), and deformity (123), 12% were smokers and 41% had revision surgery. Significant improvements in clinical and functional outcomes were reported with a 99.08% fusion rate. The authors of this industry-independent study also noted that rhBMP-related complications (seroma, ectopic bone) were rare.

In 2009, Geibel and others reported a 48 patient series undergoing PLIF procedures with rhBMP-2 at a total of 59 operative levels.[55] In this series with a mean 11.2 month follow-up, thin-slice CT in all patients demonstrated successful interbody and posterolateral fusion. No canal compromise, heterotopic bone formation, or adjacent level fusion was reported. Recently, Singh and coworkers reported retrospectively collected data from a single center's of minimally invasive transforaminal lumbar interbody fusion (MIS-TLIF) utilizing rhBMP-2.[56] In their series of 573 patients, 1.7% underwent additional surgery for ectopic bone formation and recalcitrant radiculopathy. The rate of pseudarthrosis requiring repeat operation was 6.8%.

Others have concluded that the osteolysis and ectopic bone associated with rhBMP use are clinically silent.[57,58] For example, Meisel and others reported osteoclastic activity in a 17 of their patients undergoing PLIF with 12mg of rhBMP-2 in the cages.[59] Despite this, all of the patients fused by 6 months and there were no cases of cage subsidence or poor clinical outcomes. Others have reported similar findings.[60,61] Similarly, Michielsen and others recently reported the results of a randomized trial in which 20 patients underwent a single level PLIF with rhBMP versus 20 undergoing the same procedure with autologous bone.[62] Clinical outcomes (VAS, ODI, SF-36) were similar between the groups. Osteolysis and ectopic bone formation were frequently seen in the rhBMP group and were not seen in the autograft group. That being said, there were no cases of cage subsidence or radiculopathy noted during the follow-up interval. While fusion rates were ultimately the same, in this study, interestingly, use of rhBMP2 was associated with slower fusion incorporation.

Other author groups have reached conclusions similar to Carragee et al. For example, Mindea and coworkers reported an 11.4% rate of new radicular symptoms after TLIF in their 35 MIS TLIF patients in whom rhBMP had been utilized.[63] None of their 8 non-BMP patients exhibited similar symptoms. Similarly, Rihn and others reported a 14% post-operative radiculitis in their group of 86 patients undergoing TLIF with rhBMP-2 compared with a 3% risk in their 33 patients undergoing TLIF with ICBG.[64] The authors recommended use of a hydrogel sealant which reduced their radiculitis rate to 5.4%. On the other hand, the autograft group had a higher complication rate (45.5% vs. 29.1%), but the difference was not statistically significant (p=.09). The non-union rates were 3.0 and 3.5% in the ICBG and rhBMP groups, respectively. Nearly a third of the ICBG patients had residual donor site pain and there was a 3.1% donor site infection rate.

Recently, Heida et al performed a systematic review of 29 papers meeting their criteria to assess the impact of different grafting materials on outcomes in TLIF surgery.[65] Various types of interbody cages were assessed as were local autograft, iliac crest autograft, local bone with rhBMP and local with allograft. Local bone with rhBMP conferred the best Oswestry Disability Index scores and visual pain scores.

While the YODA and other recent data must be considered when weighing the risks and benefits of this material in a given patient, rhBMP should remain available to physicians and well informed patients. Especially in patients at risk for fusion failure or without adequate volume or quality of autogenous bone in the iliac crest, rhBMP remains a viable alternative.

Item 4: Posterior Cervical or Thoracic Fusions (in adults or children)

There are relatively few high quality studies assessing the risks and benefits of rhBMP-2 utilization in the posterior cervical spine. In 2012, Hodges and others retrospectively reviewed 29 patients undergoing CT fusion assessment at least one year after posterior cervical fusion.[80] Three (10.3%) of these patients developed pseudoarthrosis, but none required additional surgery. No adverse events related to rhBMP use were reported and no evidence of heterotopic bone formation was found. The authors concluded that rhBMP "can be used safely in posterior cervical spine fusion, but additional larger studies are recommended."

In 2009, Crawford et al reported a higher, but not statistically significant, rate of complications associated with the use of rhBMP-2 for instrumented posterior cervical spine fusions relative to ICBG.[81] While the graft material was chosen at the surgeon's discretion, a consecutive series of 72 patients were included, of who 41 received rhBMP-2. One patient in the ICBG group required additional surgery at the bone harvest site. The posterior cervical wound itself required additional surgical management in 14.6% of the rhBMP and 2.8% of the ICBG patients. Other outcomes were similar between the groups. The authors concluded that additional studied are needed to clarify the issue and the "determine optimal dosing and carrier" for usage in the posterior cervical spine. Another study from the same year evaluated 83 patients undergoing posterior cervical fusion, 67 with ICBG and 16 with rhBMP-2 (dose 1.3mg/level).[82] Here, one patient in the rhBMP group had significant neck swelling that improved over 1 week with steroids. The infection rate was 12% in the ICBG group and 0% in the rhBMP group. Other outcomes were similar.

At this point, NASS feels that the available data do not support routine use of rhBMP-2 in posterior cervical fusion surgeries.

Use of rhBMP in children remains controversial, and, as with many other uses, off-label. While it would be easy to decry exposure of this vulnerable patient population to such a potent osteoinductive protein, there may be occasions in which the benefits outweigh the risks. Certainly, the use of rhBMP for pediatric spine fusion has increased. In 2013, Jain and others reported a 3.4-fold increase in rhBMP use, from 2.7% in 2003 to 9.3% in 2009.[13] Certain subgroups of patients were more likely to receive rhBMP, including congenital (versus idiopathic) scoliosis. In 2010, Fahim and others published a 17 month safety and efficacy study of rhBMP use in children.[85] In this relatively small series, CT evaluation and grading of the fusion was undertaken 3 months after surgery. While no pseudarthroses or loss of correction was identified, one of 19 patients did exhibit bony overgrowth and restenosis and required reoperation. The authors concluded that rhBMP-2 safe and efficacious adjunct to posterior spinal fusion in pediatric patients.

In another recent study of 15 children undergoing spinal fusion with rhBMP, Abd-El-Barr and coworkers reported three complications, none specifically related to rhBMP (e.g. screw malpositioning).[86] Of note, osseous fusion was achieved in each of these patients despite many having "congenital defects that historically decrease fusion rate." Other individual cases of use in salvage procedures have been described.[87]

At this point, NASS does not support routine use of rhBMP in skeletally immature patients. On the other hand, this material should be available for compassionate use in very high risk children.

Item 5: Anterior Cervical Fusion

In their review, Carragee et al[5] cited complications associated with rhBMP implantation as part of anterior cervical fusion procedures. These concerns have not been widely contested and, in fact, were previously noted by an FDA Public Health Notification in 2008. The YODA reviews did include these data.

The initial series describing use of rhBMP in the anterior cervical spine reported fusion rates consistently near 100%, few or no complications.[66-70] In 2003, Baskin and coworkers compared the use of rhBMP-2 versus IC autograft in a PRCT of anterior cervical discectomy and fusion procedures.[66] All 33 patients from both groups were fused by 6 months. At 24 months, rhBMP-2 group had significantly better improvement in neck ($P < 0.03$) and arm ($P < 0.03$) pain than autograft. No complications attributable to rhBMP were reported and those patients receiving rhBMP had avoided statistically significant pain ($P < 0.007$) from the harvest site at 6 weeks. In 2005, Boakye and colleagues reported outcomes of their retrospective review of 23 patients in whom rhBMP placed in PEEK cages in anterior cervical discectomy and fusion procedures.[67] In this cohort, 1.05 mg/level of rhBMP-2 in PEEK cages induced solid fusion with good clinical outcomes and no significant morbidity. Ectopic bone formation was observed in 3 early patients who had received twice the rhBMP dose used later.

By 2006, however, case reports and case series reported adverse events related to anterior cervical implantation of rhBMP, including airway problems and dysphagia.[69,71-73] One of the first of these reports, by Smucker and coworkers, performed a multivariate analysis and found patients receiving rhBMP-2 to have a 10.1-fold increase in risk for swelling complications compared to those that did not receive rhBMP-2.[71] That same year, Shields and colleagues retrospectively reviewed 151 ACDF with rhBMP and Plate patients. They found that 23.2% had suffered complications, including hematoma, swelling, and dysphagia. They noted that the patients in their series had a three and a half times higher rhBMP dose than that reported in Baskin et al (2.1 mg rhBMP/level vs 0.6 mg/level).

In two separate papers in 2007, Vaidya and coauthors reported higher dysphagia and graft subsidence rates in patients receiving rhBMP-2 with allograft for cervical fusion.[72,73] In 2008, Buttermann reported the results of a prospective, non-randomized study in which he compared rhBMP-2 with allograft against IC autograft in ACDF.[74] While both groups exhibited similar clinical improvements, at a dose of 0.9 mg rhBMP/level, 50% of rhBMP group suffered dysphagia compared to 14% autograft. Later that year, the FDA issued a Black Box Warning of "life threatening complications" associated with use in the anterior cervical spine.[75] Use of rhBMP-2 in the anterior cervical spine dropped thereafter.[76]

Some authors have continued to argue for its occasional use, citing reasonable complication rates when lower doses are employed. In one recent study, a relatively small series of patients undergoing anterior-posterior cervical spine surgery, rhBMP was not a predictive factor for the development of post-operative dysphagia.[77] Lu and colleagues retrospectively compared dysphagia rates in patients undergoing multilevel ACDF surgery with or without rhBMP in their cohort of 150 patients.[78] The complication rate was statistically significantly higher in the rhBMP group (13% vs. 8%, $p < 0.005$). While dysphagia rates were similar, the rhBMP group's mean dysphagia severity score was higher. Interestingly, the severity of dysphagia was similar in patients undergoing 3 and 4 level ACDF. Use of rhBMP was associated with lower pseudarthrosis rates (0% vs. 16%, $p < 0.05$). The authors concluded that "the use of rhBMP-2 appears to reduce the risk of pseudarthrosis. This benefit is most pronounced in patients who undergo 4-level ACDF and are smokers."

Klimo and Peele reported osteolysis with loss of sagittal alignment and "a high incidence of bone growth beyond the core of the PEEK spacer" in their series of 22 patients undergoing ACDF with rhBMP filled cages.[79] While they did not report any clinically significant anterior cervical swelling, they recommended reservation of rhBMP-2 in the anterior cervical spine only "n those patients who are at greatest risk of pseudoarthrosis."

Given the potential for life-threatening complications, it is currently recommended that rhBMP-2 be used in the anterior cervical spine only in occasional, high-risk patients. In a 2012 editorial, Riew and Carragee wrote: "While rhBMP can cause catastrophic complications, it is also the most powerful inducer of bone formation available commercially. We believe that judicious use of appropriate doses, in special cases, should remain an option for surgeons and well-informed patients."[2]

Specific Concerns

***Cancer Rates*:** In their 2011 review, Carragee and others associated implantation of high doses of rhBMP-2 with an increased risk of cancer.[5] They reported a 3.8% rate of new cancers in the rhBMP group compared to 0.89% in the iliac crest group with minimal overlap of confidence intervals calculated for two groups. As part of the YODA study, Simmonds and others concluded that cancer "was nearly twice as common in the rhBMP-2 recipients" with a relative risk of 1.98.[7] In their report, the 95% confidence intervals were wide, ranging from 14% lower to 454% higher. They did not identify different risk levels based on dosage. Fu and others calculated a relative risk for cancer to be 3.45 in the rhBMP group as compared to the iliac crest group.[6] However, while this difference remained statistically significant at 24 months, it was no longer significant at 4 years follow-up. They concluded that the numbers were insufficient to determine if cancer risk dose-dependent. In their review of reviews, Bono and Wetzel[23] noted that Fu et al[6] found a stronger association than both Carragee et al[5] and Simmonds et al.[7]

Since then, a number of studies have examined cancer rates in patients that had previously undergone spinal fusion with rhBMP. Most of these studies have shown low cancer rates. In a series of 502 consecutive patients from a single center, post-operative cancer prevalence was 3.4%, but did not increase with dose.[38] High doses of rhBMP-2 were used, (mean 115 mg (40-351 mg range)). A recent retrospective cohort study of Medicare beneficiaries undergoing lumbar fusion studied 146,278 subjects aged 67 and older who underwent surgery in 2003-2008.[83] Of that cohort, 15.1% received rhBMP. At any overall average follow up of 4.7 years, the rate of new cancers in the rhBMP group was 15.4% versus 17% in those undergoing surgery without rhBMP. rhBMP was also found not to relate to any individual cancer types.

On the other hand, Carragee et al re-analyzed the data from the FDA AMPLIFY trial of 463 patients.[84] At 2 years, with 86% follow-up, there were 15 new cancer events in 11 rhBMP pts versus 2 new cancer events in 2 pts. The authors calculated an incidence rate of new cancer events per 100 person-years. The rhBMP-2 group this was 3.37 (95% CI, 1.89 to 5.56) versus 0.50 (95% CI, 0.06 to 1.80) in the ICBG control.

At this point, it appears there may be a small, but significant increase in cancer risk after implantation of rhBMP-2. Perhaps the material should be avoided in patients at high risk for cancer. In others, however, the risk of treatment failure after spinal fusion leads us to conclude that the benefits of rhBMP outweigh this risk.

***Economics*:** A number of studies have examined the costs and benefits of rhBMP-2 implantation from both medical and societal perspectives. In 2009, Alt and others examined the economic impact of rhBMP-2 in lumbar fusion surgery in Germany, France, and the United Kingdom.[88] They found that,

despite rhBMP's higher initial price (2,266 to 2,970 Euros) long term costs were 8,483 to 9,191 Euros per case due to faster return to work time.

Carreon and others performed a cost-utility study comparing rhBMP-2 and ICBG in lumbar fusion patients over age 60.[89] "A dedicated hospital coder and research nurse tracked each patient to determine direct costs of inpatient care and all postoperative healthcare encounters up to 2 years after surgery. Preoperative and 2-year-postoperative SF-6D utility scores for each patient were determined." The study found that: "The mean total 2-year cost for care (excluding complication and additional spine treatment costs) was $34,235 in the ICBG group and $36,530 in the rhBMP-2/ACS group. For the entire group, the mean cost to treat a major complication was $10,888, the cost of revision surgery for nonunion was $46,852, and additional treatment for spine-related events was $5892. In the ICBG group, 8 patients had complications; 20 had additional interventions, 5 of whom required revision for nonunion. In the rhBMP-2/ACS group, 6 patients had complications, 10 had additional interventions, and 1 required revision for nonunion. The cost of using rhBMP-2/ACS was $39,967 with a 0.11 mean improvement in SF-6D; and for ICBG the cost was $42,286 with a mean improvement of 0.10 in SF-6D." The authors concluded that the increased rate of complications associated with ICBG actually accounted for its higher 2 year cost for care over rhBMP-2.

In 2003, Polly and others performed a cost analysis of rhBMP vs ICBG in a single level ALIF.[90] Using an economic model "developed from clinical trial data, peer-reviewed literature, and clinical expert opinion," the authors concluded that "the upfront price of bone morphogenetic protein ($3380) is likely to be offset to a significant extent by reductions in the use of other medical resources, particularly if costs incurred during the 2 year period following the index hospitalization are taken into account."

Several less favorable studies have recently been published. One recent study detailed the costs associated with complications of rhBMP use such as osteolysis and cage migration ($19,224 per patient), neuroforaminal bone growth $14,785, and pseudarthrosis, $20,267).[56] In 2007, Garrison and others performed a systematic review of existing RCTs to identify the costs per QALY associated with utilization of rhBMP-2 in various fracture repair and spine fusion surgeries for the British National Health.[91] Based on their estimates and indirect data, the estimated incremental cost per QALY gained was about £120,390."

***Technical Improvements*:** It appears that many of the problems reported after rhBMP implantations arise from two related factors. First, this material is labeled as an implant and surgeons previously use it that way. In truth, rhBMP is a drug. It is a powerful molecule capable of both strongly inducing bone formation, but also inducing a strong inflammatory reaction in surrounding tissue, stimulation of osteolysis and ectopic bone formation.

It's possible that the few adverse events reported in the initial rhBMP series led to a skewed understanding of the real risk-benefit ratio of rhBMP. This view, in turn, may have prompted a laissez faire attitude. As a drug, careful attention to dosing and carrier is required. Unfortunately, the utilization of rhBMP "off-label" limited the ability of the manufacturer and others to educate surgeons on proper dosing, containment, and carrier options. This left many surgeons to "reinvent the wheel" in their own practices.

Since the FDA trials, a number of changes to routine surgeon practices have occurred. These practices, including modified rhBMP dosing, use of barrier materials between the rhBMP and the dura, careful endplate preparation, and, perhaps, improved carrier materials are reported to decrease adverse events.[55,91] Even in anterior cervical spine applications, several authors have reported safer implantation of rhBMP-2 by decreasing the dose to 0.4-0.7mg per level, containing the rhBMP with DBM putty or fibrin glue, and adding 20–40 mg of methylprednisolone in wound before closure.[2,70,92,93] In posterolateral fusions for deformity, on the other hand, the pseudarthrosis rate essentially dropped to zero when the per-level rhBMP dose was above 5mg. In ALIF surgery, decreased rhBMP dose was associated with decreased RE rates.[48]

Crandall and coworkers recently reported lost rhBMP related complications (0.4% seroma, 0.6% ectopic bone growth and no cases of symptomatic osteolysis or cage subsidence.[54] They recommended backfilling the disc space with local autograft. Mannion et al, reported that very low dose rhBMP (1.4 mg/level) reduced but did not completely eliminate complications of its usage such as perineural cyst formation and heterotopic ossification.

Typically, rhBMP-2 is implanted in the spine after soaking onto a type I collage sponge. Compression resistant, often ceramic, matrices have been tested but the failure to gain FDA approval of posterior applications has limited their marketing for this purpose.[94,95] Others have reported new carriers, such as microbeads, to contain the rhBMP and decrease soft tissue complications.[96]

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Author Disclosures

Truumees, Eeric: Royalties: Stryker Spine (C, I receive partial royalties for a lumbar plate in quarterly installments. To date, each quarter has been highly variable in terms of royalty amounts paid.); Private Investments: IP Evolutions (0 Shares, 33%, This is a small group I started with two partners to develop our own IP independent of larger implant companies. It was folded in January, 2012 and is no longer an active concern.); Board of Directors: North American Spine Society (Nonfinancial, Travel Expenses are reimbursed.); Other Office: AAOS Communications Cabinet (Financial, Incoming Editor-in-Chief of AAOS Now, member of AAOS Communications Cabinet, travel reimbursement. Small monthly stipend may be paid after 1 transitional year (2015).); Other: Stryker Biotech (Nonfinancial, Along with my partners in my previous practice, I was involved in a clinical study of OP-1 (rhBMP-7) sponsored by Stryker Biotech

roughly from 2000-2004. I did not consult for Stryker Biotech nor did I directly receive compensation for study participation. Paid directly to institution/employer).