Osteochondral Allograft/Autograft Transplantation (OAT): Assessing Signals for Update

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1. Previous Coverage Decision

A Health Technology Assessment titled: *Osteochondral Allograft/Autograft Transplantation (OAT)*, was published on November 18, 2011 by the Health Care Authority. Findings and Coverage Decision was adopted on March 16, 2012. The Committee's Coverage Decision is summarized below.

Health Technology Background

Osteochondral Allograft/Autograft Transplantation (OAT) was selected in December 2010 to undergo an evidence review process. The evidence based technology report indicates that OAT referred to the use of cylindrical, dowel-shaped or geometric-shaped plugs of osteochondral material that are press fit into a defect and do not require the use of screws, pins, plates, or other fixation devices. Mosaicplasty, which involves multiple cylindrical plugs, was also included in the report. Osteochondral autograft (or allograft) transplantation or mosaicplasty involve transplantation of cartilage and subchondral bone into the defect to facilitate the growth or new tissue. These procedures can be done open or arthroscopically and are sometimes combined with other joint operations such as arthroscopic debridement or anterior cruciate ligament (ACL) repair.

Osteochondral autograft transplantation involves harvesting bone and intact articular cartilage from a non-weight bearing portion of a joint from the patient to fill a defect in the weight-bearing portion of the joint. This is a technically demanding procedure and is limited to treating defects < 4 cm^2 because of donor tissue limitations. Osteochondral allograft transplantation involves the transplantation of a piece of cartilage and subchondral bone from a source outside of the patient to fill the osteochondral defect. Osteochondral allografts are regulated by the FDA as Human Cell or Tissue Products (HCT/P), as defined in section 361 of the Public Health and Service Act.

HTCC Coverage Determination

Osteochondral Allograft/Autograft Transplantation (OAT) is a **covered benefit with conditions.**

Osteochondral Allograft/Autograft Transplantation (OAT) for joints other than the knee is a **not covered benefit with conditions.**

HTCC Reimbursement Determination

Limitations of Coverage

Osteochondral Allograft/Autograft Transplantation for the knee is a covered benefit when the following conditions are met:

- Age <50, older at the discretion of the agency;
- Excluding malignancy, degenerative and inflammatory arthritis in the joint; and
- Single focal full-thickness articular cartilage defect

Non-Covered Indicators

Osteochondral Allograft/Autograft Transplantation for joints other than the knee are not covered.

Committee Decision

Based on the deliberations of key health outcomes, the committee decided that it had the most complete information: a comprehensive and current evidence report, public comments, and agency and state utilization information. The committee concluded that the current evidence on Osteochondral

Allograft/Autograft Transplantation (OAT) for the knee demonstrates that there is sufficient evidence to cover with conditions. The committee concluded that the current evidence on Osteochondral Allograft/Autograft Transplantation (OAT) for joints other than the knee demonstrates that there is insufficient evidence to cover. The committee considered all the evidence and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable. Based on these findings, the committee voted to not cover Osteochondral Allograft/Autograft Transplantation (OAT) for joints other than the knee. Based on these findings, the committee voted to cover with conditions Osteochondral Allograft/Autograft Transplantation (OAT) for the knee.

Medicare Decision and Expert Treatment Guidelines
The committee reviewed the clinical guidelines and Medicare decision. The Centers for Medicare and Medicaid Services have no published national coverage determinations (NCD) for Osteochondral Allograft/Allograft Transplantation (OAT).

2. Purpose of Report

The purpose of this literature update is to determine whether or not there is sufficient evidence published after the original report to conduct a re-review of this technology based on the presence of preset signal criteria (see Figure 1). The key questions in the included original report are listed below. **For the signal update, updated searches were performed only for Key Questions 3, 4, 5 and 6.**

Key question 1

1. What is the case definition of a patient suitable for OATS/mosaicplasty surgery, and are there measures of reliability and validity for case identification?
   a. What are the maximum, minimum, and optimum size (volume) of the damage that is suitable for repair using OATS/mosaicplasty?
   b. What are the maximum and optimum number of lesions that can be repaired in a single OATS/mosaicplasty procedure?
   c. Are there other considerations that make OATS/mosaicplasty suitable or unsuitable (age, mobility, comorbidities, BMI)?
   d. Is there a distinction between OATS and mosaicplasty, and a related case definition difference between the two?

Key Question 2

2. What are the expected treatment outcomes of OATS/mosaicplasty, and are there validated instruments and scores to measure clinically meaningful improvement?

Key Question 3

3. What is the evidence of efficacy and effectiveness of OATS/mosaicplasty (open or arthroscopic)? Including consideration of short term and long term:
   a. Delay or avoidance of progression to osteoarthritis
   b. Impact on function, pain, range of motion, quality of life, activities of daily living and return to work
   c. Longevity of treatment effect
   d. Need for continuing and/or subsequent intervention
   e. Need for extended or continuing physical therapy
   f. Recovery time considering harvest site recovery issues
   g. Differential results from multiple versus single grafts, patterning for multiple
   h. grafts (linear arrangement versus circular arrangement)

i. Differential results between allograft and autograft procedures
j. Differential results between open and arthroscopic procedures
k. Differential results in centers of excellence

Key Question 4

4. What is the evidence of the safety of OATS surgery? Including consideration of:
    a. Adverse events type and frequency (peri-operative, cartilage plug detachment, cartilage rejection, graft fit, harvest site issues, development of fibrocartilage, mortality, other major morbidity such as DVT, deep infection, and excessive intraarticular bleeding)
    b. Revision/re-operation rates (if not addressed in efficacy)

Key Question 5

5. What is the evidence that OATS surgery has differential efficacy or safety issues in sub-populations? Including consideration of:
    a. Gender
    b. Age
    c. Psychological or psychosocial co-morbidities
    d. Baseline functional status: e.g. type of injury or lesion, extent of cartilage damage, specific damage site size, number of damage sites
    e. Other patient characteristics or evidence based patient selection criteria,
    f. especially comorbidities of diabetes and high BMI
    g. Provider type, setting or other provider characteristics
    h. Payer/ beneficiary

Key Question 6

6. What is the evidence of cost implications and cost-effectiveness for OATS/mosaicplasty? Including consideration of:
    a. Costs (direct and indirect) and cost effectiveness
    b. Short term and long term

3. Methods

3.1 Literature Searches

We conducted an electronic literature search for the period March 1, 2011 through January 10th, 2018 using identical search terms used for the original report for key questions 3 through 6. This search included 3 main databases: PubMed, Cochrane Library, and EMBASE. Additional electronic databases were searched; see Appendix A for search methodology and additional details. Osteochondral allografts are regulated by the FDA as Human Cell or Tissue Products. In addition, we searched the FDA website for updated information on such products.

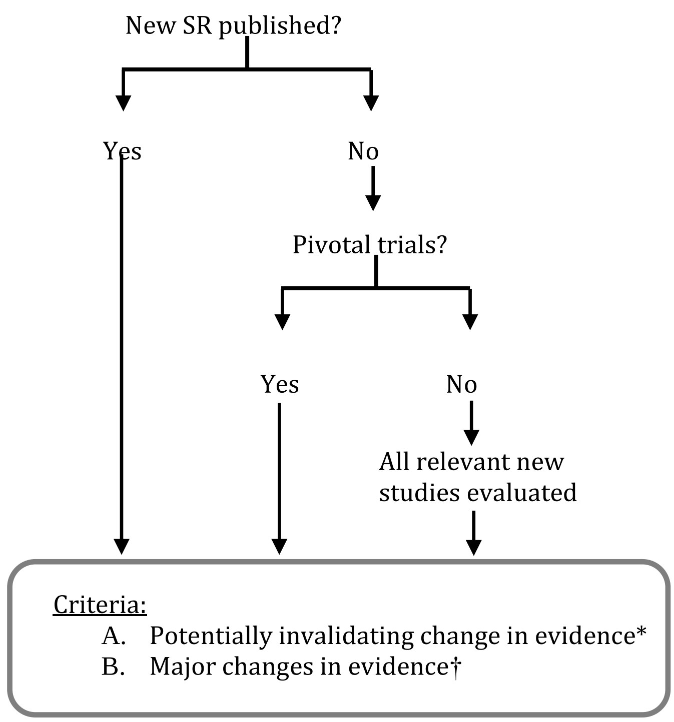
3.2 Study selection

We sought systematic reviews (SR) of randomized controlled trials (RCTs) of efficacy and safety with meta-analysis that included articles that met inclusion and exclusion criteria similar to the original report. In addition we sought systematic reviews reflecting updates or new advances for the technology. Secondary to the large number of citations returned, we focused on screening systematic reviews and meta-analyses of RCTS published between 2011 and 2018. Although quality of systematic reviews was not formally evaluated for this report, we chose systematic reviews of head to head trials for efficacy that were the most comprehensive and of higher quality based on the following: report of search strategies (two or more databases and description of dates searched), number of included relevant RCTs, pre-stated inclusion and exclusion criteria, information on methodologies used for synthesis of data, inclusion of patient reported or safety outcomes and evaluation of the strength of the body of literature using GRADE or another analogous system. Only systematic reviews of RCTs were included for efficacy. Systematic reviews focused on longer-term safety outcomes may include nonrandomized studies. A summary of the included SRs and RCTs is found in Appendix B.

3.3 Compilation of Findings and Conclusions

For this assessment we constructed a summary table that included the key questions, the original conclusions, new sources of evidence, new findings, and conclusions based on available signals. To assess whether the conclusions might need updating, we used an algorithm based on a modification of the Ottawa method, Figure 1.

Figure 1. Algorithm of the modified Ottawa Method of Identifying Signals for SR Updates



*A-1. Opposing findings: Pivotal trial or SR including at least one new trial that characterized the treatment in terms opposite to those used earlier

A-2. Substantial harm: Pivotal trial or SR whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decision making

A-3. Superior new treatment: Pivotal trial or SR whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm.

†B-1. Important changes in effectiveness short of "opposing findings"

B-2. Clinically important expansion of treatment

B-3. Clinically important caveat

B-4. Opposing findings from discordant meta-analysis or nonpivotal trial

4. Results

4.1 Search

The literature search identified 1,755 titles. After title and abstract review, 1,724 articles were excluded and 31 articles remained that addressed in part or in full key questions 3, 4, 5, and/or 6. A total of 16 articles were retained for the signal update, Figure 2. A full list of excluded studies and the reasons for exclusions can be found in Appendix C.

We identified 20 systematic reviews that addressed in part or in full key questions 3, 4, and/or 5. Systematic reviews were excluded if they did not include study types of interest and/or if they were not the most comprehensive and of the highest quality, Appendix B. Two systematic reviews related to efficacy and four systematic reviews focused on safety were retained, of which one systematic review was included for both efficacy and safety. No full health technology assessments were identified; however a 2017 Canadian Agency for Drugs and Technologies in Health Rapid Review is summarized in Appendix B for informational purposes only. One systematic review described results for differential safety (key question 5). We found two cost-effectiveness studies (Key Question 6); there were none in the previous report. Six new RCTs were identified; none were considered pivotal. Two follow-up publications of RCTs included in the previous report were also identified and included.

The FDA still regulates osteochondral allografts as Human Cell or Tissue Products (HCT/P) as defined in section 361 of the Public Health and Service Act. No updates on FDA approval have been published since our initial report.

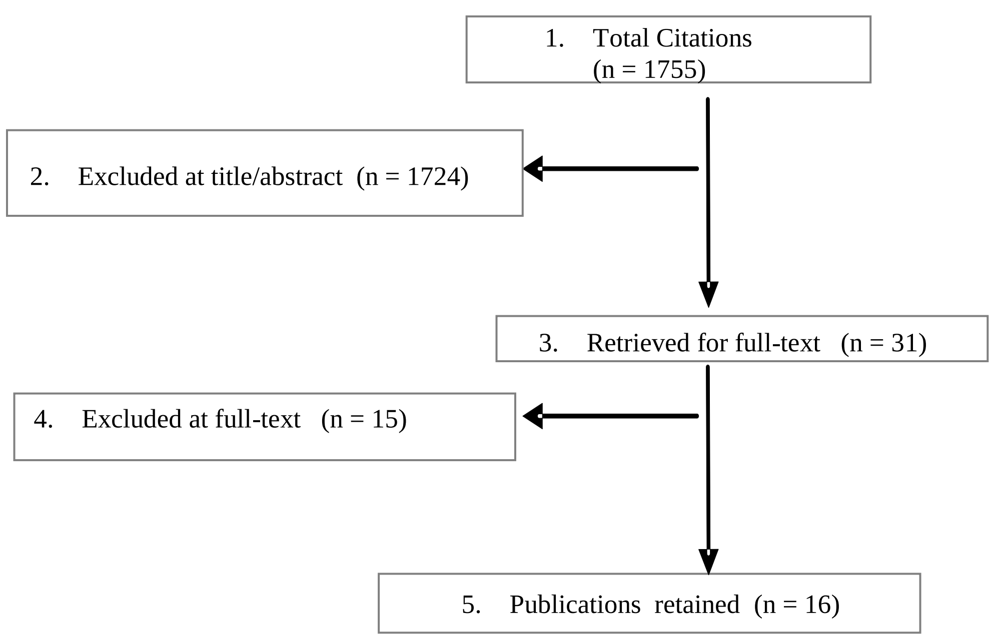


Figure 2. Flow chart showing results of literature search

4.2 Identifying signals for re-review

Tables 1- 4 show the original key questions, the conclusions of the original report, the new sources of evidence, the new findings, and the recommendations of Aggregate Analytics, Inc. (AAI) regarding the need for update (Figure 1). **For the signal update, updated searches were performed only for Key Questions 3, 4, 5 and 6.**

Table 1. Osteochondral Allograft/Autograft Transplantation Summary Table for Key Question 1. [NO UPDATED SEARCH FOR SIGNAL UPDATE]

Conclusions from CER Executive Summary	New Sources of Evidence	New Findings	Conclusion from AAI
Key Question 1. What is the case definition of a patient suitable for OATS/mosaicplasty surgery, and are there measures of reliability and validity for case identification?			
Consistent or agreed-upon case definitions: There is variability with respect to the terms used to describe the various procedures and how they are defined. No specific agreed-upon case definitions were found. Treatment algorithms (only available for the knee) cite case series. Lesion size and classification appear to be key criteria for assessing treatment options (after ligament and meniscus stability, lesion location and other factors have been determined). **Autograft (OAT or mosaicplasty)**: Based on inclusion/exclusion criteria for randomized studies for knee lesions, the most consistent characteristics defining cases for inclusion were: symptomatic (5/5 studies), isolated (4/5 studies) full-thickness lesions or Outerbridge or ICRS grades 3 or 4 lesions (4/5 studies). Exclusion criteria in three of the five studies included knee joint instability or ligamentous deficiency. The mean ages of participants in all studies was <45 years old. **Osteochondral allograft (dowel, cylinder, plug)**: No prospective comparative studies were found and limited information is available from three case series. Cases were defined as symptomatic in all three studies. Studies designed to evaluate clinical decision-making based on patient or lesion characteristics were not found **Talus**: Only one comparative study was available. Pain and presence of a full thickness lesion as inclusion criteria are consistent with criteria described above for the knee. No studies pertaining to other anatomical regions meeting the inclusion criteria were found.	NOT SOUGHT	N/A	N/A
<u>Evidence of validity and reliability (lesion classification systems):</u> • No validity studies of the Outerbridge or ICRS lesion grading systems in the population of interest were found. • Overestimation of lesion size by arthroscopy compared with open evaluation was reported in one clinical study. Inexperienced clinicians had less accurate measures. • Two clinical studies evaluated the reliability of the ICRS grading system using arthroscopy. One study reported 80.9% agreement between arthroscopic and open assessment of grade. Only one study (the smallest) reported chance-adjusted agreement between raters and suggests that there is only fair to slight agreement between raters. • Inter-rater reliability of the Outerbridge classification was evaluated in one study. The overall agreement beyond chance for the video tapes where surgeons were to discriminate between grades 2 and 3 was moderate (κ range 0.41-0.57). The authors did not apparently	NOT SOUGHT	N/A	N/A

Conclusions from CER Executive Summary	New Sources of Evidence	New Findings	Conclusion from AAI
evaluate grade 4 lesions to any large extent and thus, application to a case definition which may focus on grades 3 and 4 lesions is not clear. • No studies for anatomical regions other than the knee were found.			

Table 2. Osteochondral Allograft/Autograft Transplantation Summary Table for Key Question 2. [NO UPDATED SEARCH FOR SIGNAL UPDATE]

Conclusions from CER Executive Summary	New Sources of Evidence	New Findings	Conclusion from AAI
Key Question 2: What are the expected treatment outcomes of OATS/mosaicplasty, and are there validated instruments and scores to measure clinically meaningful improvement?			
• Review of the properties of outcomes measures used in included comparative studies is limited to those measures that were examined in samples drawn from the target population (patients with articular cartilage damage). Of these measures, five have been validated in this population: • International Cartilage Repair Society (ICRS) cartilage repair assessment • Lysholm Knee Scoring Scale (LKSS) • Modified Cincinnati Knee Rating System (MCRS) • International Knee Documentation Committee subjective knee form (IKDC SKF) • Knee Injury Osteoarthritis Outcome Score (KOOS) Four patient-reported and one clinician-based outcomes measures commonly used in studies of patients with cartilage defects in the knee have undergone psychometric analysis in these patients: • None of the five instruments were adequately tested for validity. Content validity was inadequate for all instruments, primarily because patients with chondral lesions were not involved in item selection in that particular study. Criterion validity was not tested in these studies for any instruments, likely because of the lack of a gold standard criterion. Tests of construct validity were hampered by definitional problems and small sample sizes. • Reliability was inadequately tested for the three outcome measures that were tested for internal consistency. None of the studies performed factor analysis to assess potential dimensions. While good internal consistency was shown for the KOOS and the ICRS, internal consistency for these instruments was inadequate as too few patients/raters were tested. Similarly, high values	NOT SOUGHT	N/A	N/A

Conclusions from CER Executive Summary	New Sources of Evidence	New Findings	Conclusion from AAI
for reproducibility were found for the IKDC, the LKSS, and the MCKRS in samples that were too small to meet quality criteria. • Studies that assessed responsiveness showed strong effect sizes for change from preoperative to post-operative scores on the IKDC, MCKS, LKSS, and KOOS. However, quality criteria also require that these effect sizes be supported by comparison of the minimally important clinical difference with the smallest detectable difference, analysis of receiver operating curves, or other supporting analysis. Only one study, which analyzed the IKDC and MCKS, met this criterion. • The minimal clinically important difference (MCID) for pre-op to post-op improvement was determined in one study to be from 6.3 points (6 months follow-up) to 16.7 points (12 month follow-up) on the IKDC and 14.0 points (6 months) and 26.0 points (12 months) on the MCKRS. The MCID was not reported for any other measures in patients with cartilage damage.			

Table 3. Osteochondral Allograft/Autograft Transplantation Summary Table for Key Questions 3 and 4. [UPDATED SEARCH RESULTS]

Conclusions from CER Executive Summary (Strength of Evidence)	New Sources of Evidence	New Findings	Conclusion from AAI
Key Question 3: What is the evidence of efficacy and effectiveness of OATS/mosaicplasty (open or arthroscopic)?			
Autograft versus microfracture, drilling or debridement alone			
Knee			
Efficacy: Knee (Low Evidence) • Two poor quality RCTs (N=104 total), one in young athletes, the other in children. • **Function:** OAT was associated with statistically better patient-reported and clinician-reported outcomes. • **Longevity of treatment effect**: Differences between treatments remained significant up to the last follow-up (maximum 48 months). Functional scores in young athletes improved for OAT recipients up to 36 months. In children following initial improvement at 12 months, ICRS scores decreased slightly, but remained stable up to 48 months. • **Return to activity**: A greater proportion of patients treated by OAT versus MF had returned to pre-injury activity levels at pre-specified time points.	**Systematic reviews** Graticelli 2016[1] Cochrane review (3 RCTs total, includes new RCTs Ulstein and Lim) Pareek 2016[2] (6 RCTs total, includes 3 new RCTs Gudas 2013, Ultstein and Lim and Gudas 2012 f/u) **RCTs** **Follow-up publications:** Gudas 2012[3] (*follow-up to Gudas 2005)* **New RCTS:** Solheim 2017[4] (Mosaicplasty) Ulstein 2014[5] Lim 2012[6] Gudas 2013[7] (OAT vs. MF and vs. debridement only)	**Function** *Systematic reviews*: Pareek SR: Subjective patient outcomes (International Knee Documentation Committee score [IKDC], Lysholm knee scoring scale) at 3 years favored OAT (3 trials by Gudas, one is new, SMD 0.40, 95%CI 1.04, 0.70, p = 0.008); No SOE provided. *New RCTs:* Solheim 2017 (N=40): Clinically and statistically significant difference in Lysholm score favoring OAT at 1 year and all subsequent time points. **Longevity** Gracitelli SR: Pooled mean difference from two small new trials (Lim, Ulstein, total N 72) for the Lysholm score at ≥5 years: showed no difference between OAT mosiacplasty and microfracture (pooled MD – 1.01, 95%CI -4.54, 2.33, p = 0.53) whereas 1 older trial included in prior report favored OAT on the IKDC score (MD13.97, 95%CI 13.25, 14.69. SOE was reported as very low (insufficient) Pareek SR: No difference in subjective scores (IKDC, Lysholm) at 5-10 years (3 trials pooled SMD 0.92, 95%CI -1.07, 2.9), but substantial heterogeneity is noted, only Gudas 10 year follow –up was significant. No SOE provided. Gudas 2012, 10 year follow-up to Gudas 2005 in young athletes: Authors report function continued to	Pooled data including new trials suggest no difference between OAT autograft and MF at ≥5 years for function or Tegner score. Data are from small non-pivotal trials and the evidence base is likely low or insufficient. This section of the report is still valid and does not need updating.(Criteria A1, B-1-4)

Conclusions from CER Executive Summary (Strength of Evidence)	New Sources of Evidence	New Findings	Conclusion from AAI
		be significantly better(ICRS and Tegner scores) with OAT vs. MF; *New RCTs:* Inconsistent findings at 5 years in Lysholm Score: Significant difference favoring OAT reported in Solheim (N= 40, MD 10, 955CI 0.57 to 19.4); Lim 2012 difference was not significant but point estimate tended to favor MF (N, 47, MD -2.8, 95%CI -6.64, 0.94). At 10 years there were no differences between treatments in Solheim 2017 or Ulstein 2014 (N=25) , but point estimates were in opposite directions; sample sizes are small. **Return to Activity** *Systematic reviews*: Gracitelli SR: Mean Tegner Activity Score ≥5 years was not significant for either new trial (Lim, Ulstein). Continuation of sport in older trial (Gudas 2005) and 3 years was more common with OAT vs. MF (RR 3.24 , 95%CI 1.77, 5.92) but not statistically different at 10 years (RR 2.07, 95%CI 0.81, 5.30) Authors SOE: very low (insufficient) Pareek SR: Tegner Activity score (3 – 10 years); OAT associated with better scores (3 trials, MD 0.47, 95%CI 0.14 to 0.80); Trials summarized were Gudas 2012, Gudas 2013 and Lim 2012; individually, only Gudas 2013 reached statistical significance; no SOE provided *RCT follow-up*: Gudas 2012 continuation of sport at same level at 10 years (N = 41): Mean duration of previous sport activity was statistically longer in the OAT vs. MF group.	

Conclusions from CER Executive Summary (Strength of Evidence)	New Sources of Evidence	New Findings	Conclusion from AAI
		New RCTs: In Gudas 2013, OAT was favored over debridement alone; authors do not report whether there was a statistical difference between groups with regard proportions who returned to activity.	
Effectiveness: Knee (No Evidence) • No nonrandomized comparative studies were found.	NOT SOUGHT	N/A	N/A
ANKLE			
Efficacy: Ankle (No Evidence) • No randomized controlled trials were found so efficacy could not be evaluated.	**New RCT** Sun 2016[8] (N=153)	**Function and pain at 2.3 years** Authors report no difference in changes scores of AOFAS, TAS, or Mazur ankle scoring system values between OAT and MF or in VAS pain; both OAT and MF resulted in improved AOFAS, TAS, Mazur ankle scoring and VAS pain compared with drilling.	There are new data that would update the report; however the findings from one non-pivotal trial are not sufficient to trigger an updated report. (Criterion A1)
Effectiveness Ankle (Very Low Evidence) **Function:** One small poor quality cohort (N= 32) reported differences in functional outcomes (assessed by AOFAS or SANE Scores) between OAT and chondroplasty or OAT and microfracture; however, 24-hour post-operative pain was greater among patients treated by OAT.	Not Sought	N/A	N/A
Autograft versus autologous chondrocyte implantation (ACI)			
Efficacy (Low Evidence) • Two poor quality RCTs in general (older) populations were found. One enrolled >40% of participants who had prior surgeries (N =140 total). In the other RCT, ≥50% of persons did not receive treatment (n treated = 23/44 randomized), as authors reported "spontaneous improvement" in the six months following initial debridement. • **Function:** Patient-reported outcomes were better for OAT/mosaicplasty but statistical	**Systematic Reviews** None **RCTs** **Follow-up publications** Bentley 2012[9] (*follow-up to Bentley 2003*) **New RCTS:** Lim 2012[6]	**Knee** **Function** *New RCT:* Lim 2012 (N = 40 knees): The authors reported no differences in Lysholm, Tegner, or HSS scores at a follow-up up to a mean of 5.7 years. 10 year follow-up of previously included trial, Bentley 2012: ACI continued to demonstrate a statistically significant better results than OAT in the modified Cincinnati score, however there appeared to be differential of data for this measure at 10 years that may	This section of the report is still valid and does not need updating. (Criteria A1, B-1, B-4)

Conclusions from CER Executive Summary (Strength of Evidence)	New Sources of Evidence	New Findings	Conclusion from AAI
significance was not uniformly achieved in the two small RCTS. In the largest RCT (n = 100) a significantly smaller proportion of participants receiving mosaicplasty had excellent or good outcomes (author's modification of the Cincinnati Rating Scale) and one of the smaller RCTs reported no significant differences in the Meyer score. Both these studies included substantial proportions of participants who had prior surgeries. Differences in outcomes measures used makes comparison across studies difficult. • **Longevity of treatment effect**: In one study (N =40), functional scores for both OAT and ACI increased over time for the Lysholm, Tegner and Myers scores; only for the Lysholm Knee Scoring Scale were significant differences between treatment sustained over time favoring OAT.		bias findings; 15 of 42 patients in the OAT group were evaluated for functional outcomes at the 10 year follow-up, versus 48 of 58 patients in the ACI group.	
<u>Effectiveness (No Evidence)</u> • No nonrandomized comparative studies were found.	Effectiveness, not sought	N/A	N/A
Autograft versus other treatments			
<u>Efficacy: Ankle (No Evidence)</u> • No randomized controlled trials were found so efficacy cannot be evaluated.	**<u>New RCT</u>** **Autograft vs. allograft** Ahmad 2016[10] (N=40)	There were no differences between autograft and allograft with regard to function or pain at a mean of 3.2 years. Similarly there were no differences in graft union or need for operative revision procedures.	There are new data that would update the report, however the findings from one small non-pivotal trial are not sufficient to trigger an updated report. (Criteria A1, B2)
<u>Effectiveness Knee (Very Low Evidence)</u> • Four small, poor quality nonrandomized studies compared OAT alone or in combination with other procedures. Confounding by indication was present in all and heterogeneity across studies precludes effective comparison across them.	Effectiveness, not sought	N/A	N/A

Conclusions from CER Executive Summary (Strength of Evidence)	New Sources of Evidence	New Findings	Conclusion from AAI
• **Function:** For most functional outcomes, there were no differences between treatment groups. • In one small (N =18) study, post-operative mean Modified Lysholm score was significantly less for OAT versus matrix assisted chondrocyte transplantation (MACT). • Range of motion appeared to be substantially greater among patients treated by OAT with realignment versus realignment alone in another study (n =49)			
Allograft : Osteochondral allograft using primarily press-fit dowel/cylinder or plug (not requiring hardware)			
Efficacy: No Evidence • No randomized controlled trials were found. **Effectiveness: Knee and Ankle (Very Low Evidence)** • **Comparative studies:** No statistically significant differences between treatment groups were reported for most outcomes measures across two small studies (N = 70 total). Tegner scores were improved for OA recipients compared with loose body removal and arthroscopic reduction and internal fixation in one study, and SF-12 Mental Component Scores were significantly improved in patients who received OA and MAT (meniscal allograft transplantation) compared with OA and ACI in the other. • Case series of >19 patients which primarily used press-fit plugs (dowel/cylinder/geometric) without use of fixation • **Function and QoL:** Various patient-reported, clinician based outcomes and quality of life measures were used across studies and generally indicated improved	**No new RCTs** Effectiveness not sought	No new efficacy evidence	N/A

Conclusions from CER Executive Summary (Strength of Evidence)	New Sources of Evidence	New Findings	Conclusion from AAI
function and quality of life following the allograft procedure compared with pre-operative values. • One study reported a 91% survival rate of grafts at 5 years and 76% at both 10 and 15 years (N =65).			
Key Question 4: What is the evidence of the safety of OATS surgery? Including consideration of: a. **Adverse events type and frequency (peri-operative, cartilage plug detachment, cartilage rejection, graft fit, harvest site issues, development of fibrocartilage, mortality, other major morbidity such as DVT, deep infection, and excessive intraarticular bleeding)** b. **Revision/re-operation rates (if not addressed in efficacy)**			
Autograft			
Safety: Knee and Ankle (Low Evidence) • Data from three RCTs (all knee), 3 nonrandomized comparative studies (2 knee, 1 ankle), and 15 case series of osteochondral autograft transfer (9 knee, 4 ankle, and 2 both knee and ankle) were used • Surgical complications (infection, deep vein thrombosis, and hemarthrosis) are infrequent (<7%). • In 3 RCTs, revisions of OAT procedures in the knee were performed significantly less often than revisions following microfracture (1% vs. 33%; 2 trials, mean 3-4 year follow-up). There was no clear difference for OAT compared with ACI in one trial at 2 years (0% vs. 5%, respectively). Re-operations following OATs were 17% across seven case series of the knee and 34% across three case series of the ankle (variety of procedures, unclear timeframes). • Rates of donor site morbidity were 10% in two RCTs in the knee,10% across three case series in the knee, 7% across two case series in the ankle, and 9% in one case series at both sites.	**Systematic reviews** **Knee** Pareek 2016[2] (6 RCTs total, includes 3 new RCTs Gudas 2013, Ulstein 2014 and Lim 2012 and Gudas 2012 f/u, Gudas 2009; Autograft vs. MF) Andrade 2016 [11](11 studies, includes 1 RCT, 1 prospective cohort, 4 retrospective cohorts, and 5 case-series; Autograft only) **Ankle** Andrade 2016[11] (10 studies, no new RCTs, 3 retrospective cohorts, and 7 case-series; Autograft only) **RCTs, knee** **Follow-up publications:** Gudas 2012[3], *follow-up to Gudas 2005* (Autograft vs. MF) **New RCTs:** Ulstein 2014 [5](Autograft vs. MF)	**Knee** **Surgical complications** *Systematic reviews and RCTs*: NR **Failure (as defined by authors)** *Systematic reviews*: Pareek SR, Autograft vs. MF: MF had 2.4 times the risk of failure when compared with Autograft in 4 trials (RR 2.4, 95% CI 1.05, 5.52), p=0.036; N=180; Gudas 2009, Gudas 2012, Lim 2012, Ulstein 2014) over mean follow-up of 5.6 years (range, 3-10 years). *RCTs*: Autograft vs. MF: Gudas (N=57): Significantly lower risk of failure with Autograft (14% vs. 38%, p<0.05) over a mean follow-up of 10.4 years (range, 9-11 years) Autograft vs. ACI: Bentley (N=100), large defects: Significantly greater risk of failed cartilage repair (surgical intervention) with Autograft (55% vs. 17%, p<0.001) at a minimum follow-up of 10 years (range, 10-12 years) **Reoperation (as defined by authors)** *Systematic reviews*: NR	Knee: This portion of the report is still valid. New evidence at longer term continues to suggest that OAT autograft is associated with less failure and fewer reoperations compared with microfracture. Long-term follow-up for OAT vs. ACI from one large trial still suggests OAT may have greater failure vs. ACI. (Criteria A-2, B-4) Ankle This portion is still valid as primary evidence is still from case-series.

Conclusions from CER Executive Summary (Strength of Evidence)	New Sources of Evidence	New Findings	Conclusion from AAI
• No deaths directly attributable to OAT were found in the studies reviewed.	Bentley 2012[9], *follow-up to Bentley 2003* (Autograft vs. ACI) Lim 2012[6] (Autograft vs. MF and vs. ACI) **<u>RCTs, Ankle</u>** **New RCTs:** Ahmad 2016[10] (Autograft vs. Allograft)	*RCTs*: Autograft vs. MF: Ulstein (N=25): 36% vs. 54% at median follow-up of 9.8 years (range, 5-11 years), p=NS Lim (52 knees): 5% vs. 10% at a mean follow-up of 5 years (range, 3-10 years), p=NS Autograft vs. ACI: Lim (40 knees): 5% vs. 11% at a mean follow-up of 5 years (range, 3-10 years), p=NS **Donor-site morbidity** *Systematic reviews*: Andrade SR (N=1472 knee patients): The pooled estimate for knee-to-knee transplantation was 5.9% (range 0%-92% across 11 studies) over follow-up periods ranging from 1 to 9.6 years. The most common donor-site complaints were patellofemoral disturbances (23%) (3 studies), crepitation (31%) (2 studies) and post-operative effusion (9%) (2 studies) **<u>Ankle</u>** **Revision** *Systematic reviews*: NR*RCTs*: Ahmad, Autograft vs. Allograft (N=40): 10% vs. 13% at a mean follow-up of 3.1 years (range, 1-6.4 years), p=NR **Graft nonunion** *Systematic reviews*: NR *RCTs*: Ahmad, Autograft vs. Allograft (N=40): 10% vs. 19% at a mean follow-up of 3.1 years (range, 1-6.4 years), p=NR **Donor-site morbidity** *Systematic reviews*: Andrade SR (N=254 ankle patients): The pooled estimate for knee-to-ankle transplantation was 19.6% (range 0%-55% across 10 studies) over follow-	

Conclusions from CER Executive Summary (Strength of Evidence)	New Sources of Evidence	New Findings	Conclusion from AAI
		up periods ranging from 0.5 to 6.3 years. The most common donor-site complaints were pain or instability during daily living or sports activities (44%) (3 studies) and persistent pain (13%) (2 studies)	
Allograft versus various treatments			
Safety: Knee (Low Evidence) • Rates of all re-operations following OATs using allograft were 12.5% across seven studies (2 cohorts, 5 case-series). • Rate of graft failure was 21% in two case series that used radiographs. • One case of infection (4%) was reported in one case series. • Allograft transplantation carries an extremely small potential risk of disease transmission. No study of disease transmission related to osteochondral allograft was found in our search.	**Systematic reviews** **Knee** Familiari 2017[12] (19 studies total, 1 prospective cohort, 1 retrospective cohort and 17 case series; Allograft only) Assenmacher 2016[13] (5 studies total, 1 prospective cohort and 4 case series; Allograft only) **No new RCTs**	**Knee** **Reoperation (as defined by authors)** *Systematic reviews*: Familiari SR: Mean reoperation rate across 17 studies was 30.2% (range 0%-63%) over a mean follow-up of 8.7 years. Assenmacher SR: Mean reoperation rate across all studies was 36% over a mean follow-up of 12.3 years. The most common reoperations included unicompartmental or total knee arthroplasty (37%), debridement due to symptoms (24%) and graft-related surgery (removal, fixation, and revision) (14%). **Failure (as define by authors)** *Systematic reviews*: Familiari SR: Mean failure rate across 17 studies was 18.2% (range 0%-31%) over a mean follow-up of 8.7 years. Assenmacher SR: Mean failure rate across all studies was 25% over a mean follow-up of 12.3 years A total of 72% of the failures were conversion to total (68%) or unicompartmental (4%) knee arthroplasty, and 28% involved graft removal, graft fixation, and graft revision. **Survivorship** *Systematic reviews*: Familiari SR: Kaplan-Meier analysis of mean survivorship across the included 12 studies was	New evidence does not change the conclusions from the previous report (criteria A-1 or A3), nor provide major changes in the evidence (criteria B-1 – B4) for either autograft or allograft. This section does not need updating

Conclusions from CER Executive Summary (Strength of Evidence)	New Sources of Evidence	New Findings	Conclusion from AAI
		86.7% at 5 years, 78.7% at 10 years, 72.8% at 15 years and 67.5% at 20 years. Assenmacher SR: Kaplan-Meier analysis of mean survivorship was reported by 3 studies and was 94% at 5 years, 84% at 10 years, 71% at 15 years, and 45% at 20 years. **Post-operative infection** *Systematic reviews*: Assenmacher SR: One case of deep infection (1 study) and one case of superficial cellulitis (1 study). **Disease transmission** *Systematic reviews*: NR	

Table 4. Osteochondral Allograft/Autograft Transplantation Summary Table for Key Questions 5 and 6

Conclusions from CER Executive Summary (Strength of Evidence)	New Sources of Evidence	New Findings	Conclusion from AAI
Key Question 5: What is the evidence that OATS surgery has differential efficacy or safety issues in sub populations?			
Autograft			
Efficacy: Knee (Low Evidence) • Direct comparisons within RCTs are limited and may suggest that age, defect size, and defect location may influence outcomes • Indirect comparison of factors is challenging given differences in the populations studied, study quality the comparators used.	**Systematic reviews:** Pareek 2016[2] (includes 2 new trials –Gudas 2013, Lim 2012 and 10 year follow-up, Gudas 2012)	**Systematic reviews** Pareek SR: There was no effect modifications for Tegner Activity score (3 – 10 years) by defect size (< 3cm^2, > 3cm^2), p (interaction) = 0.134 **RCTs** No formal tests for interaction were reported for subanalyses related to patient characteristics or lesion characteristics.	There are new data that would update this section of the report. However, the findings from these studies don't meet the criteria that would trigger an updated report. (Criteria B1-4)
Effectiveness: Knee and Ankle (Very Low Evidence) • No direct comparisons for any factor were made in nonrandomized comparative studies • Indirect comparisons based on case series of autograft OATS/mosaicplasty suggest that younger patients may experience better function and be better able to return to sports. Better functional outcomes may occur with one plug versus multiple plugs based on two small studies. Lesion location may influence outcome. • Allograft: Limited information from two case series is conflicting with regarding the influence of gender.	Effectiveness Not Sought	N/A	N/A
Autograft and Allograft			
Safety: Knee and Ankle(Very Low Evidence) • No comparative studies of autograft or allograft transplantation assessed differential safety • Results of case series of autograft and allograft transplantation suggested that older patients may have more risk of graft failure and that grafts of larger lesions were more likely to fail. • No full economic studies directly addressing the cost-effectiveness of either autograft or allograft	**Systematic Reviews** Pareek 2016[2] **No New RCTs**	**Systematic reviews** Pareek: There was no effect modifications for failure by lesion type (osteochondritis dissecans (OCD) and articular cartilage defect (ACD), p(interaction) =0.101	There are new data that would update this section of the report. However, the findings from these studies don't meet the criteria that would trigger an updated report. (Criteria B1-4)

Conclusions from CER Executive Summary (Strength of Evidence)	New Sources of Evidence	New Findings	Conclusion from AAI
osteochondral transplantation as described in this report were found.			
Key Question 6: What is the evidence of cost implications and cost-effectiveness for OATS/mosaicplasty?			
Knee and Ankle (No Evidence) No full economic studies directly addressing the cost-effectiveness of either autograft or allograft osteochondral transplantation as described in this report were found.	CADTH 2017 Rapid review[14]: No economic studies for shoulder, ankle **New cost effectiveness analysis** **Knee** Miller 2015[15] Schronk 2017[16]	2 studies for isolated distal femoral lesions based on systematic reviews of level 1 or 2 studies; age range 15-55 years old. **Miller 2015** (N = 134 patients) OAT vs. microfracture for mean lesion size of 2.7 cm^2 (1.0 to 6.0 cm^2): Results for cost per point improvement pre-op to post-op in functional measures based on outcomes measure used. Only the International Cartilage Repair Society (ICRS) functional measure showed statistically significant difference (difference $98.29/per point improvement; OAT $308.50 vs. microfracture $ 406.79). Authors report that cost to return patients back to their previous level of sport at 1, 3, and 10 years, demonstrated OAT to be more cost-effective than microfracture for all years. Authors' conclusion: Microfracture was found to be more cost effective by the Lysholm and HSS scores, whereas OAT was more cost-effective by the Tegner and ICRS scores. Given similar clinical outcomes, microfracture and OAT are both viable, cost-effective first-line treatment options for these injuries. **Schronk 2017** (N = 730 knees) OAT, microfracture, ACI-1 (First-Generation Autologous Chondrocyte Implantation). Mean lesion sizes ranged from 1.9 cm^2 to 5.1 cm^2, mean follow-up ranged from 36.7 to 38.3 months. The costs per point functional outcome change were OAT $313.84, MF $200.59, AC-1 $536.59. Author' conclusions: All treatments led to an increase in functional outcome scores postoperatively MF was found to be the most cost effective treatment option and ACI-1 the least cost-effective.	There are new data that would update this section of the report. However, the findings from these studies don't meet the criteria that would trigger an updated report.

5. Conclusions

Tables 1, 2, 3 and 4 show the original key questions, the conclusions of the original report, the new sources of evidence, the new findings, and the conclusions of Aggregate Analytics, Inc. (AAI) with respect to the criteria that identify a trigger for an update (Figure 1). This report focuses on Key questions 3-6.

5.1 Key Question 1: NOT PART OF SIGNAL UPDATE

5.2 Key Question 2: NOT PART OF SIGNAL UPDATE

5.3 Key Question 3 (Efficacy):

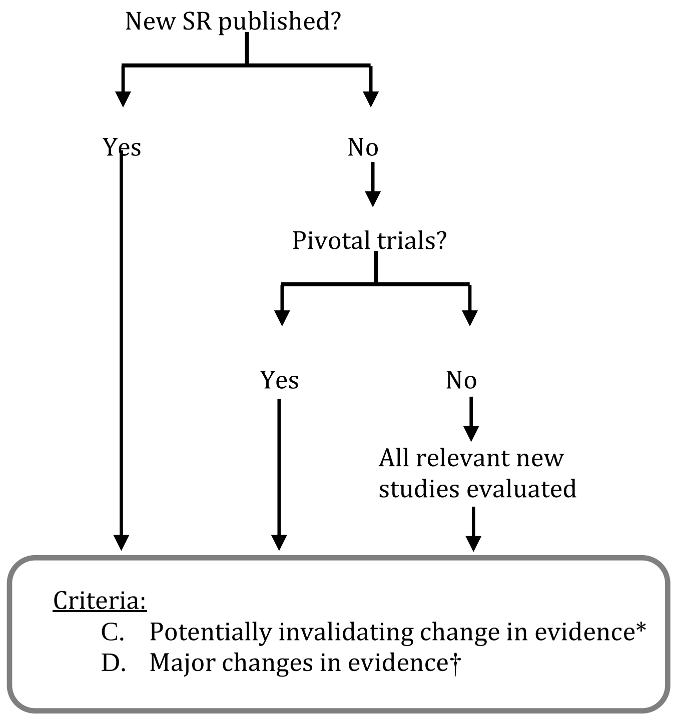
- OAT/mosaicplasty vs. microfracture, drilling or debridement alone
  - **Knee:** Two systematic reviews incorporating new RCTs and one additional RCT (not incorporated in to systematic reviews) comparing OAT and microfracture and describing longer-term outcomes were identified. Pooled data including new trials suggest no difference between OAT autograft and microfracture at ≥5 years for function or Tegner score. Data are from small non-pivotal trials; the evidence base is likely low or insufficient. This section of the report is still valid and does not need updating. (Criteria A1, B-1-4)
  - **Ankle:** One new RCT comparing OAT with microfracture and with drilling was identified, however the trial is not considered pivotal and doesn't meet the criteria that would trigger a report update. (Criteria A-1, A-3, B2).
- OAT/mosaicplasty vs. ACI (Knee)
  - One new, small RCT and 10 year follow-up from a previously included trial comparing OAT with ACI were identified. Results are consistent with the previous report; there are no major changes in evidence (criteria B 1-4). This section does not need updating.
- Autograft vs. Allograft (Ankle)
  - One small new trial evaluating OAT autograft with allograft in the ankle/talus was identified but is not considered pivotal. The findings don't meet the criteria that would trigger an updated report (criterion A-1).

5.4 Key Question 4 (Safety): New evidence does not change the conclusions from the previous report (criteria A-1 or A3); there are not any major changes in the evidence base (criteria B-1 – B4) for either autograft or allograft. This section does not need updating

5.5 Key Question 5 (Differential efficacy or safety): There is limited information from one systematic review suggesting that lesion size or type do not modify treatment with regard to the outcomes of activity or implant failure. However, the findings don't meet the criteria that would trigger an updated report (Criteria B1-4).

5.6 Key Question 6: Two cost-effectiveness studies comparing OAT with microfracture have been published since the previous report. However, the findings don't meet the criteria that would trigger an updated report.

Figure 2. Algorithm of the modified Ottawa Method of Identifying Signals for SR Updates



*A-1. Opposing findings: Pivotal trial or SR including at least one new trial that characterized the treatment in terms opposite to those used earlier

A-2. Substantial harm: Pivotal trial or SR whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decision making

A-3. Superior new treatment: Pivotal trial or SR whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm.

†B-1. Important changes in effectiveness short of "opposing findings"

B-2. Clinically important expansion of treatment

B-3. Clinically important caveat

B-4. Opposing findings from discordant meta-analysis or nonpivotal trial

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APPENDIX A. SEARCH STRATEGIES

Search strategy for PubMed: Search dates: March 1, 2011 through January 10, 2018

	Search terms	Number of articles
#1	("osteochondral autograft transfer" OR "mosaicplasty" OR "mosaicplasties")	197
#2	(chondral OR osteochondral) OR ("Cartilage, Articular"[MeSH] OR "Osteochondritis Dissecans"[MeSH] OR "osteochondritis dissecans")	9202
#3	#1 OR #2	9218
#4	(transplant OR transplants OR transplantation* OR implant OR implants OR implantation* OR graft OR grafts OR grafting OR autograft* OR autologous OR autotransplant* OR ("Transplantation, Autologous"[MeSH]) OR allograft* OR allogeneic OR homograft* OR allotransplant* OR ("Transplantation, Homologous"[MeSH]))	374,476
#5	#3 AND #4	2519
#6	rabbit* OR "mouse" OR "mice" OR "rat" OR "rats" OR "dog" OR "dogs" OR "Models, Animal"[MeSH] OR (Animals[MeSH] NOT "Humans"[MeSH])	1,100,143
#7	("Case Reports"[Publication Type] OR "case report")	375,523
#8	#6 OR #7	1,467,032
#9	#1 OR #5 NOT #8	1668

Search strategy for Cochrane: Search dates: March 1, 2011 through January 10, 2018

	Search terms	Number of articles
#1	("osteochondral autograft transfer" OR "mosaicplasty" OR "mosaicplasties")	15
#2	(chondral OR osteochondral) OR ("Cartilage, Articular"(MeSH) OR "Osteochondritis Dissecans"(MeSH) OR "osteochondritis dissecans")	182
#3	#1 OR #2	187
#4	(transplant OR transplants OR transplantation* OR implant OR implants OR implantation* OR graft OR grafts OR grafting OR autograft* OR autologous OR autotransplant* OR ("Transplantation, Autologous"(MeSH)) OR allograft* OR allogeneic OR homograft* OR allotransplant* OR ("Transplantation, Homologous"(MeSH)))	30988
#5	#3 AND #4	89
#6	rabbit* OR "mouse" OR "mice" OR "rat" OR "rats" OR "dog" OR "dogs" OR "Models, Animal"(MeSH) OR (Animals(MeSH) NOT "Humans"(MeSH))	4248
#7	("Case Reports"(Publication Type) OR "case report")	4556
#8	#6 OR #7	8609
#9	#1 OR #5 NOT #8	76*

*4 technology assessments and 1 economic evaluation were excluded. All were either structured or provisional abstracts and/or were not study types of interest

Additional electronic databases were searched using key words and included EMBASE, ClinicalTrials.gov, AHRQ, National Guideline Clearinghouse and INAHTA for eligible studies, including health technology assessments (HTAs), systematic reviews, primary studies and FDA reports.
Additional searches yielded 11 articles not previously captured but none met inclusion criteria.

APPENDIX B. SUMMARY OF INCLUDED STUDIES

Appendix Table B1. Summary of systematic reviews included for efficacy

Assessment *Search dates*	Purpose	Condition	Treatment vs. comparators	Primary Outcomes	Evidence- base Used	Primary Conclusions
Gracitelli 2016 Cochrane review *Database inception to February 5th, 2016*	To assess the relative effects (benefits and harms) of different surgical interventions (microfracture, drilling, mosaicplasty, and allograft transplantation) for treating isolated cartilage defects of the knee in adults.	Knee cartilage defects	OAT vs MF	Knee function assessed by validated tools, QoL measures, failure of treatment and adverse effects	3 RCTs (2 new RCTs: Lim 2012, Ulstein 2014) (n=133)	**OAT vs MF efficacy:** In a pooled analysis of Lysholm scores at a follow-up of 5 years or longer (SoE very low/insufficient), the authors report no difference in outcomes (2 new trials, pooled difference -1.10, 95% CI -4.54 to 2.33). One older trial (included in prior report) favored OAT on the IKDC score (MD13.97, 95%CI 13.25, 14.69) (SoE very low/insufficient) **OAT vs MF return to activity:** Mean Tegner score at a follow-up of 5 years or longer was not statistically significant for either new trial (Lim 2012, Ulstein 2014). Continuation of sport in Gudas 2005 was more common in OAT (RR 3.24, 95% CI 0.81, 5.40) but statistical significance was not reached at 10 years (RR 2.07, 95%CI 0.81, 5.30) (SoE very low/insufficient) **OAT vs MF safety:** Across 3 trials at a follow-up of five years or longer, authors report failure of treatment and adverse events occurred at a statistically significant lower rate in OAT (SoE very low/insufficient) (3 trials [2 new trials], pooled RR 0.47, 95% CI 0.24, 0.9)
Pareek 2016 *January 1st 1995 to May 1st 2015*	To compare OAT and MF surgical techniques to determine postoperative activity level, subjective patient outcomes, failure rates, and assess if any lesion characteristics favored one	Knee articular cartilage damage	OAT vs MF	Activity related scores, subjective clinical scores, and failure rate	6 RCTs (3 new RCTs: Lim 2012, Ulstein 2014, Gudas 2013; 1 new follow-up publication: Gudas 2012) (n=249)	**OAT vs MF efficacy:** In a pooled analysis of subjective scores at a follow-up of 3 years (SoE not reported), OAT demonstrated statistically significant improved scores (3 trials [1 new trial], pooled SMD 0.40, 95% CI 0.10 to 0.70). The difference was not statistically significant at a follow-up of 5 to 10 years (3 trials [3 new trials], pooled SMD 0.92, 95% CI -1.07 to 2.90) but substantial heterogeneity was noted, only the 10 year follow-up reported in Gudas 2013 was significant.

Assessment *Search dates*	Purpose	Condition	Treatment vs. comparators	Primary Outcomes	Evidence- base Used	Primary Conclusions
	technique over the other.					**OAT vs MF return to activity:** Across 3 trials with a follow-up of 3 to 10 years (SoE NR), authors report statistically significant better Tegner scores in OAT (3 trials [3 new trials], pooled SMD 0.469, 95% CI 0.140 to 0.798). In Gudas 2012, mean duration of previous sport activity was statistically longer in OAT compared to MF. In a subgroup analysis of lesion size, the authors found that OAT performed statistically significantly better in lesions > 3 cm^2 (2 trials [2 new trials], pooled SMD 0298, 95% CI -0.076 to 0.673) but not in lesions < 3 cm^2 (1 trial [1 new trial], SMD 0.768, 95% CI 0.281 to 1.256). No modification by defect size was found (p (interaction) = 0.134).

ACI: autologous chondrocyte implantation; CI: confidence interval; MF: microfracture; OA: osteoarthritis; OAT: osteochondral autologous transplantation; QoL: quality of life; RCT: randomized controlled trial; RR: risk ratio; SMD: standardized mean difference; SoE: Strength of Evidence

Appendix Table B2. Summary of systematic reviews included for safety

Assessment *Search dates*	Purpose	Condition	Population	Primary Outcomes	Evidence- base Used	Primary Safety Conclusions
Andrade 2016 *Database inception to October 2016*	To provide an overview of donor-site morbidity associated with harvesting osteochondral plugs from the knee joint in mosaicplasty procedure*	Full-thickness cartilage lesions of weight-bearing joints in the knee or ankle*	N=21 articles (N=1726 patients) Knee: 11 articles (N=1472 patients, mean age 33.2 years, follow-up 12 to 115 months) Ankle: 10 articles (N=254 patients, mean age 34.8 years, follow-up 12 to 76 months)	Presence of donor-site morbidity after mosaicplasty	**Level I:** n=1 (1 knee) **Level II:** n=1 (1 knee) **Level III:** n=7 (4 knee, 3 ankle) **Level IV:** n=12 (5 knee, 7 ankle)	The donor-site morbidity for knee-to-ankle (19.6%, range across studies 0%-55%) was greater than knee-to-knee (5.9%, range across studies 0%-92%) mosaicplasty procedures, without any significant correlation between rate of donor-site morbidity and size of the defect, number and size of the plugs. Most common donor-site morbidity complaints for the knee were patellofemoral disturbances (23 %) and crepitation (31%); post-op effusion (9%). For the ankle, complaints were pain or instability during daily living or sports activities (44 %), patellofemoral disturbances (13 %), knee stiffness (13 %) and persistent pain (13 %)
Assemacher 2016 *January 1, 1995 to June 1, 2015*	To evaluate long-term clinical outcome scores, reoperation, and failure rates of osteochondral allograft and to examine if certain factors predispose patients to worse outcomes	Full-thickness cartilage defects of articular cartilage and subchondral bone in the knee	N=5 studies (N=291 patients, 55% male, age 34.8 years, mean 12.3 years follow-up, 10 to 17.1 years)	Clinical outcomes, reoperation rates, failure rates	**Level II**: n=1 study **Level IV:** n=4 studies	Across all studies at final follow-up, mean failure rate was 25% and mean reoperation rate was 36%. Post-operative infection was reported by 2 studies: one reported 1 case of deep infection and one reported a case of superficial cellulitis. Survivorship was reported by 3 studies and was 94% at 5 years, 84% at 10 years, 71% at 15 years, and 45% at 20 years. Results are similar to failure and reoperation rates for alternative cartilage restoration techniques. Reoperation for patellofemoral grafts was significantly higher (83%), but most of the procedures (mean 1.8, range 0 to 6) were for debridement and hardware removal. Femoral condyle grafts have slightly improved survivorship. Patellofemoral grafts are less successful than tibial and femoral grafts, as seen in this review
Familiari 2017 *1980 to March 2017*	To review clinical outcomes and failure rates after osteochondral allograft	Chondral defects of the knee	N=19 studies (N=1036 patients, mean 31.5 years (10-82), mean	Clinical outcomes and failure rates	**Prospective cohort:** n=1 study **Retrospective cohort:** n=1 study	OCA transplantation of the knee yielded good survival rates at 5 to 10 year follow-up. Mean 5-year survival rate across the studies included in this review was 86.7%, while the mean 10-year survival rate was 78.7%. The survival rates were 72.8% at 15

Assessment *Search dates*	Purpose	Condition	Population	Primary Outcomes	Evidence- base Used	Primary Safety Conclusions
	transplantation in the knee at a mean 2 years' follow-up		follow-up 8.7 years (2-32 years))		**Case series:** n=17 studies	years and, subsequently, 67.5% at 20 years. OCA transplantation was associated with considerable reoperation (30.2%, range 0%-63%) (17 studies) and failure (18.2%, range 0%-31%) (17 studies) rates at final follow-up.
Pareek 2016 *January 1st 1995 to May 1st 2015*	To compare OAT and MF surgical techniques to determine postoperative activity level, subjective patient outcomes, failure rates, and assess if any lesion characteristics favored one technique over the other.	Knee articular cartilage damage	N=6 studies (N=249)	Activity related scores, subjective clinical scores, and failure rate	**Randomized controlled trials**: n=6 trials	Pooled analysis of failure of treatment across 4 trials found OAT had a statistically significant lower rate of failure† (4 trials [3 new trials], pooled SMD 2.417, 95% CI 1.059 to 5.519). The difference remained statistically significant when a sub-analysis was performed on trials reporting on both articular cartilage defect and osteochondritis dissecan lesions (3 trials [3 new trials], pooled SMD 1.959, 95% CI 1.033 to 3.713), compared to osteochondritis dissecan lesions alone (1 trial, SMD 21.478, 95% CI 0.476 to 39.703).

CI: confidence interval; MF: microfracture; OAT: osteochondral autologous transplantation; OCA: osteochondral allograft transplantation; SMD: standardized mean difference
*All donor sites were in the knee but cartilage lesions occurred in either the knee or ankle
†Authors note in discussion that an important limitation of the meta-analysis is the variability in the definition of "failure" between studies

Appendix Table B3. Summary of CADTH Rapid Review

Assessment *Search dates*	Purpose	Condition	Treatment vs. comparators	Primary Outcomes	Evidence- base Used	Primary Conclusions
The Use of Osteochondral Allograft for the Ankle, Knee, and Shoulder: Clinical Effectiveness and Cost-Effectiveness CADTH Rapid Response Report (2017) *January 1, 2012 to January 10, 2017*	The report aimed to provide evidence on the clinical benefits, harms, and cost-effectiveness of the use of fresh, prolonged fresh, or frozen osteochondral allografts for the lesions of the ankle, knee, and shoulder.	Painful lesion of the ankle, knee, or shoulder involving cartilage or cartilage with bone that has failed non-operative and primary treatment	**Knee** Osteochondral allograft transplantation* vs before the operation. Three SRs reported some patients were treated with concomitant procedures† **Ankle** Osteochondral allograft transplantation‡ vs before the operation **Shoulder** Osteochondral allograft transplantation vs before the operation	Clinical effectiveness, functional outcomes, and cost-effectiveness	**Knee** 4 SRs of cohort or case-series studies **Ankle** 2 SRs of case-series and/or other nonrandomized studies **Shoulder** 1 SR of case-series studies No economic evaluations were identified	**Knee** <u>Function</u>*:* All SRs reported improved functional outcomes compared to before surgery. <u>Return to activity</u>*:* One SR reported patients returned to full activity 5.9 months on average after surgery. Another SR reported most patients returned to sports and preinjury-level performance by 30 months and 9.6 months, respectively. SRs (number not reported) reported improved Tegner scores compared to before surgery. <u>Pain:</u> All SRs reported improved pain outcomes compared to before surgery <u>Patient satisfaction:</u> One SR reported that 86% of patients were extremely or mostly satisfied with the operation. <u>Failure and reoperation:</u> One SR reported that 36% of patients had reoperations. Two SRs reported that 18% to 25% of all operations were considered failures, requiring conversion to knee arthroplasty or graft revision or removal. **Ankle** <u>Function:</u> SRs reported improved functional scores after surgery. <u>Pain:</u> One SR reported improved VAS scores compared to before surgery. <u>Patient satisfaction:</u> One SR reported that 71% of patients reported good to excellent satisfaction with the operation. <u>Failure and reoperation:</u> One SR reported that 25% of patients required at least one reoperation of any kind and that 13% of all operations were considered failures §. **Shoulder** <u>Function:</u> The one SR reported higher shoulder stability after surgery and the no recurrence of

Assessment *Search dates*	Purpose	Condition	Treatment vs. comparators	Primary Outcomes	Evidence- base Used	Primary Conclusions
						shoulder instability. Range of motion was restored or increased compared to before the operation. <u>Complication rates:</u> SR reported 74% of patients with shoulder instability had complications after the operation**.

CADTH: Canadian Agency for Drugs and Technologies in Health; SR: systematic review

*One SR included only fresh allografts, another included fresh, prolonged-fresh, and fresh-frozen allografts, and the remaining two SRs did not specify restrictions on the type of allograft
†Concomitant procedures included tibial tubercle transfer and extensor mechanism realignment, osteotomy, meniscal transplantation, ligamentous reconstruction, and retinacular release
‡One SR included only fresh allografts; the other SR did not specify any restriction on allograft type
§Defined as postoperative graft nonunion, resportion, or persistence of symptoms leading to subsequent arthrodesis or arthroplasty
**Complications included spontaneous avascular necrosis and collapse, persistent pain, clicking, catching, stiffness, and flattening

Appendix Table B4. Study characteristics of new RCTs and new follow-up publications

Author (Year)	Demographics	Results	Conclusions	Comments
Knee: Autograft vs. MF or Debridement alone				
Solheim 2017	N= 40 Age at surgery, mean (IQR): 32 (18-48) years % Male: 70% F/U: 1, 5, 10, 15 years Lesion size: 3.5 cm^2 Lesion description: full-thickness articular chondral defects on the condyles or trochlea Area: NR <u>OAT (Autograft , mosaicplasty)</u> After arthroscopic evaluation and debridement to subchondral bone, grafts were harvested from the periphery of the patellofemoral joint and transplanted into corresponding bur holes in the defect <u>MF</u> After arthroscopic evaluation and debridement to subchondral bone, angled awls were used to make holes in the subchondral bone plate were made 3 to 4 mm apart.	<u>Function: OAT vs. MF</u> Lysholm Score, mean (SD), p: • Baseline: 56 (15) vs 50 (16), p = 0.2 • 1 year: 85 (12) vs. 72 (22), p = 0.015 • 5 years: 83 (9) vs 67 (18), p < 0.001 • 10 years: 81 (16) vs 65 (22), p = 0.020 • ≥15 years: 77 (17) vs 61 (22), p = 0.011 (difference of >9 points considered clinically significant) Minimum 15 years success, n/N (%), p: • Lysholm <64 (poor outcome): 4/20 (20%) vs 13/20 (65%), p = 0.004 • Lysholm ≥80 (good outcome): 12/20 (60%) vs 4/20 (20%), p = 0.010 <u>Later surgical procedure</u> • Knee replacement, n (%): 3 (15%) vs. 1 (5%), p =0.292	**Function**: at all time points through minimum of 15 years, mosaicplasty was associated with a statistically and clinically relevant improvement in function with more mosiacplasty patients reporting good outcome at 15 years. Additional Surgery: No significant differences between groups; any other safety or adverse outcomes were reported.	The authors declare no conflict of interest Funding NR
Ulstein 2014	N= 25 Age, mean (SD): 32.3 (7.7) years % Male: 56% F/U, median (IQR): 9.8 (4.9 to 11.4) years Lesion size, mean (range): 2.8 (2.0 to 6.0) cm^2 Lesion description: chondral or osteochondral lesion of ICRS grade III-IV Area, n/N (%) trochlea vs n/N (%) medial vs n/N (%) lateral: 2/25 (8%) vs 20/25 (80%) vs 3/25 (12%)	<u>Function: OAT vs MF</u> Lysholm Score mean change (95% CI), (MD, 95% CI), p: • 9.8 (4.9-11.4) years: 13.4 (0.9 to 25.8) vs 21.6 (3.7 to 39.4), (MD 8.2, 95% CI -11.7 to 28.1), p NS KOOS pain mean change (95% CI), (MD, 95% CI), p: • 9.8 (4.9-11.4) years: 11.8 (-2.8 to 26.4) vs 20.6 (2.8 to 38.3), (MD 8.8, 95% CI -12.7 to 30.3), p NS KOOS symptoms mean change (95% CI), (MD, 95% CI), p:	**Function**: There were no significant differences in Lysholm score or KOOS, at median follow-up of 9.8 years.	Included in Gracitelli 2016 Cochrane Review and Pareek 2016 SR Restricted shuffling approach for randomization may not be true randomization (see Schulz 2002) Authors declare no conflict of interest

Author (Year)	Demographics	Results	Conclusions	Comments
Knee: Autograft vs. MF or Debridement alone				
	<u>OAT (Autograft mosaicplasty)</u> Procedure was performed though medial parapatellar arthrotomy or a mini-invasive arthrotomy. Osteochondral grafts from periphery of the femoral condyles were transplanted using "press-fit" method into lesion site <u>MF</u> Procedure was done arthroscopically. Debridement of all damaged/unstable cartilage was done. An arthroscopic awl was used to make multiple holes 3 to 4 mm apart	• 9.8 (4.9-11.4) years: 8.5 (-3.5 to 20.6) vs 17.4 (2.6 to 32.2), (MD 8.9, 95% CI -8.9 to 26.7), p NS KOOS activities in daily living mean change (95% CI), (MD, 95% CI), p: • 9.8 (4.9-11.4) years: 7.5 (-4.3 to 19.3) vs 13.0 (-3.8 to 29.8), (MD 5.5, 95% CI -13.4 to 24.4), p NS KOOS function in sport and recreation mean change (95% CI), (MD, 95% CI), p: • 9.8 (4.9-11.4) years: 41.3 (23.7 to 58.9) vs 32.4 (13.3 to 51.6), (MD -8.9, 95% CI -33.4 to 15.7) p NS KOOS quality of life mean change (95% CI), (MD, 95% CI), p: • 9.8 (4.9-11.4) years: 25.0 (10.6 to 39.3) vs 34.6 (15.1 to 54.0), (MD 9.6, 95% CI -12.7 to 31.9), p NS <u>Reoperation: OAT vs MF</u> Reoperation, n/N (%), p: 5/14 (36%) vs 6/11 (54%), p NS		Funding: Grant from Akershus University Hospital and the Foundation of Sophies Minde
Gudas 2013	N= 136 (102 randomized, 34 matched controls) Age, mean: 32.7 years w/o control, 32.0 w/control Male: 63% w/o control, 65% w/control F/U: Lesion size, mean (SD): 2.9 (4.2) Lesion description: articular cartilage damage grades III-IV in the femoral condyle Area: medial <u>OAT (Autograft) (n=34)</u> Performed under arthroscopic control simultaneously with ACL reconstruction. Eight mm plugs from	<u>Function: OAT vs MF</u> IKDC subjective score, mean (SD): • Preoperative: 45.5 vs 46.5 • 3 years*: 86.8 (2.6) vs 86.0 (3.5), p = 0.024 <u>Return to activity: OAT vs MF</u> Tegner score, mean (SD): • Preoperative: 2.5 vs 2.7 • 3 years: 7.1 vs 6.9 <u>Function: OAT vs debridement</u> IKDC subjective score, mean (SD): • Preoperative: 45.5 vs 47.1 • 3 years*: 86.8 (2.6) vs 84.5 (2.6), p = 0.018	**Function:** at a follow-up of 3 years, OAT had statistically significant improved IKDC scores compared to MF and debridement. **Return to activity:** At a 3 year follow-up, OAT had slightly higher Tegner scores than both MF and debridement but statistical significance was unclear.	Included in Pareek 2016 SR Authors declare no conflicts of interest

Author (Year)	Demographics	Results	Conclusions	Comments
Knee: Autograft vs. MF or Debridement alone				
	medial and/or lateral margin of femoral trochlea were used <u>MF (n=34)</u> Awls used to make perforations 3 to 4 mm apart <u>Debridement (n=34)</u> Unstable cartilage was debrided and the calcified cartilage layer was removed	<u>Return to activity: OAT vs debridement</u> Tegner score, mean (SD): • Preoperative: 2.5 vs 2.5 • 3 years: 7.1 vs 6.2		
Lim 2012†	N= 109 patients (120 knees) randomized, 69 patients (70 knees) evaluated Age, mean (range): 28.5 (18-42) years % Male: 57% F/U, mean (range): 5.7 (3 to 10.5) years Lesion size: 2.74 cm^2 Lesion description: single symptomatic articular cartilage lesion of the knee Area, n/N (%) medial vs n/N (%) lateral: 55/70 (79%) vs 15/70 (21%) <u>OAT (Autograft mosaicplasty) (n=22 knees)</u> Performed after arthroscopic examination and debridement of fibrillated cartilage. Plugs of 4, 6, and 8 mm were inserted using press-fit method <u>MF (n=30 knees)</u> After arthroscopic examination, tapered awls were used to make 0.5 to 1 mm diameter holes 4 mm deep and placed 3 to 4 mm apart	<u>Function: OAT vs MF ‡</u> Lysholm, mean (SD), (MD, 95% CI): • Preoperative: 53.2 (7.2) vs 51.2 (6.2) • 5 years: 84.8 (5.5) vs 85.6 (6.8), (-0.8, 95% CI -4.5 to 2.9), p = 0.66 HSS, mean (SD), (MD, 95% CI): • Preoperative: 78.66 (7.23) vs 78.22 (9.12) • 5 years: 88.12 (4.15) vs 87.60 (4.56), (MD 0.52, 95% CI -2.06 to 3.09), p = 0.69 <u>Return to activity</u> Tegner, mean (SD), (MD, 95% CI): • Preoperative: 2.7 (1.5) vs 2.8 (1.4) • 5 years: 5.3 (1.2) vs 5.1 (1.5), (MD 0.2, 95% CI -0.6 to 1.0), p = 0.62 <u>Reoperation: OAT vs MF§</u> Reoperation, n/N (%), (RR, 95% CI), p: 1/22 (5%) vs 3/30 (10%), (RR 0.45, 95% CI 0.1 to 4.1), p = 0.47	**Function:** There were no differences in functional scores measured with Lysholm or HHS at a five year follow-up **Return to activity:** At a five year follow-up, there were no differences in return to activity as measured by Tegner **Reoperation:** There was no difference in number of reoperations at a five year follow-up	109 patients enrolled, only 69 underwent procedures Authors declare no conflicts of interest Funding NR

Author (Year)	Demographics	Results	Conclusions	Comments
Knee: Autograft vs. MF or Debridement alone				
Gudas 2012** **(follow-up to Gudas 2005)**	N= 60 Age, mean (range): 24.3 (15 to 40) years % Male: 63% F/U: 3 and 10 years Lesion size: 2.8 (1.4) cm^2 Lesion description: articular cartilage defect or osteochondral defect of the knee Area, % medial vs % lateral: 84% vs 16% OAT (Autologous) Residual cartilage and calcified layers of subchondral bone were removed. 5.5 mm plugs from lateral and/or medial margin of the femoral trochlea were used and transplanted into defect using "press-fit" method. MF Debridement of unstable cartilage was done and calcified layer was removed. Arthroscopic awl made multiple holes 2 to 4 mm apart.	Function: OAT vs MF ICRS, mean (SD): • 10 years: p < 0.005 Return to activity: OAT vs MF Return to preinjury sports activities: • p < 0.001 Average duration of return to previous sports activities: • p < 0.005 Failure: OAT vs MF Reoperation during 10 year follow-up, n/N (%), p: 4/28 (14%) vs 11/29 (38%). p < 0.05 Authors report subanalysis based on lesion type ACD and OCD as well as on age less than 25 and greater than 25 but do not provide formal test for interaction.	**Function:** At a 10 year follow-up, a statistically significant difference in ICRS scores was found in favor of OAT **Return to activity:** In terms of return to preinjury sports activities and duration of continuation of sports after surgery was statistically significantly better in OAT at a 10 year follow-up. **Failure:** Over 10 year period, OAT had a statistically significant lower rate of reoperation.	Authors declare no conflict of interest Funding NR
Ankle/Talus: Autograft vs. MF or drilling or allograft				
Sun 2016	N= 153 Age, mean (SD): 33.6 (6.9) % Male: 59% F/U: mean 27.4 months Lesion size: NR Lesion description: osteochondral lesions of the talus Area: NR A. OAT (Autograft) (n=52) Follow debridement, 4-9 mm holes 5.0 mm in depth were drilled into	Function: OAT vs. MF AOFAS, mean (SD), p: • 2.3 (1.7 to 3.0) years: 79.6 (6.5) vs 76.7 (8.4), p = NS AOFAS, mean change (SD), p: • 2.3 (1.7 to 3.0) years: 25.1 (1.3) vs 24.3 (1.6), p = NS Mazur ankle scoring system, mean (SD), p: • 2.3 (1.7 to 3.0) years: 95.2 (8.8) vs 92.3 (7.4), p = NS Mazur ankle scoring system, mean change (SD), p:	**Function:** Authors report no difference in changes scores of AOFAS or Mazur ankle scoring system values between OAT and MF; both OAT and MF resulted in improved AOFAS and Mazur ankle scoring compared with drilling. **Return to activity:** No difference in Tegner scores were reported between OAT	Authors declare no conflict of interest Funding NR No description of how randomization was done and no description of concealed allocation

Author (Year)	Demographics	Results	Conclusions	Comments
Knee: Autograft vs. MF or Debridement alone				
	the cartilage surface under arthroscopy. Grafts were taken from the outside of the ipsilateral patellofemoral joint and transplanted into the defects. Ankle fracture fixation and/or ligament repair was done and the joint capsule was sutured. B. MF (n=53) Following debridement, holes of depth 3 to 4 mm were made 3 to 4 mm apart under arthroscopy. C. Drilling (n=48) Following debridement, the fracture surface was trimmed under arthroscopy. Holes with depths 1.0 to 1.5 cm were drilled.	• 2.3 (1.7 to 3.0) years: 41.8 (3.2) vs 40.5 (4.1), p = NS Return to activity: OAT vs MF Tegner, mean (SD), p: • 2.3 (1.7 to 3.0) years: 4.7 (2.1) vs 4.6 (1.3), p = NS Tegner, mean change (SD), p: • 2.3 (1.3 to 3.0) years: 2.8 (0.3) vs 2.8 (0.7), p = NS Pain: OAT vs MF VAS (0-10), mean (SD), p: • 2.3 (1.7 to 3.0) years: 2.4 (0.4) vs 2.7 (0.3), p = NS VAS (0-10), mean change (SD), p: • 2.3 (1.7 to 3.0) years: 5.1 (1.2) vs 4.9 (0.7), p = NS, Function: OAT vs. drilling AOFAS, mean (SD), p: • 2.3 (1.7 to 3.0) years: 79.6 (6.5) vs 64.9 (9.8), AOFAS, mean change (SD), p: • 2.3 (1.7 to 3.0) years: 25.1 (1.3) vs 11.2 (0.7), $p < 0.05$ Mazur ankle scoring system, mean (SD), p: • 2.3 (1.7 to 3.0) years: 95.2 (8.8) vs 80.1 (9.8), $p < 0.05$ Mazur ankle scoring system, mean change (SD), p: • 2.3 (1.7 to 3.0) years: 41.8 (3.2) vs 28.0 (1.7), $p < 0.05$ Return to activity Tegner, mean (SD), p: • 2.3 (1.7 to 3.0) years: 4.7 (2.1) vs 3.6 (1.1), Tegner, mean change (SD), p:	and MF, but both OAT and MF resulted in improved Tegner scores compared to drilling. **Pain:** Authors report no difference in pain VAS between OAT and MF; both OAT and MF resulted in improved pain VAS compared with drilling.	

Author (Year)	Demographics	Results	Conclusions	Comments
Knee: Autograft vs. MF or Debridement alone				
		• 2.3 (1.3 to 3.0) years: 2.8 (0.3) vs 1.8 (0.2), $p < 0.05$, Pain: OAT vs drilling VAS (0-10), mean (SD), p: • 2.3 (1.7 to 3.0) years: 2.4 (0.4) vs 5.2 (0.8), $p < 0.05$ VAS (0-10), mean change (SD), p: • 2.3 (1.7 to 3.0) years: 5.1 (1.2) vs 2.3 (0.4), $p < 0.05$		
Ahmad 2016	N= 40 Age, mean (range): 40.5 (14-63) years Male: 58% F/U: 2 weeks, 6 weeks, 3 months, 6 months, 1 year, final F/U mean of 3.2 years Lesion size, mean: 1.6 cm^2 Lesion description: recurrent or large osteochondral lesions of the talar dome (OLT) Area, n/N (%) anterior or central, n/N (%) posteromedial: 19/36 (53%) vs 17/36 (47%) OAT (Autograft) Open ankle arthrotomy with or without malleolar osteotomy was done. Osteochondral autografts from the extra-articular superolateral distal femoral condyle were transplanted into defects using "press-fit" method Allograft Open ankle arthrotomy with or without malleolar osteotomy was done. Fresh talar allografts were	Function: OAT vs allograft FAAM, mean (range): • 3.2 (1 to 6.4) years: 85.5 (56 to 97.6) vs 80.7 (56 to 95.2), $p = 0.25$ Pain: OAT vs allograft VAS Pain: • 3.2 (1 to 6.4) years: 2.2 (0 to 8) vs 2.7 (1 to 8), $p = 0.15$ Safety/complications: OAT vs allograft§ Revision operative procedure, n/N (%), (RR, 95% CI), p: • 3.2 (1 to 6.4) years: 2/20 (10%) vs 2/16 (13%), (RR 0.80, 95% CI 0.13 to 5.1), $p = 0.81$ Graft nonunion, n/N (%), (RR, 95% CI), p: • 3.2 (1 to 6.4) years: 2/20 (10%) vs 3/16 (19%) (RR 0.53, 95% CI 0.10 to 2.8), $p = 0.46$	**Function:** There was no difference between OAT and allograft in FAAM at a mean follow-up of 3.2 years **Pain:** There was no difference between OAT and allograft in pain VAS at a mean follow-up of 3.2 years **Safety and complications:** There was no difference between OAT and allograft in graft nonunion or in revision operative procedures at a mean follow-up of 3.2 years	Authors declare no conflict of interest No external funding reported 4 patients in allograft group were excluded after randomization for having OLTs with significant involvement of either medial or lateral shoulder of the talar dome. Patients were treated with hemi-talus allograft.

Author (Year)	Demographics	Results	Conclusions	Comments
Knee: Autograft vs. MF or Debridement alone				
	harvested and transplanted into defects using "press-fit" method			
KNEE: Autograft vs. ACI				
Lim 2012	N= 109 patients (120 knees) randomized, 69 patients (70 knees) evaluated Age, mean (range): 28.5 (18-42) years Male: 57% F/U, mean (range): 5.7 (3 to 10.5) years Lesion size: 2.74 cm^2 Lesion description: single symptomatic articular cartilage lesion of the knee Area, n/N (%) medial, n/N (%) lateral: 55/70 (79%) vs 15/70 (21%) <u>OAT (Autograft mosaicplasty) (n=22 knees)</u> Performed after arthroscopic examination and debridement of fibrillated cartilage. Plugs of 4, 6, and 8 mm were inserted using press-fit method <u>ACI (n=18 knees)</u> First stage was arthroscopic harvest of 1 cm by 1 cm fragments from the margin of the trochlea. Fragment underwent enzymic digestion to release cells for culture. Six weeks later, arthrotomy procedure was done to place periosteal flap, harvested from the tibia, over defect, fixed with sutures, and sealed with fibrin glue. Solution of expanded chondrocytes was injected underneath flap.	<u>Function: OAT vs ACI</u> Lysholm, mean (SD), p: • 5 years: 84.8 (5.5) vs 84.6 (6.1), p NS HSS, mean (SD), p: • 5 years: 88.12 (4.15) vs 82.51 (4.58), p NS <u>Return to activity: OAT vs ACI</u> Tenger, mean (SD), p: • 5 years: 5.3 (1.2) vs 5.2 (1.3), p NS <u>Reoperation: OAT vs ACI§</u> Reoperation, n/N (%), (RR, 95% CI), p: 1/22 (4%) vs 2/18 (11%), (RR 0.41, 95% CI 0.04 to 4.2), p = 0.44	**Function:** The authors reported no differences in Lysholm or HSS scores at a follow-up up to a mean of 5.7 years **Return to activity:** The authors reported no differences Tegner at a follow-up up to a mean of 5.7 years **Reoperation:** There was no difference in rates of reoperation between OAT and ACI	109 patients enrolled, only 69 underwent procedures Authors declare no conflicts of interest Funding NR

Author (Year)	Demographics	Results	Conclusions	Comments
Knee: Autograft vs. MF or Debridement alone				
Bentley 2012 (follow-up to Bentley 2003)	N= 100 Age, mean (range): 31.3 (16 to 49) years % Male: 57% F/U: ≥10 years Lesion size, mean: 4.2 cm^2 Lesion description: symptomatic articular cartilage defect of the knee Area, n/N (%) medial, n/N (%) lateral, n/N (%) patella, n/N (%) other/unknown: 17/100 (17%), 50/100 (50%), 24/100 (24%), 9/100 (9%) <u>OAT (Autograft, mosaicplasty)</u> Parapatelar arthrotomy was done. After defect was debrided, 4.5 mm grafts were harvested from the margin of the trochlea and transplanted into the defect. <u>ACI</u> Biopsy of articular cartilage was harvested from the margin of the trochlear. Three to five weeks after enzymatic digestion, parapatellar arthrotomy was performed. The defect was debrided and covered with the cells at 3 to 4 mm intervals.	<u>Function: OAT vs ACI</u> Modified Cincinnati score, n/N (%): • Excellent (80-100): 4/15 (27%) vs 28/48 (58%) • Good (55-79): 5/15 (33%) vs 7/48 (15%) • Fair (30-54): 4/15 (27%) vs 6/48 (13%) • Poor (<30): 2/15 (13%) vs 2/48 (4%) • p-value: 0.02 Stanmore Bentley score, n/N (%): • Score of 0: 2/15 (13%) vs 7/48 (15%) • Score of 1: 4/15 (27%) vs 23/48 (48%) • Score of 2: 5/15 (33%) vs 3/48 (6%) • Score of 3: 2/15 (13%) vs 6/48 (13%) • Score of 4: 2/15 (13%) vs 4/48 (8%) • p-value: 0.27 <u>Failure of operation: OAT vs ACI</u> Failed cartilage repairs, n/N (%), p: 23/42 (55%) vs 10/58 (17%), p < 0.0001	**Function:** At a minimum of a 10 year follow-up, ACI demonstrated statistically significant better results than OAT in the modified Cincinnati score, while results of the Stanmore-Bentley functional rating showed no difference. **Failure of operation:** ACI showed statistically significant lower rates of failed cartilage repair at a minimum of 10 years follow-up.	Only 15 of 42 patients in the OAT group were evaluated for functional outcomes at the 10 year follow-up, compared to 48 of 58 patients in the ACI group. Authors declare no conflict of interest Funding NR

ACI: Autologous Chondrocyte Implantation; ACD: articular cartilage defect; AOFAS: American Orthopedic Foot and Ankle Society score; CI: confidence interval; FAAM: Foot and Ankle Ability Measure Sports scoring system; F/U: follow-up; HSS: Hospital for Special Surgery score; ICRS: International Cartilage Repair Society score; IQR: interquartile range; KOOS: Knee Injury and Osteoarthritis Outcome Score; MD: mean difference; MF: microfracture; NR: not reported; OAT: osteochondral autograft transplantation; OCD: osteochondral defect; RR: risk ratio; VAS: visual analog scale

*Estimated from graph

†Trial population included three groups; OAT, MF, and ACI. Comparison between OAT and ACI is included in corresponding section

‡MDs, CIs, and p values calculated by AAI

§RRs, CIs, and p values calculated by AAI

**Population was exclusively athletes

APPENDIX C. SYSTEMATIC REVIEWS EXCLUDED AT FULL TEST REVIEW

Excluded systematic reviews

Citation	Reason for exclusion
Bexkens R, Ogink PT, Doornberg JN, et al. Donor-site morbidity after osteochondral autologous transplantation for osteochondritis dissecans of the capitellum: a systematic review and meta-analysis. Knee Surg Sports Traumatol Arthrosc 2017;25:2237-46.	Evaluated chondral lesions of the elbow; elbow was not a region of interest
Camp CL, Stuart MJ, Krych AJ. Current concepts of articular cartilage restoration techniques in the knee. Sports Health 2014;6:265-73.	No quantitative synthesis
Chalmers PN, Vigneswaran H, Harris JD, Cole BJ. Activity-Related Outcomes of Articular Cartilage Surgery: A Systematic Review. Cartilage 2013;4:193-203.	No new RCTs included
Chawla A, Twycross-Lewis R, Maffulli N. Microfracture produces inferior outcomes to other cartilage repair techniques in chondral injuries in the paediatric knee. Br Med Bull 2015;116:93-103.	No RCTs included
Devitt BM, Bell SW, Webster KE, Feller JA, Whitehead TS. Surgical treatments of cartilage defects of the knee: Systematic review of randomised controlled trials. Knee 2017;24:508-17.	No quantitative synthesis
Haien Z, Jiachang W, Qiang L, Yufeng M, Zhenwei J. Osteochondral Autologous Transplantation Compared to Microfracture for Treating Osteochondral Defect: An Updated Meta-analysis of Randomized Controlled Trials. J Knee Surg 2017.	Lower quality review and substantial cross-over with included trials
Li Z, Zhu T, Fan W. Osteochondral autograft transplantation or autologous chondrocyte implantation for large cartilage defects of the knee: a meta-analysis. Cell Tissue Bank 2016;17:59-67.	Lower quality review and substantial cross-over with included trials
Lynch TS, Patel RM, Benedick A, Amin NH, Jones MH, Miniaci A. Systematic review of autogenous osteochondral transplant outcomes. Arthroscopy 2015;31:746-54.	Lower quality review and substantial cross-over with included trials
Mundi R, Bedi A, Chow L, et al. Cartilage Restoration of the Knee: A Systematic Review and Meta-analysis of Level 1 Studies. Am J Sports Med 2016;44:1888-95.	No new RCTs included
Naveen S, Robson N, Kamarul T. Comparative analysis of autologous chondrocyte implantation and other treatment modalities: A systematic review. European Journal of Orthopaedic Surgery and Traumatology 2012;22:89-96.	No new RCTs included
Riboh JC, Cvetanovich GL, Cole BJ, Yanke AB. Comparative efficacy of cartilage repair procedures in the knee: a network meta-analysis. Knee Surg Sports Traumatol Arthrosc 2017;25:3786-99.	Not a meta-analysis head-to-head of trials, network meta-analysis
Richter DL, Schenck RC, Jr., Wascher DC, Treme G. Knee Articular Cartilage Repair and Restoration Techniques: A Review of the Literature. Sports Health 2016;8:153-60.	Lower quality review and substantial cross-over with included trials
Smith MV, Bedi A, Chen NC. Surgical treatment for osteochondritis dissecans of the capitellum. Sports Health 2012;4:425-32.	No RCTs included
Westermann RW, Hancock KJ, Buckwalter JA, Kopp B, Glass N, Wolf BR. Return to Sport After Operative Management of Osteochondritis Dissecans of the Capitellum: A Systematic Review and Meta-analysis. Orthop J Sports Med 2016;4:2325967116654651.	No RCTs included

Excluded randomized controlled trials

Citation	Reason for exclusion
Clave A, Potel JF, Servien E, Neyret P, Dubrana F, Stindel E. Third-generation autologous chondrocyte implantation versus mosaicplasty for knee cartilage injury: 2-year randomized trial. Journal of orthopaedic research : official publication of the Orthopaedic Research Society 2016;34:658-65.	Product used ACI intervention not FDA approved

ACI: Autologous Chondrocyte Implantation; FDA: Food and Drug Administration