Washington State Health Care Authority

Health Technology Assessment

# Cervical Spinal Fusion for Degenerative Disc Disease

## Draft Evidence Report - Public Comments

**February 21, 2013**

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# Cervical Spinal Fusion for Degenerative Disc Disease

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## Draft Evidence Report
## Public Comment and Response

February 21, 2013

# Response to Public Comments

*The Institute for Clinical and Economic Review (ICER) is an independent vendor contracted to produce evidence assessment reports for the Washington HTA program. For transparency, all major comments received during the public comment period are included in this response document. Comments related to program decisions, process, or other matters not pertaining specifically to the project scope or draft evidence assessment report are acknowledged through inclusion only.*

This document responds to comments from the following parties:

**Draft Key Questions**

- Ian Zhao, Ph.D., Medical Program Specialist III, Washington State Department of Labor & Industries
- Christina Farup, M.D., Vice President, Evidence-Based Medicine, DePuy Synthes Spine, Inc.
- Dena Scearce, J.D., Director, State Government Affairs, Medtronic, Inc.
- Mitchel S. Berger, M.D., President, American Association of Neurological Surgeons; Ali R. Rezai, M.D., President, Congress of Neurological Surgeons; Joseph S. Cheng, MD, MS, Chairman, AANS/CNS Section on Disorders of the Spine and Peripheral Nerves; Jens R. Chapman, M.D., Chairman, AOSpine North America; K. Daniel Riew, MD, President, Cervical Spine Research Society; Charles Mick, M.D., President, North American Spine Society; John K. Hsiang, M.D., President, Washington State Association of Neurological Surgeons; Lyle Sorensen, M.D., President, Washington State Orthopaedic Association; and John R. Tongue, M.D., President, American Association of Orthopaedic Surgeons

| | Comment | Response |
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| ***Ian Zhao, Ph.D., Washington State L&I (on behalf of Agency Medical Directors)*** | | |
| 1 | Given the key questions and the evidence at hand, it would still be important to differentiate in summary on the outcomes (effectiveness, safety, and cost-effectiveness) for the 2 main clinical categories of DDD: 1) patients with radiculopathy, who are undergoing a decompressive procedure (laminectomy, discectomy) with or without an add-on fusion, and 2) patients with DDD with chronic neck pain but not radiculopathy. We suspect these are the 2 categories that will drive the clinical committee's decision process. | *Thank you for your comments. We will clarify the key clinical categories for rating the evidence in the Executive Summary.* |
| 2 | The results and findings of the Decision Analytic Model are very interesting. It will certainly be helpful in making coverage decisions. However, this is a very complex model. It would be beneficial to add additional interpretation to the key methodological concepts, how the model is developed in detail and how the results are derived from the model. The information may be included in an appendix as reference. | *New introductory language has been added to the Executive Summary to try to give some context to the terms used regarding the design and analysis of the simulation model. Moving forward, we will work with the Agency Medical Directors and the Health Technology Clinical Committee to develop more detailed information on modeling efforts that will meet their needs.* |
| 3 | The reviewers considered the overall comparative clinical effectiveness of cervical fusion to conservative treatment "Comparable". The reviews also suggested an "Incremental" rating on clinical effectiveness for cervical fusion comparing to ongoing conservative treatment for faster relief of the patients with severe and disabling symptoms. This seems to be a reasonable rating. However, to give a complete and balanced assessment, the reviewers should also explicitly include an "Inferior" rating for cervical fusion compared to conservative treatment for patients who have milder symptoms particularly in the long term given the diminished effect of fusion over time with increased depression (page 65) and higher rates of adverse events (pages 71-75), including death (page 20). This is important to call out in the executive summary. | *The possibility of such a rating for patients with milder symptoms has been added to the Executive Summary.* |
| 4 | The NNT and NNH approach was not included in the review to compare the clinical effectiveness or harm of the technology with comparators, which might have strengthened robustness of the appraisal. | *These measures have been added for further context, particularly with regard to the model.* |
| 5 | Page 4. The report states that "Data on harms and/or subgroups of interest were also obtained from large (>50 patients), long-term (≥12 months of follow-up) case series evaluating cervical fusion". Some of the more serious adverse events may be | *Case reports do not provide any information on denominator, making it impossible to estimate the frequency or rarity of event rates with any precision. FDA MAUDE reports frequently do not include sufficient information on the clinical nature* |

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| | more rare, e.g., 1/1000 cases. In these cases, even single case reports, or FDA MAUDE reports, may be informative. Since the committee is explicitly charged with considering safety and rare but serious events cannot be captured in trials smaller than occurrence rates, these kinds of studies should not be excluded. | *of the event that has occurred.* |
| 6 | Page 4. The report states that "The criteria, which related to issues of study design, reporting, and minimization of bias, are presented in Appendix B". It is actually in Appendix A. | *This has been corrected.* |
| 7 | Page 6. The report states that "(NOTE: 5-10 point changes on VAS score represent the minimum change that would be considered "clinically important")". The IMMPACT group and others have recommended CMI to be more like 20-30% in pain and function. It is particularly important for beneficiaries to achieve more than minor palliative relief, thus if meaningful functional improvement is not evident, this should definitely be pointed out. | *We have expanded the text to include ranges from the IMMPACT publication, but note that similar ranges are described in both publications for "minimum clinically-important improvement".* |
| 8 | Page 8. The report states "In this study, an assessment of 292 patients receiving either PMMA fusion or posterior foraminotomy (Korinth, 2006); long-term outcome was assessed after a mean of 6 years". This seems to be an incomplete sentence. | *This has been corrected.* |
| ***Christina Farup, M.D., DePuy Synthes, Inc.*** | | |
| 1 | …a base-case economic model that includes an ill-defined subgroup of patients with "mild-to-moderate" cervical radiculopathy lacks relevance for real-world clinical decision-making. | *Thank you for your comments. The reference case for the model included patients with moderate symptoms; a mistaken reference was made to "mild to moderate" in the economic section, which has been removed. We also note, however, that populations in available RCTs were relatively heterogeneous, with standard deviations of 25-50% in baseline measures of pain and disability. This is true even in large trials comparing cervical fusion with artificial discs. For example, baseline NDI scores in a trial of the Bryan artificial disc[1] averaged 50.2, which equates to the lower end of severe disability.[2] However, the standard deviation was 15.3, which equates to moderate disability on the lower end and very severe disability on the upper end.* |

[1] Sasso RC, et al. *J Bone Joint Surg Am* 2011;93:1684-92.

[2] Vernon H, Mior S. *J Manipulative Physiol Ther* 1991 Sep;14(7):409-15.

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| 2 | We also disagree with the report's contention that patients represented within high quality studies of ACDF versus cervical disc arthroplasty "have more severe forms of cervical degenerative disc disease" than exhibited by the broad population of candidates for cervical fusion. | *This comment was primarily made in comparison to trials of fusion vs. conservative care, in which baseline measures of pain and function were not as severe.* |
| 3 | Important data about the health-related quality of life (HRQoL) burden of cervical radiculopathy as reported by Carreon et al. were omitted on the basis of comparative disutility for myocardial infarction or stroke. | *There were additional concerns regarding the methods used by Carreon et al., including face validity of SF-36 scores (e.g., individuals with no neck disability had mean SF-36 score of 0.68), did not estimate size or SD of prediction errors, and use of one method to map utilities. We thank the reviewer for describing the publication by Richardson in some detail, a study that we were not previously aware of that is not vulnerable to these concerns. We have revised the utility estimates in the model to use values from Richardson as their basis.* |
| 4 | Estimates used for the cost-utility model were derived from data sources irrelevant for quality-of-life measurement for patients with cervical radiculopathy. | *Our initial rationale for use of the study by Kadanka was its inclusion of a measure of treatment success. We recognize, however, that this moved the focus of the model away from the target population. We have revised the model to focus on data culled from studies of patients with radiculopathy.*<br><br>*Because we also recognize that discussion of evidence from studies conducted primarily in myelopathy populations has caused considerable confusion, we have eliminated such discussion throughout the report (myelopathy studies remain summarized in evidence tables and are separately flagged as such).* |
| 5 | The model relies on a flawed assumption about the course of treatment response after ACDF. | *While our focus in the model was on the relative treatment response over time, we recognize that the pattern illustrated in the Kadanka study does not mirror that in other randomized comparisons of fusion to other forms of surgery or conservative care. Our revision to the model mirrors the pattern of response to fusion presented in the reviewer's comments. We do note, however, that early clinical benefits seen with fusion vs. alternative treatments do tend to converge over time, which the revised model also now reflects.* |
| ***Dena Scearce, JD, Medtronic, Inc.*** | | |
| 1 | Executive Summary Does Not Provide Answers to the Key Questions | *Thank you for your comments. The executive summary is not designed to include every component of the full report. Because it follows the flow of the 4 key questions, we were unable to conceive of a structure for the report that would be mor fit for purpose.* |

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| 2 | Structure of Report Difficult to Follow | *Where feasible, we have amended presentation of the data to include the number of studies, and have created an index to Appendix C.* |
| 3 | Inappropriate Comparators: Conservative Care and CSM | *Conservative care was the primary comparator of interest for the Washington state Agency Medical Directors who provided guidance on the scope of this review. Having completed our review we agree with them that conservative care is a valid comparator given that randomized and cohort comparisons of fusion vs. conservative care exist. In addition, there is substantial heterogeneity in the duration of prior conservative treatment or symptoms in available studies; in some of these, no data on the duration of conservative treatment is provided.*<br><br>*As noted on page 5, we recognize that inclusion of studies conducted In patients with a primary complaint of myelopathy was problematic, and have removed these studies from the main body of the report and executive summary.* |
| 4 | Decision Analytic Model Has Limitations | *The model has been revised to more accurately reflect utilities and treatment response in a radiculopathy population. Limitations have been noted in both the executive summary and main body of the report.* |
| 5 | Mortality Harms are Presented Out of Relevant Context | *The probability of death has been revised in the model to more accurately reflect the slightly increased peri-operative risk alone.* |
| ***Specific Comments*** | | |
| 1 | The Marawar article may not be relevant to the assessment as it provides statistics on Medicare beneficiaries and includes a variety of cervical spine pathologies (herniated disc, spondylosis with myelopathy, spondylosis without myelopathy, and spinal stenosis). A citation to a more age-relevant population would be appropriate or, at a minimum, clarification should be provided. | *This study was based on data from the National Hospital Discharge Survey, a probability survey of all hospital discharges in the US (not just Medicare). This is reflected in the mean age of participants, which ranges from 47-50 years across time periods. Patient selection was done by procedure; no data were available on indication for these procedures.* |
| 2 | The McLaughlin study cited is not a comparison of anterior to posterior, it pertains only to 2-level anterior. | *While we were attempting to make a point about both anterior vs. posterior and single- vs. multi-level fusion, we agree that this is not the appropriate citation. It has been replaced and the text modified for clarity.* |
| 3 | This is a broad statement that is not well supported; case series are useful for various outcomes, including assessment of potential harms in large cohorts. | *We have revised the text to clarify our intent in not rating study quality for case series.* |
| 4 | The discussion of Mayer and quality of life notes that Beck Depression is higher for surgery at 12 months. This is accurate. However, these patients also had higher depression scores at baseline, which is not mentioned. There is no | *This text has been modified, given that the Mayer study does not calculate change in BDI scores from baseline.* |

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| | discussion in terms of "improvement." | |
| 5 | The meta-analysis comparing fusion to discectomy includes only 2 studies for Odom's criteria in Figure ES2. A third study reported Odom's criteria (Appendix C lists Abd-Alrahman/1999 at 24 mos), yet it is not included. Additionally, the Barlocher and Van den Bent studies have different follow-up intervals but the data are combined (Barlocher/2002 data at 6 and 12 mos, and van den Bent at 24 mos). | *Abd-Alrahman was not included in primary analyses of this measure because it was rated as a lower-quality study. It is included in secondary analyses, however. Study results are presented as of the latest timepoint analyzed (i.e., 12-24 months), as examination of the observed data showed relatively stable results across these timepoints within each study.* |
| 6 | The time interval for quality of life is not indicated here; Appendix C appears to indicate it is one year. | *The timeframe for quality of life in Xie 2007 was 12 months; the text has been modified accordingly.* |
| 7 | The meta-analysis comparing fusion to discectomy includes only four studies. It seems the selection was limited to studies with 12-24 months assessment. This seems to bias against any differences occurring earlier. Other studies in Appendix C provided shorter term data on return to work. Likewise, of the four studies, two studies had 24 months data and others had only 12 months; it is not clear that combining the data is appropriate. | *Only two studies provided shorter-term data (6 months) on return to work. These have now been analyzed in a separate meta-analysis; results did not differ statistically.* |
| 8 | The above reference to Figure ES3 notes that the pooled estimate directionally favors discectomy, which is noted as 'control,' but is not statistically significant. However, the figure seems to depict an outcome favoring fusion, which is noted as 'experimental.' | *When the meta-analysis is based on a rate ratio, and the outcome is positive (i.e., return to work), any pooled estimate <1.0 indicates a lower likelihood of the positive outcome and therefore favors the comparator category (i.e., control).* |
| 9 | The potential harms reference two studies by Shamji 2008/2009. These studies are not conducted in a typical cervical DDD population. As noted in Appendix C, they are multi-level surgeries (4-8 levels) with higher risks and the intent was to compare anterior to posterior. In addition, both studies include patients with CSM.<br><br>In terms of studies on potential harms, a recent large database study by Memtsoudis/2011 on complications with ACDF versus posterior surgery is not included. From this study, complications and mortality rates 4.1%/0.26% and 15.4% /1.4%, respectively. Comparable rates were reported by Wang/2007. These rates are both lower than the complications cited for general surgery risks in the report (see p. 75 perioperative complications cited in Table 5 and mortality rates in the narrative 1.2% - 21.5%). | *Shamji 2009 has now been excluded because of its focus on myelopathy and multilevel surgery. Shamji 2008, which includes primarily patients without myelopathy, has been retained.*<br><br>*Memtsoudis 2011 was not selected because, unlike the Shamji study, there was no information on patient selection, and we could not determine if acute trauma, congenital deformities, etc. were included.*<br><br>*Wang 2007 was not initially selected because it appeared initially to be a single-arm case series with information on only the hospital stay. Information on differences in harms by anatomic approach from this has been added to the report for further context.* |

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| 10 | Table ES3 is not meaningful without number of studies reporting, sample size, and confidence intervals. Additionally, peri-operative and immediate post-operative should be differentiated from long term complications. And, in the Long Term Events statistics, the mortality lower end for surgery should be "0." | *Information on the characteristics of each study are available in Appendix C. We cannot include all such characteristics in a table intended to summarize data across studies, but have included the number of studies contributing to each outcome for further context.* |
| 11 | It is accurate that the most frequent complication for fusion is dysphagia and hoarseness, however, it is also the most frequent complication for discectomy alone. In 4 studies of fusion versus discectomy (Haueberg, Xie, Ruetten 2008 and 2009), the first two report no differences in rates of dysphagia and the latter two studies did not report statistical significance. The report's comment "there was overlap" does not clearly communicate these differences. | *We have modified the text to make clear that rates were similar when compared between fusion and discectomy.* |
| 12 | It is not clear how the 55 reports of the case series were selected or how they are used in the analysis. The narrative makes general note of exclusion of articles comparing surgical techniques (see p. 53), yet it appears that some of these articles were included (e.g., Guo 2011). No further information is provided later in the detailed section of the document. Providing clarification would perhaps enhance the merit and usefulness of the analysis. | *The selection criteria for case series were clear, based on size (>50 cases) duration (12+ months) and data either on the outcomes of interest or featuring a prespecified comparison according to a subgroup of interest. Data from the Guo 2011 study were selected for information on level of surgery only.* |
| 13 | There is no indication of the follow-up period for these annualized rates. Nor is there indication of the numbers of patients, confidence intervals, or duration of follow-up. | *Variation in the duration of follow-up is precisely the reason for annualization of rates in this table, which is focused on long-term harms only.* |
| 14 | This is an error; the results for nonsmokers should be reversed as they had less pain (see App, C, p. 47) | *Thank you for identifying the error. It has been corrected.* |
| 15 | The Kristof 2009 is a study of multi-level myelopathy and like Tominaga 2002 was intended to be excluded from the study, according to the authors. The report should have included the Memtsoudis/2011 study in this anterior versus posterior discussion. The narrative does not address the possible variance in indications between posterior versus anterior with the former typically consisting of more multi-level procedures. | *As described previously, studies focusing primarily on myelopathy patients have been removed.* |
| 16 | This section of the report provides a broad brush on single level versus multi-level. Providing additional context and sample sizes of subgroups would be useful. | *An attempt was made to focus on the key findings of these studies. Details for each study are available in Appendix C.* |

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| 17 | Riley 2005 study on dysphagia is cited. The same author has provided a later systematic review that should be included. | *While our focus was on primary studies only, we have added corroborative data from Riley 2010 to the text.* |
| 18 | In this age discussion, the authors mostly cited studies with CSM patients that were intended to be excluded. | *As with other sections of the report, this section has been rewritten to exclude studies that included a majority of myelopathy patients.* |
| 19 | The health state diagram does not allow for patients to transition from worsening pain to no change in cervical pain or improvement. It assumes that after each cycle a patient in the worsening health state can only continue to get worse or die after each three month cycle. Similarly, the model also assumes that patients who improve may only continue to improve or get worse and does not allow for a transition to the no-change-in-cervical-pain health state after each three month cycle. In addition, the model does not allow for transitions between no-change-in-cervical-pain to death unless a patient transitions through worsening cervical pain. The transition probabilities to the death state should reflect only the all-cause mortality for the age-adjusted patient population being simulated in the model, therefore a patient should be able to transition from no-change to death. | *To increase transparency, the model has been simplified to 3 states (improvement, no improvement, death), as data on symptom worsening came primarily from Kadanka et al.* |
| 20 | As BMP is not FDA-approved for cervical fusion, reference to BMP for use in cervical fusion should be removed. | *Our scope in describing clinical practice is not limited to FDA-approved uses of tests or treatments. Given that clinical experts have described use of BMP in cervical fusion we have decided to leave the text unchanged.* |
| 21 | Bowel or bladder incontinence is not related to cervical spine surgery; this reference should be removed. | *This text will be removed.* |
| 22 | The authors note assessment of complications within 30 days yet the report tables provided depict annual rates. | *Annual rates are used for what are termed "longer-term" adverse events in the report table and text, not for peri-procedure complications. This is clearly noted in the headers and footnotes on the table.* |
| 23 | Exclusion of articles comparing "one type of fusion to another" and inclusion of articles on anterior versus posterior approaches warrants further consideration. Is relevant information being excluded (i.e., particularly more contemporary evidence) and is not relevant information included? More contemporary studies may represent comparison of methods as ACDF in general is considered standard of care. Of the 90 selected studies, only approximately 18 (20%) were published in the past three years (i.e., 1/15 RCT, 5/20 comparative and 12/55 observational). | *The Washington HCA is interested in the evidence on cervical fusion in comparison to alternative treatments. The subgroups regarding anterior vs. posterior and single- vs. multi-level fusion were included based on consultation with individual clinical experts as well as public comments on the draft key questions from the North American Spine Society.* |

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| 24 | "Training Standards and Relationship to Outcomes" is included, yet this was not raised in the four key questions. | *It is nevertheless critical to understand whether there are any published training standards or data on procedure "learning curve" as possible indicators of variation in practice and outcome.* |
| 25 | These data include complications from ALL general surgical procedures, not just spine, for 30-day readmission. While the data is useful, the narrative ought to put these general surgical risks in context relative to cervical fusion surgery. | *This information was specifically requested by the Washington HCA as additional context on what might be expected in typical surgical practice. We have nevertheless added text to the report to put the estimates into context.* |
| 26 | Comments on page 11 and 12 related to Tables 9 and 10 of the model. | *The revised model structure and inputs address these concerns.* |
| 27 | There is no justification for the cost of repeat surgery being 25% higher than ACDF. While there is no data, a more appropriate assumption would be the same cost of ACDF: $29,722. | *This assumption was based on Carreon et al. (2012), and was in fact more conservative (Carreon assumed a cost for repeat surgery nearly twice that of the index procedure). Nevertheless, we have assumed the same cost as the index procedure in our revised base case.* |
| 28 | The report specifically excludes the extensive literature on cervical disc arthroplasty versus ACDF. These studies include RCTs with standard outcomes and long term follow-up. | *These comparisons were deemed to be out of scope by the Washington HCA. We have nevertheless used these data as the basis of the population in our revised model.* |
| 29 | The basis for inclusion of articles in the reference list is unclear. Approximately 90 "studies" were included in the systematic review; the reference list includes 182 citations. Some possibly unrelated references (e.g., Juratli's 2009 mortality study for lumbar fusion, Gore 2012 on back pain, Kim 2009 cervical discs, Sasso 2011 cervical discs, Spinal Kinetics M6-cervical disc web site, Deyo for lumbar stenosis) are included without rationale. And, it is not clear which articles represent the selected comparative and observational studies included in the analysis. The bases for inclusion should be explained. | *As is customary for systematic reviews, articles cited by guidelines as well as editorials and other articles are read by staff as part of their seeking to understand the clinical context. The studies selected through the literature search process for inclusion in analyses of clinical benefits and harms are clearly labeled by first author and year of publication.* |
| 30 | As currently organized, review of these data is very cumbersome. An index would be useful for expedited data review. | *As mentioned previously, this has been done.* |
| ***Multiple Specialty Society Response*** | | |
| | NOTE: Responses to selected concerns are noted below, as many concerns raised have already been addressed earlier in this document. | *Thank you for your comments.* |
| 1 | For instance, while the report notes that it does not include patients presenting with a primary complaint of myelopathy, a citation from Key Question #4 nevertheless uses results of a myelopathy study to predict outcomes in treatment of cervical radiculopathy patients (7). This approach produces<br>critical errors, using outcomes for surgery from one distinct clinical entity (cervical myelopathy) | *As noted previously, discussion of data from studies primarily focused on myelopathy has been removed from the report, and the model has been restructured to focus on patients with cervical radiculopathy.* |

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| | to construct a value-of-care model on a completely different clinical entity (cervical radiculopathy). | |
| 2 | The choice of articles upon which the report is based is curious. There are 15 randomized, controlled trials (RCTs) listed as sources in Appendix C. However, only 6 were published in the last 10 years and most are much older. Only three of the RCTs are from U.S. centers. These unusual choices for foundational data introduce a source of bias in the report's results. | *As noted previously, the search focused on studies comparing cervical fusion to an alternative treatment modality, NOT on different variants of fusion. The exceptions to this were comparisons of anterior to posterior fusion as well as single- vs. multi-level surgery, as suggested by individual clinical experts and the North American Spine Society in its response to the draft key questions.* |
| 3 | In discussing non-operative treatments, this rigorous approach to assessment of article quality was not applied. In non-operative therapies, observational case series are reported as adequate foundation for intervention. The rationale for greater leniency in evaluation of the literature in nonoperative treatments is not explained in the report. This leads to the unusual situation where uncommon conservative interventions, with limited support in the literature (e.g., chemonucleolysis, coblation nucleoplasty), are placed upon equal literature-based footing with anterior cervical discectomy and fusion -- an operative treatment with over 60 years of clinical experience. This illustration of further potential confirmation bias questions the validity of the report's conclusions. | *We fear that the reviewers are perhaps confusing our introductory section, which provides an overview of the types of interventions that possibly can be used for cervical DDD, with the evidence review itself. We applied the same criteria to all RCTs and comparative cohorts, regardless of the comparator to fusion. Case series data were focused on fusion alone; we used no case series of non-fusion treatment in our evidence review.* |
| 4 | There have been a number of recent cervical arthroplasty versus cervical fusion prospective, randomized, FDA sanctioned, IDE studies published in the literature. The report notes these were not included in this assessment due to some of these articles being previously reviewed by the Washington State HCA. However, the goal of this report is to evaluate the effect of surgical fusion on the clinical outcomes in patients with cervical degenerative disease, not to update previous Washington State HCA publications. While some of these articles may have been previously reviewed in other HCA processes, they are still material to this assessment and failing to include them is a source of bias in this report. | *Cervical arthroplasty procedures were not in the scope of this evidence review as considered by the Washington HCA.* |
| 5 | Options provided by HTA include physical therapy, cervical collar immobilization, spinal manipulation | *We again fear that the reviewers are confusing introductory text with the conclusions of the review. We have made no assertion that all forms of* |

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| | (chiropractic), medication (analgesics, muscle relaxants, opioids), alternative therapy (yoga, acupuncture) and self-care (educational materials, home stretching). These represent a variety of nonsurgical options available for consideration for the management of cervical spondylosis and radiculopathy. The assertion stated in the HTA that all forms of conservative management (e.g., physical therapy, spinal manipulation) have approximately equal clinical effectiveness is simply not valid. | *conservative management have equal effectiveness. Nevertheless, we have provided further detail in our evidence rating section regarding the modalities that have actually been compared to fusion (physical therapy, cervical collar immobilization) to further clarify the comparisons being made.* |
| 6 | The HTA also describes radiographic evidence of radiculopathy: radiculopathy is a clinical diagnosis; radiographic studies can confirm or negate the working hypothesis that a compressive phenomenon exists. | *We regret the confusion caused by our wording, and have amended the text to focus on radiographic evidence of nerve root compression.* |
| 7 | Therefore, in determining risk of surgery for cervical DDD, combining disparate study populations from multiple RCTs and comparative cohort studies leads to variable, inconclusive results. | *While it is true that data from heterogeneous populations will produce variable rates of harm, this is precisely why we (a) present results as ranges instead of using measures of central tendency; and (b) did not attempt to meta-analyze harms data. We also note that data from the NIS and other large observational datasets are in fact presented in our review.* |
| 8 | Therefore, the risk for a given adverse event (e.g. hoarseness) or the overall cumulative surgical risk may be markedly different for anterior versus posterior surgery. Lumping these procedures together when reporting potential harm thus results in misleading and invalid conclusions. | *We appreciate the nuances involved in determining the appropriate surgical approach for individual patients, but it is also impractical to attempt to summarize harms in one table that considers all possible factors. We hope that our interpretation of the factors associated with greater or lesser surgical risk in the text provides the reader with the appropriate context.* |
| 9 | We have reviewed the studies that are reported to describe how anterior fusions lead to fewer complications when compared to posterior fusions. Most surgeons will agree that anterior cervical fusions have superior clinical outcomes when compared to posterior cervical fusions; however the vast majority of posterior cervical fusions are for patients that have 4-8 levels being fused. It is very important to compared fusion levels when making such a comparison. The Shamji study did not evaluate which levels were being fused, and the posterior group is very likely to include patients with more pathological levels and more multiple comorbidities. Most surgeons resort to a posterior | *We appreciate the clinical distinctions made, and have added language similar to this to make clear that the choice of anatomic approach is often tied to clinical need.* |

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| | approach when more four or levels need be performed, intraoperative time is shorter and dysphagia requiring peg tubes less likely. The Shamji study confirmed the greater incidence of dysphagia in the anterior group (2). There usually are very concrete and distinct reasons to either perform an anterior<br>or posterior fusion or both, and it is extremely difficult to make a blanket statement that favors one<br>approach over another other, as each patients pathology location differs. | |
| 10 | Multiple comments regarding the inappropriate use of data from Kadanka et al. in the model. | *As previously described, the revised evidence review and model address these concerns.* |
| 11 | We also note inaccuracies in the assignment or estimations of utility (QALY-gain) for cervical surgery. | *As previously described, a new approach has been taken in estimating the disutility of cervical symptoms and the gain from resolving neck and arm pain based on data from Richardson et al.* |
| | 1) In assessing measurable spinal instability in cervical spine fusion, again, conditions that increase susceptibility to instability include those mentioned above, pertaining to bone quality, and progression of disease following fusion to adjacent cervical levels requiring further operations [6-9].<br><br>2) Technical approach to fusion: There is no measureable differential effectiveness in the technical approach to fusion. What can be discerned from a safety perspective is that although a posterior approach to cervical spine in multiple studies may have a slight increase in infection risk, this is not long term or insurmountable and does not preclude that approach particularly if the disease pathology is best approach from that surgical exposure [10,11]. Another study focused on the rate of neurological deficits in spine surgery also mentioned a slightly higher rate of injury with combined approaches [12] and dysphagia [10]. Yet again, cases such cases requiring anterior and posterior (combined) approaches typically involved high complexity and patients with more advanced disease beyond average. | *We will assess this factor with conditions associated with spinal instability in mind.*<br><br>*All issues regarding comparisons of different technical approaches to fusion will be considered, including the potential for selection and other biases in comparisons across study populations.* |

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| | 3) In comparing treatment setting (ambulatory versus inpatient) for differential effectiveness, a careful review needs to be done to avoid confounding the indications and safety with regard to patient selection for both facilities. Often patients with multiple comorbidities have surgery as inpatients, and are not candidates for ambulatory surgery. As such, a comparison of complications in ambulatory and inpatient settings may result in drawing incorrect conclusions [2,13]. | *As above, we will consider the potential for selection and other biases in comparisons across treatment settings.* |
| 4 | Comments on Key Question 4:<br><br>Because economic value is increasingly becoming more important in the era of health care policy decision-making, and variety of studies are being published to establish the overall cost-effectiveness of the procedures we provide. A recent study evaluated the cost-effectiveness of single-level anterior cervical discectomy and fusion five years after surgery [1]. At five year follow-up, single-level cervical fusion was found to be both effective and durable resulting in a favorable cost per quality adjusted life year (QALY) gained as compared to other widely accepted healthcare interventions. The important point in this study is the long-term nature of it: surgery is often misconceived as an expensive alternative to conservative measures when examined at less than 1 year of follow-up. The durability of conservative treatment is very limited, and a significant percentage of these patients move into the realm of surgical intervention. In this cited study, the resultant cost/QALY gained at one year was $104,831; $53,074 at year two; $37,717 at year three; $28,383 at year four; and $23,460 at year five. Clearly, the data demonstrates that the durability of the treatment is much more relevant that the upfront cost.<br><br>Unfortunately there are no published studies in the literature comparing the long term costs and cost-<br>effectiveness of cervical fusion and alternative approaches. There is, however, literature on the comparison of surgical treatment of lumbar disease with conservative treatment. Using data | *Thank you for your comments. No changes to Key Question 4.*<br><br>*The review will evaluate all published reports on the costs and cost-effectiveness of all relevant management approaches for cervical degenerative disc disease, including the study described here.*<br><br>*The scope of the review is limited to management approaches for cervical degenerative disc disease; as such, studies focused on other conditions such as lumbar disease will not be considered.* |

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| | from the<br>Spine Patient Outcomes Research Trial (SPORT), Tosetson et al. was able to demonstrate substantial reductions in cost per quality-adjusted life year when using four year follow-up data [2]. Again demonstrated here is the fact that surgical intervention provides durable long-term benefit, such that cost/QALY gained goes down substantially as more long term data is collected. One can easily extrapolate that fusion for the treatment of cervical disease will be quite comparable, or even better than the durability demonstrated in the SPORT data. Long-term studies comparing the cost-effectiveness of cervical fusion relative to alternative approaches are needed. | |
| *Dena Scearce, JD, Medtronic, Inc.* | | |
| | Comment on Population:<br><br>Suggested wording: "Adults (>17y) with chronic or subacute cervical DDD with or without spondylosis<br>and/or radiculopathy and/or myelopathy, who have failed six weeks of conservative treatment. Patients with acute trauma, systemic symptoms, and/or severe neurologic impairment will be excluded, as surgical intervention is typically the only<br>available course of action for these individuals."<br><br>Comment on Population: The definition of the patient population is key to the evidence assessment. Patients with cervical DDD who do not have radiculopathy and/or myelopathy are not usual candidates for spinal fusion. Clarification is required. In addition, patients who receive spinal fusion should have failed conservative treatments. | *Thank you for your comments. No changes to Population other than wording changes previously described (page 1). Studies of cervical fusion will be included regardless of duration of prior conservative or other therapy.* |
| | Comment on Intervention:<br><br>Suggested wording: "The major technical approaches to one-level, two-level, or greater than two- level cervical fusion, performed as both an initial surgical intervention and as a subsequent or repeat procedure."<br><br>Comment on Intervention: Multi-level procedures should be differentiated as two-level and greater than two-level. Clarification as to the type of "major" technical approaches would be | *Thank you for your comments. The Intervention section has been amended to reflect these suggestions and will now read as follows: "The intervention of interest will be the major technical approaches to cervical fusion, categorized according to anatomic approach (anterior vs. posterior) and number of levels involved (single, 2-level, or >2-level). Studies of instrumented fusion will be included regardless of type of hardware utilized."* |

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| | useful (e.g. anterior procedures including discectomy with fusion/graft discectomy with fusion/graft and instrumentation). | |
| | Comment on Comparators:<br><br>As noted, patients who are treated with cervical fusion have failed six or more weeks of conservative treatment; therefore, comparison to conservative care is an invalid comparator. The relevant comparator to cervical fusion is other surgical intervention with various types of discectomy. We would encourage the HTA to consider the appropriate comparator to ensure a fair and balanced review. | *Thank you for your comments. No changes to the Comparators section. Conservative care will remain a comparator of interest, as stated in the response to comments on page 4.* |
| | Comment on Outcomes:<br><br>Suggested wording changes:<br>• Patient and clinician-reported measures of pain, function, and disability<br>• *Neurological function*<br>• *Radiographic assessments, such as fusion, alignment*<br>• Measures of "treatment success" or "clinically meaningful change" in clinical symptoms<br>• Requirements for repeat surgery or other retreatment, *with clarification on type of initial surgery*<br>• Return to work and/or resumption of normal activities<br>• Complications and adverse events of treatment<br>• Mortality, *with clarification on cause(s) of death*<br>• Treatment strategy costs and cost-effectiveness relative to comparators<br><br>Comment on Outcomes: It is our recommendation that the above underlined items be included to better describe the treatment outcomes. Additionally, the added clauses will provide clarity to types of surgery and reasons for mortality, which may have no association to the surgical intervention. | *Thank you for your comments. Neurological function will be assessed as part and parcel of the first-listed outcome. Evidence on requirements for repeat surgery and/or retreatment will be assessed according to type of initial surgery, and evidence on mortality will be examined according to categorical or discrete causes of death as available. Radiographic assessment will NOT be considered an outcome of interest, as measures of fusion success are poorly correlated with improvements in pain and function.*[1]<br><br>[1] *Kaiser MG, Mummaneni PV, Matz PG, et al. Radiographic assessment of cervical subaxial fusion. J Neurosurg Spine 2009;11(2):221-7.* |
| 1 | Comments on Key Question 1:<br><br>Suggested wording: What is the clinical effectiveness of cervical fusion for DDD with radiculopathy and/or myelopathy, who have | *Thank you for your comments. No further changes to Key Question 1 other than those described on page 4.* |

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| | failed six weeks of conservative treatment relative to that of conservative management approaches and other alternatives?<br>Question #1 - Comment: The definition of DDD should be clarified as noted above. In addition, we believe the comparison in this question is misguided. As we have stated above, the patient population receiving fusion has already failed conservative options. In order to be valid, the comparison here should instead be discectomy alone versus fusion. Potential benefits should also be assessed. It is also our opinion that the clinical effectiveness comparisons should include appropriate description of the specific population, unique indication(s) and surgical procedures utilized to ensure an accurate and reasonable comparison. | *As described previously, no attempt will be made to limit studies of cervical fusion based on duration of prior conservative or other treatment. Conservative care will remain a comparator of interest for the reasons described on page 4. Studies of fusion will be included regardless of indication for surgery.* |
| 2 | Comments on Key Question 2:<br><br>Suggested wording: What are the adverse events and other potential safety issues associated with cervical fusion compared to conservative management approaches?<br><br>Question #2 - Comment: Again, we think the comparison in this question is misguided. The patient population receiving fusion has already failed conservative options. In order to be valid, the comparison here should instead be discectomy alone versus fusion. It is also our opinion that the phrase "harms" is biased against fusion and instead we recommend utilization of the term "safety issues." We also believe this question should include an acknowledgement that there is a general lack of data on natural disease progression and conservative management, and more data available on cervical fusion; this will inevitably adversely bias against cervical fusion. | *Thank you for your comments. No further changes to Key Question 2 other than those described on page 5. As described previously, the review will encompass all potential harms of all relevant management approaches.* |
| 3 | Comments on Key Question 3:<br><br>What is the differential effectiveness and safety of cervical fusion? Consider the following factors: age, sex, race or ethnicity, measurable spinal instability, technical approach to fusion, impact of wait time on the efficacy of surgical treatment, ancillary use of a brace, insurance status (e.g. workers' compensation vs. other), | *Thank you for your comments. No further changes to Key Question 3 other than those described on page 6. The list of factors was intended to be illustrative, not exhaustive. Nevertheless, we will consider the additional factors described in your comment during our review of the evidence.* |

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| | and treatment setting (e.g. inpatient vs. outpatient vs. ambulatory surgery center)?<br><br>Ouestion #3 - Comment: It is our recommendation that the above underlined items be included to present a comprehensive list of factors. | |
| ***Michael Heggeness, MD, PhD, North American Spine Society*** | | |
| 1 | Comments on Key Question 1:<br><br>Comment: The main problem with the question as worded is that it causes confusion as to the diagnosis and symptoms being treated. As worded the question will have different meanings to different practitioners. With all due respect, this is simply a poorly worded question. It mixes terms that mean different things and have different indications for evaluation and treatment. The answers will only be as good as the questions. Unfortunately, the question is currently overly broad and encompasses such a wide variety of disease entities it will likely lead to diverse and non-directed answers.<br><br>The terms DDD and spondylosis are not necessarily synonymous. When asking the questions it will be important to specifically define DDD and spondylosis. Not only the presence of the conditions but also the severity are critical for appropriate decision making These underlying conditions will result in spinal degeneration with or without stenosis. The stenosis can be central resulting in spinal cord compression or foraminal resulting in nerve root compression or both. As a result, patients may present four categories of complaints. The first is "no complaint", they have a degenerative condition but are asymptomatic. The other three are axial pain, radiculopathy, or myelopathy, or a combination. In summary, the comments should be directed towards management of the degenerative condition (be specific) that results in (type of stenosis) with clinical presentation of (no symptoms vs. axial pain vs. myelopathy vs. radiculopathy).<br>The most clinically important question focuses on whether or not the spondylosis has created neurologic impingement by disc degeneration, | *Thank you for your comments. No further changes to Key Question 1 other than those described on page 4. As noted previously, language relating to specific types of symptoms or indications for surgery has been removed from the question. We will make note of the distinctions made in your comment when reviewing the evidence, however, in order to appropriately categorize the studies identified.* |

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| | collapse or loss of structural integrity or by the development disc osteophytes causing either spinal cord or nerve root compression. Further distinction then needs to be made for early myelopathic symptoms (prior to severe neurologic impairment) versus radiculopathy. | |
| 2 | Comments on Key Question 2:<br><br>This is an important question, as there are potential adverse events. It is important to recognize that the adverse events are substantially dependent on the condition being treated. Thus appropriateness of fusion or non-surgical treatment will change based on risk vs. benefit of the treatment. This in turn will depend on the distinction between presence or absence of stenosis and the presence of no symptoms vs. axial pain vs. radiculopathy vs. myelopathy.<br><br>The potential harms associated with not treating myelopathy (until "there is severe neurologic impairment") are great and should be treated separately. Likewise the treatment of DDD with radiculopathy is different from myelopathy but still may have significant neurologic consequences when treated non-operatively.<br><br>Additionally, cervical fusion should be divided into anterior and posterior fusion as the risk profiles are different for the two procedures. The risks of surgery are more inherent to the approach than to "cervical fusion" in general. | *Thank you for your comments. No further changes to Key Question 2 other than those described on page 5. As mentioned previously, we will explore all possible harms of all relevant management approaches.*<br><br>*We will consider potential harms to include those correlated with delay in corrective treatment.*<br><br>*Categorization of cervical fusion will include that of anatomic approach as you suggest, as well as the number of disc levels involved.* |
| 3 | Comments on Key Question 3:<br><br>NASS believes that age will need to be stratified.<br><br>While asking questions regarding sex, race and ethnicity is part of any good database, we do not expect significant differences in regard to the outcomes of cervical fusion.<br><br>Spinal instability requires further definition. As defined it is ambiguous and surgery is generally indicated for true instability. In general, use of this term should be either well defined or avoided.<br><br>Technical approach to fusion should be divided into anterior vs. posterior approaches. This can be further divided into standard vs. minimally invasive approaches. | *Thank you for your comments. No further changes to Key Question 3 other than those described on page 6.*<br><br>*To the extent that available studies stratify according to this factor, we will make note of how it is defined in each study and identify any areas of variability in the definition.*<br><br>*These stratifications are planned for the review.*<br><br>*We agree with these concerns; this is why insurance status was listed as a stratum of specific interest. We will seek to identify both clinical trials and observational studies that involve multiple treatment* |

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| | | *settings.* |
| | Workmen's compensation has many well-known and defined confounders to both operative and non-operative treatment and should be treated as a separate entity.<br>Treatment setting is also interesting and should be recorded in databases that assess outcomes with both short and long term complications, repeat admission and or return to the operating room. | |
| 4 | Comments on Key Question 4: | |
| | In order to determine cost-effectiveness there needs to be definitions for length of treatment (a single episode of symptomatology to resolution vs. lifetime treatment). The more difficult problems with cost-effectiveness involve defining time off work, return to work, progression to disability and time on disability. When a patient changes from insurance to disability (Centers for Medicare and Medicaid Service [CMS] covered care) do the health care costs show as stopping or will the costs be carried on? What is the patient's level of function? While alternative treatment may be the most cost-effective perhaps the degree of disability takes away any cost advantages. If the patient is on such significant opioids in pain management what is the cost to the patient, family structure and workplace? | *Thank you for your comments. No changes to Key Question 4.*<br><br>*An "all-payer" perspective will be taken with the planned cost-effectiveness evaluation. As such, a patient moving from traditional insurance to disability will continue to incur costs. Progression to disability will be assumed to incur additional costs (including those of lost productivity) as well as decrements in health-related quality of life.* |
| | While this is an important question to ask, it is also very difficult information to obtain. There are many variables to consider, and the collection of the data is vulnerable to heterogeneity, making comparative analysis flawed and often inappropriate. Great care must be taken to precisely define the methodology to insure homogeneous data and accurate conclusions. | *As with any economic evaluation, heterogeneity and residual uncertainty are expected and will be addressed using a variety of well-accepted techniques such as probabilistic and deterministic sensitivity analysis.* |

**Agency Medical Directors Comments on HCA Draft Evidence Report:**
Cervical Spinal Fusion for Degenerative Disc Disease

**Vendor:** ICER (Institute for Clinical and Economic Review)

**Report Date:** January 8, 2013

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1. The evidence was very strong that cervical fusion added onto other forms of surgery, such as discectomy, does not have additional benefit to patients with cervical DDD symptoms (Page 65 to 69). Given the key questions and the evidence at hand, it would still be important to differentiate in summary on the outcomes (effectiveness, safety, and cost-effectiveness) for the 2 main clinical categories of DDD: 1) patients with radiculopathy, who are undergoing a decompressive procedure (laminectomy, discectomy) with or without an add-on fusion, and 2) patients with DDD with chronic neck pain but not radiculopathy. We suspect these are the 2 categories that will drive the clinical committee's decision process.
2. Page 89. The results and findings of the Decision Analytic Model are very interesting. It will certainly be helpful in making coverage decisions. However, this is a very complex model. It would be beneficial to add additional interpretation to the key methodological concepts, how the model is developed in detail and how the results are derived from the model. The information may be included in an appendix as reference.
3. Page 24. The reviewers considered the overall comparative clinical effectiveness of cervical fusion to conservative treatment "Comparable". The reviews also suggested an "Incremental" rating on clinical effectiveness for cervical fusion comparing to ongoing conservative treatment for faster relief of the patients with severe and disabling symptoms. This seems to be a reasonable rating. However, to give a complete and balanced assessment, the reviewers should also explicitly include an "Inferior" rating for cervical fusion compared to conservative treatment for patients who have milder symptoms particularly in the long term given the diminished effect of fusion over time with increased depression (page 65) and higher rates of adverse events (pages 71-75), including death (page 20). This is important to call out in the executive summary.
4. The NNT and NNH approach was not included in the review to compare the clinical effectiveness or harm of the technology with comparators, which might have strengthened robustness of the appraisal.
5. Page 4. The report states that "Data on harms and/or subgroups of interest were also obtained from large (>50 patients), long-term (≥12 months of follow-up) case series evaluating cervical fusion". Some of the more serious adverse events may be more rare, *e.g.,* 1/1000 cases. In these cases, even single case reports, or FDA MAUDE reports, may be informative. Since the committee is explicitly charged with considering safety and rare but serious events cannot be captured in trials smaller than occurrence rates, these kinds of studies should not be excluded.
6. Page 4. The report states that "The criteria, which related to issues of study design, reporting, and minimization of bias, are presented in Appendix B". It is actually in Appendix A.

7. Page 6. The report states that "(NOTE: 5-10 point changes on VAS score represent the minimum change that would be considered "clinically important")". The IMMPACT group and others have recommended CMI to be more like 20-30% in pain and function. It is particularly important for beneficiaries to achieve more than minor palliative relief, thus if meaningful functional improvement is not evident, this should definitely be pointed out.
8. Page 8. The report states "In this study, an assessment of 292 patients receiving either PMMA fusion or posterior foraminotomy (Korinth, 2006); long-term outcome was assessed after a mean of 6 years". This seems to be an incomplete sentence.

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February 8, 2013

Washington State Healthcare Authority
Health Technology Assessment Program
Josh Morse, MPH
Program Director
P.O. Box 42712
Olympia, WA 98504-2712

Dear Mr. Morse,

*DePuy Synthes Spine*, part of the *DePuy Synthes Companies of Johnson & Johnson*, is grateful for the opportunity to provide the Washington State Health Care Authority with comments on its draft evidence report for Cervical Spinal Fusion for Degenerative Disc Disease (DDD). *DePuy Synthes Spine* is a leading manufacturer of medical devices for treatment of spinal pathology.

We agree with the determination that cervical fusion typically is not performed for patients with neck pain due to DDD in the absence of either radiculopathy or spinal cord compression. However, due to the following issues adressed in detail below, we feel that the decision analytic model used to address key question four (KQ4) should have no influence on coverage policies for patients with cervical radiculopathy.

- The draft report does not accurately characterize the health-related quality of life burden borne by patients with cervical radiculopathy who are candidates for surgical intervention;
- Estimates used for the cost-utility model were derived from data sources irrelevant for quality-of-life measurement for patients with cervical radiculopathy; and
- The model relies on a flawed assumption about the course of treatment response after anterior cervical fusion and discectomy.

* * * * *

***The draft report does not accurately characterize the health-related quality of life burden borne by patients with cervical radiculopathy who are candidates for surgical intervention***

By definition—and in accordance with common payer policies—fusion for cervical radiculopathy is reserved for patients whose intractable pain and/or neurological impairment directly impedes activities of daily living (ADLs) despite an adequate trial of nonoperative treatment (1). Thus, a base-case economic model that includes an ill-defined subgroup of patients with "mild-to-moderate" cervical radiculopathy lacks relevance for real-world clinical decision making.

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We also disagree with the report's contention that patients represented within high-quality studies of anterior cervical discectomy and fusion (ACDF) versus cervical disc arthroplasty "have more severe forms of cervical degenerative disk disease" (draft evidence report page 95, paragraph 3) than exhibited by the broad population of candidates for cervical fusion. While the clinical trial population is likely to be more homogenous (e.g., isolated, single-level radiculopathy) than patients who receive fusion in the general population, there is no evidence to suggest systematic differences in measures of disease severity.

Important data about the health-related quality of life (HRQoL) burden of cervical radiculopathy as reported by Carreon et al. and other researchers (2–4) were omitted from the report and decision analytic model on the basis of comparative disutility for patients with myocardial infarction or stroke (draft evidence report page 95, paragraph 3). Given that these diseases can affect distinct patient populations and aspects of HRQoL, such a complex value judgement should bear no influence on this evidence review. Instead, the review should reflect community or patient preferences—as derived from validated measures such as the EQ-5D or SF-6D specifically for patients with *cervical radiculopathy*—as a basis for utility estimates.

Our analysis of short-form 36 (SF-36) and SF-6D data from the ACDF control arm of the PRODISC® C Total Disc Replacement Investigational Device Exemption (IDE) study corroborates findings within the published literature indicating that cervical radiculopathy has significant, detrimental impact on HRQoL and utility (4). At baseline, patients randomized to ACDF had SF-36 physical component scores (PCS) well below United States norms (35 versus 50, respectively) (5). These deficits are consistent with meaningful impairment in ADLs, debilitating pain, and a reduced ability to function at work (5). Using Brazier's method for deriving SF-6D utility values from the SF-36 (6), we determined mean (SD) baseline utility among this clinical trial population (n =104) to be .53 (.078). This estimate is consistent with independently calculated values reported in the published literature (2,4), which should not be disregarded on the basis of comparisons with other disease states or the assumption that this trial population differs in severity from patients treated outside of the investigational setting.

***Estimates used for the cost-utility model were derived from data sources irrelevant for quality-of-life measurement for patients with cervical radiculopathy***

The studies used to inform the economic model include distinct patient populations (e.g., patients with cervical myelopathy); incorrect outcome measures; and/or limitations that preclude conclusions about the relative effectiveness of cervical fusion versus nonopeartive management. The following are among such limitations:

- Kadanka, 2002 and 2011 (7,8): This study compared fusion to conservative care for patients with *cervical myelopathy*, and does not include a preference-based measure of health-related quality of life. The authors of the draft evidence report correctly acknowledge that this pathology is out of scope for this assessment. Despite this, this study nonetheless serves as a key input for the structure of the economic model.

- Persson, 2001 (9): This trial compared fusion vs. physiotherapy vs. collar (three arms with 27 patients in each). This small study is unlikely to have been powered to detect clinically relevant between-group differences in pain and function (no justification for sample size was provided). Additionally, systematic differences in baseline total scores for the Disability Rating Index (DRI) for patients assigned to surgery versus physiotherapy suggest that balanced treatment assignment was unsuccessful (i.e., there was a failure of randomization). All DRI items were worse at baseline for patients assigned to surgery, and baseline total DRI scores were more than 20% worse for the surgical group relative to physiotherapy. Finally, the outcomes within the surgery arm of this study are inconsistent with results from high quality studies of ACDF versus cervical disc arthroplasty (discussed below).

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- Mayer, 2002 (10): The non-concurrent conservatively managed cohort was deemed not appropriate for surgery, as follows: "Surgical treatment was ruled out by a determination made by at least one orthopedic or neurosurgeon not directly connected to the rehabilitation program, as well as a surgeon evaluator associated with the multidisciplinary program." Therefore, comparisons between the two clinically distinct patient populations in this study are subject to treatment-by-indication bias.

- Van der Velde, 2008 (11): This decision analytic model included a patient population with "neck pain seeking care of a physician...with neck pain ≥ two weeks duration". This nondescript, heterogeneous population is unlikely to be representative of the subpopulation of patients with cervical radiculopathy significant enough to warrant surgery.

- Sullivan, 2006 (12): EQ-5D index scores were estimated for International Classification of Diseases, 9th-revision, clinical modification (ICD-9-CM) code 723 (other disorders of the cervical region). This code group represents a variety of cervical spine pathologies, and lacks precision for quantification of disutility applicable specifically to surgical candidates with a diagnosis of cervical radiculopathy.

***The model relies on a flawed assumption about the course of treatment response after ACDF***

The decision analytic model is built around the assumption that patients who receive ACDF have declining quality of life over time (evidence report page 84, Tables 7-8). However, as discussed above, the source documents from the systematic review completed for the evidence report do not provide a sound basis for this assumption. In contrast, high-quality, long-term data from the ACDF control arm of the PRODISC C Total Disc Replacement IDE study for treatment of cervical radiculopathy strongly refute this assumption. This patient population experienced dramatic, sustained improvements from baseline through 2, 5, and 7-years of follow up in utility (Table 1)(13) and SF-36 PCS scores (Table 2)(13–15).

**Table 1: Utility Estimates derived from SF-6D, Baseline to 84 Months, ACDF for cervical radiculopathy** (13)

| Time point (months) | Sample size | Lower 95% confidence limit | Mean Utility (SF-6D) | Upper 95% confidence limit |
|---|---|---|---|---|
| 0 | 106 | 0.52 | 0.53 | 0.55 |
| 2 | 96 | 0.60 | 0.63 | 0.66 |
| 3 | 91 | 0.66 | 0.69 | 0.72 |
| 6 | 86 | 0.67 | 0.71 | 0.75 |
| 12 | 76 | 0.67 | 0.71 | 0.75 |
| 18 | 79 | 0.67 | 0.71 | 0.75 |
| 24 | 101 | 0.69 | 0.73 | 0.76 |
| 36 | 55 | 0.64 | 0.69 | 0.73 |
| 48 | 51 | 0.66 | 0.70 | 0.74 |
| 60 | 61 | 0.69 | 0.73 | 0.78 |
| 72 | 61 | 0.72 | 0.76 | 0.79 |
| 84 | 73 | 0.70 | 0.73 | 0.77 |

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**Table 2: SF-36 PCS Scores, Baseline to 84 Months, ACDF for cervical radiculopathy** (13)

| Time point (months) | Sample size | Lower 95% confidence limit | Mean SF-36 PCS | Upper 95% confidence limit |
|---|---|---|---|---|
| 0 | 106 | 33.8 | 35.2 | 36.6 |
| 2 | 96 | 38.6 | 40.5 | 42.4 |
| 3 | 91 | 40.9 | 43.1 | 45.3 |
| 6 | 86 | 44.1 | 46.3 | 48.5 |
| 12 | 76 | 43.1 | 45.4 | 47.6 |
| 18 | 79 | 42.7 | 45.1 | 47.5 |
| 24 | 101 | 43.4 | 45.6 | 47.8 |
| 36 | 55 | 41.9 | 45.0 | 48.2 |
| 48 | 51 | 42.0 | 44.7 | 47.3 |
| 60 | 61 | 43.7 | 46.4 | 49.2 |
| 72 | 61 | 45.3 | 47.6 | 50.0 |
| 84 | 73 | 45.4 | 47.8 | 50.1 |

* * * * *

*DePuy Synthes Spine* encourages the final assessment report and underlying decision analytic model to thoughtfully consider professional society treatment guidelines (16,17), Medicare and commercial payer policies, and the body of literature in its entirety to inform its policy for cervical fusion for patients with cervical radiculopathy. Please do not hesitate to contact me at your convenience to address any questions about these comments.

Sincerely,

Christina Farup, MD
Vice President, Evidence Based Medicine

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CA #11081A

Page 6 of 6

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February 14, 2013

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SENT VIA E-MAIL: josh.morse@hca.wa.gov
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**RE: Comments on Draft Evidence Report for Cervical Spinal Fusion for Degenerative Disc Disease**

Dear Mr. Morse,

Thank you for the opportunity to provide comment on the Draft Evidence Report for Cervical Spinal Fusion for Degenerative Disc Disease (DDD). As you are probably aware, Medtronic Spinal and Biologics manufactures products that treat a variety of disorders of the spine. These products are utilized by spinal and orthopedic surgeons to treat patients and restore their quality of life.

We have reviewed the Draft Report prepared by the Institute for Clinical and Economic Review (ICER) and wish to provide comments for your attention. We offer our comments in two parts: broad, macro-level observations, followed by an attachment with our specific micro-level comments with references to the evidence cited in the report. We understand the volume of information reviewed for these technology reviews, and have attempted to be as brief and concise as possible while still making our points. Should you have questions, please do not hesitate to contact me for additional information.

**Broad Comments**

- **Executive Summary Does Not Provide Answers to the Key Questions**
  The Executive Summary of this report does not function as a high-level overview of the report; instead it appears to represent a full appraisal of the entire document – but with key elements missing. It is lengthy and does not provide straight-forward, understandable answers to the four Key Questions outlined in the report. A large portion of the summary focuses on the Decision Analytic Model, yet there is no mention of the potential and noted limitations provided later in the report. The summary also ought to include reference or highlights of various medical societies and insurance providers' recommendations for cervical spinal fusion. As noted on pages 43 and 44 of the report, the North American Spine Society (NASS), the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS), American College of Occupational and Environmental Medicine (ACOEM), the Work Loss Data Institute and UpToDate recommend cervical discectomy and fusion after a course of conservative care for the noted indications.

- **Structure of Report Difficult to Follow**
  We offer the general observation that the report, as drafted and structured, is difficult to follow. Matching narrative with the appropriate tables proves challenging. Certain tables in the document include calculated statistics on combined outcomes from various studies. However, in most cases, the table does not provide a perspective on the generalizability of the data based on the number of studies, the sample size, or confidence intervals. Inclusion of this perspective would enhance both the reader's understanding of the cited evidence, as well as the robustness of the evidence. Additionally, an index for all of the supporting information contained in Appendix C would be helpful; it is voluminous and cumbersome.

- **Inappropriate Comparators: Conservative Care and CSM**
  We again reiterate our point made in our submitted comments (October 2012) on the Key Questions that the comparison of cervical fusion to conservative care is an invalid one because patients who are treated with cervical fusion have already failed six or more weeks of conservative treatment. Severity of illness in patients treated conservatively is lower and not comparable to those patients treated with cervical fusion; this yields inappropriate comparisons of relative effectiveness between groups. Consequently, it is not surprising that there is limited evidence comparing cervical fusion to conservative care, as reflected in ICER's ratings on p. 23. The relevant comparator to cervical fusion is other surgical intervention with various types of discectomy.

  Additionally, regarding indications, the report notes that the focus is cervical radiculopathy. Accordingly, on page 3, the narrative indicates that patients whose primary complaint was cervical spine myelopathy (CSM) would be excluded as these cases are generally a neurologic emergency. However, the report includes studies with CSM patients, including the base case for the Decision Analytic Model. CSM patients tend to be older with more co-morbidities, experience other causes of mortality, and suffer multi-level disease. Integrating the CSM patients likely tends to bias the results.

  Following is a list of examples of studies with CSM patients included in the report with the first author's name/publication year:
  - ✓ Kadanka/2011: RCT/all CSM
  - ✓ Hasegawa/2007: CC/all CSM
  - ✓ Kawakami/2000: CC/all CSM
  - ✓ Koakutsu/2010: CC/all CSM
  - ✓ Nagata/1996: CC/all CSM
  - ✓ Tominaga/2002: CC/all CSM
  - ✓ Steiber/2005: CC/all CSM
  - ✓ Gandhoke/2011: CC/stenosis/OPLL $\geq$ 2 levels
  - ✓ Hirai/20111: CC/all CSM
  - ✓ Iwasaki/2007: CC/all CSM
  - ✓ Kristof/2009: CC/all CSM
  - ✓ Highsmith/2011: CC/all CSM
  - ✓ Yoshida/1998: CC/majority CSM in surgery groups/mix in conservative care
  - ✓ Shamji/2008 and 2009: majority CSM

- **Decision Analytic Model Has Limitations**
  A majority of the narrative focuses on ICERs Quality Adjusted Life Years (QALY) or Decision Analytic Model. While this is certainly relevant today with focus on comparative effectiveness, we have general concerns regarding the robustness of the model and its inputs. The drafters of the report

indicate that the weaknesses of the analysis warrant discussion, that certain findings should be interpreted with caution and that the comparability of evidence was limited due to variation in patient populations, study designs and outcome definitions. Yet this crucial information regarding results was not presented in the Executive Summary as an important point. The Decision Analytic Model simulates chronic neck pain patients treated with conservative care compared to cervical fusion.

As noted above, the comparison of conservative care to cervical fusion is an inappropriate one given that patients receiving cervical fusion have already failed conservative treatment. Therefore, conservative care and cervical fusion should not be considered treatment substitutes since patients are not at the same severity level at baseline. Rather, chronic neck pain patients progress through a treatment pathway from conservative care to more invasive and surgical treatments such as cervical fusion, if their pain does not improve. The comparison of conservative care to cervical fusion subsequently skews the relative effectiveness of the treatments and cost-effectiveness ratios. A more appropriate comparison for relative effectiveness would be two surgical treatment options for patients of similar severity levels, such as cervical fusion and discectomy.

Decision Analytic Models rely on a foundation of robust clinical evidence. The quantity and quality of the evidence selected for the comparison of conservative care to cervical fusion is limited, yielding a weak evidence base with high levels of uncertainty. This uncertainty is then combined with additional model assumptions regarding parameter estimates, and transition probabilities, which subsequently results in unstable estimates of the relative cost and clinical effectiveness from the Decision Analytic Model.

Sensitivity analyses were conducted surrounding some of the parameters included in the Decision Analytic Model. However, there was not a comprehensive sensitivity analysis conducted that would vary cost and QALY parameters to include ranges cited in the literature (e.g. Carreon 2012). It is unclear why certain parameter estimates were selected over others and a more comprehensive sensitivity analysis would provide insight into how the cost-effectiveness ratios vary based on underlying clinical evidence.

- **Mortality Harms are Presented Out of Relevant Context**
  It should be noted that mortality is an infrequent occurrence following cervical fusion surgery. As for general surgery and spine surgery, it is an intra-operative and immediate post-operative risk but more typically is related to general surgery risks and patient conditions versus specifically resulting from cervical fusion. Long-term mortality is not a relevant outcome.

  And, while it is customary to include death as an absorbing state in decision analytic models to account for attrition in the simulated cohort, the transition probabilities to the death state are problematic. The model assumes cervical fusion cases have a 1.1% higher probability of death compared to conservative care during the first year and eventually a 3.1% higher probability of death at year 3(p 89). The difference in mortality seems high given that the patients should be assumed to have the same baseline characteristics such as age. The probability of death should reflect the same age-adjusted mortality and include a slight adjustment for mortality risk related to surgery. The difference in probability of death is higher than expected and it is unclear how the probability of death differentially increases in the cervical fusion arm relative to the conservative care arm given the only difference in mortality should be related to mortality risk at surgery, which occurs within one year. Potential explanations for the model's assumption of increased relative probability of death for cervical fusion are frequency of repeat surgeries and the reference case including myelopathy patients. Further clarification on the repeat surgery assumptions, as well as the inclusion of myelopathy patients in the estimates, is warranted.

As we mentioned above, we have included our specific comments as an attachment for your review. We thank you again for the opportunity to comment on the Draft Evidence Report for Cervical Spinal Fusion for Degenerative Disc Disease and to participate in the HTA process. We stand ready to answer any questions on these comments and will gladly respond to non-proprietary information requests from ICER.

Sincerely,

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## ATTACHMENT

**Specific Comments**

Our specific comments are listed below, each with the language excerpt (in italics) from the report, the corresponding page number and our comments and/or suggestions for improvement and increased accuracy. Please note that our comments for pages 1-23 may also apply to the remainder of the report where the narrative is identical. The comments for the remaining pages address unique information not covered in the Executive Summary.

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- *The rate of spinal fusion has increased dramatically in recent years; an analysis of U.S. hospital discharge data from 1990-2004 showed an 8-fold increase in the utilization of anterior fusion procedures, even while the overall rate of hospital admissions for cervical DDD remained steady (Marawar, 2010). [page 2]*

**Comment**: The Marawar article may not be relevant to the assessment as it provides statistics on Medicare beneficiaries and includes a variety of cervical spine pathologies (herniated disc, spondylosis with myelopathy, spondylosis without myelopathy, and spinal stenosis). A citation to a more age-relevant population would be appropriate or, at a minimum, clarification should be provided.

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- *Studies that compared anterior to posterior anatomic approaches to fusion as well as single level, 2-level, and multi-level fusion were included, however, as evidence suggests that rates of mortality and certain complications may differ between these approaches (Shamji, 2009; McLaughlin, 1997). [page 4]*

**Comment**: The McLaughlin study cited is not a comparison of anterior to posterior, it pertains only to 2-level anterior.

---

- *Study quality was not assessed for case series, as the biases inherent in such study designs were felt to equate to poor quality universally. [page 4]*

**Comment**: This is a broad statement that is not well supported; case series are useful for various outcomes, including assessment of potential harms in large cohorts.

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- *Quality of life was also evaluated in the cohort study comparing fusion and interdisciplinary rehabilitation to rehabilitation alone (Mayer, 2002). Patients undergoing surgery reported statistically-significantly greater levels of depression on the Beck Depression Inventory at 12 months (mean [SD] = 10.7 [8.4] vs. 7.5 [8.4] for rehabilitation alone; p=.03). [page 7]*

**Comment**: The discussion of Mayer and quality of life notes that Beck Depression is higher for surgery at 12 months. This is accurate. However, these patients also had higher depression scores at baseline, which is not mentioned. There is no discussion in terms of "improvement."

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- *Figure ES2. Meta-analysis of treatment success, based on Odom's criteria. [page 9]*

**Comment**: The meta-analysis comparing fusion to discectomy includes only 2 studies for Odom's criteria in Figure ES2. A third study reported Odom's criteria (Appendix C lists Abd-Alrahman/1999 at 24 mos), yet it is not included. Additionally, the Barlocher and Van den Bent studies have different follow-up intervals but the data are combined (Barlocher/2002 data at 6 and 12 mos, and van den Bent at 24 mos).

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- *Data on quality of life were found in the Xie RCT comparing fusion with or without instrumentation to discectomy (Xie, 2007). [page 10]*

**Comment**: The time interval for quality of life is not indicated here; Appendix C appears to indicate it is one year.

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- *Figure ES3. Meta-analysis of likelihood of return to work at 12-24 months, fusion vs. discectomy. [page 11]*

**Comment**: The meta-analysis comparing fusion to discectomy includes only four studies. It seems the selection was limited to studies with 12-24 months assessment. This seems to bias against any differences occurring earlier. Other studies in Appendix C provided shorter term data on return to work. Likewise, of the four studies, two studies had 24 months data and others had only 12 months; it is not clear that combining the data is appropriate.

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- *As shown in Figure ES3 on the following page, the pooled estimate directionally favored discectomy in terms of return to work at 12-24 months, but this difference was not statistically significant. [page 11]*

**Comment**: The above reference to Figure ES3 notes that the pooled estimate directionally favors discectomy, which is noted as 'control,' but is not statistically significant. However, the figure seems to depict an outcome favoring fusion, which is noted as 'experimental.'

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- *In contrast, rates of in-hospital and 30-day mortality from large database studies, while <1%, were certainly nonzero (Shamji, 2008; Shamji, 2009). [page 11]*

**Comment**: The potential harms reference two studies by Shamji 2008/2009. These studies are not conducted in a typical cervical DDD population. As noted in Appendix C, they are multi-level surgeries (4-8 levels) with higher risks and the intent was to compare anterior to posterior. In addition, both studies include patients with CSM.

The narrative on page 11 notes that "*observational studies examined in this review suggest that risks of surgical interventions [sic, should be complications] may be higher than reported in RCTs.*" RCTs are often not "sized" for complication reporting; therefore, rates may not reflect data from large observational studies. This supports the usefulness of large cohort studies on safety outcomes.

In terms of studies on potential harms, a recent large database study by Memtsoudis/2011 on complications with ACDF versus posterior surgery is not included. From this study, complications and mortality rates 4.1%/0.26% and 15.4% /1.4%, respectively. Comparable rates were reported by

Wang/2007. These rates are both lower than the complications cited for general surgery risks in the report (see p. 75 perioperative complications cited in Table 5 and mortality rates in the narrative 1.2% - 21.5%).

Memtsoudis SG, Hughes A, Ma Y, Chiu YL, Sama AA, Girardi FP. Increased in-hospital complications after primary posterior versus primary anterior cervical fusion. Clin Orthop Relat Res 2011; 469(3): 649-57.

Wang MC, Chan L, Maiman DJ, Kreuter W, Deyo RA. Complications and mortality associated with cervical spine surgery for degenerative disease in the United States. Spine 2007;32(3): 342-7.

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- *Table ES3. Reported ranges of rates of potential harms from RCTs and comparative cohort studies, by type of study and comparator. [page 12]*

**Comment**: Table ES3 is not meaningful without number of studies reporting, sample size, and confidence intervals. Additionally, peri-operative and immediate post-operative should be differentiated from long term complications. And, in the Long Term Events statistics, the mortality lower end for surgery should be "0."

---

- *Among perioperative complications, the most frequently reported for fusion included dysphagia, hoarseness, and infection. [page 13]*

**Comment**: It is accurate that the most frequent complication for fusion is dysphagia and hoarseness, however, it is also the most frequent complication for discectomy alone. In 4 studies of fusion versus discectomy (Haueberg, Xie, Ruetten 2008 and 2009), the first two report no differences in rates of dysphagia and the latter two studies did not report statistical significance. The report's comment "*there was overlap*" does not clearly communicate these differences.

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- *Long-term data on harms were reported in 55 reports of case series, describing events in nearly 7,000 patients. [page 13]*

- *Importantly, we generally did not include studies comparing only one type of fusion to another (e.g. with vs. without plating), as recent systematic reviews have concluded that data are not sufficient to distinguish the performance of these approaches (Jacobs, 2011; Nishizawa, 2012; Gebremariam, 2012). [page 53]*

**Comment**: It is not clear how the 55 reports of the case series were selected or how they are used in the analysis. The narrative makes general note of exclusion of articles comparing surgical techniques (see p. 53), yet it appears that some of these articles were included (e.g., Guo 2011). No further information is provided later in the detailed section of the document. Providing clarification would perhaps enhance the merit and usefulness of the analysis.

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- *Table ES4. Reported ranges of annualized rates of potential harms from fusion case series. [page 14]*

**Comment**: There is no indication of the follow-up period for these annualized rates. Nor is there indication of the numbers of patients, confidence intervals, or duration of follow-up.

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- *In the RCT comparing fusion to physical therapy and cervical collar immobilization (Persson, 2001), the improvement in VAS pain among those undergoing surgery was found to be better among smokers vs. nonsmokers (p<.05)... [page 15]*

**Comment**: This is an error; the results for nonsmokers should be reversed as they had less pain (see App. C, p. 47)

---

- *Comparisons of anterior vs. posterior fusion techniques were performed in 1 good-quality and 3 fair-quality retrospective cohort studies. In the good-quality study, 103 patients underwent either anterior corpectomy with fusion or posterior laminectomy with fusion (Kristof, 2009). No statistically-significant differences were observed for any perioperative complication, functional outcome, or pain score. In a fair-quality study comparing anterior cervical decompression with fusion or posterior laminoplasty with fusion in patients with cervical myelopathy (Tominaga, 2002)... [page 15]*

**Comment**: The Kristof 2009 is a study of multi-level myelopathy and like Tominaga 2002 was intended to be excluded from the study, according to the authors. The report should have included the Memtsoudis/2011 study in this anterior versus posterior discussion. The narrative does not address the possible variance in indications between posterior versus anterior with the former typically consisting of more multi-level procedures.

---

- *Single- vs. Multi-Level Surgery*
  *Subgroup analyses of patients undergoing single- and multi-level fusion procedures were analyzed in 18 case series. In most of these studies, increases in the number of levels involved were associated with increased rates of pseudarthrosis, although the statistical significance of any observed differences was often not tested. [page 16]*

**Comment**: This section of the report provides a broad brush on single level versus multi-level. Providing additional context and sample sizes of subgroups would be useful.

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- *In one series, rates of dysphagia were reported for patients undergoing 1-, 2-, and 3+ level anterior fusion; these rates increased according to the number of levels involved (11% vs. 24% vs. 43%, significance not tested) (Riley, 2005). [page 16]*

**Comment**: Riley 2005 study on dysphagia is cited. The same author has provided a later systematic review that should be included.

Riley LH 3rd, Vaccaro AR, Dettori JR, Hashimoto R. Postoperative dysphagia in anterior cervical spine surgery. Spine 2010; 20;35(9 Suppl):S76-85.

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- *Age*
  *Eight case series provided data on patient subgroups based on age; three of these showed statistically-significant differences based on patient age in rates of adverse events and neurologic outcomes (Cabraja, 2011; Kadoya, 2003; Heidecke, 2000). For example, the rate of neurologic improvement significantly declined with increasing age, from 71.0% among those age <40 years to 11.1% among patients age 70 years or older (p= 0.014) (Kadoya, 2003).*

**Comment** In this age discussion, the authors mostly cited studies with CSM patients that were intended to be excluded.

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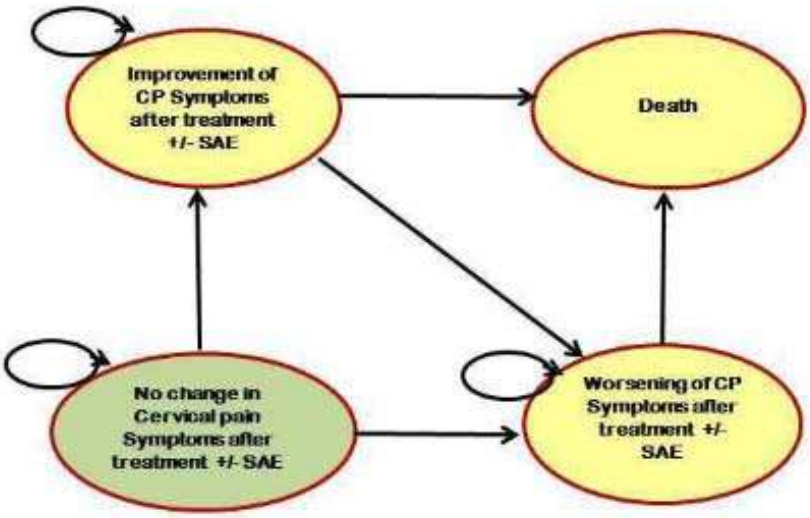
- *The decision model designed for this evaluation is shown in Figure ES4 below.*
  *ES4. Markov Disease State Diagram for Cervical Degenerative Disc Disease.*




*[page 18]*
*Despite its strengths, this analysis has certain limitations that warrant discussion. First, there were considerable weaknesses in available clinical evidence. As a result, findings from the economic evaluation should be interpreted with caution. There was a limited body of direct (and indirect) evidence comparing spinal fusion with alternative treatments other than surgery. Further, there was considerable variation in patient populations, study design, and outcome definitions across studies, which limits the comparability of evidence. [page 94-95]*

**Comment** In building a "base case" for its spinal fusion compared to conservative care model, the report uses a CSM study (Kadanka 2002) as its base (as well as data from CSM studies for other inputs). CSM patients are to be excluded as their patient characteristics are not comparable to radiculopathy.

The health state diagram does not allow for patients to transition from worsening pain to no change in cervical pain or improvement. It assumes that after each cycle a patient in the worsening health state can only continue to get worse or die after each three month cycle. Similarly, the model also assumes that

patients who improve may only continue to improve or get worse and does not allow for a transition to the no-change-in-cervical-pain health state after each three month cycle. In addition, the model does not allow for transitions between no-change-in-cervical-pain to death unless a patient transitions through worsening cervical pain. The transition probabilities to the death state should reflect only the all-cause mortality for the age-adjusted patient population being simulated in the model, therefore a patient should be able to transition from no-change to death.

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- *The spine is stabilized by fusing two or more vertebrae together, using bone grafts from the patient or bone bank; in some cases, bone-related products such as bone morphogenetic proteins (BMP) or synthetic products such as polymethylmethacrylate (PMMA) may be used as graft material instead (American Academy of Orthopaedic Surgeons, June 2010). [page 39]*

**Comment**: As BMP is not FDA-approved for cervical fusion, reference to BMP for use in cervical fusion should be removed.

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- *Risks associated with spinal fusion include nerve root damage, bowel or bladder incontinence, cerebrospinal fluid leakage, bleeding, and infection. [page 40]*

**Comment**: Bowel or bladder incontinence is not related to cervical spine surgery; this reference should be removed.

---

- *Our recording of data on potential harms of fusion and other surgical procedures included "peri-procedure" fatalities and complications occurring during the procedure or within 30 days following. [page 50]*

**Comment**: The authors note assessment of complications within 30 days yet the report tables provided depict annual rates.

---

- *Comparators of interest in this review included all management options compared to fusion in RCTs and comparative cohort studies. These included conservative management approaches such as physical therapy, spinal manipulation, immobilization (i.e., via a cervical collar or brace), medication, and other approaches; minimally-invasive procedures such as spinal injections, radiofrequency denervation, and percutaneous procedures; and other forms of surgery, including decompressive procedures such as discectomy or laminectomy without fusion, laminoplasty, and foraminotomy. Importantly, we generally did not include studies comparing only one type of fusion to another (e.g. with vs. without plating), as recent systematic reviews have concluded that data are not sufficient to distinguish the performance of these approaches (Jacobs, 2011; Nishizawa, 2012; Gebremariam, 2012). Exceptions to this rule included studies where the comparison was of anatomic approach or number of levels fused. [page 53]*

**Comment**: Exclusion of articles comparing "one type of fusion to another" and inclusion of articles on anterior versus posterior approaches warrants further consideration. Is relevant information being excluded (i.e., particularly more contemporary evidence) and is not relevant information included? More contemporary studies may represent comparison of methods as ACDF in general is considered standard of care. Of the 90 selected studies, only approximately 18 (20%) were published in the past three years (i.e., 1/15 RCT, 5/20 comparative and 12/55 observational).

---

- ***Training Standards and Relationship to Outcomes***
  *The benefits and harms associated with all procedures vary to some extent according to the skills of the operator….*
  *Studies examining the relation of procedure volume to outcome in patients with cervical disorders are relatively few in number. [page 62]*

**Comment**: "Training Standards and Relationship to Outcomes" is included, yet this was not raised in the four key questions.

---

- *Table 5. Frequency of perioperative surgical complications in a cohort of 1,442 patients, by type of complication. [page 75]*

**Comment**: These data include complications from ALL general surgical procedures, not just spine, for 30-day readmission. While the data is useful, the narrative ought to put these general surgical risks in context relative to cervical fusion surgery.

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- *Table 9: Clinical Parameters and Probabilities for the Decision Model [page 85]*

**Comment**: Repeat surgery base estimate is assumed to be 0.75. It is unclear what data this assumption is based on and whether it is applied to all surgical treatment options included in the model, or is specific to laminoforaminotomy, or to ACDF. If it is specific to laminoforaminotomy, or ACDF what are the repeat surgery estimates for the other surgical treatment options included in the decision analytic model?

Regarding the Clinical Subgroup Risk Multipliers: No methodology or justification is provided for the selection of the sources for the rates used in the model. The relevance of some of the citations is not clear. For example:

  - Relative risk of pain resolution; posterior versus anterior: Gore 2012 study follows 50 patients for 21 years following ACDF.
  - Odds of mortality, posterior versus anterior: Shamji 2009. Appendix C p 30 notes all patients with myelopathy. Perhaps reference is Shamji 2008 where subgroups with or without myelopathy and mortality for each group provided in Appendix C p 43 (note mortality higher with myelopathy).
  - Odds of mortality, multiple versus single fusion. Deyo 2010 is a study of "lumbar" stenosis, not relevant to cervical.

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- *Table 10: Adverse Events Incorporated into the Decision Model [page 86]*

**Comment**: No methodology or justification is provided for the selection of the sources for the rates used in the model. The relevance of some of the citations is not clear. For example:
ACDF perioperative complications: Korinth 2006. Study includes two groups with neither fusion per se (i.e., discectomy with "cement" versus foraminotomy).

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- *We also applied a[n] incremental cost of $17,564 associated with adjacent segment disease and $5,000 for perioperative complications for spinal fusion to 13.6% and 6.5% of patients respectively, as well as a disutility estimate of 0.20 (due to the need for subsequent surgery in these patients) [page 86]*

**Comment**: It is unclear what literature these estimates and assumptions are based on; citations are needed.

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- *Table 12. Cost Information for Treatment Considered [page 87]*

Comment: There is no justification for the cost of repeat surgery being 25% higher than ACDF. While there is no data, a more appropriate assumption would be the same cost of ACDF: $29,722

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- *Table 16. Results of Sensitivity & Variability Analysis [page 92]*

**Comment**: Cost, QALYs, and parameter inputs should be included in the univariate sensitivity analysis and include the full range of values found in the literature (e.g. Carreon 2012).

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- *Finally, this analysis is based on data from trials for cervical disc arthroplasty, in which patients have more severe forms of cervical degenerative disk disease. [page 95]*

**Comment**: The report notes that cervical disc arthroplasty patients included in Carreon's analysis are "more severe." The basis for this is not defined and its absence leaves the reader uninformed.

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- *However, the current body of evidence also suffers from a lack of rigor and applicability, as nearly all randomized studies have been small, conducted in single, specialized centers, and have not employed standard techniques for measuring or evaluating outcomes. [page 96]*

**Comment**: The report specifically excludes the extensive literature on cervical disc arthroplasty versus ACDF. These studies include RCTs with standard outcomes and long term follow-up.

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- *References Section [page 98-114]*

**Comment**: The basis for inclusion of articles in the reference list is unclear. Approximately 90 "studies" were included in the systematic review; the reference list includes 182 citations. Some possibly unrelated references (e.g., Juratli's 2009 mortality study for lumbar fusion, Gore 2012 on back pain, Kim 2009 cervical discs, Sasso 2011 cervical discs, Spinal Kinetics M6-cervical disc web site, Deyo for lumbar stenosis) are included without rationale. And, it is not clear which articles represent the selected comparative and observational studies included in the analysis. The bases for inclusion should be explained.

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- *Appendix C*

**Comment**: As currently organized, review of these data is very cumbersome. An index would be useful for expedited data review.

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February 14, 2013

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**Subject: Draft Evidence Report for Cervical Spinal Fusion for Degenerative Disc Disease**

Dear Mr. Morse:

On behalf of the Washington State Association of Neurological Surgeons (WSANS), Washington State Orthopaedic Association (WSOA), American Association of Neurological Surgeons (AANS), American Association of Orthopaedic Surgeons (AAOS), AOSpine North America, Cervical Spine Research Society (CSRS), Congress of Neurological Surgeons (CNS), AANS/CNS Joint Section on Disorders of the Spine and Peripheral Nerves and North American Spine Society (NASS), we would like to thank the Washington State Health Care Authority for the opportunity to comment on the draft Health Technology Assessment (HTA) draft evidence report on "Cervical Spinal Fusion for Degenerative Disc Disease." As leaders in cervical spine care, our organizations have worked with policymakers for many years to help ensure that patients have access to this important treatment when appropriate.

We appreciate the Washington State Health Care Authority's attempt to summarize the literature on surgical treatment of the cervical spine in this draft evidence report. Unfortunately, the technology assessment makes a number of critical errors, which undermine the validity of the report's analysis and strongly questions the quality of the assessment's final conclusions.

**Background**

Regrettably, cervical DDD is a "catch all" diagnosis, applied to a variety of different cervical degenerative conditions. This illustrates one significant failing of International Classification of Disease-9-Clinical Modification coding used in administrative data, where one code may refer to a variety of different patients. Both a young patient with a small disc bulge and mild radicular symptoms with no motor or sensory deficits, and an elderly patient with severe ossification of the posterior longitudinal ligament and advanced cervical myelopathy who is wheelchair dependent, may each be coded in administrative datasets as having cervical DDD. Hence, any literature review or assessment of administrative data must initially determine how to identify patients with separate categories of cervical symptomatology: axial neck pain, cervical radiculopathy and cervical myelopathy.

Axial neck pain, as noted in the report's Introduction, is very common and often necessitates medical evaluation. Axial neck pain may be present in cases of cervical radiculopathy or myelopathy as well. However, surgical treatment for axial neck pain in isolation is unusual. Sources for axial neck pain include cervical disc degeneration and musculoskeletal injury, as seen in whiplash associated disorders.

Cervical radiculopathy develops from focal impingement upon a nerve root producing radiating pain. While usually following a benign clinical course, cervical radicular symptoms failing to improve with conservative therapy or producing motor deficit may require operative therapy. Interestingly, the report fails to cite multiple reports published from recent randomized, prospective U.S. Food and Drug Administration (FDA) Investigational Device Exemption (IDE) trials establishing the clinical value of operative treatment in cervical radiculopathy and the maintenance of these beneficial effects at up to 6 years following surgery. These articles share rigorous study design, clear inclusion and exclusion criteria for enrolled patients and excellent follow-up rates (1-4).

Cervical myelopathy classically develops from chronic compression of the spinal cord as a result of cervical degenerative changes. Narrowing of the spinal canal produces both trophic and dynamic effects upon spinal cord morphology and vascular supply, producing neurologic loss of function. The natural history of cervical myelopathy arising from cord compression is one of gradual, steady deterioration (5). In cases of functional loss from myelopathy, recovery is difficult to predict, with many patients continuing to harbor significant deficits after surgery; a prime goal of operative intervention is prevention of further functional loss (5-7). Many operatively treated patient will only see stabilization of their symptoms, with up to 30 percent of patients in prospective studies not enjoying a return of pre-operative lost function (7).

The patient populations, indication for surgery, and goals of treatment in axial neck pain, myelopathy and radiculopathy patients are clearly distinct. Most studies focus on the evaluation and management of one of these patient populations; unfortunately, the draft HTA does not observe these distinctions, and freely mixes between the three groups of patients in their analysis. This inattention to detail and mixing of distinct clinical entities limits the value of the report's conclusions.

For instance, while the report notes that it does not include patients presenting with a primary complaint of myelopathy, a citation from Key Question #4 nevertheless uses results of a myelopathy study to predict outcomes in treatment of cervical radiculopathy patients (7). This approach produces critical errors, using outcomes for surgery from one distinct clinical entity (cervical myelopathy) to construct a value-of-care model on a completely different clinical entity (cervical radiculopathy). Further detail is provided in the comments below on Key Question #4.

Unfortunately, comparable to its lack of attention to detail in consideration of different patient populations, the report also lumps a wide variety of operative treatments for cervical degenerative disc disease together. Operative indications and expectations of patient outcome for a single level discectomy, versus a multiple level laminectomy and fusion, are as different as the patients themselves. Ignoring these clinically vital details introduces further sources of potential selection bias to the report.

**Literature Quality**

The choice of articles upon which the report is based is curious. There are 15 randomized, controlled trials (RCTs) listed as sources in Appendix C. However, only 6 were published in the last 10 years and most are much older. Only three of the RCTs are from U.S. centers. These unusual choices for foundational data introduce a source of bias in the report's results.

In discussing non-operative treatments, this rigorous approach to assessment of article quality was not applied. In non-operative therapies, observational case series are reported as adequate

foundation for intervention. The rationale for greater leniency in evaluation of the literature in non-operative treatments is not explained in the report. This leads to the unusual situation where uncommon conservative interventions, with limited support in the literature (e.g., chemonucleolysis, coblation nucleoplasty), are placed upon equal literature-based footing with anterior cervical discectomy and fusion -- an operative treatment with over 60 years of clinical experience. This illustration of further potential confirmation bias questions the validity of the report's conclusions.

There have been a number of recent cervical arthroplasty versus cervical fusion prospective, randomized, FDA sanctioned, IDE studies published in the literature. The report notes these were not included in this assessment due to some of these articles being previously reviewed by the Washington State HCA. However, the goal of this report is to evaluate the effect of surgical fusion on the clinical outcomes in patients with cervical degenerative disease, not to update previous Washington State HCA publications. While some of these articles may have been previously reviewed in other HCA processes, they are still material to this assessment and failing to include them is a source of bias in this report.

We believe these findings indicate deficiencies not in the extant literature, but rather in the choice of articles summarized in the report. We feel this represents another potential for confirmation bias.

Moving beyond these preliminary observations, the remainder of our comments will address each of the report's Key Questions.

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**Key Question #1: Evidence on Comparative Clinical Effectiveness**

Beginning with the language of KQ1, there is significant ambiguity as this is a broad topic: "What is comparative clinical effectiveness of cervical fusion for DDD relative to that of conservative management approaches, minimally-invasive procedures, and other forms of surgery?" Examples of each of these interventions are described in the policy put forth by the HTA, and are further detailed below. Per the HTA brief, the policy presents a consensus where "…the focus of this appraisal was on adults (>17 years of age) with cervical DDD symptoms, including neck pain, arm pain, and/or radiculopathic symptoms…[and] did not include myelopathic patients…." Below, the provided comparators are broken down and medical care concerns identified.

***Cervical Fusion***

Cervical fusion surgery is not a distinct clinical term. In patients undergoing cervical fusion, many factors may impact clinical outcomes. Not only do the number of levels involved potentially affect patient results, but so do approach (anterior only, posterior only, anterior and posterior), whether procedures are completed with or without discectomy, with or without laminar decompression, with or without interbody fusion, with or without corpectomy, with or without bone fusion and with or without instrumentation. When instrumented, great heterogeneity exists in types of instrumentation employed. For example, in posterior instrumentation there is variability in lateral mass plates versus lateral mass screws, pedicle screws, facet screws and spinous process wiring. The phrase "cervical fusion" is therefore extremely broad and encompasses a huge variety of patients.

***Conservative Therapy***

Options provided by HTA include physical therapy, cervical collar immobilization, spinal manipulation (chiropractic), medication (analgesics, muscle relaxants, opioids), alternative therapy (yoga, acupuncture) and self-care (educational materials, home stretching). These represent a variety of nonsurgical options available for consideration for the management of cervical spondylosis and radiculopathy. The assertion stated in the HTA that all forms of conservative management (e.g., physical therapy, spinal manipulation) have approximately equal clinical effectiveness is simply not valid.

***Spinal Injections***

Included options provided by HTA are spinal injections of steroids, nerve blocks, chemonucleolysis and botulinum toxin. The use of epidural steroid injections in the cervical spine is much more technically challenging and involves higher risk due to anatomical concerns. There are very limited numbers of providers able to do cervical epidural steroid injections (ESI), and as such there is significant limitation to patient access. The risks are higher than in the lumbar spine because of the presence of the cervical spinal cord and the smaller allowable volume. Selective nerve root blocks (SNRB) in the cervical spine likewise have high risk challenges for the provider and patient due to anatomy. Additionally, even if a patient consents to this treatment by someone willing and able to provide the cervical steroid injection (whether ESI or SNRB), these often involve multiple injections over the course of a year or more; thus it is not necessarily a one-time cost.

Finally, the risk of steroid injections in the central nervous system was brought into sharp focus recently when a large number of patients died from contaminated product. This has further limited the enthusiasm of patients and providers to use this therapeutic option. Chemonucleolysis, when chosen, is a technique typically used in the lumbar spine to manage disk degenerative issues, and is more akin to the next section, which addresses minimally invasive/percutaneous procedures. While botulinum injection can be very helpful for dystonia/torticollis that can cause neck pain, or even exacerbate cervical degenerative issues including radiculopathy, using botulinum toxin alone is not indicated for classic radicular pain of the arm/hand -- and, in fact, has been cited to cause cervical

radiculopathy as a complication of its use in treatment of dystonia (1). There are no articles in the past decade of PubMed listings to support this use.

***Minimally Invasive Procedures***

Less invasive procedures listed by the HTA are radiofrequency ablation and coblation nucleoplasty. These listed procedures are better labeled as percutaneous procedures, since they do not have the visualization, intensity, outcomes or acceptance similar to surgical interventions (i.e., open, minimally-invasive and mini-open surgical techniques are much more similar to each other than the percutaneous techniques). Radiofrequency ablation, chemonucleolysis and coblation nucleoplasty are not generally used in the management of cervical disk degeneration with radiculopathy.

In a PubMed search, few recent articles support these treatments for radiculopathy. Rather, these procedures are more typically used, if chosen, in the lumbar spine. Because of the anatomy involved (i.e., spinal cord, vascular anatomy, smaller epidural space and smaller disk space), they are not typically performed in the cervical spine. Radiofrequency ablation therapies may be used in facetogenic pain, which is a potential contributor to neck pain, but this is a scenario different than the one indicated by the HTA. We agree with the statement that "no comparative data were available comparing fusion to minimally-invasive nonsurgical management options such as spinal injections, RFR or coblation nucleoplasty."

***Other Surgeries (Non-fusion Surgeries)***

As noted in the HTA, non-fusion surgeries include discectomy, foraminotomy and laminectomy/laminoplasty. The examples given for these procedures in the HTA are, however, confounded by heterogeneity. Discectomy can be achieved ventrally or posteriorly (the latter in very select scenarios). As compared to the lumbar spine, a discectomy via a posterior approach in the cervical spine is a more complex technical issue and entails greater risk given the anatomy of the spinal cord and nerve root in such a small space as the cervical canal. It can therefore only be used in select patients with more laterally-positioned soft discs. Foraminotomy may be a component of laminectomy, laminotomy or laminoplasty, and may or may not also be done with discectomy – in the vignette describing foraminotomy as provided by the HTA, discectomy is described with it. Inconsistencies in describing the procedures, or intent of procedures, muddy the interpretation. Foraminotomies can also be done via a ventral approach. Decompression of the central canal by laminectomy or laminoplasty is not the typical procedure for management of cervical radiculopathy – decompression of the central canal is the typical procedure for cervical stenosis/myelopathy. Laminectomy or laminoplasty combined with foraminotomy and or discectomy is the more typical posterior approach for management of radiculopathy, when a posterior approach is chosen. To combine this variety of "other" non-fusion surgeries into an arbitrarily singular category limits the clinical relevance of these observations.

Some application of the data chosen to support the position statements of the HTA are flawed (see KQ 4). With respect given to ICER's definitions of quality, the majority of the cited articles are Levels III/IV evidence. Most of the studies cited by the HTA are not RCTs, and none are Level I evidence.

When conservative measures fail, or when significant neurologic impairment exists, surgical intervention is reasonable to consider. Neck pain alone is not considered a typical indication for operative therapy. Anatomic considerations and surgeons' experiences must factor into decision of approach. The goal of surgical intervention is protection and decompression of neural elements while ensuring spinal stability. The HTA also describes radiographic evidence of radiculopathy: radiculopathy is a clinical diagnosis; radiographic studies can confirm or negate the working hypothesis that a compressive phenomenon exists. When compression of the nerve root is confirmed, surgery can be an appropriate option. Not every radiculopathy co-exists with an

identifiable compressive phenomenon; in such situations, various conservative measures including those listed in the HTA may provide benefit.

While it is true that not all non-surgical measures are equal, so too is it true that not all surgical measures are equal. Having varied approaches for assorted patient needs is of the utmost consideration of a physician/surgeon.

***Previously Developed Guidelines***

What other information is available? In utilizing evidence-based medicine techniques, in the last three years, there are two major guidelines published regarding the management of cervical radiculopathy, and these are available online from the National Guideline Clearinghouse and the National Quality Measures Clearinghouse/AHRQ. The first is from the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS). In August 2009, the AANS and CNS jointly published guidelines regarding the diagnosis and treatment of cervical radiculopathy in patients with degenerative disorders. This squarely fits the stated intentions of this Washington State HTA. Management, surgical and nonsurgical and functional outcomes are analyzed in a consistent and structured fashion, and the data behind the guidelines and recommendations are amassed in the August 2009 issue of the *Journal of Neurosurgery Spine* (2). Additionally, in January 2011, the North American Spine Society (NASS) published additional clinical guidelines entitled "Evidence- Based Clinical Guidelines for Multidisciplinary Spine Care Diagnosis and Treatment of Cervical Radiculopathy from Degenerative Disorders." in the *Spine Journal* (3). The AANS/CNS guidelines report found level 1 literature evidence for superior clinical efficacy of anterior cervical decompression and fusion in comparison to conservative therapy in patients with radiculopathy from cervical degenerative disease. The NASS guidelines detail further literature support for operative treatment of cervical radiculopathy.

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**Key Question #2: Adverse Events and Other Harms Associated w/Cervical Fusion**

The draft report reviews several RCTs and comparative cohort studies in order to determine the incidence of potential harm after surgical treatment for cervical DDD. While it is clear that surgery of any kind introduces risk, determining the true incidence of adverse events after surgery is complex. This Washington State HTA's approach to addressing surgical risk for cervical DDD is inherently limited as it assumes that cervical DDD is a single disease entity with: a) uniform risk factors for adverse events; and b) that various surgical treatment approaches carry similar and equivalent potential risk.

Cervical DDD is not a singular disease but a diagnosis associated with a larger spectrum of clinical conditions, which can include myelopathy, radiculopathy, axial neck pain, or can be asymptomatic. As such, the underlying patient's condition and pre-existing disability not only factor into the indication for surgery, but also significantly impact surgical morbidity. Wang, et al in a review of 932,009 hospital discharges with the diagnosis of cervical DDD from the Nationwide Inpatient Sample (NIS) found an overall low rate of complications and mortality after cervical spine surgery (1). Notably however, they observed that the most significant factor in determining morbidity and mortality after surgery was associated preoperative myelopathy. The impact of pre-existing disability on surgical morbidity has similarly been reported in other observational studies (2, 3). Therefore, in determining risk of surgery for cervical DDD, combining disparate study populations from multiple RCTs and comparative cohort studies leads to variable, inconclusive results.

There are various potential surgical approaches for patients with symptomatic cervical DDD, with surgical decision-making dependent on the patient's underlying condition, age, comorbidities, spinal alignment, and extent of involved levels (among other factors). Large NIS observational studies confirm that the type of surgery performed is frequently correlated with these patient factors (1, 4, 5), thereby creating uniquely different risk profiles. Surgical risk can be categorized as those inherent to the type of procedure, and those incurred secondary to the severity of the underlying condition. For example, hoarseness is a known, yet infrequent, complication associated with anterior cervical surgery that does not occur after posterior surgery. Alternatively, posterior cervical surgery is often preferred in patients with myelopathy, multilevel disease and advanced age, and is associated with higher risk than anterior surgery for less severe conditions. Therefore, the risk for a given adverse event (e.g. hoarseness) or the overall cumulative surgical risk may be markedly different for anterior versus posterior surgery. Lumping these procedures together when reporting potential harm thus results in misleading and invalid conclusions.

Certain adverse events are unique to fusion surgery and warrant critical evaluation. As this HTA points out, pseudarthrosis is intrinsic to fusion procedures and can be considered a potential harm as it may lead to disability or need for reoperation. The impact of these surgical risks, however, must be weighed against the consequence of the underlying disease if left untreated. In 2009, the AANS/ CNS Joint Section on Disorders of the Spine and Peripheral Nerves performed an evidence-based review and formulated guidelines regarding the management of cervical DDD. They found the natural history of untreated patients with severe, long-standing cervical spondylotic myelopathy demonstrates stepwise worsening deterioration without improvement (6). Progressive myelopathy not only impacts individual disability, it creates a heavy burden on caregivers and society. Therefore, while surgery does carry a small risk of adverse events such as pseudarthrosis and reoperation, this must be viewed in light of the improved quality of life and reduction in socioeconomic costs with proper surgical treatment (7).

Last, this HTA points out the challenge of determining surgical risk using the available literature. RCTs are often too small to capture reliable data on complications that occur infrequently. Traynelis, et al in a review of 720 patients undergoing cervical spine surgery reported only a 0.4 percent risk for new postoperative neurologic deficit (8). The number of subjects necessary to conduct a comparative effectiveness trial with respect to potential harm would be unfeasible at that low incidence. Further, the exclusion criteria of many RCTs eliminates patients with significant disability or who are otherwise at high risk, thereby resulting in a subject group that does not accurately reflect the as-treated patient population. Alternatively, although large administrative patient databases such as the NIS allow for analysis of considerable numbers of cases, they have limitations including variations in reporting, sampling bias, coding inconsistencies, and the inability to determine causal relationships between diagnosis, interventions, and outcomes. Moving forward, multicenter prospective clinical outcomes registries will likely provide us with the necessary information for better defining risk of adverse events with accurate generalizability.

We applaud the efforts of the HTA for reviewing the literature and attempting to ascertain surgical risk associated with cervical DDD. While it is clear that overall complications are rare, based on the reasons outlined above, it is unlikely that we will be able to come to any significant useful conclusions regarding potential harm using the present analysis.

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**Key Question #3: Effectiveness and Safety of Cervical Fusion vis-à-vis Certain Factors**

***Single versus 2-Level Surgery***

The authors make reference to a 1976 RCT comparing ACDF to posterior discectomy with foraminotomy, and report the conclusion that for single level disease, the fusion group did better, but for 2 level disease, the posterior non-fusion group did better. It is important to recall that this paper compares the Cloward technique to the posterior decompression. This operative approach to anterior cervical discectomy predates the use of plate fixation and is no longer routinely used. There is a known incidence of cervical kyphosis using the Cloward technique without anterior plate fixation (1). A two-level Cloward operation without a plate could lead to even more kyphosis, perhaps negatively impacting the clinical results in these patients.

This paper does not apply to the current medical practice standards, which includes plating with two-level fusions, and hence the conclusion that posterior decompression is superior to anterior two-level fusion may not be correct using modern techniques.

***Gender***

Although male gender was found in the Rosensorn study to be associated with better outcomes, it does not make practical sense to favor offering fusion procedures to the male gender. The majority of patients in this study were males; hence an extended sample size and more rigorous analysis will likely rule gender out as a factor to consider in offering fusion procedures to patients. If females are denied equal access to fusion procedures, the social implications will be extreme.

***Inpatient versus Outpatient Fusion***

The Silvers 1996 study concluded that inpatient surgical candidates were more than twice as likely to require revision operations. There was no statistical testing on this. It makes sense that the inpatients were more likely to have revision surgeries. Most surgeons elect to perform outpatient surgery on healthy individuals with minimal or absent comorbidities (3), while inpatients are those who have multiple comorbidities and hence are more likely to experience complications leading to increased rates of re-operation.

***Anterior versus Posterior Fusion***

We have reviewed the studies that are reported to describe how anterior fusions lead to fewer complications when compared to posterior fusions. Most surgeons will agree that anterior cervical fusions have superior clinical outcomes when compared to posterior cervical fusions; however the vast majority of posterior cervical fusions are for patients that have 4-8 levels being fused. It is very important to compared fusion levels when making such a comparison. The Shamji study did not evaluate which levels were being fused, and the posterior group is very likely to include patients with more pathological levels and more multiple comorbidities. Most surgeons resort to a posterior approach when more four or levels need be performed, intraoperative time is shorter and dysphagia requiring peg tubes less likely. The Shamji study confirmed the greater incidence of dysphagia in the anterior group (2). There usually are very concrete and distinct reasons to either perform an anterior or posterior fusion or both, and it is extremely difficult to make a blanket statement that favors one approach over another other, as each patients pathology location differs.

***Duration of symptoms***

We agree that increased duration of symptoms prior to surgery often lead to worsening outcomes. We often recommend surgical intervention prior to the completion of conservative treatment measures for fear of this phenomenon. It is not unusual for us to encourage patients to come to the ER for expedited treatment in the setting of a patient who has been denied coverage for an operation.

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Multi-society Comments on Cervical Spine Fusion Evidence Report
February 14, 2013


**Key Question #4: Cost of Cervical Fusion versus Alternative Treatments**

Regarding clinical effectiveness, throughout the draft report, studies examining patients with cervical myelopathy are combined with analyses examining patients with and without radiculopathy (i.e. neck pain only). Combining three very different diseases (radiculopathy, myelopathy and neck pain with radiographic signs of DDD) is not clinically appropriate. In particular, degenerative disc disease (DDD) is a radiographic entity and not a clinical spine diagnosis per se.

Although cervical myelopathy is given as an exclusion criterion, many studies including myelopathy are included in the evidence review and results. Separate reports should be created for these three very distinct diseases; they should not be lumped together.

With regards to the Markov decision model which estimates the probability of events (one of four outcomes) and assigns an estimated utility and cost to those four outcomes, the clinical inputs and evidenced-based assumptions are flawed. The model is only as strong as the evidence that drives the assumption and the likelihood of a particular outcome. Because all other values that are estimated downstream are based on whether one treatment or another makes a patient better, worse, the same, or results in death, these downstream statistical "adjustments" do not overcome the errors made upstream. In fact, this "frame-shifting" leads to a dramatic negative effect on the integrity of the analytical output.

The largest error we have identified relates to the clinical inputs that drive the model on the probability of the four outcomes. The model is based on the assumption that the percentage of patients getting worse, better or same after surgery for DDD (with associated radiculopathy) will be similar to the Kadanka (2002) paper (1). Table 8 is identical to Kadanka 2002. However, the Kadanka paper is a study of myelopathy, not neck and arm pain. Importantly, Kadanka, et. al. reported better, same and worse outcomes for treatment of myelopathy (and based on myelopathy specific -- i.e., spinal cord -- function), not DDD associated neck pain or arm pain. Therefore, the model of probabilities of outcome is based on the wrong disease and the wrong endpoint (spinal cord function) for better/worse/same.

We also note inaccuracies in the assignment or estimations of utility (QALY-gain) for cervical surgery. The QALY health state for pre-treatment DDD (with radiculopathy) associated neck pain is based on population norms for "neck pain" patients in general from large population surveys (2). Again, these are not surgically relevant patients, nor is there any evidence that these patients have DDD or radiculopathy. Based on the prevalence of various forms of cervical disease, this baseline population norm reference more likely reflects "neck strains" than DDD with radiculopathy. Furthermore, the assumed utility or QALY-gain or loss for better/worse/same outcome was based on Van der Velde et al. study (3). The +/-0.9 utility assigned in the model and from the Van der Velde study was what was reported for general neck pain patients in a pain clinic when they were asked whether they had "no troublesome neck pain" = 0.80 QALY or "yes, troublesome neck pain" = 0.71 QALY- regardless of type of medical treatment or whether they ever had neck treatments (Table 1 of Van der Velde). In fact, there is no evidence that this utility was applied in patients with DDD (with or without radiculopathy) associated neck pain. Neck pain does not, by definition, represent the disease being studied in the report. Neck pain is a symptom, not a disease. To further the analogy, "cough" does not necessarily equate to lung cancer. Cough is a symptom of pneumonia, viral flu, allergy, or cancer. Utility of treatment of cough is not a valid proxy for utility of treatment for lung cancer.

The Value of a treatment is most dependent on the effectiveness of that therapy versus that of an alternative. The definition of effectiveness likelihood (Kadanka 2002) and assignment of utility values (Van der Velde) to represent Utility are both flawed in this analysis. The model does not accurately estimate the parameters of benefit in the [benefit/cost] value equation.

The flaws in the benefit estimation are insurmountable and produce extremely misleading results.

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**Conclusion**

On behalf of the undersigned organizations and the surgeons and patients we serve, we thank you for the opportunity to comment on the Washington State Health Care Authority's Health Technology Assessment on Cervical Spinal Fusion for Degenerative Disc Disease. It is imperative that patients have a wide range of treatment options available to them, and so we encourage you to carefully consider our comments and amend the draft report accordingly. **We therefore specifically request that as the Health Technology Clinical Committee considers its recommendations regarding the surgical treatment for cervical degenerative disease, that careful consideration be given to the multispecialty guidelines recently published by the AANS/CNS Joint Section on Disorders of the Spine and Peripheral Nerves and NASS.** These guidelines are referenced in the responses to Key Question #1 above and attached herein.

If you have any questions or need additional information, please do not hesitate to contact us. In the meantime, we look forward to the opportunity to present our views in person at the March 22, 2013 Health Technology Clinical Committee meeting.

Sincerely,

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