Washington State Health Care Authority

Treatment of Chondral Defects of the Knee

Peer review and public comment on draft evidence report

August 21, 2024

Health Technology Assessment Program (HTA)

Washington State Health Care Authority

PO Box 42712
Olympia, WA 98504-2712
(360) 725-5126
www.hca.wa.gov/hta
shtap@hca.wa.gov

Prepared by:
RTI International–University of North Carolina Evidence-based Practice Center
Research Triangle Park, NC 27709
www.rti.org

This document was created in response to peer review and public comments on a Draft Health Technology Assessment (HTA) report prepared by the RTI-UNC Evidence-based Practice Center through a contract to RTI International from the State of Washington Health Care Authority (HCA). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the State of Washington HCA and no statement in this document should be construed as an official position of the State of Washington HCA.

The information in the document is intended to help the State of Washington's independent Health Technology Clinical Committee make well-informed coverage determinations. This document and its associated Evidence Report are not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this document and the associated Evidence Report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

Acknowledgments

The following individuals contributed to the report associated with this document:
Lead Investigator: Shivani Reddy, MD, MS
Co-Investigators: Leila Kahwati, MD, MPH; Caroline Rains, MPH
Research Assistant: William Tanner, MS
Clinical Advisor: Joseph Marchese, MD
Project Coordinator: Caroline Rains, MPH
Scientific Reviewer: Gerald Gartlehner, MD, MPH
Library/Document Preparation: Mark Howell, MLS

Contents

List of Tables

Peer Review Comments and Responses

Three independent, external peer reviewers were invited to provide comments on the Draft Evidence Report and were provided with an honorarium for their review. The peer reviewer's name, affiliations, and conflicts of interest are reported in ***Table 1***.

Table 1. External Peer Reviewer of the Draft Evidence Report

Name	Title/Affiliation	Summary of Conflicts of Interest Reported
Jack Anavian, MD (Reviewer 1)	Sports Medicine and Orthopedic Trauma, Southern California Permanente Medical Group; Team Physician, US Ski and Snowboard Associations	Financial conflicts: Peer reviewer has received general payments of $166 in the year 2023 from Linvatec Corporation for food and beverage. Non-financial conflicts: Peer reviewer has a primary clinical specialty of orthopedic surgery and performs the procedures reviewed in this HTA.
Daniel B.F. Saris, MD, PhD (Reviewer 2)	Chair of Sports Medicine, Professor of Orthopedics and Regenerative Medicine Department of Orthopedic Surgery, Mayo Clinic Rochester MN	Financial conflicts: Peer reviewer has received general payments of $124 from Medacta USA, Inc. for food and beverage and associated research funding of $1,500 from Anthrex, Inc. in the year 2023. The reviewer is a consultant and chair of the scientific advisory board for ReLive Biotechnologies, which makes the cell therapy Spherox. Spherox is not approved or available in the US and was excluded from this review. Non-financial conflicts: Peer reviewer has a primary clinical specialty of orthopedic surgery and performs the procedures reviewed in this HTA. He has authored many publications on chondral defect repair.
Louise Thoma, PT, DPT, PhD (Reviewer 3)	Assistant Professor, Thurston Arthritis Research Center, Injury Prevention Research Center, Department of Health Sciences Department of Physical Therapy, University of North Carolina at Chapel Hill	Financial conflicts: None Non-financial conflicts: Peer reviewer provides clinical care for patients with chondral defects, as well as provides medical education for physical therapy students on this topic.

The peer reviewers did not identify any missing studies and did not identify any studies that should have been excluded from the report. We addressed many of the comments submitted by the reviewers in the Final Evidence Report, though some comments or suggestions were outside the scope of the HTA. We considered the revisions made based on peer review comments as minor revisions. Specific peer review comments and responses are provided in ***Table 2***.

Table 2. Peer Reviewer Comments on Draft Evidence Report and Response

Item	Comment	Response
Introduction		
Are there any additional issues you think we should cover in the introduction?	Reviewer 1: Overall, the introduction is well presented. I would include a brief discussion of the long-term impact and implications of chondral defects in the pediatric and young adult populations. In addition to debilitating pain and functional limitations of chondral defects in this population, post-traumatic and early onset osteoarthritis remains a major concern. Reviewer 2: The introduction is very clear well focused and concise, properly addressing the content of the review I do not feel there is anything that needs to be added or omitted. Reviewer 3: Inclusion of current treatment utilization data is important. Looks like this data will be included later.	Reviewer 1: We have added information about this issue in pediatric populations to the Introduction. We thank reviewers 2 and 3 for their comments.
Do you see anything inaccurate, superfluous, or unclear?	Reviewer 1: There is nothing inaccurate, superfluous, or unclear in the introduction/background section of the executive summary or the final technical report. Reviewer 2: To the best of my knowledge, I feel that this is properly representing the current understanding of literature given the fact that there are many interpretations of various papers that are done differently by different authors, reviewers and clinical specialists. Reviewer 3: Nothing noted.	We thank the reviewers for their comments.
Any additional comments?	Reviewer 1: No further comments on the Introduction. Reviewer 2: None. Reviewer 3: Generally, make clear early that this HTA is focused on the knee, and not the treatment of chondral defects in other joints.	We thank Reviewers 1 and 2 for their comments. Reviewer 3: We appreciate the reviewer's comment and have added text in several parts of the introduction that this HTA addresses the knee and no other joints.
Methods		
Do you see any problems with our methods?	Reviewer 1: I do not see any major problems with the methods. The overall methodology employed in this technical report is sound and of high-level quality, via the selection of RCTs, NRSIs, and cost-effectiveness studies that have been conducted in highly developed countries using English language. A distinction is made between the MACI procedure and earlier 1st and 2nd generation ACI procedures that have been excluded in this analysis. This distinction is important and the exclusion of earlier generation ACI procedures is appropriate, as they are no longer employed by most surgeons. The limitations of the studies included are acknowledged and well documented	Reviewer 1: We thank the reviewer for his comment regarding stratification of results by size, depth, and location and understand that these are important factors in determining outcomes of these procedures. While we did abstract subgroup analyses, only 3 studies presented stratified results by either location or size, which did not permit us to make conclusions about how these lesion characteristics impact outcomes. We have added this point in the limitations section of the discussion.

	in the report. One limitation that is not well discussed that I feel is important, is the fact that this report is a comparative analysis of treatments for chondral defects as a general category. The analysis does not stratify chondral defects based on size, depth, and location of the defect. These factors are important when deciding on treatment for chondral defects and can greatly impact outcomes of any particular treatment. This is arguably the most significant limitation of this analysis based on the criteria used. There is some acknowledgement that comparative effectiveness studies are not always based on lesion-specific characteristics and therefore do not represent clinical care, and that surgeons will pick a treatment based on lesion-specific characteristics. Reviewer 2: These are appropriate extensively described and properly applied. I feel this was meticulously devised and well executed review using the currently best practice techniques. Reviewer 3: To confirm, there were no studies that compared OCA to any other procedure besides OATS? Was the Marx Activity Score included as an outcome measure? This scale has been used to assess return to activity, similar to the Tegner Activity Scale, which was included in Table 5.	Reviewer 2: We thank the reviewer for his comments. Reviewer 3: We confirm that the only comparative study of OCA used OATS as a comparator. We considered, and for the most part included, all patient-centered outcomes that were reported by the included studies. The Marx Activity Scale was not reported by any of the studies.
Any additional comments about the Methods section?	Reviewer 1: While I can understand and appreciate why only RCTs, NRSIs, and cost-effectiveness studies that have been selected for this analysis, it is important to consider and acknowledge that outcome data available for some of the less frequently employed treatments (e.g. OCA) are limited to mostly non-comparative or lower-level outcome studies. Therefore, by nature of the selection criteria used, the true efficacy and value of such treatments may be under-estimated as compared to other treatment options. Reviewer 2: None Reviewer 3: Was there a minimal time for follow up needed? E.g., minimum follow up one year? - Was there any consideration for evaluating the role of defect location in the effectiveness? E.g. Is the efficacy of treatment A compared to treatment B different in patellofemoral vs. tibiofemoral defects? If not, consider commenting on the ability of the current literature to evaluate this consideration. - Was Patient Acceptable Symptom State (PASS) considered related to MCID and clinically relevant thresholds? Given the often pronounced effect that chondral defects can have on pain and function, it is possible that these interventions result in a sizeable	Reviewer 1: We appreciate the reviewer's concerns about potentially missing information about procedures which are less likely to undergo evaluation in comparative studies. We have added this concern to the limitations section of the discussion. Reviewer 2: We thank the reviewer for his comment. Reviewer 3: We did not set a threshold for minimum time to followup. The range of follow-up was 6 months to 15 years. To address the comment of defect location: we did abstract subgroup analyses, although only 2 studies reported results stratified by defect location. We have added the lack of effectiveness results by location and size as a limitation. To address the comment about the PASS scale, we did not identify any studies with this outcome.

	change in outcomes (>MDIC) yet remain less than acceptable to patients.	
Results		
Are there any studies you believe we may have missed?	Reviewer 1: I do not believe there are any studies that have been missed using the criteria described. It is clear that majority of the of data present for comparison is focused on MACI vs MF and OATS vs MF. In comparison to the 2011 review, this review more accurately compares ACI to other treatments by limiting the analysis to 3rd generation ACI (MACI). There is also data to support use of MACI as a first-line treatment vs MF with reduced need for reoperation, despite higher upfront cost. Again, outcome data available for some of the less frequently employed treatments, such as OCA, are mostly limited to mostly non-comparative or lower-level outcome studies. Therefore, it is difficult to determine the efficacy and value of such treatments, especially as they pertain to chondral defects of considerable size/depth for which these treatments are often employed. Reviewer 2: No, these studies and the paper selected to the best of my knowledge represent the current state of literature relevant to the topic. Reviewer 3: Not to my knowledge.	Reviewer 1: See comment above. This concern is addressed by adding it to the limitations section of the discussion. We thank Reviewers 2 and 3 for their comments.
Are there studies that you believe we should have excluded?	Reviewer 1: I do not believe any of the studies discussed should have been excluded. Reviewer 2: No. Reviewer 3: Not that I noted	We thank the reviewers for their comments.
Do you believe we have inaccurately described any studies?	Reviewer 1: No. Reviewer 2: No I feel the studies have been properly described, the only issue that might be with some further evaluation or discussion is the size of defects and how this relates to treatment selection various sizes between 2, 3 and 4 cm have been used in different papers or similar reviews in clinical practice in all reality most frequent defect sizes are between 2 and 4 cm in my opinion most clinical algorithms and decision-making select autologous osteochondral grafts for smaller defects below 1- 2 cm, microfracture is definitely no longer the gold standard or preferred comparator. Allograft are used for many defects 15 mm and up. MACI is indicated for defects larger than 3 cm the sizes are typically applied for the projected defect size after debridement. Reviewer 3: Of the outcomes extracted, they seem accurately described.	Reviewer 1 and 3: We thank the reviewers for their comments. Reviewer 2: We thank the reviewer for his comment regarding stratification of results by size, depth, and location and understand that these are important factors in determining outcomes of these procedures. While we did abstract subgroup analyses, only 3 studies presented stratified results by either location of size, which did not permit us to make conclusions about how these lesion characteristics impact outcomes. We have added this point in the limitations section of the discussion.

Any additional comments about the Results?	Reviewer 1: No. Reviewer 2: None Reviewer 3: Regarding Table 5: - Are the MCIDs or clinically relevant thresholds specific to those with chondral defects, or are these from other knee injury populations? Should identify and highlight chondral defect specific metrics when available. - Should identify if the number is an MCID or a clinically relevant threshold. - Tegner activity score is not reflective of "return to", rather current participation. Regarding Table 9: - In summary of effect, consider adding indicators of directionality in the descriptions; For example, change in IKDC score was greater in MACI compared to MF, however it does not state that this change represents an improvement (and not worsening). For reoperation outcome in NRSIs: Summary of effect could be further clarified. In the SOE, it seems one study reported RRR of 43%, but unclear direction. Is this 43% RRR for MACI relative to MF?	Reviewer 1 and 2: We thank the reviewers for their comments. Reviewer 3: Regarding Table 5, we appreciate the reviewer's comments that some scales were designed to measure pain and/or function in different types of knee injuries. We have specified the measures that specifically include chondral defects in their description in the text preceding the table. The numbers in the last column of Table 5 indicate an MCID and this has been corrected in the column header. We have also corrected the description of the Tegner score. Regarding Table 9, the direction of effect is indicated in the last column of the table. For reoperation outcome in NRSIs of MACI vs MF, we have clarified the direction of effect in the COE table.
Discussion		
Do you think we missed any important points?	Reviewer 1: Overall, the Discussion section is well formulated and gives a comprehensive overview of the results and limitations of the analysis. There is mention that the largest body of evidence is seen with comparison of MACI vs MF and OATS vs MF and that MF is still considered first-line therapy for reason mentioned in the discussion. There is also data to support use of MACI as a first-line treatment vs MF with reduced need for reoperation, despite higher upfront cost. One reason given is that a failed MF may deem a subsequent MACI unsuccessful due to destabilization of underlying subchondral bone. I would consider a discussion of the limitations of such an analysis when size, depth and location of the chondral defect is not factored in, especially as it pertains to comparison of first-line MACI or OCA to second-line treatments. Reviewer 2: The discussion is lengthy and somewhat fragmented, but this is mainly because of the complex and extensive nature of the topic reviewed I do feel that the points are well made a properly described. Reviewer 3: Consider adding a discussion on the importance of considering time when evaluating the evidence. For example, a proposed advantage of	Reviewer 1: We appreciate the reviewer's comments about including lesion characteristics in the analysis. As stated above, few studies included these analyses and we have added this is a limitation to the discussion section. Reviewer 2: We thank the reviewer for his comment. Reviewer 3: We appreciate the reviewer's comments about the timing of outcome evaluation. We have added text to the discussion about how timing of follow-up can impact our assessment of results. We agree with the reviewer that there was limited and inconsistent reporting of harms. We have added text about this in the discussion. We prioritized patient-reported outcomes for this HTA. We specifically did not include studies reporting imaging or pathology results. We agree with the reviewer that a

	advanced procedures (MACI/OATS/OCA) is their longevity vs. MF. Yet, likely driven by the lack of consistency in the available data, the time frame upon which conclusions are drawn are not discussed or presented to a limited extent. However, the timing of the outcome collection, including for efficacy and harms, is critical to understanding the tradeoffs between procedures. Procedures that may seem comparable at 6 months and 1 year may not be comparable at 5 years. Consider expanding upon the limited discussion of harms among the included studies. The report acknowledges that other non-comparative studies may better report harms over time, however the number of studies that report no harms in this report was shocking. Cartilage restoration procedures are major orthopedic surgeries. Harms are expected and the results of this report suggest that they may be under-reported. The report authors have a unique perspective on the status of the current evidence and literature. Do the report authors have any comments regarding the outcome measures used across studies that may inform future study design? For example, to what extent were the outcome measures so variable that they prevented synthesis of studies. Were there outcome measures that were not included in extraction but should be considered by future efforts? Are there aspects of health that should be better captured?	range of outcomes were reported by included studies. The most commonly reported were the KOOS subscales and the IKDC, though they accounted for less than half of RCTs and NRSIs. The lack of standardized outcomes did indeed prevent more in-depth synthesis of the studies, though poor reporting also played a role. Many studies did not provide enough data to perform more robust quantitative synthesis other not reporting within-group or between-group analysis, not reporting statistical testing, and, for NRSIs, not controlling for confounding. Including a standardized set of outcomes and data reporting would allow for more robust quantitative synthesis. Other relevant outcomes for which we planned to obtain data included measure rehabilitation time, time to return to work, and time to return to ADLs. A few studies reported time to return to sport or presurgical activity, either as a discrete outcome or within a PRO. Discrete measurement of rehabilitation time and time to return to ADLs or work would capture outcomes important to patients who may be very active but not athletes. We have added text regarding the above to the discussion.
Do you disagree with any of the discussion items?	Reviewer 1: No. Reviewer 2: There is room for some different interpretation on the final advice and evaluation of the technologies as they are described in the discussion however based on the interpretation of the literature and the goal of this review, I understand the positioned described in the discussion and do not have any significant issues that would need to be changed. Reviewer 3: Page 54, last paragraph “This may signal that a second procedure may still have significant benefits after a failed first procedure without additional harms” The rationale for this conclusion is unclear, based on the preceding sentences. The preceding evidence indicates that first line procedure have greater or comparable effectiveness, lower failure, and similar harms. This still favors first line procedures. Figure 5 also favors first line procedure, albeit very low COE. Perhaps the statement could still acknowledge some uncertainty, or recognize that existing evidence favors	Reviewer 1 and 2: We thank the reviewers for their comments. Reviewer 3: We have revised the text to clarify the discussion point.
Any additional comments	Reviewer 1: No additional comments. Reviewer 2: None.	Reviewer 1 and 2: We thank the reviewers for their comments.

about the Discussion?	Reviewer 3: From page 54 "The three comparative studies of ACI and MF included in the last HTA showed comparable effectiveness of ACI and OATS or greater effectiveness of OATS." Comment: This sentence is not clear to me. It seems to start with a comment of ACI and MF but ends with comments on ACI vs. OATS. Consider clarifying the point here.	Reviewer 3: We thank the reader for highlighting this error. We have corrected it in the text.
Other Sections		
Any comments on the structured abstract, conclusion, figures, tables, and appendices?	Reviewer 1: These are all well formulated and early to follow. Reviewer 2: The figures tables and the appendix are extensive which makes for a volume in this document that will probably make for difficult read for the general audience they do have ever properly represent the data necessary for extensive evaluation of the comprehensive review presented here. Reviewer 3: Figure 5/Appendix F: Consider adding the number of studies/total sample size that contributed to each COE rating, as the study size and number of studies for each comparison varied widely and may influence interpretation of the figure. I think it could be added within the cell in small print under the favored treatment/"comparable" text. Make explicitly clear throughout that this HTA is specific to knee chondral defects. It does get specified eventually but should be clear from page 1. Perhaps even the title.	Reviewer 1 and 2: We thank the reviewers for their comments. Reviewer 3: We agree that the number of studies and participants may be helpful for readers if added to the summary COE Table (Figure 5/Appendix F). However, when we attempted to do this, the figure became more difficult to view. We refer the readers to the COE table for each section.
General Comments		
Is the report clearly written, adequately detailed and of an appropriate length?	Reviewer 1: Yes. Reviewer 2: This is a very lengthy report but represents a comprehensive review of the field and I found it to be well written. Reviewer 3: The report is generally very well written, appropriately prioritizes information, highlights many relevant issues and nuances of studying chondral defect treatment. It is adequately detailed and appropriate length. In particular, there is important discussion on the built-in confounding and challenges of study related to how defect size, depth, and location drive treatment options, and for RCTS, inclusion and exclusion criteria. There are also important points made on the lack of information regarding rehabilitation and return to work.	We thank the reviewers for their comments.

Please make any additional comments you feel would help us improve the report.	Reviewer 1: No further comments Reviewer 2: None. Reviewer 3: The report appropriately synthesizes and appraises the current available evidence to address the HTA questions. Serious considerations and conversations are needed regarding what future evidence is needed to guide policy and decision making. As highlighted in the HTA, there are important challenges inherent to treating chondral lesions that limit our ability to rely on RCTs to evaluate treatment. For example, when the indications for all the procedures are remarkably different regarding lesion size, depth, and location, what are the best available and ethical study designs needed to best inform future policies and treatment decisions. It is surprising that the leading national and international associations for orthopedic surgery and cartilage restoration have not published clinical practice guidelines, as these organizations should be leading the discussions on these treatments. Perhaps this reflects the quickly evolving history of treatment for these injuries. However, such efforts may lead to stronger studies that meaningfully guide policy decisions.	Reviewer 1 and 2: We thank the reviewers for their comments. Reviewer 3: We agree with the reviewer about the lack of studies in which procedures are studied under their optimal conditions as well at the inherent limitations of RCTs to study these procedures. We have included text regarding these limitations in the discussion.

Public Comments and Responses

The Draft Workplan and Key Questions were posted for public comment.

The Draft Evidence Report was posted for public comment from June 27, 2024 to July 30, 2024. Two public comments were submitted. The names and affiliations of those submitting comments are summarized in ***Table 3.***

Table 3. Individuals or Organizations Submitting Public Comments on the Draft Evidence Report

Name	Title/Affiliation
No specific names identified (Public Commentor 1)	Washington State Department of Labor & Industries
Carolyn J. Graziano, MD (Public Commentor 2)	Director Strategic Reimbursement, Value Generation, and Market Access; Smith & Nephew, Inc.

Public comments and responses to comments are detailed in ***Tables 4 and 5***. Complete copies of the comments submitted by individuals follow the table.

Table 4. Public Comments on Draft Evidence Report and Specific Responses (Commentor 1)

Public Comment	Response
The evidence report concludes that "Both MACI and OATS had comparable harms to MF" based on the 10 comparative studies	We presented study design criteria during a call with Agency Medical Directors during the scoping phase of the

that provided evidence for safety. MACI is a newer technology and the number of subjects included in the comparable studies is limited. Case series and cohort studies are usually included in quest of infrequent AEs and SAEs. Please remind us of the reason why case series and cohort studies are excluded for safety question? Any relevant search outcome from the FDA MAUDE database?	HTA and these criteria were posted for draft comment from June 27, 2024 to July 30, 2024. Including case series and non-comparative cohort studies would increase the yield beyond what is feasible within resource and schedule constraints, though we do agree that such studies may yield some information to help with bounding of harm outcomes in the absence of comparative studies. We did query the FDA MAUDE database and obtained only 3 records. All 3 records reported that technicians noted the sterile culture dish was leaking fluid. Surgeries did not move forward for any of these patients.
For the 3 RCTs comparing MACI to MF, is it possible to carry out a meta-analysis for PROs and response? It would be helpful to see the pooled results.	In our methods, we note that we will only perform meta-analysis if data from at least 3 studies were available. Only 2 of the 3 studies reported the data necessary to perform a meta-analysis.
pES-9. Regarding the cell free aragonite implant (Agili-C) and autologous matrix-induced chondrogenesis (AMIC). These two products are not introduced and described sufficiently in the "Technology Description" section. Are these products being used as an independent (stand-alone) technology or in conjunction with another procedure, or both? Table 2 on page 5 seems to indicate that they are used in conjunction with another procedure. But the description of study (Autologous Matrix-Induced Chondrogenesis vs. MF) on page ES-9 implies that AMIC was used as stand-alone technology. Page 3 describes AMIC as "AMIC combines MF with a collagen membrane to stabilize the clot and enhance repair." It would be helpful to have more description on AMIC.	Additional details have been added to the introduction of the HTA report. AMIC is a MF procedure in which a collagen membrane covers the microfracture site. The cell-free implant is a stand-alone procedure, using an inorganic implant to fill the defect.
pES-10. "Across all groups, 13 AEs were reported in 9 patients; no SAE related to the treatment was reported for any patient (COE very low for comparative effectiveness)" Should it be "COE very low for harms" instead?	Thank you for catching this error. It has been corrected in the text.
p3. Table 1. Indications for Chondral Defect Repair Procedures by Size and Subchondral Involvement. The information in the table is very useful. Are the approximate size indications for each procedure and depth of the lesion displayed in the table supported by good evidence or mostly experts' opinion?	Most of this data comes from single arm studies, single arms of RCTs only (non-comparative data), review articles, and expert opinion, which were not eligible for this study. The size and depth indications are culled from these studies and review articles. Our orthopedic surgery consultant and the expert peer reviewers suggest that these size/depth indications are not rigid rules to be applied mechanistically. There may be valid clinical reasons for selection of procedures that are not reflected solely in this table.
p41. Regarding effectiveness and adverse events of cell-free implants. "Greater improvement in PROs and in response to treatment in the cell-free implant (Agili-C) group compared to MF/chondroplasty (moderate COE for greater effectiveness and moderate COE for fewer harms of cell-free implant)." There is only one RCT on Agili-C included in the report. The study is industry funded and has high overall risk of bias (Table E-5, pE-5; Altschuler et al. 2023). How can COE for effectiveness and harms be graded as moderate based on this single RCT with high risk of bias (and unknown consistency)?	GRADE methodology states that the concept of inconsistency cannot exist in the context of single study bodies of evidence; therefore, certainty cannot be downgraded for that reason (see Chapter 14 Cochrane Handbook). The results reported for patient-reported outcomes and response were precise (statistically significant), so the certainty of evidence was downgraded once for high risk of bias. The certainty of evidence was corrected to low for harms as we downgraded for risk of bias and precision.

ES-6 "This review did not include first- and second-generation autologous chondrocyte implantation (ACI) because this procedure has been superseded by the third-generation procedure MACI, which has fewer complications than first- and second-generation procedures, and it is more likely to be used in current and future clinical practice" What is the evidence supporting this conclusion? ACI was included in the earlier HTA decision, so excluding it does not allow proper updating of that decision. Was the conclusion that it is no longer used from manufacturers' materials or publications with industry funding? And similarly, on ES-12, "Limiting our scope to the more modern MACI procedure, gives us a clearer picture of the comparative effectiveness of cell-based restoration to MF." We believe this reasoning may be flawed and not supportable.	The decision to exclude 1st and 2nd generation ACI procedures was discussed with Agency Medical Directors at a call during the scoping phase. This decision was made based on several narrative reviews we identified during scoping and based on input from our clinical subject matter expert that these procedures were obsolete and no longer performed by the surgical community because of inferior results as compared to the 3rd generation procedures. Further, one of our expert peer reviewers agreed with the decision to exclude them from the review because they are no longer being performed. The prior review did not make a coverage decision on cell-based regeneration procedures (ACI/MACI). This will be the first time that cell-based regeneration procedures will be evaluated for coverage. In a randomized trial comparing 1st generation ACI and 3rd generation ACI (MACI), over half of the patients in the 1st generation ACI group had graft hypertrophy (18/33) over 2 years compared with MACI in which there was 1 graft hypertrophy over 2 years. (1/35) The study planned to enroll 100 patients but was stopped early for the disproportionate number of harms in the 1st generation ACI group. This study was conducted in the UK and did not report funding. This UK study (Gooding et al., 2006) is cited in the background section of the HTA report. Additionally, a systematic review authored by Shanmugaraj et al., 2019 that evaluated ACI and MACI reported a higher rate of graft hypertrophy for 1st generation ACI vs MACI (20% vs 13%); this study also reported the proportion of 1st generation ACI among chondral defect repairs was less than 10% from 2013 to 2018. We have added this additional study to the background of the HTA report. The one FDA approved 2nd generation product was removed from the market in 2017. As discussed during the scoping call, Given these findings, we determined it would not be valuable for the committee to consider an older procedure with greater harm and less use for coverage. Likewise, combining ACI and MACI studies into one category did not seem appropriate for the two procedures when there are clear outcome differences between them and in which the results of the ACI studies would obscure the effectiveness and harms of the procedure which is more clinically relevant.
ES-10 ES 3.10 First-line Procedures vs. Second-line Procedures (MACI and OCA): I don't believe looking at failed surgery would be in the scope of this technology assessment	The intention of including first-line vs second-line procedure was to offer information to help the committee's consideration of covering a second chondral defect repair surgery should the first one fail. This comparison was presented discussed during the at the scoping call with the Agency Medical Directors.
ES-12 "This may reflect the practice community's assessment …" Throughout the report, there is reference to the practice community. While this may be true regarding lesion size, what is the evidence on lesion size? Wasn't that an important issue from the prior report, and how was it dealt with at that time. There is too	Few studies in this HTA performed subgroup analyses based on defect characteristics. As described above, the evidence on lesion size is derived from single arm studies, single arms of RCTs only (non-comparative data), review articles, and expert opinion, which were not eligible for this

much emphasis in this report on what the clinical community thinks. This is an evidence report.	study. In the context of limited direct evidence on important considerations such as size, surgeons and patients need to tailor individual decisions to the clinical context as we do with most evidence-based medicine and recommendations.
Throughout the report, there is no clear indication of the bias related to industry funded studies and how that may have affected the confidence of evidence determinations. This may be particularly important for studies conducted in Europe since there is no routine reporting of financial conflict of interest as there is in the US with CMS Open Payments reporting.	We thoroughly searched the included studies for funding sources. Unfortunately, many did not report this study characteristic. Six of the 23 studies reported industry funding, including 4 RCTs and 2 NRSIs. This information is summarized as part of study characteristics in the Results section and is also included at the study level in Appendix C.

Table 5. Public Comments on Draft Evidence Report and Specific Responses (Commentor 2)

Public Comment	Response
The inclusion of products and technology beyond the scope of draft key questions for comment is encouraging as surgeons continue to seek more readily available, single step, cost effective, safe, treatments demonstrating strong outcomes to address this clinical need. Physicians and patients alike are seeking solutions that minimize the number of patient procedures and time to procedure through ready to use implants.	We thank the commentor for their comment.
Page 26, Table 2 of the Draft Report incorrectly identifies the regulatory pathway for Agili-C as "361 HCT/P". The correct FDA pathway for Agili-C is PMA Breakthrough Device Status. The US Food and Drug administration granted Breakthrough Device designation in 2020 and Premarket Approval (PMA) in March of 2022 (P210034). https://www.fda.gov/medical-devices/device-approvals-denials-and-clearances/pma-approvals.	We thank the commentor for highlighting this error; it has been corrected in the report.
Further, Page ES-4, under Regulatory Status ES1.4, the following statement is included: "A product used in OCA and a cell-free implant (Agili-C) are approved through a pathway that does not require an investigational new drug application or premarket approval to be commercially sold (DeNovo NT). Additional materials used in cartilage repair surgeries, which have either been FDA approved, designated with FDA Breakthrough Device status, or are in Phase III trials, were included in this HTA." Again, CartiHeal Agili-C has a premarket approval with breakthrough device status.	We thank the commentor for highlighting this error; it has been corrected in the report.
While "cell-free implants" (e.g., Agili-C) were not included in the Summary of Evidence (ES-10) as not being among the technologies with the largest number of studies, it is worth noting that as a new entrant into the clinical space, the evidence for CartiHeal Agili-C is compelling. The Draft Report evidence analysis concludes CartiHeal Agili-C "cell free implant" compared to Microfracture/Chondroplasty, demonstrates moderate certainty of evidence (COE) in four of the comparison categories of the HTA: PRO's, Responder, Treatment Failure, and Harms. Only one other treatment, MACI vs Microfracture, demonstrates moderate certainty of evidence (COE) in only two categories: PROs and Responder.	We agree with commentor that newer technologies hold promise for improved outcomes and lower harms, and include this information in our discussion, including information about moderate certainty of evidence for patient-reported outcomes and response. We have also updated Figure ES 4.1 and Table 5 of the final report.

(Appendix F: Summary of COE ratings) Comparing the quantity of evidence vs. the quality of evidence by treatment, some procedures such as OATS have a greater volume of studies, but the certainty of evidence is low. Page 43, Table 21, includes only 1 RCT comparing cell-free implant to Microfracture/chondroplasty. However, the assessment provided is accurate and captures the merits of the study. Again, the demonstration of moderate confidence of evidence for 4 out of 5 comparison categories certainly places CartiHeal Agili-C in position for consideration for coverage for HCA members when compared to other treatments, particularly as more evidence is being developed.	
Commentary on the study gaps is appreciated for future publications and upcoming CartiHeal Agili-C clinical trials. Manuscripts are in submission showing positive 4-year and 5-year outcomes from the Altschuler et al study and will include re-operation data with anticipated publication within the coming year. The opportunity to comment on the Draft Report is greatly appreciated.	We appreciate the commentor's information about future research.