

WASHINGTON STATE HEALTH CARE AUTHORITY

# Peer Reviews, Public Comments & Responses

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Health Technology Assessment

**OAT/Mosaicplasty Health**

**Date: Friday, October 14, 2011**

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**Health Technology Assessment Program**

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# Peer Reviews, Public Comments & Responses

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OAT/Mosaicplasty Health  
Technology Assessment

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**Note:** Spectrum is an independent vendor contracted to produce evidence assessment reports for WA HTA program. For transparency, all comments received during the comments process are included or otherwise made publically available. However, comments related to the key questions (and their formulation), context provided regarding the key questions, program decisions, process, policy decisions, or other matters not pertaining to the evidence presented in the report are acknowledged through inclusion, but are not within the scope of response for report accuracy and completeness

## Peer review comments and Spectrum Research response

Section and/or page	Comment	Spectrum Research Response
INTRODUCTION Comments  Page 7 Line 12	I don't think it is generally agreed that OCD is due to lack of blood supply. There are several etiologies. You may be referring to avascular necrosis here instead? OCD only accounts for maybe 5 % of cartilage lesions in any case.	Sentence changed in text
Page 7 Line 18	Autologous chondrocyte transplantation is probably reparative rather than reconstructive since one is not replacing the structure but inducing a growth process. Many now believe that the cells used in ACI may not actually make the cartilage but rather stimulate growth from subchondral bone.	Changed text to (Cole, 2009 and Shah, 2007 describe ACI as "restorative techniques")
Page 7 Line 22	"Transplantation of cartilage and subchondral bone into the defect is intended to facilitate the growth of new tissue." I think as a reconstructive technique that growth is secondary. The primary goal is to directly replace structure.	Changed sentence (per Shah, 2007):
Page 32 Line 7  Background Comments	The description of OCD does not appear accurate. It is not a common cause of cartilage lesions and its etiology is not clearly vascularity related. The OATS literature may emphasize OCD since the OATS procedure replaces subchondral bone affected by OCD as well as articular cartilage.	Corrected the text accordingly.
Page 34 Line 1	ACI is reparative, not reconstructive.	Cole, 2009 and Shah, 2007 describe ACI as "restorative" techniques, so the description was corrected accordingly.
Page 39 Line 24	Thermal necrosis was never properly examined in the literature. Recent data shows bone necrosis around microfracture holes (Chen et al JOR 2009).	Removed reference to necrosis; Chen 2009 study shows necrosis in a rabbit model, but not known if data present in humans.

<p>Page 40      Line 10</p>	<p>There is limited evidence for some of your description of ACI. Note that passaged chondrocytes are no longer chondrocytes and so what is injected are “dedifferentiated chondrocytes”. The following statement is not correct “The initial FDA approval in 1997 was for treatment of secondary, contained Outerbridge grades 3 and 4 defects of the femoral condyle and trochlea in patients &gt; 18 years old”. ACI is only approved after failure of MF. The following statement is also incorrect “Studies have demonstrated efficacy in additional populations”. There has been no RCT to date that has demonstrated efficacy of ACI in any population compared to a control group like MF. One RCT Knutsen 2004 and Knutsen 2007 concludes that ACI and MF are not different.</p>	<p>Corrected text to “dedifferentiated” chondrocytes. Changed FDA 1997 reference to quote from FDA approval letter and added 2000 restricted revision. All the studies Mithoefer cites in demonstrating efficacy are case series; corrected the text accordingly.</p>
<p>REPORT OBJECTIVES &amp; KEY QUESTIONS</p>	<p>The objective is very general while the key questions highly specific. I would have expected an intermediate level of detail, perhaps listing specific objectives prior to the very detailed key questions.</p>	
<p>METHODS Comments</p> <p>Page 65      Line 10</p>	<p>Appendix D containing key information on LoE is cited but not present in the document.</p>	<p>For some reason, the Appendices, which were sent as a separate document, were not posted on the State’s website at the time of the Draft publication</p>
<p>Page 65      Line 10</p>	<p>You have not addressed some of the methodological issues that are specific to surgical studies as described in Ref 52 Mithoefer.</p>	<p>Some additional context has been added to the “Key considerations highlighted by clinical experts”. Each medical discipline has its own unique features and study concerns. Methodologically rigorous studies can take a number of the unique features into account. While many procedures may not lend themselves to RCTs, well-designed prospective cohort studies (and other designs depending on the study question) can provide high quality evidence when steps are taken to reduce bias and enhance internal validity.</p>

<p>RESULTS Comments</p>	<p>There is a very high level of detail in the results section without appropriate interpretation and synthesizing of the information into a limited number of conclusions and take home points. The latter are certainly presented in the summary but the connection between the highly detailed results and the summary points are not easy to follow.</p> <p>A greater level of attention to formatting text, tables and figures to be visually communicative and easily digested and retained needs to be brought to the document</p>	<p>We have attempted to create transition sentences and enhance the tables and flow of information. Additional context in the “Key considerations” section was added. The primary focus is on presentation of the data so readers can draw their conclusions with some interpretation provided in text surrounding figures and tables.</p>
<p>CONCLUSIONS Comments</p>	<p>I believe the extent and comprehensiveness of the report and conclusions are very strong. The level of rigor is very high however the surgical community may have difficulty placing this approach into their context since it is a very general approach that may not account for some specific features that are often present in surgical treatments and studies. Although the latter may not change the actual results or conclusions it is important to address these issues.</p>	<p>Some additional context has been added to the “Key considerations highlighted by clinical experts”. In general each medical discipline has its own unique features and study concerns. Methodologically rigorous studies can take a number of the unique features into account</p>
<p>OVERALL PRESENTATION and RELEVANCY Comments</p>	<p>I think some work is required to smooth out the details and interpret some of the findings in a more common and general sense. A vast amount of information is presented but is somewhat difficult to get a global handle on. Direct statements interpreting some of these findings would help the clarity and flow of the report.</p>	
<p>Quality of Report</p>	<p>Good</p>	

## Provider comments and Spectrum Research response

**Email message sent to the HTAP by Brian L. Cole, MD, MBA (Full message following response to industry comments)**

Not sure where to begin on this issue of OATS and OA graft transplantation except to say that OATS has data that is level 1 in support of it and there is abundant level 2 and 3 data for both procedures. This is essentially a thesis in terms of addressing the approval pathway based upon the existing science. This needs to have clinicians involved when making these decisions to assist in your interpretation of the literature

Please let me know if I can assist

Check out my website for peer reviewed literature [cartilagedoc.org](http://cartilagedoc.org)

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Brian J. Cole, MD, MBA

**Spectrum Research response:** No specific issues to respond to. We looked at the website provided and found no studies that met the inclusion criteria that were not already included.

## Spectrum Research response to public comments

### Industry Comments

#### Appendix A: Detailed comments

Smith & Nephew, Advanced Surgical Devices Division, Dr. Paul M. Just

#### Detailed comments: From Smith and Nephew's

Page	Concern	Detail	Spectrum Research Response
11, 19, 146	Case definition	OATS and mosaicplasty are restorative procedures used to repair cartilage damage. Expectation that a public health or epidemiologic description for a case definition of a cartilage repair procedure exists in surgical literature is not realistic. It is the patient who may require such a procedure that must be defined. If a case definition is to be demanded, it should be of the diagnostic requirements of cartilage damage. Cartilage lesions are most accurately identified by diagnostic arthroscopy. <sup>1, 2</sup> Reasonable diagnostic assessment of suspected cartilage damage has been described. <sup>2, 3</sup> However, one must recognize that, as stated by Magnussen, et al, "Articular cartilage defects frequently are discovered at arthroscopy and may not be anticipated before the procedure." <sup>4</sup>	Information on evaluation of cartilage damage classification and arthroscopic determination of lesion characteristics are presented for Key Question 1.  As stated in the body of the report (beginning on page 72), treatment algorithms from review and instructional articles provide similar advice and do not provide evidence-based case definitions or cite evidence supporting the decision tree for determining characteristics that point to the best treatment options.  The references suggested by the commenter provide general information about the diagnostic assessment and description of lesions and describe options for treatment in general.
12, 19, 25, 146	Statement that "lesion size and classification appear to be the primary criteria for assessing treatment options."	Determination of the most suitable treatment for cartilage damage is complex. Consideration on treatment options begin with which joint is involved. Outcomes have been related to the location within a joint of a lesion (using the knee as example, whether it is located on the medial femoral condyle, lateral femoral condyle, patella, etc.) <sup>1, 5, 6</sup> , the lesion surface area (<1 cm <sup>2</sup> , 1-4 cm <sup>2</sup> , or >4cm <sup>2</sup> ) <sup>6-11</sup> , lesion depth, lesion etiology (acute or insidious), and symptom duration <sup>12</sup> .	The main body of the report (KQ1, beginning on page 72) does discuss the complexity of determining treatment options and presents information from treatment algorithms. After assessing alignment, ligament stability and meniscal deficiency, and other considerations, recommendations for use of OATS (autograft) versus osteochondral allograft do appear to have lesion size, and classification as key elements for determining treatment in addition whether the patient is "high

			<p>demand” or “low demand” regarding their physical activity.</p> <p>Portions of the summary and text have been reworded.</p>
12, 79-82, 146	<p>Challenge to the validity of the Outerbridge and ICRS grading systems in patients with cartilage damage.</p>		<p>It is not clear what the concern is.</p>
14, 20, 98, 102, 147	<p>Comparing outcomes of OAT/ mosaicplasty to ACI.</p> <p>The interpretation as stated is challenged.</p> <p>Comment that the two RCTs mentioned are “poor quality.”</p>	<p>The statements are erroneous as made clear on page 102 of the draft report. These sections fail to accurately report the results of the three prospective randomized controlled trials<sup>6, 13, 14</sup> comparing OATS/mosaicplasty to ACI.</p> <p>Contrary to the statements in the draft report, a recent Cochrane Review of ACI identified that Dozin et al 2005<sup>13</sup> and Horas et al 2003<sup>14</sup> demonstrated a non-significant trend toward superior outcomes for OATS/ mosaicplasty (their Figure 3).<sup>15</sup></p> <p>Bentley et al 2003 concluded ACI had superior outcomes to mosaicplasty but issues with the study population include that the average lesion size was larger than recommended for mosaicplasty and that the osteochondral plug was placed proud to the surrounding surface.<sup>6</sup> It is this study that helps define that OAT/mosaicplasty should be limited to lesions smaller than 4 cm<sup>2</sup>. It is this study that helped later define that OAT/mosaicplasty should be limited to lesions smaller than 4 cm<sup>2</sup>.</p> <p>Horas et al 2003 concludes mosaicplasty is superior to ACI and reports significantly faster recovery at six, 12 and 24 months after surgery by the LKSS for OATS/mosaicplasty compared to ACI.<sup>14</sup> Please reread the authors’ conclusion on page 189 of the study and correct the interpretation presented throughout the draft report. The authors’ state, “...according to the postoperative Lysholm score, the recovery of the patients treated</p>	<p>The data and figures for the Horas study have been corrected and text edited accordingly.</p> <p>The Cochrane review did not state that there was a non-significant trend in the Horas and Dozin studies; they said it was a “non-significant result with no preference for one treatment over the other.” Vasiliadis 2010 Cochrane Review: It is not clear what figure the commenter is referring to. The Vasiliadis figure 3 they cite summarizes the methodological quality of included studies. We assume that the commenter is referring to Figure 2 (page 12) and the corresponding Analysis 1.5 (page 42), which is described as an “exploratory analysis” of “satisfactory outcome of success” or analysis 1.4. The following statements are taken directly from the Cochrane report:</p> <ul style="list-style-type: none"> <li>• Description from Cochrane Review: “Although outcome measurement differed in the three trials, and the categorization of continuous scales into crude categories is generally unsatisfactory; two analyses featuring all three trials are presented on an exploratory basis..... Analysis 1.4 presenting</li> </ul>

		<p><i>with autologous chondrocyte implantation was significantly slower than that of the patients treated with osteochondral cylinder transplantation; this was found at six months (<math>P \leq 0.0015</math>), twelve months (<math>P \leq 0.001</math>), and at twenty-four months (<math>P \leq 0.012</math>).<sup>14</sup> Also see their Figure 1.</i></p> <p>Although Dozin et al 2005 had a small population, of those who completed the final LKSS assessment, 15 of 18 (83.3%) OATS/ mosaicplasty compared to 10 of 19 (52.6%) ACI patients were classified as experiencing a complete success (LKSS &gt;90).<sup>13</sup> The result was not statistically significant and the authors concluded there was no difference between treatments.</p> <p>Three prospective RCTs compared OATS/ mosaicplasty to ACI.<sup>6,13, 14</sup> Bentley et al 2003<sup>6</sup> and Horas et al 2003<sup>14</sup>, respectively, have been identified as level 1 and level 2 studies by three systematic and one comprehensive review applying international standards based on established levels of evidence, modified Coleman Methodology Score and risk of bias.<sup>4, 5, 7, 16</sup> Similarly, Dozin et al 2005<sup>13</sup> was identified by a systematic review as a level 2 study.<sup>7</sup> Two other systematic reviews of ACI surgery identify all three as level 2 studies.<sup>17, 18</sup></p> <p>There appears to be some difference of opinion on the quality of any evidence. However, stating these are “poor quality” trials may result in reader bias. One would expect this would be avoided by an objective report</p>	<p>results for an ‘excellent’ outcome shows the disparity between the results of the three trials. Analysis 1.5 shows the pooled results for “satisfactory outcome of success”.”</p> <ul style="list-style-type: none"> <li>• Results as stated in Cochrane: “The analysis revealed a non-significant result, with no preference to one treatment over the other (Figure 2), but also considerable heterogeneity (<math>I^2 = 79\%</math>)”</li> </ul> <p>Examination of the forest plot for figure 2 (Analysis 1.5): While the point estimates for Dozin and Horas may suggest that mosaicplasty might be favored, the results were not statistically significant (this is consistent with this HTA report) and the third study by Bentley shows a marginally significant effect favoring ACI (i.e. the effect is in the opposite direction). Thus it is not clear that a conclusion of “nonsignificant trend favoring mosaicplasty” is supported when all 3 studies are considered. The findings should be interpreted with caution given the significant heterogeneity across studies (79% of the pooled effect might be due to heterogeneity), combined with the methodological concerns regarding these studies.</p> <p><i>Horas Study:</i></p> <p>Although Horas, et al conclude that recovery was slower following ACI versus OAT and the figure suggests higher mean values for OAT earlier in time, no formal statistical comparison of the curve slopes (i.e. rate of</p>
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			<p>recovery) was presented. The p-values presented appear to relate to the statistical differences between mean values for the study groups at the same time points, not the rate of recovery.</p> <p><i>Dozin Study:</i></p> <p>Data presented in Dozin’s Table 3 is reflected in the report in Table 23 as it appears that the authors included the groups that showed “subjective improvement” but had no LKSS and those that were “lost to follow-up” in their evaluation of statistical significance. In our table 23, these later two groups are both considered lost to follow-up. From Dozin’s table 3 it appears that only 17 mosaicplasty patients and 16 ACI patients completed LKSS and that 15/17 (88.2%) and 10/16 (62.5%) for mosaicplasty and ACI respectively had “complete success” based on LKSS with the corresponding RR and 95% CI in the text of our report being 1.4 (0.93, 2.14) p = 0.12. This result is not statistically significant.</p> <p><i>Critical appraisal and level of evidence:</i></p> <p>All three of the RCTs comparing OAT/mosaicplasty with ACI and the two comparing OAT with microfracture were given ratings of IIb using the Level of Evidence (LoE) system developed <i>a priori</i> used for evaluating study quality in our Health Technology Assessments as described in Appendix D and E. The description of these studies as “poor quality” is consistent with the description in the methods. (The appendices were provided with the draft report but for some reason were not posted to the State’s Website.) The rating system was</p>
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			<p>developed based on the sources cited (including domains suggested by the AHRQ) and reflects the potential for bias in studies. An RCT does not automatically get classified as “Level I” evidence as sources of bias are also considered, creating a downgrade to a Level II or IIb. RCTs, as any other study design, may be rated as poor if there is significant potential for bias as described in the objective rating scheme and critical appraisal. Very high quality prospective cohort study may provide evidence that may be of equal (or higher) quality than a very poorly conducted RCT that has significant potential for bias (e.g. significant loss to follow-up). The intent is to put study results in the context of the internal validity and potential for bias by using a formal rating system and applying the description based on criteria set <i>a priori</i>.</p>
<p>14, 98</p>	<p>On Longevity of treatment effect.</p>	<p>State results clearly.</p> <p>Gudas etal 2005, a prospective RCT, found “significant superiority of OAT [n=28] over microfracture [n=29]” in “active young athletes under the age of 40” “at an average of 37.1 months” as measured by HSS and ICRS.<sup>19</sup></p> <p>Gudas etal 2009, a prospective RCT, reported “at an average of 4.2 years follow-up” that OAT (n=25) had “significant superiority” over microfracture (n=22) in their population of children under 18 years old measured by ICRS functional and objective assessment.<sup>20</sup></p> <p>In a prospective quasi-RCT, Horas etal 2003 reported that LKSS revealed faster recovery through 24 months in the OAT group compared to the ACI group.<sup>14</sup></p> <p>Prospective case series have reported</p>	<p>Gudas studies:</p> <p>The previous section states that OAT recipients had significantly better functional outcomes. The section on longevity accurately describes the “trends” over the various follow up time and that the significant differences favoring OAT were sustained. Data are presented in figures and tables. Detailed text, specifying mean follow-up time is also presented.</p> <p>Horas:</p> <p>See previous comments regarding speed of recovery.</p> <p>The focus of the HTA with regard to evaluation of efficacy and effectiveness is on the highest</p>

		<p>long-term favorable outcomes from mosaicplasty. Hangody et al 2010 reported that depending on location of repair, 74% to 91% of 354 athletes followed for 9.6 years on average (range 2-17 years) after mosaicplasty had favorable outcomes.<sup>21</sup> Solheim et al 2010 reported that at a median 7 years (range 5-9 years) after mosaicplasty, improvement over baseline was maintained, albeit at a lower level than at one year post-surgery.<sup>22</sup></p>	<p>quality studies which compare treatments. Given that comparative studies were available for autograft OAT/mosaicplasty, case series were not included. The Hangody 2010 information on athletes is in the report under "special populations".</p>
16	<p>Under Safety, 5<sup>th</sup> bullet, "it is not possible to attribute this progression to the graft procedure."</p>	<p>"Attribute" is not a neutral term. Rather, to objectively assess the data, a more appropriate conclusion is that without a comparison group, it is not possible to evaluate how OAT surgery may interact with the development of osteoarthritis.</p>	<p>Wording revised.</p>
20	<p>The draft report calls two prospective RCTs comparing microfracture to OATS/mosaicplasty "low quality."</p>	<p>Three systematic reviews and one comprehensive review identify Gudas et al 2005 as a level 1 study.<sup>4, 5, 7, 10</sup> There appears to be some difference of opinion on the quality of any evidence. However, stating these are "poor quality" trials may result in reader bias. One would expect this would be avoided by an objective report.</p>	<p>Please see previous response regarding LoE assessment and Appendices D and E of the report. Information on the determination of "Overall Strength of Evidence" is found in Appendix D as well..</p>
23	<p>Key Question 6 is not accurately reflected in the summary table.</p>	<p>Key Question 6 on page 9 and 25 of the draft report is: What is the evidence of cost implications and cost-effectiveness for OATS/mosaicplasty? Including consideration of:</p> <ul style="list-style-type: none"> <li>a. Costs (direct and indirect) and cost effectiveness</li> <li>b. Short term and long term</li> </ul>	<p>The full form of the questions is given in several places and is not repeated in the summary tables.</p>
24	<p>Calling ACI a less invasive procedure than OATS/mosaicplasty</p>	<p>It is incorrect to use autologous chondrocyte injection as an example of a less invasive procedure than OAT/mosaicplasty. It is not. ACI is a two-stage procedure meaning that it cannot be completed in a single surgery.<sup>23</sup> Although the first stage, harvesting, may be</p>	<p>This phrase is taken from the context provided by Health Technology Assessment Program from their published key questions document.</p>

		performed arthroscopically, the second stage, implantation, is performed by arthrotomy. <sup>24</sup>	
37	The "ideal" patient	Appears to be opinion based.	The term is taken directly from the references used which may be the opinion of the references/authors. The text has been clarified to reflect this. Added a caveat to the text.
41	NICE guidance	<p>Considering that the principal prospective RCTs referenced in the draft report compare OAT/mosaicplasty to ACI, it is reasonable to include the current NICE Guidance for ACI in addition to that included for mosaicplasty.</p> <p>The current NICE Guidance for ACI was issued in May 2005 and reviewed in May 2008. It states, "Autologous chondrocyte implantation (ACI) is not recommended for the treatment of articular cartilage defects of the knee joint except in the context of ongoing or new clinical studies that are designed to generate robust and relevant outcome data, including the measurement of health-related quality of life and long-term follow-up." (From Technology Appraisal 16)</p>	The focus of the report is on OAT and mosaicplasty, not ACI. ACI is one of the comparators, not the primary topic. Guidelines for other alternative treatments are not provided either.
55	Private insurer coverage policies	We found no reviewed commercial insurer not to cover OATS/mosaicplasty. (see Appendix B)	We are required to present only two bell-weather payers and any CMS NCD in the HTA. We presented three bell-weather payers: AETNA, CIGNA, and Premera Blue Cross of Washington and Alaska. Added a coverage requirement for Premera Blue Cross: coverage for ankle, defect must be focal. Verified information for three payer policies.
61	What is OA or mosaicplasty?	<p>OATS or Osteochondral Autograft Transfer System is the name of a proprietary system to perform Osteochondral Autograft Transplantation (OAT). The latter not the former is appropriate for inclusion throughout the HTA report.</p> <p>Mosaicplasty is a variant of OAT that</p>	<p>The bulleted information is taken from the context provided by Health Technology Assessment Program from their published key questions document.</p> <p>We have attempted to use OAT</p>

		applies multiple small osteochondral plugs rather than a single large plug to fill a prepared cartilage lesion site resulting in a mosaic like appearance.	consistently throughout the report. The wording of the key questions is presented as written in the State's document. The background contains a description of these that is consistent with this comment.
68	For Horas 2003 the report states it is unclear if OATS open or arthroscopic	Page 187 of Horas et al 2003 states, "depending on the location, a medial or lateral arthrotomy was used." <sup>14</sup>  Magnussen et al identifies Horas 2003 as using open surgery. <sup>4</sup>	This has been corrected
98	Return to work or pre- injury activity levels	In addition to the evidence listed by the draft report, Mithoefer et al 2009 provides a systematic review of return to sport in athletes following articular cartilage surgery of the knee. <sup>12</sup> They included data from 20 studies reporting on 1363 patients. Principal comparisons completed were between microfracture, OAT and ACI (they called it ACT).  Good and excellent repair ratings were as follows: <ul style="list-style-type: none"> <li>• Microfracture 67% ± 7%</li> <li>• ACI 82% ± 7%</li> <li>• OAT 93% ± 5%, P=0.01 to MF</li> </ul> Overall return to sports were as follows: <ul style="list-style-type: none"> <li>• Microfracture 66% ± 6%</li> <li>• ACI 67% ± 17%</li> <li>• OAT 91% ± 2%, P=0.01 to MF</li> </ul> Time to return to sports were as follows: <ul style="list-style-type: none"> <li>• Microfracture 8 ± 1 months</li> <li>• ACI 18 ± 4 months</li> <li>• OAT 7 ± 2 months</li> </ul> The authors stated that the best "durability" was associated with ACI (96% ± 4%) followed by microfracture (52% ± 6%, P=0.079) and OAT (52% ± 21%, P=0.002). <sup>12</sup>  Thus, more athletes returned to sport and did so faster following the OAT procedure compared to microfracture and ACI. However, of those who did return, more who received ACI continued for a longer period of time. <sup>12</sup>	This section describes evidence on efficacy, which is derived from RCTs. Information on effectiveness (from observational studies) is presented later in the section.  The systematic review by Mithoefer was briefly summarized in section 1.4, table 8 and is mentioned under KQ 5. This paper combines data from a range of study designs, but primarily case series, thus statistical comparisons between treatment groups are not appropriate. (These are not direct, head to head comparisons of treatments in the same underlying study populations.)

		<p>They found several factors to be associated with the ability to return to sports<sup>12</sup>:</p> <ul style="list-style-type: none"> <li>• Younger age (between 25 and 40 years of age)</li> <li>• Time between injury and surgery (those receiving surgery within 12 months of injury were significantly more likely to return to sport). This was most significant in adolescents because all returned if surgery occurred within 12 months post injury compared to only 1/3 if surgery took place more than 12 months post injury.</li> <li>• Lesion size under 2 cm<sup>2</sup> in the microfracture and OAT groups was associated with higher rate of return to sports. Lesion size in ACI patients did not impact return to sport.</li> </ul>	
102	<p>Presentation of data from Bentley et al (draft report reference 88)</p>	<p>While Bentley et al 2003 is often cited as Level 1 evidence, it contains significant shortcomings when put in context with present knowledge of procedure selection for patients with cartilage defects.</p> <p>Kish and Hangody immediately responded with a letter to the editor commenting on the trial following its publication stating:</p> <p><i>“The authors noted that the mean size of the lesions treated in both groups was 4.66cm<sup>2</sup>. As has been repeatedly reported in the literature by us and others,(their reference 2-8) the prime indication for the mosaicplasty is for chondral or osteochondral lesions in the range of 1 cm to 4 cm<sup>2</sup>. In these defects, the mosaicplasty continues to provide good to excellent results in approximately 90% of cases.</i></p> <p><i>For lesions greater than 4 cm<sup>2</sup> and when the patient has undergone previous surgery, we consider mosaicplasty as a salvage procedure offering a significantly lower success rate.”<sup>11</sup></i></p> <p>Additionally, they expressed concern about the rehabilitation strategy</p>	<p>We agree that there are methodological short comings to this study and the other RCTs as well. Those based on study design methodology are described in Appendix E; This was rated as a LoE IIb study. (poor quality RCT).</p> <p>Mean lesion sizes for all studies is provided in Table 12. Some additional context has been added to the results.</p> <p>Editorials, letters to the editor do not meet the inclusion criteria for the HTA report.</p> <p>The “indications and contraindications” section of the background summarizes what appear to be the recommendations for treatment. As noted in the text, it appears that the case series are the sources usually cited in support of many recommendations.</p> <p>The Safran review article suggested by the commenter has as one of its conclusions:</p>

		<p>followed by the study.<sup>11</sup></p> <p>Safran and Sieber<sup>5</sup> identify methodological challenges with the trial design as well, stating:</p> <p><i>“Key features of the study include proud placement of the Osteochondral plugs, immediate weight bearing for all patients, cylinder cast placement for 10 days postoperatively, and lack of continuous passive motion device usage, all of which are nonstandard postoperative recommendations by the investigators who champion their respective procedures.”<sup>5</sup></i></p>	<p>“Comparative studies have not clearly demonstrated the superiority of either ACI or OAT.”</p> <p>Additional context has been added in the “Key considerations by clinical experts” section of the report.</p>
102	Incorrect interpretation of the study of Horas et al (Draft report reference 5)	Refer to our comments for draft report pages 14 and 106 and others.	The data and figures for the Horas study have been corrected and text edited accordingly. See previous responses.
102	Rating two prospective RCT’s and one prospective quasi-RCT lower than several other peer-reviewed systematic reviews have done.	<p>Three prospective RCTs compared OATS/ mosaicplasty to ACI.<sup>6,13, 14</sup> Bentley etal 2003<sup>6</sup> and Horas et al 2003<sup>14</sup>, respectively, have been identified as level 1 and level 2 studies by three systematic and one comprehensive review applying international standards based on established levels of evidence, modified Coleman Methodology Score and risk of bias.<sup>4, 5, 7, 16</sup> Similarly, Dozin et al 2005<sup>13</sup> was identified by a systematic review as a level 2 study.<sup>7</sup> Two other systematic reviews of ACI surgery did identify all three as level 2 studies.<sup>17, 18</sup></p> <p>There appears to be some difference of opinion on the quality of any evidence. However, stating these are “poor quality” trials may result in reader bias. One would expect this would be avoided by an objective report.</p>	See previous response regarding LoE, overall strength of evidence (SoE) as well as Appendices D and E.
102	For Dozin et al (draft report reference 6) one interpretation only is provided for the fact that some enrolled patients did not choose to have surgery.	While accurate that 1/3 of enrolled patients chose not to have reconstruction surgery six months after receiving arthroscopic debridement, 2/3 did choose to have reconstructive surgery. Had this been the intent of the trial, rather than a prospective report of what occurred, a different conclusion might be reached that	Additional comments have been added to the “Key considerations highlighted by clinical experts” section.

		<p>debridement alone did not provide adequate relief to 2/3 of the evaluated population by six months after a conservative procedure.</p> <p>Hubbard reported one-year and five-year results of a prospective RCT of 76 patients with symptomatic single Outerbridge grade III or IV lesions of the medial femoral condyle treated with arthroscopic debridement or washout. At one year, 32 of 40 patients with debridement and 5 of 36 patients with washout (100% follow-up) were pain free. At five years, of the 76% of patients available for follow-up, 19 of 32 debridement and 3 of 26 washout patients were pain free.<sup>25</sup></p> <p>In clinical practice, many surgeons today would recommend an immediate marrow stimulation or OAT/mosaicplasty procedure at the time of the initial arthroscopy documenting Outerbridge Grade III or IV lesions of an appropriate size and intra-articular location rather than wait six months to perform the definitive procedure.</p>	
104	“Myers score steadily increased....”	In reviewing Figure 1 in the study by Horas et al 2003 <sup>14</sup> this statement is rather ambitious. Compare the change in Meyers and Tegner scores to that in the Lysholm Score.	The scores (corrected) for all three measures are presented in the report and their respective trends described in the text.
104	Draft report states that in the Horas et al study (draft report reference 5) 5 of 7 patients receiving OAT complained of pain at the donor site on squatting.	This statement should be balanced with one made by the authors in their discussion of the study results. <sup>14</sup> They said, <i>“Donor site morbidity does not seem to be a disadvantage of osteochondral cylinder transplantation compared with autologous chondrocyte implantation, since the level of activity and other scores were similar to, or even higher than, those in the group treated with autologous chondrocyte implantation.”</i> <sup>14</sup>	This appears to be the opinion of the author. The HTA report does describe the scores for the various outcomes and detailed data abstraction is available in the Appendices allowing readers to draw their own conclusions about the relative pros and cons based on the various measures.
106	The draft report continues the incorrect interpretation of Figure 1 from Horas etal (draft report	Please recognize in Figure 1 of Horas etal 2003 <sup>14</sup> that “x” represents ACI and the solid dot represents OAT. The statement in the draft report should read:  “mean LKSS scores were significantly	The data and figures for the Horas study have been corrected and text edited accordingly.

	reference 5).	higher for <b><u>osteochondral cylinder patients</u></b> at 6, 12 and 24 months.”	
107	Recovery time The draft report states, “there is little evidence to suggest that overall recovery time differed by treatment.”	<p>Although we concur that studies do not directly address this result, it should be recognized that ACI (ACT) is a two-stage procedure while OAT/mosaicplasty is completed in one-stage.<sup>23</sup> Two surgeries offer two opportunities for morbidity and two separate recovery and rehabilitation periods.</p> <p>Furthermore, a systematic review of return to sports following articular cartilage repair of the knee in athletes found that time to return to sport following respective surgery was 7 ± 2 months after OAT, 8 ± 1 months after microfracture and 18 ± 4 months after ACI.<sup>12</sup></p>	<p>The studies that we summarize only report recovery time post-surgery, not including the ACI harvest recovery.</p> <p>See previous comments regarding the systematic review. This systematic review does not provide data on donor site recovery or morbidity specifically.</p>
108	Summary of functional outcomes table.	Comment should be made within the table for the Bentley et al 2003 <sup>6</sup> study per our comments for page 102 of the draft report. The poorer outcomes in the mosaicplasty arm should be interpreted in balance with the fact that the patients receiving the treatment, on average, had larger lesions than are recommended for an OAT/mosaicplasty surgery.	Mean lesion size is documented in a number of places in the report. The introductory paragraph to the table indicates that there are differences not only in lesion size, but other patient and study characteristics as well. It is not possible to disentangle the influence of the various factors to arrive a single conclusion.
124	Infection	Vasiliadis et al 2010 <sup>26</sup> report that the one superficial infection reported by Bentley et al 2003 <sup>6</sup> was in the ACI group.	Bentley’s study did not break down complications by treatment group. The review article cited in the S&N letter (Vasiliadis, Wasiak, Salanti 2010) includes a table of complications in 9 studies; in this table, <u>all</u> of the complications in the Bentley study (not just infection) are attributed to the ACI group. The text of this review paper discusses the complication of all of the other studies in the table, but not Bentley. It appears that this table of complications is in error with regards to the Bentley study. A Cochrane review by the same authors (Vasiliadis & Wasiak 2010) states twice that the Bentley study did not report complications by treatment group: “Bentley 2003 reported complications but did not mention whether any further surgery was

			required. Moreover, the authors did not split the complications by treatment group. In total, one participant developed calf-vein thrombosis and required anticoagulants and one developed a superficial infection,” and “Bentley 2003 failed to indicate the treatment group of the five participants with complications.”
138	Table 35	To more accurately assess outcomes for OAT/mosaicplasty in Bentley et al 2003, results should be adjusted for lesion size and other factors that have been associated with less good outcomes in these patients like proud placement of the autograft.	While it would be important to adjust for factors that may be different between treatment groups aside from the intervention, no such data are provided and adjustment is not possible.
139	Table 36	Per page 138 comments	See above
140	Table 37	Per page 138 comments	See above

142	Athletes paragraph 1	<p>Among athletes who returned to sport, it is accurate that those who received ACI compared to microfracture or OAT/mosaicplasty were better able to “continue participation at the preinjury level after 3 to 5 years.” However, the highest and quickest rate of return to sport was in the OAT/mosaicplasty treated athletes.<sup>12</sup> Details under comments for page 98.</p>	See response to comment related to page 98.
145-146	<p>Cost implications as a component of Key Question 5 have disappeared.</p>	<p>Upmeier, et al 2007<sup>27</sup> performed a retrospective cross-sectional study in patients treated for knee cartilage lesions in seven German centers between 1997 and 2001. Procedures applied included debridement, abrasion arthroplasty, subchondral drilling, microfracture, chondroplasty, Osteochondral autografts or allografts and ACI. Analysis was as treated.</p> <p>Prospective inclusion and exclusion criteria were established and the data retrospectively collected. Patients completed a questionnaire on element driving cost. Follow-up costs, but not operative costs were collected. Costs over the five year period following surgery were evaluated.</p> <p>An interesting element of the study was that patients diagnosed with but not treated for cartilage defects were included in the evaluation. Of 4031 patients meeting inclusion criteria, 1991 completed the patient questionnaire and following protocol exclusions. Patients completed a questionnaire on elements driving cost. Both direct and indirect costs were considered.</p> <p>Of 4031 patients meeting inclusion criteria, 1991 completed the patient questionnaire, and following protocol exclusions, 1708 were included in the final analysis.</p> <p>Two potentially relevant findings for health care decision makers are revealed by this investigation. Indirect costs were higher than direct costs and in years one, four and five, the untreated patients accounted for</p>	<p>The full key questions are stated in numerous places in the report and are abbreviated in the summary tables.</p> <p>Upmeier is a costing study only, not a full economic analysis and therefore did not meet inclusion criteria. A full economic analysis would include comparison of both cost and effectiveness for competing alternative treatment and presentation of an incremental cost-effectiveness ratio or similar measure. Cost information is in Euros and based healthcare systems that are very different than those in the United States.</p>

		the highest costs. <sup>27</sup>	
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147	The draft report continues the incorrect interpretation of Figure 1 from Horas et al (draft report reference 5).	Refer to our comments for draft report pages 14, 102 and 106 and others.	The data and figures for the Horas study have been corrected and text edited accordingly.
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## Provider Comments

Public comment for OATS

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**From:** Brian Cole [<mailto:bcole@rushortho.com>]

**Sent:** Monday, September 26, 2011 6:12 AM

**To:** HCA ST Health Tech Assessment Prog

**Subject:** Public Comment for: Osteochondral Allograft Transplantation and Autograft Transfer System (OATS/Mosaicplasty)

Not sure where to begin on this issue of OATS and OA graft transplantation except to say that OATS has data that is level 1 in support of it and there is abundant level 2 and 3 data for both procedures. This is essentially a thesis in terms of addressing the approval pathway based upon the existing science. This needs to have clinicians involved when making these decisions to assist in your interpretation of the literature

Please let me know if I can assist

Check out my website for peer reviewed literature [cartilagedoc.org](http://cartilagedoc.org)

--

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[www.myshoulderelbow.org](http://www.myshoulderelbow.org) <<http://www.myshoulderelbow.org/>>

[www.LiveActiveNow.org](http://www.LiveActiveNow.org) <<http://www.liveactivenow.org/>>

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Thank you

## Public Comments

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Josh Morse  
Program Director, Washington State Health Care Authority  
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Olympia, WA 98504-2712

VIA E-MAIL

September 30, 2011

Dear Mr. Morse:

Smith & Nephew, Inc. is a global medical technology business specializing in Orthopaedics (Trauma and Total Joint Reconstruction), Endoscopy and Advanced Wound Management. Smith & Nephew is a global leader in the development and manufacture of devices used in arthroscopic surgery.

We appreciate that the Washington State Health Care Authority Health Technology Assessment Program has invited comments on the draft Health Technology Assessment (HTA) on Osteochondral Allograft/Autograft Transplantation (OAT) conducted by Spectrum Research, Inc.

Untreated cartilage and osteocartilaginous lesions are believed to “worsen and lead to secondary degenerative lesions.”<sup>1</sup> Indirect support for this comes from a five-year German health cost study of over 1700 patients considered for cartilage repair surgery.<sup>2</sup> Comprehensive direct and indirect costs were captured for five years after these patients accepted or rejected surgery. Total costs in years one, four and five were highest in those patients who were not treated.<sup>2</sup>

A recent Norwegian study compared quality of life measured by the Knee Injury and Osteoarthritis Outcome Score (KOOS) between patients enrolled in ongoing or recently completed prospective randomized controlled or case series studies of patients scheduled for knee surgery. Results from patients scheduled for repair of focal cartilage lesions were compared to those scheduled for surgery for anterior cruciate ligament (ACL) injury, or those scheduled for surgery for knee replacement or osteotomies around the knee related to osteoarthritis. Patients with cartilage lesions averaged 28 years and 15 years younger than patients scheduled for arthroplasty or osteotomy, respectively. The authors concluded that “patients with focal cartilage lesions have major problems with pain and functional impairment. Their complaints are worse than those of ACL-deficient patients, and quality of life is affected to the same extent as in patients scheduled for knee replacement.”<sup>3</sup>

As an avascular tissue, isolated cartilage damage of less than full thickness heals at best poorly. Full thickness cartilage damage has a greater capacity for healing with appropriate intervention. Farr and colleagues earlier outlined a reasonable approach for treatment of cartilage lesions subject to patient and defect characteristics.<sup>4</sup> They originally categorized treatment approaches as non-operative, palliative, reparative and restorative. Evidence-based evolution in the considerations and the techniques involved in restoration of normal joint function in patients with cartilage lesions have resulted in categorization of advanced treatment into procedures

which are intended to stimulate chondrogenesis or those delivering osteochondral reconstruction.<sup>5</sup>

Palliative procedures include articular lavage and debridement and are documented not to have prolonged effects.<sup>4,6</sup> Marrow stimulation procedures, abrasion arthroplasty, subchondral drilling and microfracture are most useful in treating small cartilage defects in non-arthritic joints in younger patients.<sup>5</sup> Unfortunately, initially favorable results tend to deteriorate over time.<sup>7,9</sup>

Osteochondral autologous transplantation (OAT), typically described as a single osteochondral graft, mosaicplasty, described as multiple similar or dissimilar sizes of cylindrical osteochondral grafts combined together to fill a defect, and autologous chondrocyte implantation (ACI) are the most common restorative procedures selected for use in appropriate patients with appropriate lesions. The latter is not within the scope of this evaluation but has been frequently referred to as a treatment alternative. Significant additional resources are required for ACI because it is a two-stage procedure requiring arthrotomy for the second, implantation, stage.

Current marrow stimulation procedures are unable to reestablish type II hyaline cartilage. Rather, these procedures produce a fibrocartilage repair and this is considered to be the reason for functional deterioration following the repair. Osteochondral transplantation or mosaicplasty is considered the only technique that “recreates type II collagen hyaline cartilage in normal cartilage matrix.”<sup>10</sup> A recent histopathologic evaluation of mosaicplasty treated cartilage lesions demonstrated that the surface of the former lesion was comprised of 74% hyaline cartilage and 26% fibrocartilage leading the authors to conclude, “Mosaicplasty is the only surgical technique which ensures the transfer of autologous hyaline cartilage, structured and viable, at the lesion level, allowing the restoration of articular congruency.”<sup>1</sup> In addition, they documented that localized healing continued through two years in 21 second look arthroscopy patients.<sup>1</sup>

For the knee, two prospective randomized controlled trials (RCT) have documented superior outcomes up to 48 months following surgery for OAT and mosaicplasty compared to microfracture.<sup>8,9</sup> One prospective RCT<sup>11</sup> and one prospective quasi-RCT<sup>12</sup> have reported no difference and superiority, respectively, of mosaicplasty compared to ACI. Although one prospective RCT<sup>13</sup> has reported ACI to have superior outcomes compared to mosaicplasty, methodological issues confound this interpretation.<sup>14,15</sup> The average size of the treated lesions as reported in this study are larger than recommended today for first-line treatment with OAT/mosaicplasty and the osteochondral plugs were inserted above the level of the surrounding cartilage tissue. Such placement has been associated with increased intra-articular pressures and surgical failure and is not recommended.

There are many choices to be made by physicians and informed patients together regarding the choice of treatment strategies that offer the highest probability of a high quality and long lasting favorable clinical outcome for patients with focal cartilage lesions. An additional confounding factor is highlighted by Magnussen et al, “Articular cartilage defects frequently are discovered at arthroscopy and may not be anticipated before the procedure.”<sup>16</sup> When a reconstructive procedure is considered, the best available evidence supports that patients and physicians should have access to safe and effective procedures such as OAT and mosaicplasty.

Detailed review comments of Spectrum’s draft HTA report on OAT follow as Appendix A. Commercial payer policies comprise Appendix B. One major interpretative error was found to persist throughout the report and requires correction as it may influence the report conclusion. Additional information of relevance is also provided.

We acknowledge the voluntary medical review of these comments by: Louis F. McIntyre, MD  
Westchester Orthopedic Associates, and Chairman, Health Policy and Practice Committee, Arthroscopy Association of North America  
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Please contact us should additional clarification be required. Sincerely,

Paul M. Just, PharmD, BCPS Director, Healthcare Economics

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Appendix A. Detailed comments

Page	Concern	Detail
11, 19, 146	Case definition	OATS and mosaicplasty are restorative procedures used to repair cartilage damage. Expectation that a public health or epidemiologic description for a case definition of a cartilage repair procedure exists in surgical literature is not realistic. It is the patient who may require such a procedure that must be defined. If a case definition is to be demanded, it should be of the diagnostic requirements of cartilage damage. Cartilage lesions are most accurately identified by diagnostic arthroscopy. <sup>1,2</sup> Reasonable diagnostic assessment of suspected cartilage damage has been described. <sup>2,3</sup> However, one must recognize that, as stated by Magnussen, et al, "Articular cartilage defects frequently are discovered at arthroscopy and may not be
12, 19, 25, 146	Statement that "lesion size and classification appear to be the primary criteria for assessing treatment options."	Determination of the most suitable treatment for cartilage damage is complex. Consideration on treatment options begin with which joint is involved. Outcomes have been related to the location within a joint of a lesion (using the knee as example, whether it is located on the medial femoral condyle, lateral femoral condyle, patella, etc.) <sup>1, 5, 6</sup> , the lesion surface area (<1 cm <sup>2</sup> , 1-4 cm <sup>2</sup> , or >4cm <sup>2</sup> ) <sup>6-11</sup> , lesion depth, lesion etiology (acute or insidious), and symptom duration <sup>12</sup> .
12, 79-82, 146	Challenge to the validity of the Outerbridge and ICRS grading systems in patients with cartilage damage.	

<p>14, 20, 98, 102, 147</p>	<p>Comparing outcomes of OAT/ mosaicplasty to ACI.</p> <p>The interpretation as stated is challenged.</p>	<p>The statements are erroneous as made clear on page 102 of the draft report. These sections fail to accurately report the results of the three prospective randomized controlled trials<sup>6, 13, 14</sup> comparing OATS/mosaicplasty to ACI.</p> <p>Contrary to the statements in the draft report, a recent Cochrane Review of ACI identified that Dozin etal 2005<sup>13</sup> and Horas etal 2003<sup>14</sup> demonstrated a non-significant trend toward superior outcomes for OATS/ mosaicplasty (their Figure 3).<sup>15</sup></p> <p>Bentley etal 2003 concluded ACI had superior outcomes to mosaicplasty but issues with the study population include that the average lesion size was larger than recommended for mosaicplasty and that the osteochondral plug was placed proud to the surrounding surface.<sup>6</sup> It is this study that helps define that OAT/mosaicplasty should be limited to lesions smaller than 4 It is this study that helped later define that OAT/mosaicplasty should be limited to lesions smaller</p>
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Page	Concern	Detail
	<p>Comment that the two RCTs mentioned are “poor quality.”</p>	<p>Horas et al 2003 concludes mosaicplasty is superior to ACI and reports significantly faster recovery at six, 12 and 24 months after surgery by the LKSS for OATS/mosaicplasty compared to ACI.<sup>14</sup></p> <p>Please reread the authors’ conclusion on page 189 of the study and correct the interpretation presented throughout the draft report. The authors’ state, “...according to the postoperative Lysholm score, the recovery of the patients treated with autologous chondrocyte implantation was significantly slower than that of the patients treated with osteochondral cylinder transplantation; this was found at six months (<math>P \leq 0.0015</math>), twelve months (<math>P \leq 0.001</math>), and at twenty-four months (<math>P \leq 0.012</math>).”<sup>14</sup> Also see their Figure 1.</p> <p>Although Dozin et al 2005 had a small population, of those who completed the final LKSS assessment, 15 of 18 (83.3%) OATS/ mosaicplasty compared to 10 of 19 (52.6%) ACI patients were classified as experiencing a complete success (LKSS &gt;90).<sup>13</sup> The result was not statistically significant and the authors concluded there was no difference between treatments.</p> <p>Three prospective RCTs compared OATS/ mosaicplasty to ACI.<sup>6, 13, 14</sup> Bentley et al 2003<sup>6</sup> and Horas et al 2003<sup>14</sup>, respectively, have been identified as level 1 and level 2 studies by three systematic and one comprehensive review applying international standards based on established levels of evidence, modified Coleman Methodology Score and risk of bias.<sup>4, 5, 7, 16</sup> Similarly, Dozin et al 2005<sup>13</sup> was identified by a systematic review as a level 2 study.<sup>7</sup></p> <p>Two other systematic reviews of ACI surgery identify all three as level 2 studies.<sup>17, 18</sup></p> <p>There appears to be some difference of opinion on the quality</p>

14, 98	On Longevity of treatment effect.	<p>State results clearly.</p> <p>Gudas etal 2005, a prospective RCT, found “significant superiority of OAT [n=28] over microfracture [n=29]” in “active young athletes under the age of 40” “at an average of 37.1 months” as measured by HSS and ICRS.<sup>19</sup></p> <p>Gudas etal 2009, a prospective RCT, reported “at an average of 4.2 years follow-up” that OAT (n=25) had “significant superiority” over microfracture (n=22) in their population of children under 18 years old measured by ICRS functional and objective assessment.<sup>20</sup></p>
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Page	Concern	Detail
		<p>In a prospective quasi-RCT, Horas et al 2003 reported that LKSS revealed faster recovery through 24 months in the OAT group compared to the ACI group.<sup>14</sup></p> <p>Prospective case series have reported long-term favorable outcomes from mosaicplasty. Hangody et al 2010 reported that depending on location of repair, 74% to 91% of 354 athletes followed for 9.6 years on average (range 2-17 years) after mosaicplasty had favorable outcomes.<sup>21</sup> Solheim et al 2010 reported that at a median 7 years (range 5-9 years) after mosaicplasty, improvement over baseline was maintained, albeit at a lower level than at one year post-surgery.<sup>22</sup></p>
16	Under Safety, 5 <sup>th</sup> bullet, “it is not possible to attribute this progression to the graft procedure.”	“Attribute” is not a neutral term. Rather, to objectively assess the data, a more appropriate conclusion is that without a comparison group, it is not possible to evaluate how OAT surgery may interact with the development of osteoarthritis.
20	The draft report calls two prospective RCTs comparing microfracture to OATS/mosaicplasty “low quality.”	<p>Three systematic reviews and one comprehensive review identify Gudas et al 2005 as a level 1 study.<sup>4,5,7,10</sup></p> <p>There appears to be some difference of opinion on the quality of any evidence. However, stating these are “poor quality” trials may result in reader bias. One would expect this would be avoided by an objective report.</p>
23	Key Question 6 is not accurately reflected in the summary table.	<p>Key Question 6 on page 9 and 25 of the draft report is:</p> <p>What is the evidence of cost implications and cost-effectiveness for OATS/mosaicplasty? Including consideration of:</p> <p>a. Costs (direct and indirect) and cost effectiveness</p>
24	Calling ACI a less invasive procedure than OATS/ mosaicplasty	It is incorrect to use autologous chondrocyte injection as an example of a less invasive procedure than OAT/mosaicplasty. It is not. ACI is a two-stage procedure meaning that it cannot be completed in a single surgery. <sup>23</sup> Although the first stage, harvesting, may be performed arthroscopically, the second stage, implantation, is performed by arthrotomy. <sup>24</sup>
37	The “ideal” patient	Appears to be opinion based.

41	NICE guidance	<p>Considering that the principal prospective RCTs referenced in the draft report compare OAT/mosaicplasty to ACI, it is reasonable to include the current NICE Guidance for ACI in addition to that included for mosaicplasty.</p> <p>The current NICE Guidance for ACI was issued in May 2005 and reviewed in May 2008. It states, "Autologous chondrocyte implantation (ACI) is not recommended for the treatment of articular cartilage defects of the knee joint except in the context</p>
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Page	Concern	Detail
		of ongoing or new clinical studies that are designed to generate robust and relevant outcome data, including the measurement of health-related quality of life and long-term follow-up.” (From Technology Appraisal 16).
55	Private insurer coverage policies	We found no reviewed commercial insurer not to cover OATS/ mosaicplasty. (see Appendix B)
61	What is OATS or mosaicplasty?	<p>OATS or Osteochondral Autograft Transfer System is the name of a proprietary system to perform Osteochondral Autograft Transplantation (OAT). The latter not the former is appropriate for inclusion throughout the HTA report.</p> <p>Mosaicplasty is a variant of OAT that applies multiple small osteochondral plugs rather than a single large plug to fill a prepared cartilage lesion site resulting in a mosaic like appearance.</p>
68	For Horas 2003 the report states it is unclear if OATS open or arthroscopic	<p>Page 187 of Horas etal 2003 states, “depending on the location, a medial or lateral arthrotomy was used.”<sup>14</sup></p> <p>Magnussen etal identifies Horas 2003 as using open surgery.<sup>4</sup></p>
75	Table 16	Table is incomplete. Bentley etal 2003 identifies that their criteria included patient with lesions $\geq 1 \text{ cm}^2$ and that patients’ age range was 16 to 49 years old. <sup>6</sup>

<p>98</p>	<p>Return to work or pre-injury activity levels</p>	<p>In addition to the evidence listed by the draft report, Mithoefer et al 2009 provides a systematic review of return to sport in athletes following articular cartilage surgery of the knee.<sup>12</sup> They included data from 20 studies reporting on 1363 patients. Principal comparisons completed were between microfracture, OAT and ACI (they called it ACT).</p> <p>Good and excellent repair ratings were as follows:</p> <ul style="list-style-type: none"> <li>☐ Microfracture 67% ± 7%</li> <li>☐ ACI 82% ± 7%</li> <li>☐ OAT 93% ± 5% , P=0.01 to MF</li> </ul> <p>Overall return to sports were as follows:</p> <ul style="list-style-type: none"> <li>☐ Microfracture 66% ± 6%</li> <li>☐ ACI 67% ± 17%</li> <li>☐ OAT 91% ± 2%, P=0.01 to MF</li> </ul> <p>Time to return to sports were as follows:</p> <ul style="list-style-type: none"> <li>☐ Microfracture 8 ± 1 months</li> <li>☐ ACI 18 ± 4 months</li> <li>☐ OAT 7 ± 2 months</li> </ul> <p>The authors stated that the best “durability” was associated with ACI (96% ± 4%) followed by microfracture (52% ± 6%, P=0.079) and OAT (52% ± 21%, P=0.002).<sup>12</sup></p>
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Page	Concern	Detail
		<p>Thus, more athletes returned to sport and did so faster following the OAT procedure compared to microfracture and ACI. However, of those who did return, more who received ACI continued for a longer period of time.<sup>12</sup></p> <p>They found several factors to be associated with the ability to return to sports<sup>12</sup>:</p> <ul style="list-style-type: none"> <li>☐ Younger age (between 25 and 40 years of age)</li> <li>☐ Time between injury and surgery (those receiving surgery within 12 months of injury were significantly more likely to return to sport). This was most significant in adolescents because all returned if surgery occurred within 12 months post injury compared to only 1/3 if surgery took place more than 12 months post injury.</li> <li>☐ Lesion size under 2 cm<sup>2</sup> in the microfracture and OAT groups was associated with higher rate of return to sports. Lesion size in ACI patients did not impact return</li> </ul>

<p>102</p>	<p>Presentation of data from Bentley etal (draft report reference 88)</p>	<p>While Bentley etal 2003 is often cited as Level 1 evidence, it contains significant shortcomings when put in context with present knowledge of procedure selection for patients with cartilage defects.</p> <p>Kish and Hangody immediately responded with a letter to the editor commenting on the trial following its publication stating:  <i>“The authors noted that the mean size of the lesions treated in both groups was 4.66cm<sup>2</sup>. As has been repeatedly reported in the literature by us and others,(their reference 2-8) the prime indication for the mosaicplasty is for chondral or osteochondral lesions in the range of 1 cm to 4 cm<sup>2</sup>. In these defects, the mosaicplasty continues to provide good to excellent results in approximately 90% of cases. For lesions greater than 4 cm<sup>2</sup> and when the patient has undergone previous surgery, we consider mosaicplasty as a salvage procedure offering a significantly lower success rate.”<sup>11</sup></i></p> <p>Additionally, they expressed concern about the rehabilitation strategy followed by the study.<sup>11</sup></p> <p>Safran and Sieber<sup>5</sup> identify methodological challenges with the trial design as well, stating:  <i>“Key features of the study include proud placement of the Osteochondral plugs, immediate weight bearing for all patients, cylinder cast placement for 10 days postoperatively, and lack of continuous passive motion device usage, all of which are nonstandard postoperative</i></p>
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Page	Concern	Detail
102	Incorrect interpretation of the study of Horas etal (Draft report reference 5)	Refer to our comments for draft report pages 14 and 106 and others.
102	Rating two prospective RCT's and one prospective quasi-RCT lower than several other peer-reviewed systematic reviews have done.	<p>Three prospective RCTs compared OATS/ mosaicplasty to ACI.<sup>6, 13, 14</sup> Bentley etal 2003<sup>6</sup> and Horas etal 2003<sup>14</sup>, respectively, have been identified as level 1 and level 2 studies by three systematic and one comprehensive review applying international standards based on established levels of evidence, modified Coleman Methodology Score and risk of bias.<sup>4, 5, 7, 16</sup> Similarly, Dozin etal 2005<sup>13</sup> was identified by a systematic review as a level 2 study.<sup>7</sup> Two other systematic reviews of ACI surgery did identify all three as level 2 studies.<sup>17, 18</sup></p> <p>There appears to be some difference of opinion on the quality of any evidence. However, stating these are "poor quality" trials may result in reader bias. One would expect this would be avoided by an objective report.</p>
102	For Dozin etal (draft report reference 6) one interpretation only is provided for the fact that some enrolled patients did not choose to have surgery.	<p>While accurate that 1/3 of enrolled patients chose not to have reconstruction surgery six months after receiving arthroscopic debridement, 2/3 did choose to have reconstructive surgery. Had this been the intent of the trial, rather than a prospective report of what occurred, a different conclusion might be reached that debridement alone did not provide adequate relief to 2/3 of the evaluated population by six months after a conservative procedure.</p> <p>Hubbard reported one-year and five-year results of a prospective RCT of 76 patients with symptomatic single Outerbridge grade III or IV lesions of the medial femoral condyle treated with arthroscopic debridement or washout. At one year, 32 of 40 patients with debridement and 5 of 36 patients with washout (100% follow-up) were pain free. At five years, of the 76% of patients available for follow-up, 19 of 32 debridement and 3 of 26 washout patients were pain free.<sup>25</sup></p> <p>In clinical practice, many surgeons today would recommend an immediate marrow stimulation or OAT/mosaicplasty procedure at the time of the initial arthroscopy documenting Outerbridge Grade III or IV lesions of an appropriate size and</p>
104	"Myers score steadily increased...."	In reviewing Figure 1 in the study by Horas etal 2003 <sup>14</sup> this statement is rather ambitious. Compare the change in Meyers and Tegner scores to that in the Lysholm Score.

Page	Concern	Detail
104	Draft report states that in the Horas et al study (draft report reference 5) 5 of 7 patients receiving OAT complained of pain at the donor site on squatting.	This statement should be balanced with one made by the authors in their discussion of the study results. <sup>14</sup> They said, <i>“Donor site morbidity does not seem to be a disadvantage of osteochondral cylinder transplantation compared with autologous chondrocyte implantation, since the level of activity and other scores were similar to, or even higher than, those in the group treated with autologous chondrocyte implantation.”</i> <sup>14</sup>
106	The draft report continues the incorrect interpretation of Figure 1 from Horas et al (draft report reference 5).	Please recognize in Figure 1 of Horas et al 2003 <sup>14</sup> that “x” represents ACI and the solid dot represents OAT. The statement in the draft report should read:  <i>“mean LKSS scores were significantly higher for <b>osteochondral cylinder patients</b> at 6, 12 and 24 months.”</i>
107	Recovery time The draft report states, “there is little evidence to suggest that overall recovery time differed by treatment.”	Although we concur that studies do not directly address this result, it should be recognized that ACI (ACT) is a two-stage procedure while OAT/mosaicplasty is completed in one-stage. <sup>23</sup> Two surgeries offer two opportunities for morbidity and two separate recovery and rehabilitation periods.  Furthermore, a systematic review of return to sports following articular cartilage repair of the knee in athletes found that time to return to sport following respective surgery was 7 ± 2 months after OAT, 8 ± 1 months after microfracture and 18 ± 4 months after ACI. <sup>12</sup>
108	Summary of functional outcomes table.	Comment should be made within the table for the Bentley et al 2003 <sup>6</sup> study per our comments for page 102 of the draft report. The poorer outcomes in the mosaicplasty arm should be interpreted in balance with the fact that the patients receiving the treatment, on average, had larger lesions than are recommended for an OAT/mosaicplasty surgery.
124	Infection	Vasiliadis et al 2010 <sup>26</sup> report that the one superficial infection reported by Bentley et al 2003 <sup>6</sup> was in the ACI
138	Table 35	To more accurately assess outcomes for OAT/mosaicplasty in Bentley et al 2003, results should be adjusted for lesion size and other factors that have been associated with less good outcomes in these patients like proud placement of the
139	Table 36	Per page 138 comments
140	Table 37	Per page 138 comments

Page	Concern	Detail
142	Athletes paragraph 1	Among athletes who returned to sport, it is accurate that those who received ACI compared to microfracture or OAT/ mosaicplasty were better able to “continue participation at the preinjury level after 3 to 5 years.” However, the highest and quickest rate of return to sport was in the OAT/mosaicplasty treated athletes. <sup>12</sup> Details under comments for page 98.
145-146	Cost implications as a component of Key Question 5 have disappeared.	<p>Upmeier, etal 2007<sup>27</sup> performed a retrospective cross-sectional study in patients treated for knee cartilage lesions in seven German centers between 1997 and 2001. Procedures applied included debridement, abrasion arthroplasty, subchondral drilling, microfracture, chondroplasty, Osteochondral autografts or allografts and ACI. Analysis was as treated.</p> <p>Prospective inclusion and exclusion criteria were established and the data retrospectively collected. Patients completed a questionnaire on element driving cost. Follow-up costs, but not operative costs were collected. Costs over the five year period following surgery were evaluated.</p> <p>An interesting element of the study was that patients diagnosed with but not treated for cartilage defects were included in the evaluation. Of 4031 patients meeting inclusion criteria, 1991 completed the patient questionnaire and following protocol exclusions. Patients completed a questionnaire on elements driving cost. Both direct and indirect costs were considered.</p> <p>Of 4031 patients meeting inclusion criteria, 1991 completed the patient questionnaire, and following protocol exclusions, 1708 were included in the final analysis.</p> <p>Two potentially relevant findings for health care decision makers are revealed by this investigation. Indirect costs were higher than direct costs and in years one, four and five, the untreated patients accounted for the highest costs.<sup>27</sup></p>
147	The draft report continues the incorrect interpretation of Figure 1 from Horas etal (draft report reference 5).	Refer to our comments for draft report pages 14, 102 and 106 and others.

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Appendix B. Commercial Insurance Coverage Policies for OATS/mosaicplasty

Medical Policies for Mosaicplasty/OATS							
PAYOR	STATE	NON-COV POLICY	NO POLICY	POSITIVE POLICY	LAST REVIEW	POLICY #	CODES
Aetna	National			√	10/15/2010	637	27416, 29886, 29887
Cigna	National			√	10/15/2010	197	27415, 27416, 29866, 29867
Humana	National			√	8/26/2010	0494-001	27412, 27415, 29866, 29867
UHC	National		√				
Healthnet	National			√	12/1/2010	NMP284	27415, 29866, 29867
UniCare	National			√	02.17.11	SURG.00093	27412, 27415, 27416, 29866, 29867
Harvard Pilgrim	All		√				
Premera	All			√	05.10.11	7.01.506	27415, 27416, 29866, 29867
Independence BC	PA			√	01.11.11	11.14.09d	27416, 29866
Carefirst BCBS	DC, MD, VA, DE			√	07.18.11	7.01.045	None given
Anthem	All		√				
Regence	OR, UT		√				
Empire BCBS	NY		√				
Highmark BCBS	WV			√	01.17.11	S-185	27416, 29866
Highmark BCBS	Western PA			√		S-185	27416, 29866
Wellmark BCBS	IA, SD			√	8.2011	07.01.01	29867, 27412, 27415, 27416
BCBS AR	AR			√	7.2011	not given	27416, 29866,
BCBS FL	FL		√				
BCBS IL,NM,OK,TX	IL, NM, OK, TX			√	02.15.10	SUR705.020	27415, 27416, 29866, 29867
BCBS NC	NC			√	7.2011		27415, 27416, 29866, 29867
BCBS SC	SC			√	8.2011	not given	None given
BCBS VT	VT			√	07.01.11	not given	27415, 27416, 29866, 29867
Health Plan of Nevada/Sierra Health (A UHC Company)	NV			√	04.25.10	SUR038	27415, 27486, 27487, 29866, 29867

**Allografting Coverage Criteria**

1. Osteochondral allograft transplant for a chondral defect that is > 2 cm<sup>2</sup> total
2. Condition involves a focal, full thickness, (\*\*Grade III or IV).
3. Adolescent patients should be skeletally mature with documented closure of growth plates (e.g., 15 years or older). Adult patients should be too young to be considered an appropriate candidate for total knee arthroplasty or other reconstructive knee surgery (e.g. younger than 55 years).
4. Magnetic resonance imaging (MRI) or arthroscopy demonstrating chondral defect on the weight-bearing portion of the lateral or medial femoral condyle, or trochlear region of the knee
5. No evidence of arthritis on the corresponding tibial surface
6. Disabling localized knee pain that is unresponsive to conservative treatment (i.e., medication, physical therapy)

**Autografting Coverage Criteria**

1. Size of cartilage defect is between 1.0 to 2.5 sq cm.
2. Condition involves a focal, full thickness, (\*\*Grade III or IV).
3. Adolescent patients should be skeletally mature with documented closure of growth plates (e.g., 15 years or older). Adult patients should be too young to be considered an appropriate candidate for total knee arthroplasty or other reconstructive knee surgery (e.g. younger than 55 years).
4. Magnetic resonance imaging (MRI) or arthroscopy demonstrating chondral defect on the weight-bearing portion of the lateral or medial femoral condyle, or trochlear region of the knee
5. No evidence of arthritis on the corresponding tibial surface
6. Disabling localized knee pain that is unresponsive to conservative treatment (i.e., medication, physical therapy)

\*\* Grade III: loss of more than 50% of cartilage thickness, but without exposure of subchondral bone.

\*\* Grade IV: complete loss of cartilage with subchondral bone exposure.

**Summary:**

In summary we reviewed 23 Insurance Payors and none of them had a non coverage determination for the Mosaicplasty/OATS Procedure. Of the 23 payors researched 6 of them had no policy for the procedure and 17 had a positive policy as long as the criteria was satisfied.