Washington State Health Care Authority

Treatment of Chondral Defects of the Knee

Draft Evidence Report

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Health Technology Assessment Program (HTA)

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This evidence report is based on research conducted by the RTI–University of North Carolina Evidence-based Practice Center through a contract between RTI International and 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 represent the views of the Washington HCA, and no statement in this report should be construed as an official position of Washington HCA.

The information in this report is intended to help the State of Washington's independent Health Technology Clinical Committee make well-informed coverage determinations. This report is 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 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).

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List of Abbreviations

ACI	autologous chondrocyte implantation
ADL	activities of daily living
AE	Adverse event
AMIC	autologous matrix-induced chondrogenesis
BMI	body mass index
CBER	Center for Biologics and Evaluation and Regulation
CI	confidence interval
CKRS	Cincinnati Knee Rating System
COE	certainty of evidence
CQ	cost question
EQ	efficacy question
FDA	U.S. Food and Drug Adminstration
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HCT/P	Human Cells, Tissues, and Cellular and Tissues-Based Products
HTA	health technology assessment
HTCC	Health Technology Clinical Committee
ICD	International Classification of Disease
IKDC	International Knee Documentation Committee
MACI	matrix-induced autologous chondrocyte implantation
MD	mean difference
MF	microfracture
NRSI	nonrandomized studies of interventions
OATS	osteochondral autologous transplantation
OCA	osteochondral allograft transplantation
PRO	patient-reported outcomes
RCT	randomized controlled trial
RR	risk ratio
SAE	serious adverse events
SQ	safety question

Executive Summary

Structured Abstract

Purpose: This health technology assessment (HTA) reviews the comparative effectiveness, safety, and cost-effectiveness of selected treatments of chondral defects of the knee, including microfracture, drilling, osteochondral autologous transplantation (OATS), osteochondral allograft transplantation (OCA), and matrix-induced autologous chondrocyte implantation (MACI).

Data Sources: PubMed and Cochrane Library from inception to November 30, 2023; clinical trial registry; government, payor, and clinical specialty organization websites; hand searches of systematic reviews.

Study Selection: Using a priori criteria, we selected English-language primary research studies that were conducted in very highly developed countries that reported comparative effectiveness, safety, or cost-effectiveness for various chondral defect repair procedures. We selected randomized controlled trials (RCTs), non-randomized studies of interventions (NRSIs), and cost-effectiveness studies. Eligible outcomes included change in patient-reported outcomes (PROs) for severity of symptoms and function as measured by validated instruments, clinical response, treatment failure, reoperations, serious adverse events, adverse events, and cost-effectiveness from studies that used U.S.-based cost data.

Data Abstraction and Analysis: One research team member extracted data, and a second checked for accuracy. Two investigators independently assessed the risk of bias of included studies. When quantitative synthesis was appropriate, we used random-effects models to generate pooled estimates of effect. We graded the certainty of evidence (COE) for each comparison of procedures and category of outcomes using Grading of Recommendations Assessment, Development, and Evaluation.

Data Synthesis: We included 23 studies (10 RCTs, 12 NRSIs, 1 cost-effectiveness study). Twenty-three studies provided evidence on efficacy, 10 studies provided evidence for safety, and 1 study provided evidence on cost-effectiveness. Most studies evaluated outcomes at posttreatment only. The largest bodies of evidence were for comparisons of MACI vs. MF (n = 5), OATS vs. MF (n = 7), and first-line vs. second-line chondral restoration procedures (n = 4). For the MACI vs. MF comparison, we found *moderate* COE among RCTs for greater effectiveness of MACI compared to MF for PROs and response to treatment. NRSIs reported similar results, though with *very low* COE for greater effectiveness of MACI. RCTs and NRSIs reported comparable results for treatment failure, reoperations, and harms. RCTs comparing OATS and MF reported similar effectiveness (*low* to *very low* COE), with the exception of greater effectiveness of OATS for the outcome of response to treatment (*low* COE) and fewer treatment failures for OATS in 1 NRSI (*low* COE). Four NRSIs reported greater improvement of PROs and lower treatment failure for first-line restoration procedures of either MACI or OCA

(*very low* COE for MACI, very *low* COE for OCA) compared with second-line restoration procedures after failed MF. Few studies reported harms which were generally comparable.

Limitations: This HTA included many RCTs and NRSIs with high risk of bias, and we identified only 1 cost-effectiveness study. We limited the scope to peer-reviewed studies published in English. We did not include data or results presented solely in conference abstracts. We only included validated measures for disease specific patient-reported outcomes; we did not include general quality of life outcomes. We did not include first- or second-generation autologous chondrocyte implantation procedures as such procedures are no longer used in practice. We included only comparative study designs.

Conclusions: This HTA examined the comparative effectiveness, safety, and cost-effectiveness of treatments for chondral defects of the knee. MACI has low to moderate evidence for greater effectiveness compared to microfracture for patient-reported outcomes and response to treatment among RCTs. OATS and MF were comparable for outcomes indicating similar benefit of these procedures. Both MACI and OATS had comparable harms to microfracture, though our certainty of evidence was low. The evidence base was limited with respect to other comparisons.

ES 1. Background

This health technology assessment (HTA) reviews the efficacy, safety, and cost-effectiveness of treatment for chondral defects to assist the State of Washington's Health Technology Clinical Committee in determining coverage of microfracture (MF), osteochondral autologous transplantation (OATS), osteochondral allograft transplantation (OCA), and matrix-induced autologous chondrocyte implantation (MACI).

ES 1.1 Condition Description

Chondral defects refer to damage of the surface cartilage lining the bones where they connect with other bones in synovial joints (i.e., the articular cartilage). Chondral defects can cause pain and reduced function. Articular cartilage has a limited ability to regenerate and over time is associated with scarring, progressive cartilage degeneration, and increased risk for osteoarthritis. Treatments for chondral defects aim to repair, restore, or replace damaged tissue with healthier cartilage. These procedures are alternatives to total or partial knee replacement (arthroplasty) in patients who are younger and more active than typical candidates for arthroplasty.

ES 1.2 Disease Burden

Individuals with chondral defects can experience symptoms of pain, catching or locking of the joint, swelling, and impaired function.[1] Chondral defects can also have a significant impact on quality of life. Using validated surveys for patient-reported outcomes (PROs) of knee injuries, some patients with chondral defects have similar quality of life scores to those with severe osteoarthritis and reported pain and functional impairment similar to patients scheduled for knee replacement.[2]

ES 1.3 Technology Description

The 3 major categories of chondral repair procedures are bone marrow stimulation, osteochondral replacement, and cell-based restoration. Bone marrow stimulation techniques induce a healing response to generate new cartilage.[3] ***Microfracture (MF)*** involves using a small, sharp pick to create channels in the subchondral bone for mesenchymal stem cells from the bone marrow to migrate to the bone surface and create new cartilage. Osteochondral replacement procedures aim to replace a higher quality cartilage than MF. The procedures are conducted in a single surgery and transplant articular cartilage into the focal osteochondral defect.[3] The cartilage tissue is obtained from a non–weight-bearing portion of the patient's joint in ***osteochondral autologous transplantation (OATS)*** or from a cadaveric source for ***osteochondral allograft transplantation (OCA)***. Cell-based restoration procedures (***matrix-induced autologous chondrocyte implantation [MACI])*** can be performed for surface lesions and proceed in 2 surgical stages.[3] In the first stage, chondrocytes (cartilage cells) are harvested from lesser weight-bearing articular cartilage and then cultured outside of the body for 6 to 8 weeks on a porcine or synthetic scaffold. In the second stage, the scaffold with cultured chondrocytes is implanted back into the chondral defect. OATS, OCA, and MACI procedures generate a more durable hyaline cartilage than the fibrocartilage generated with microfracture, though these procedures demand higher technical skill and more resources.

ES 1.4 Regulatory Status

The surgical procedures microfracture, drilling, and OATS do not involve products or devices regulated by the U.S. Food and Drug Administration (FDA).[4] MACI is the only autologous product approved by FDA through the rigorous 351 Human Cells, Tissues, and Cellular and Tissues-Based Products pathway.[5] 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).[4,6,7] Additional materials used in cartilage repair surgeries, that have either been FDA approved, designated with FDA Breakthrough Device status, or are in Phase III trials, were included in this HTA.

ES 1.5 State of Washington Utilization Data

The State of Washington Health Care Authority will provide data related to chondral defect treatments in the State of Washington.

ES 1.6 Policy Context

The State of Washington Health Care Authority selected treatment of chondral defects of the knee for a HTA because of medium concerns of efficacy and high concerns for safety and cost.

ES 2. Methods

This section describes the methods we used to conduct this HTA.

ES 2.1 Research Questions and Analytic Framework

We developed the following research questions to guide this HTA (***Figure ES-1***):

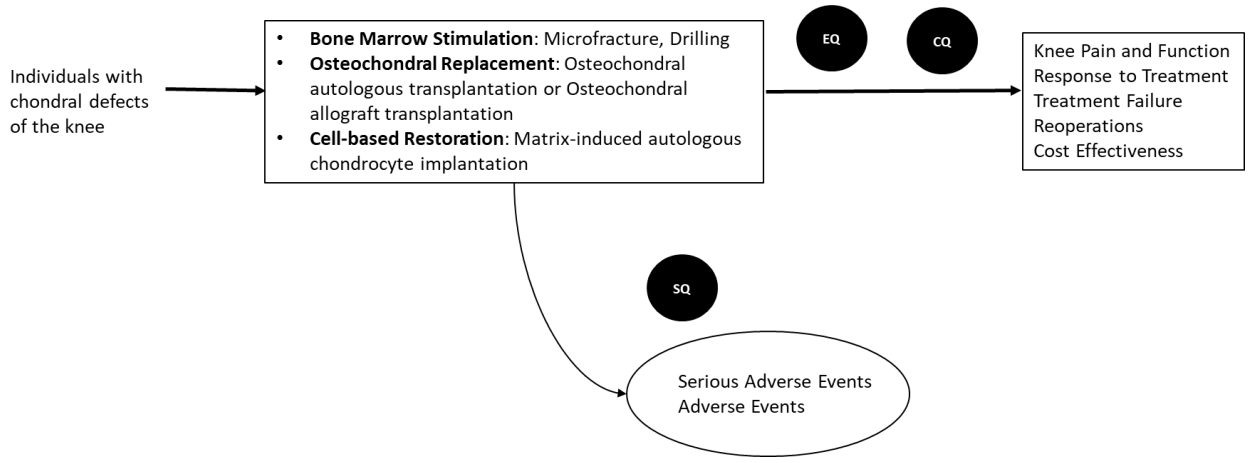
Efficacy Question (EQ). What is the efficacy of the following cartilage defect treatments for chondral defects of the knee?

- Bone marrow stimulation procedures: MF and drilling
- Osteochondral replacement: OATS and OCA
- Cell-based restoration: MACI

Safety Question (SQ). What are the harms associated with treatments for chondral defects of the knee listed above?

Cost Question (CQ). What is the cost-effectiveness of treatments for chondral defects of the knee listed above?

Figure ES-1. Analytic Framework Depicting Scope of this HTA for Treatments of Chondral Defects of the Knee



Abbreviations: CQ = cost question; EQ = efficacy question; HTA = health technology assessment; SQ = safety question.

The State of Washington HTA Program posted a draft of these research questions and proposed scope for public comment from December 22, 2023, and January 5, 2024. No public comments were received. The final key questions were published on the Program's website on January 5, 2024.[8] A draft of this report will undergo external peer review and be posted for public comment between June 29, 2024, and July 30, 2024.

ES 2.1.1 Data Sources and Search

We searched PubMed and the Cochrane Library for relevant studies published in English from inception to November 30, 2023. To ensure comprehensive identification of studies of relevant interventions, we used medical subject headings and keyword terms. The detailed search strategy is presented in ***Appendix B***. In addition, we reviewed the reference lists of relevant studies, systematic reviews, practice guidelines, and other HTAs on the topic to identify any relevant primary research studies not found through the electronic search.

ES 2.1.2 Study Selection

Two reviewers independently screened titles and abstracts and full-text articles based on the following study inclusion criteria. (Complete details are in ***Table 2*** of the Full Technical Report.)

- **Population:** Individuals with a defect of the articular cartilage of the knee only. Studies could include individuals of any age. We excluded studies that assessed treatment of chondral defects in a joint other than the knee. We also looked for subgroup analyses based on age, sex or gender, race or ethnicity, disability, or additional subgroups that the study may have reported.

- **Interventions:** We selected studies that evaluated one of the eligible chondral defect treatment surgeries for this HTA: bone marrow stimulation techniques, primarily MF (including drilling), OATS, OCA, or MACI. We also included studies of a procedure if it was FDA approved, had received FDA Breakthrough Device designation, or was in a phase 3 clinical trial.

- **Comparators:** For MF, comparators included nonsurgical interventions or conservative therapy, sham surgery, knee replacement, and chondroplasty. For OATS and OCA, MF was an additional eligible comparator. For MACI, OATS and OCA were additional eligible comparators.

- **Outcomes:** For the EQ, primary study outcomes of change in PROs of symptoms, function, or both. Return to work and sport, rehabilitation time, clinical response, treatment failure, reoperation, and avoidance of osteoarthritis were eligible. For the SQ, studies reporting serious adverse events (SAEs), adverse events (AEs), or side effects, including procedure-related complications, were included. For the CQ, we selected studies that reported on the cost-effectiveness of chondral defect repair surgery.

- **Study design**: For the EQ and SQ, we selected studies that used randomized controlled trials (RCTs), and nonrandomized studies of interventions (NRSIs) including controlled trials and observational cohort studies with a comparison group. For the CQ, we included cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis studies that were performed from the societal or payor perspective.

- **Setting**: Studies in any care setting conducted in countries with a development rating designated as *very high* by the United Nations Human Development Index. For cost studies, only studies conducted using U.S.-based cost inputs.

- **Other:** English-language only.

ES 2.1.3 What Is Excluded From This HTA

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.[9] Exclusion of ACI limits the review to procedures typically performed in contemporary clinical practice and allows the Health Technology Clinical Committee (HTCC) to make a coverage decision based on procedures that will not become obsolete in the near future. This review did not include studies published in languages other than English or conducted in countries that are not very highly developed based on the United Nations Human Development Index.[10]

ES 2.1.4 Data Abstraction and Risk-of-Bias Assessment

One team member extracted relevant study data into a structured abstraction form in DistillerSR, and a senior investigator checked those data for accuracy. Two team members conducted independent risk-of-bias assessments on all included studies. We used the Cochrane Risk of Bias (RoB 2.0) tool to assess the risk of bias for each included RCT level,[11] unless different outcomes within a single study required outcome-level risk-of-bias ratings. We used the Risk Of Bias In Nonrandomized Studies of Interventions (ROBINS-I) tool to assess risk of bias of nonrandomized studies of interventions.[12] We used the Quality of Health Economic Studies Instrument to assess the risk of bias of included cost analyses.[13]

ES 2.1.5 Data Synthesis and Quality-of-Evidence Assessment

We qualitatively synthesized study characteristics and results for each research question by clinical diagnosis category in tabular and narrative formats. To determine whether quantitative synthesis was appropriate, we assessed the number of studies and the clinical and methodological heterogeneity present based on established guidance.[14,15] We required a minimum of 3 studies to conduct meta-analyses. We also required at least 50% of studies for a condition with a similar intervention and comparator with the same outcome measured at approximately the same follow-up timepoint to calculate a pooled treatment effect for that comparison. For meta-analyses, we used random-effects models using the inverse variance method of DerSimonian and Laird to generate pooled mean differences for continuous outcomes[16] used to conduct all quantitative analyses.[17]

We graded the certainty of evidence (COE) for each procedure, category of outcomes, and study design type using the Grading of Recommendations Assessment, Development, and Evaluation approach.[18] COE can be graded as *very low*, *low*, *moderate*, or *high* and reflects our certainty in the findings.

ES 3. Results

ES 3.1 Literature Search and Overview of Measures Reported

We identified and screened 4,099 unique citations. We excluded 3,982 citations after title and abstract review. We reviewed the full text of 117 articles and included a total of 23 studies reported in 27 articles published between 2003 and 2023. Twenty-two studies were included for the EQ, 9 studies for the SQ, and 1 study for the CQ.

ES 3.2 MACI Compared to Chondroplasty

We identified 1 NRSI comparing the effectiveness of MACI to chondroplasty.[19] The study did not specify the specific type of MACI used. For the rehabilitation protocol, all patients underwent rehabilitative physiotherapy, which involved the early mobilization of the joint followed by progressive weight-bearing exercises. Key findings are reported below.

- One year post-surgery, the percentage of participants who reported resuming normal sport and work activities was 71% and 60% for MACI and chondroplasty, respectively. COE in results were very low for comparative effectiveness.

ES 3.3 MACI Compared to MF

We identified 5 studies comparing the effectiveness of MACI to MF, 3 of which were RCTs[20-22] and 2 were NRSIs.[23,24] Two of the studies used a porcine scaffold for MACI procedures,[20,22] 2 studies used an alternative scaffold,[21,23] and 1 study did not report the type used.[24] When the rehabilitation protocol was reported, it was the same for both MACI and MF groups and, in general, allowed return to usual activity at 6 months and return to high-impact sports at 12 months. Four studies reported follow-up duration of 18 to 26 months,[21-24] and 1 study evaluated outcomes up to 5 years of follow-up.[20] Key findings are reported below.

- Three RCTs reported statistically and clinically significant improvements in PROs, with greater effectiveness of MACI compared with MF (moderate COE for RCTs). Two studies reported greater response to MACI compared to MF (Moderate COE). The 1 NRSI reported similar results for PROs and response (very low COE).

- Few harms were reported across studies. In general, there were few or 0 events reported or similar numbers of AEs in both groups (COE low for comparable harms).

ES 3.4 MACI Compared to OATS

We identified 2 NRSIs comparing MACI to OATS.[19,25] Key findings are as follows:

- Limited evidence supports a lower effectiveness of MACI compared to OATS (COE very low).

ES 3.5 OCA Compared to OATS

We identified 2 NRSIs comparing the effectiveness of OCA to OATS.[26,27] One study conducted among patients age 21 or younger used data from the Pediatric Health Information System for patients undergoing OCA or OATS. Study follow-up ranged from 0.6 to 54.8 months.[26] The other used the PearlDiver Mariner database, which combines administrative data from private insurances and Medicare;[28] data from 2010 to 2018 were queried to identify individuals undergoing OCA or OATS.[27] Key findings are reported below.

- Studies reported no statistically significant differences between OCA and OATS groups (low COE for comparable effectiveness).

- No harms were reported for either study.

ES 3.6 OATS Compared to Chondroplasty

We identified 1 NRSI comparing the effectiveness of OATS to chondroplasty.[19] For the rehabilitation protocol, all patients underwent rehabilitative physiotherapy, which involved the early mobilization of the joint followed by progressive weight-bearing exercises. Key findings are reported below.

- One year post-surgery, the percentage of participants who reported resuming normal sport and work activities was 100% and 60% for OATS and chondroplasty, respectively (low COE for greater effectiveness of OATS).

ES 3.7 OATS Compared to Bone Marrow Stimulation Procedures

We identified a total of 7 studies examining the comparative effectiveness of OATS with bone marrow stimulation procedures, including 5 RCTs comparing OATS to MF[29-33] and 2 NRSIs comparing OATS to MF or drilling.[34,35] Rehabilitation protocols were the same for both groups across all studies, with goals of recommended return to pre-operative activity levels at 6 months[30,35,36] and return to sport at 6[32,33] to 12 months[30] postoperatively for studies that reported

this information. There was a wide range of mean follow-up durations: 1 study followed study participants for 2 years,[32] 4 studies from 3 to 10 years,[30,31,33,35], and 2 studies exceeding 10 years.[29,34] Key findings are as follows:

- Based on RCT and NRSI evidence, OATS and MF groups reported similar improvements in PROs (low COE for comparable effectiveness in RCT and NRSI study designs, respectively).
- One small RCT (N = 40) reported greater response to treatment for the OATS group compared to the MF group[29] (low COE).
- Treatment failure was similar for both groups for 3 RCTs (low COE) and favored OATS for fewer treatment failures in 1 NRSI (moderate/low COE).
- Harms were similar for each procedure, though there were 0 or few events (very low COE for comparable harms).
- The one study of cost-effectiveness reported mixed results on whether OATS or MF were more cost-effective[37] (low COE).

ES 3.8 Cell-free Implants Compared to MF/Chondroplasty

We identified 1 RCT comparing a cell-free aragonite implant (Agili-C) used to plug osteochondral lesions to a comparator group of MF or chondroplasty, described by the authors as surgical standard of care.[38] Key findings include:

- Greater improvement in PROs and in response to treatment in the cell-free implant group compared to MF/chondroplasty (moderate COE for greater effectiveness of cell-free implant).
- Any adverse events were lower in the cell-free implant group compared to MF/chondroplasty (moderate COE for fewer harms in the cell-free implant group).

ES 3.9 Autologous Matrix-Induced Chondrogenesis vs. MF

We identified 1 RCT comparing the effectiveness of autologous matrix-induced chondrogenesis (AMIC) to MF.[39] The study used sutured and glued AMIC procedures with Chondro-Gide, a collagen type I/III matrix. The rehabilitation protocol was the same for the sutured AMIC, glued AMIC, and MF groups and allowed full weight-bearing after 8 weeks, jogging after 6 months, and contact sports at 18 months. The study evaluated outcomes through 5 years of follow-up. Key findings are reported below.

- Cincinnati Knee Rating System improved at 1 year for AMIC and MF groups; at 5 years follow-up, improvements were sustained in the AMIC groups only while the MF group experienced a score degradation. AMIC had greater effectiveness for this outcome at both timepoints (low for greater effectiveness of AMIC).

- 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).

ES 3.10 First-line Procedures vs. Second-line Procedures (MACI and OCA)

We identified 4 studies comparing a first-line surgery with the same procedure performed as a second-line surgery after an earlier failed chondral restoration procedure. One NRSI compared first-line MACI to second-line MACI,[40] and 3 NRSIs compared first-line OCA to second-line OCA, both second-line procedures performed after failed bone marrow stimulation.[41-43] Rehabilitation protocols for OCA allowed for return to sports within 6 to 8 months postoperatively, whereas those undergoing MACI were allowed to return to high-impact sports 12 months after surgery. The follow-up time for the MACI study was 6 to 36 months; follow-up duration for the OCA studies ranged from 3 to 11 years. Key findings are reported below.

- There were more treatment failures and reoperations for second-line MACI and OCA procedures compared to first-line MACI and OCA procedures (COE very low for greater effectiveness of first-line procedures).

- First-line MACI procedures reported greater improvement in PROs compared to MF (COE very low for first-line MACI); PRO results for first-line and second-line OCA were similar (COE very low for comparable effectiveness).

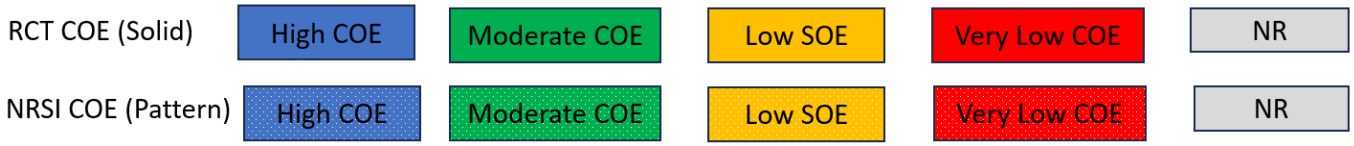
ES 4. Discussion

ES 4.1 Summary of the Evidence

A summary of the COE ratings for comparisons with the largest bodies of evidence are provided in ***Figure ES-2***; detailed visual representation of COE ratings for all comparison are provided ***Appendix F***.

Figure ES-2. Summary of COE Ratings for Selected Comparisons of Chondral Defect Procedures of the Knee Included in This HTA

Comparison[a]	*MACI vs MF*	*OATS vs MF*	*1st Line vs 2nd Line[c]*
PROs	***MACI***	***Comparable***	
	MACI	***Comparable***	***1st line***
Responder	***MACI***	***OATS***	
	MACI		
Re-operation	***Comparable***	***Comparable***	
	MACI		***1st line***
Treatment Failure	***Comparable***	***Comparable***	
	Comparable	***OATS***	***1st line***
Harms[b]	***Comparable***	***Comparable***	
	Comparable		



Notes: Solid-colored cells indicate RCT study design. Speckled cells indicate NRSI study design. Gray cells indicates no evidence. Text inside cells indicates whether one of procedures has greater effectiveness or the procedures are of comparable effectiveness.
[a] Comparisons with a minimum of three studies were highlighted in this table. See ***Appendix F*** for figure of all comparisons.
[b] Includes harms for both AEs and SAEs. Color represents the highest COE of the two outcomes.
[c] Includes both MACI and OCA.

Abbreviations: AE = adverse events; COE = certainty of evidence; MACI = matrix-induced autologous chondrocyte implantation; MF = microfracture; NRSI = nonrandomized studies of interventions; OATS = osteochondral autologous transplantation; PROs = patient-reported outcomes; RCT = randomized controlled trial; SAE = serious adverse events.

We identified the largest bodies of evidence for comparisons of MACI vs. MF and OATS vs. MF. MF is often considered first-line therapy due to being less technically difficult, limited morbidity, and low cost,[38,44] and is a clinically relevant comparator for the more involved procedures of MACI and OATS. For the MACI and MF comparison, we found moderate COE among RCTs for greater effectiveness of MACI compared to MF for PROs and response to treatment. NRSIs reported similar results, though with very low COE primarily driven by high risk of bias and small study samples resulting in imprecision. Both RCTs and NRSIs reported

comparable effectiveness of MACI and MF for treatment failure, reoperations, and harms. Outcomes from OATS and MF comparisons were similar for most outcomes with low to very low COE, with the exception of greater effectiveness of OATS for the outcome of response to treatment and reoperations (low COE). One NRSI also reported less treatment failure in the OATS group (low COE). The reasons for low COE were generally related to high risk of bias.

The 2011 State of Washington Health Care Authority HTA on OCA and OATS[45] determined evidence to be insufficient for the comparison of OATS to MF based on 2 studies that were also included in this present HTA, both of which were included in this review.[32,33] Studies in the last HTA that were excluded in this HTA related to a different scope to the prior review. The prior HTA had a key question related to validation of measures used to assess results of studies and included single arm studies and 1st and 2nd generation ACI. The scope of this HTA was limited to the knee, comparative studies, and 3rd generation ACI (MACI) Limiting the scope to comparative studies raises the robustness of our review. The three comparative studies of ACI and OATS included in the last HTA showed comparable effectiveness of ACI and OATS or greater effectiveness of OATS. Limiting our scope to the more modern MACI procedure, gives us a clearer picture of the comparative effectiveness of cell-based restoration to MF.

MF is the most common procedure performed to repair articular cartilage defects in clinical practice and is often used as a "standard of care" comparator for more technically involved procedures in comparative effectiveness research.[38] However, MF may not be appropriate for some lesions, based on size, depth, or location. Comparative effectiveness studies are not always based on lesion-specific characteristics (e.g., eligibility criteria allowing a wide range of lesion sizes) which does not represent clinical care. Our results should be interpreted in light of the different contexts of clinical care versus clinical studies. In many cases, surgeons will pick a procedure based on lesion-specific characteristics which may obviate consideration of another procedure.

Chondroplasty can be an option for patients with symptoms from chondral defects. In our HTA, we found only 1 small study (N = 47) reporting 1 outcome comparing MACI or OATS to chondroplasty, limiting our ability to make a judgment about the comparative effectiveness of these procedures compared to chondroplasty. This may reflect the practice community's assessment of chondroplasty as an inferior option, as it is not a reparative technique.

Given that cartilage repair, replacement, or restoration is often a procedure for younger, active patients for whom arthroplasty is not the optimal choice, when a cartilage defect repair surgery fails to improve a patient's symptoms or function, a surgeon and patient may consider a second-line cartilage procedure. Among the studies comparing MACI to MF and OATS to MF, many studies reported few reoperations, limiting precision resulting in low COE for reoperation outcomes. A few NRSIs reported lower reoperations or treatment failure in the MACI group or OATS group compared with MF.[23,24,34] Studies comparing first-line MACI or OCA to second-line MACI or OATS observed greater or comparable effectiveness of a first-line MACI or OCA procedure, reduced treatment failure for first-line MACI or OCA procedures, and similar harms whether the MACI or OCA was performed as first or second line surgery as compared to first-line bone marrow stimulation procedures.[40,43] This may signal that a second procedure may have

still have significant benefits after a failed first procedure without additional harms. Additionally, first-line treatment with MACI compared to the more standard treatment of MF, may result in a reduced need to reoperate and could be considered as first-line treatment despite higher upfront costs.[46] One postulated mechanism is that though MF is generally used to treat surface lesions, the procedure may affect the underlying bone, making MACI less successful.[46]

MF is the most commonly performed cartilage repair procedure, with lower cost being one consideration.[47-49] We only identified 1 study evaluating the cost-effectiveness of OATS compared to MF.[37] The results from this decision-analysis were mixed based on cost per point improvement on validated knee function and pain scores without a clear indication of which procedure is more cost-effective. However, based on return to play outcome, OATS appears to be more cost-effective at 1, 3 and 10 years of follow-up. This appears to be driven by higher failure rates for MF over time, which offsets the higher initial cost of OATS. However, this study is limited since costs were derived from a single institution. Further research on cost-effectiveness of all cartilage defect treatment surgeries would provide more data for policy makers to consider in coverage decisions.

The other comparisons identified in this HTA included MACI vs. OATS, OCA vs. OATS, and AMIC vs. MF. For all of these comparisons, we identified a few NRSIs reporting few outcomes that we rated as low to very low COE. This limited amount of evidence may be related to the differential use of these procedures for different sized lesions and subchondral bone involvement (***Table 1***). For example, OCA is usually selected over OATS for patients with larger lesions and so studies directly comparing these procedures are less likely be conducted. We identified few studies evaluating OCA due to the size and depth of lesions treated and that the most appropriate comparator to OCA may be arthroplasty. Surgeons and patients may be trying to avoid arthroplasty due to young age and activity level and, clinically, the same surgeon may not have expertise in both articular cartilage repair and arthroplasty. OCA also requires a size and location matched donor and cadaveric tissue is only viable for a short amount of time, limiting the feasibility of this procedure, particularly in a study context.

We identified 1 RCT comparing a cell-free implant, analogous to OCA, to MF or chondroplasty, in which patients receiving the cell-free implant had greater increases in PROs and higher response to therapy (moderate COE) and treatment failure and harms with comparable effectiveness (low COE). These results suggest that AEs in surgical products and techniques may yield superior results to repair procedures commonly performed in current clinical practice.

A limited number of studies reported harms and when they were reported, the COE was low or very low due to few events and high risk of bias in the evidence base. More robust and systematic ascertainment of harms in future studies would facilitate pooling across studies and would likely increase the COE ratings that could be assigned to harm outcomes.

The inclusion and exclusion criteria of this systematic review varied significantly from prior reviews and the 2011 HTA on OATS.[45] Foremost, we excluded first- and second-generation ACI procedures, which use a periosteal patch rather than a porcine or synthetic scaffold on which to culture chondrocytes (MACI). MACI has fewer complications[9] and has largely replaced ACI in

practice. We also excluded studies without a comparator group to limit the review to higher quality evidence for drawing causal inferences. We excluded intermediate outcomes, including imaging and pathologic findings, opting to focus on PROs and other outcomes more relevant to patients and policy makers.

ES 4.2 Limitations of the Evidence Base

This HTA included many RCTs and NRSIs with high risk of bias due to lack of transparency about the randomization process, limited adjustments for confounders, and not reporting missing data and if analyses to limit bias from missing data were performed. Many of the included studies had extended follow-up times, which are often associated with significant attrition, and many studies did not report the number of patients with follow-up data available at various timepoints. Studies with small sample sizes also resulted in imprecise effect estimates. Studies with more robust methodology are needed to increase the certainty of the evidence. Reducing the high risk of bias in NRSIs includes thorough consideration of confounding factors, reporting of missing data, and use of statistical methods to limit bias.

ES 4.3 Clinical Practice Guidelines

We identified only 3 organizations with treatment guidelines for chondral defect treatments of the knee, 1 of which was related to rehabilitation after articular cartilage surgery.[50] United Kingdom guidelines[51] and the American Society of Pain and Neuroscience guidelines[52] made conflicting recommendations about mosaicplasty, which is similar to OATS though used from larger lesions, for which other procedures may be preferred in current clinical practice.

ES 4.4 Payer Coverage

No Medicare national coverage determination or local coverage determinations for chondral defect treatment procedures were identified. We also conducted a scan of commercial payer coverage documents for chondral defect treatments (***Table 28***). Four payers had coverage policies for ACI or MACI, 3 payers had policies for OATS or OCA, and 1 payer had a policy for MF or drilling. The clinical criteria for coverage varied across the payers and procedures (***Table 29***). All policies required individuals with closed growth plates; some had specific requirements for full-thickness focal lesions and lesion size dependent on procedures (e.g., lesions < 4 cm^2 for MF). Other requirements also included failed conservative therapy, age too young to be considered for a total knee replacement (e.g., age < 55 years), and BMI less than 35.

ES 4.5 Limitations of This HTA

This HTA was limited to peer-reviewed studies published in English. We did not include data or results presented solely in conference abstracts. We only included validated measures for disease specific PROs; we did not include general QOL outcomes. We did not include first- or second-generation ACI procedures given fewer complications of third-generation MACI and limiting this review to procedures in current practice. We included only comparative study designs, which raises the quality of effectiveness results but may not offer a comprehensive assessment of longer-term benefits and harms. Studies conducted in countries other than *very high* on the United Nations Human Development Index were also excluded from this review. Finally, we

only included cost studies based on U.S. dollar inputs as this offers the most applicable results for HTCC decision making.

ES 4.6 Ongoing and Future Research

We identified 2 ongoing trials that were relevant to the comparisons in this review. One trial focuses on MACI compared to MF in individuals ages 10 to 17 years, is funded by industry, and is expected to be completed in 2027. The other trial compares MACI to MF in adult patients and it also expected to be completed in 2027.

ES 5. Conclusion

This HTA examined the comparative effectiveness, safety, and cost-effectiveness of treatments for chondral defects of the knee. MACI has low to moderate evidence for greater effectiveness compared to microfracture for PROs and response to treatment among RCTs, the highest level of COE identified in this HTA. OATS and MF were comparable for outcomes indicating similar benefit of these procedures. Both MACI and OATS had comparable harms to MF, though the COE was low. The rest of the evidence base was limited with respect to the other comparisons examined. Rigorous study design, consistent reporting of outcomes, particularly harms, would strengthen the evidence base for comparative effectiveness of these procedures.

Full Technical Report

1. Background

Chondral defects refer to damage of the surface cartilage lining the bones where they connect with other bones in synovial joints (i.e., the articular cartilage). Chondral defects can cause pain and reduced function. Articular cartilage has a limited ability to regenerate and over time is associated with scarring, progressive cartilage degeneration, and increased risk for osteoarthritis. Chondral defect treatments aim to repair, restore, or replace damaged tissue with healthier cartilage.

This health technology assessment (HTA) reviews the efficacy, safety, and cost-effectiveness of selected chondral defect restoration procedures of the knee, including microfracture, drilling, osteochondral autologous transplantation (OATS), osteochondral allograft transplantation (OCA), and matrix-induced autologous chondrocyte implantation (MACI).

1.1 Natural History

Articular cartilage lines the surface of bones that meet at a joint (***Figure 1***). Smooth and lubricated, articular cartilage reduces friction as the bones glide against each other in motion.[3] Histologically, more than 90% of articular cartilage is composed of hyaline cartilage, a type 2 collagen.[53] Cartilage is poorly vascularized and innervated and, if damaged, has limited ability to repair and regenerate new cartilage.[54] As a result, damaged articular cartilage is replaced with fibrocartilage composed primarily of type 1 collagen, which is stiffer and more prone to wear.[55] Progressive cartilage degeneration is associated with risk of osteoarthritis.[44,56,57]

Figure 1. Knee Anatomy

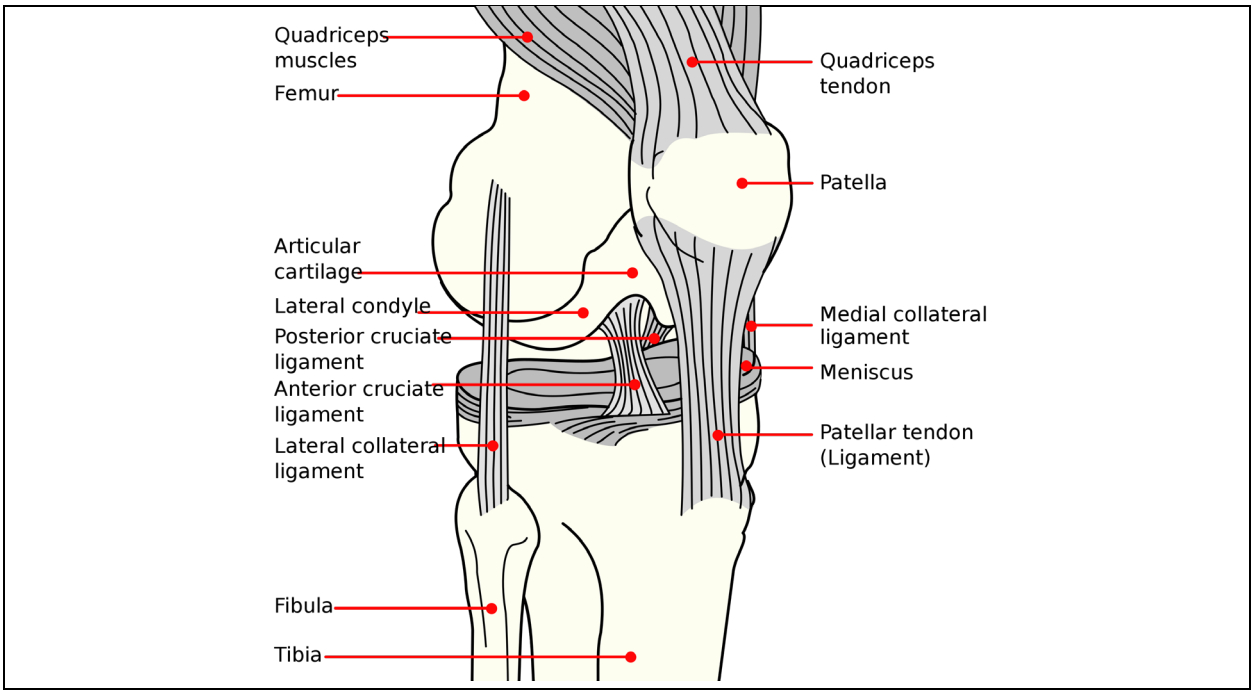


Image by Mikael Haggstrom, MD. Public domain (CC0 1.0) under CC0.

1.2 Epidemiology

The true incidence of chondral defects is unknown, though damage to the articular cartilage is commonly found in magnetic resonance imaging of asymptomatic individuals or incidentally during arthroscopy or surgery for other indications.[44] In a cross-sectional study, the incidence of chondral defect procedures was approximately 4 procedures per 1,000 patients over 10 years in a commercial claims database.[58] Prospective and retrospective cohort studies estimate chondral defects in 60% to 66% of knee arthroscopies.[59,60] Chondral defects can present acutely in the setting of trauma or have an insidious onset due to overuse and microtrauma; younger populations are more likely to present with acute trauma.[61] Other etiologies include anatomical abnormalities such as malalignment, developmental defects such as osteochondritis dissecans, or acquired metabolic factors such as avascular necrosis.[61]

1.3 Burden of Chondral Defects

Individuals with chondral defects can experience symptoms of pain, catching or locking of the joint, swelling, and impaired function.[1] Chondral defects can also have a significant impact on quality of life. Using validated surveys for patient-reported outcomes (PROs) of knee injuries, some patients with chondral defects have similar quality of life scores to those with severe osteoarthritis and reported pain and functional impairment similar to patients scheduled for knee replacement.[2]

1.4 Technology Description

Conservative management of chondral defects includes physical therapy, weight loss, anti-inflammatory medications, and joint injections. A historically routine, simple surgical intervention for focal articular cartilage defects is chondroplasty, or debridement of the damaged tissue. The primary purpose of chondroplasty is to decrease mechanical symptoms related to damaged cartilage flaps, although this treatment does not repair or replace the damaged cartilage.[48]

Patient factors that guide clinical consideration of these procedures are age, activity level, comorbidities such as osteoarthritis, limb alignment, and concurrent ligament injury. Lesion characteristics include the size, depth (surface vs. subchondral), and location of the chondral defect of the knee.[62] ***Table 1*** outlines approximate size indications for each procedure and depth of the lesion, specifically whether the defect extends to subchondral bone, or the bony layer beneath the hyaline cartilage. These procedures are alternatives to total or partial knee replacement (arthroplasty) in patients who are younger and more active than typical candidates for knee replacement. They are often considered as salvage procedures to avoid or delay knee replacement.

Table 1. Indications for Chondral Defect Repair Procedures by Size and Subchondral Involvement[63]

Procedure	Size of defect	Subchondral involvement
Chondroplasty	< 2 cm^2	No
Microfracture/drilling	< 4 cm^2	No
Osteochondral autologous transplantation (OATS)	2 cm^2 to 4 cm^2	Yes
Osteochondral allograft transplantation (OCA)	> 4 cm^2	Yes
Matrix-induced autologous chondrocyte implantation (MACI)	> 4 cm^2	Minimal

The 3 major categories of chondral restoration procedures are bone marrow stimulation, osteochondral restoration, and cell-based restoration.

Bone marrow stimulation techniques induce a healing response to generate new cartilage.[3] ***Microfracture (MF)*** involves using a small, sharp pick to create channels in the subchondral bone for mesenchymal stem cells from the bone marrow to migrate to the bone surface and create new cartilage. ***Drilling*** is a similar procedure that uses a surgical drill to create the holes. The bone marrow stimulation techniques typically generate fibrocartilage, which is not as durable as hyaline cartilage, and are generally used for patients with small (< 4 cm^2), single defects. MF is the most commonly performed chondral restoration process in the United States,[64] due to its wide availability, minimal invasiveness, simpler surgical technique, and lower costs.[47-49] MF is often considered the standard of care comparator for other chondral defect repair procedures.[38,65] Autologous matrix-induced chondrogenesis (AMIC) combines MF with a collagen membrane to stabilize the clot and enhance repair.[44]

Osteochondral replacement procedures aim to replace a higher quality cartilage than MF. The procedures are conducted in a single surgery and transplant articular cartilage into the focal chondral defect.[3] The cartilage tissue is obtained from a non–weight-bearing portion of the patient's joint in ***osteochondral autologous transplantation (OATS)*** or from a cadaveric source for ***osteochondral allograft transplantation (OCA)***. In an OATS procedure, cylindrical osteochondral plugs from non–weight-bearing portions of the knee are harvested and then inserted into the chondral defect. OATS procedures are used for smaller lesions due to limitations in the amount of tissue that can be harvested. (***Mosaicplasty*** is similar to OATS but is employed for larger lesions using multiple osteochondral plugs.) In contrast, OCA procedures use cartilage tissue from a cadaver donor and can accommodate larger defects; they run the risk of graft-host reactions or failure to incorporate. Osteochondral replacement procedures transfer hyaline cartilage with a greater proportion of type 2 cartilage, which is more durable than the fibrocartilage generated in bone marrow stimulation techniques.[47]

Cell-based restoration procedures can be performed for surface lesions and proceed in 2 surgical stages.[3] In the first stage, chondrocytes (cartilage cells) are harvested from lesser weight-bearing articular cartilage and then cultured outside of the body for 6 to 8 weeks. In the second stage, the cultured chondrocytes are implanted back into the chondral defect. The first-generation cell-based restoration procedure was known as ***autologous chondrocyte implantation (ACI)***, in which the surgeon implanted liquid culture cells into the defect and covered it with a periosteal patch.[3,66] Second-generation ACI implemented a collagen membrane over a periosteal patch. Most recently, ACI has evolved into ***matrix-induced autologous chondrocyte implantation (MACI)***, which uses a porcine or synthetic scaffold to transplant cultured chondrocytes, reducing complications from ACI such as periosteal patch hypertrophy.[9,67] Similar to OATS and OCA, MACI procedures generate a more durable hyaline cartilage than the fibrocartilage generated with MF, though MACI procedures demand higher technical skill and more resources.

1.5 Regulatory Status

Some products used in cartilage repair procedures are regulated by the U.S. Food and Drug Administration (FDA) Center for Biologics and Evaluation and Regulation (CBER) and are categorized as Human Cells, Tissues, and Cellular and Tissues-Based Products (HCT/P). The 2 regulation pathways for HCT/P products are the 351 HCT/P pathway requiring rigorous evidence of efficacy and safety and the 361 HCT/P pathway requiring donor screening and infectious disease testing only.[4] The surgical procedures microfracture, drilling, and OATS do not involve products or devices regulated by FDA.[4] MACI is the only autologous product approved by FDA CBER through the 351 HCT/P pathway (***Table 2***).[5] A previously FDA CBER–approved product for ACI (Carticel) was removed from the market in 2017. A product used in OCA is approved through the 361 HCT/P pathway (DeNovo NT),[4,6] as well as the collagen membrane (Agili-C) used for AMIC.[7] Additional materials used in cartilage repair surgeries that have either been FDA approved, designated with FDA Breakthrough Device status, or are in phase 3 trials that have been identified for this review, as shown in ***Table 2***.

Table 2. FDA Status of Biologic Materials for Chondral Defect Repair

Manufacturer	Product(s)	Restoration Procedure and Description	FDA Pathway	Year
CartiHeal	Agili-C[68]	OCA with cell-free implant: Cell-free implant composed of inorganic calcium carbonate (aragonite).	361 HCT/P	2022
Geistlich	Chondro-gide[7]	AMIC: Type I/III resorbable collagen membrane used to cover lesions that have undergone microfracture and promote cell differentiation and new cartilage.	Breakthrough Device status	2021
Ocugen	NeoCart	MACI: Collagen scaffold on which chondrocytes are cultured and implanted into the defect in a separate surgery.	Phase 3 clinical trial	NA
Vericel Corporation	MACI® (Autologous Cultured Chondrocytes on a Porcine Collagen Membrane)	MACI: Indicated for the repair of single or multiple symptomatic, full-thickness cartilage defects; it is a scaffold product to culture chondrocytes.	351 HCT/P	2016
Zimmer Biomet	DeNovo NT	OCA: Tissue from cadaver donor procured from licensed tissue banks. Embedded in fibrin glue at the time of implantation into a chondral defect.	361 HCT/P	2007

Abbreviations: AMIC = Autologous matrix-induced chondrogenesis; FDA = U.S. Food and Drug Administration; HCT/P = Human Cells, Tissues, and Cellular and Tissues-Based Products; MACI = matrix-induced autologous chondrocyte implantation; NT = natural tissue; OATS = osteochondral autologous transplantation; OCA = osteochondral allograft transplantation.

1.5 Policy Context

The State of Washington Health Care Authority selected treatment of chondral defects of the knee for a HTA because of medium concerns of efficacy and high concerns for safety and cost.

1.6 Washington State Agency Utilization Data

The State of Washington Health Care Authority will provide data related to chondral defect treatments in the State of Washington. This data will be provided in ***Appendix A***. The data provided includes utilization and costs for Medicaid (fee for service and managed care organization), the Department of Labor and Industries Workers' Compensation Program, and the Public Employee Benefit Board Uniform Medical Plan. In 2011, the Health Technology Clinical Committee (HTCC) approved coverage of OATS/OCA with conditions.

2. Methods

This section describes the methods we used to conduct this HTA. The present HTA is related to a 2011 HTA on OATS and OCA conducted for the State of Washington Health Care Authority.[69] However, the scope of the present HTA has been updated to reflect contemporary procedures and comparators and to limit the scope to knee joints.

2.1 Research Questions and Analytic Framework

We developed the following research questions and analytic framework (***Figure 2***) to guide the systematic evidence review of primary research studies:

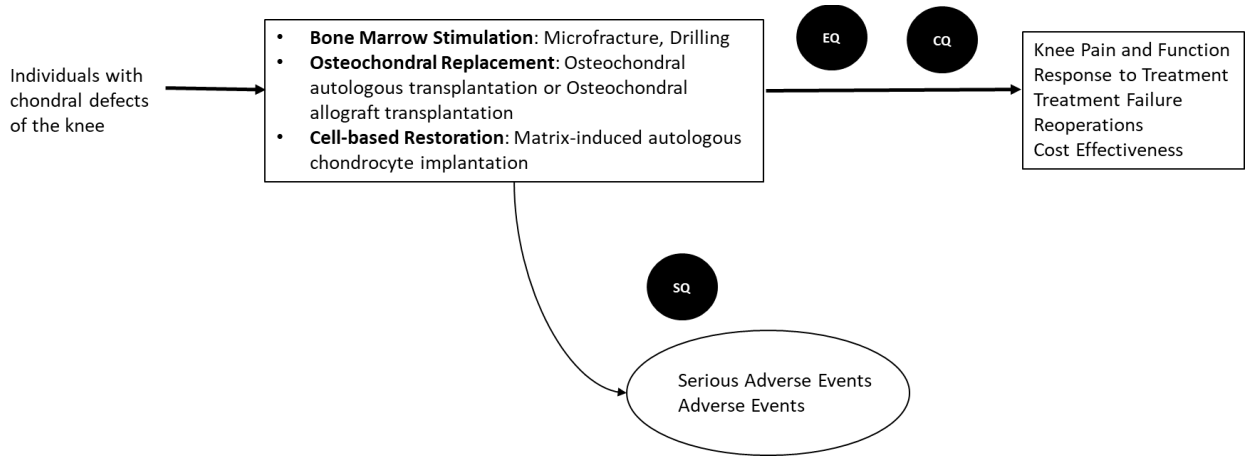
Efficacy Question 1 (EQ). What is the efficacy of the following cartilage restoration treatments for chondral defects of the knee?

- Bone marrow stimulation procedures: microfracture and drilling
- Osteochondral replacement: OATS and OCA
- Cell-based restoration: MACI

Safety Question 1 (SQ). What are the harms associated with treatments for chondral defects of the knee listed above?

Cost Question 1 (CQ). What is the cost-effectiveness of treatments for chondral defects of the knee listed above?

Figure 2. Analytic Framework Depicting Scope of this HTA for Treatments of Chondral Defects of the Knee



Abbreviations: CQ = cost question; EQ = efficacy question; HTA = health technology assessment; SQ = safety question.

The State of Washington HTA Program posted a draft of these research questions and proposed scope for public comment from December 22, 2023, and January 5, 2024. No public comments were received. The final key questions were published on the Program's website on January 5, 2024.[8] A draft of this report will undergo external peer review and be posted for public comment between June 29, 2024, and July 30, 2024.

2.2 Data Sources and Searches

We searched PubMed and the Cochrane Library for relevant studies published in English from inception to November 30, 2023. To ensure comprehensive identification of studies of relevant interventions, we used medical subject headings and keyword terms. The detailed search strategy is presented in ***Appendix B***. In addition, we reviewed the reference lists of relevant studies, systematic reviews, practice guidelines, and other HTAs on the topic to identify any relevant primary research studies not found through the electronic search.

2.3 Study Selection

Table 3 summarizes the study selection criteria related to the population, intervention, comparator, outcomes, timing, study design, and setting that defined the scope of this HTA, which are further described in the sections following the table. Two review team members independently screened titles, abstracts, and full-text articles based on these study selection criteria using DistillerSR version 2.35 (DistillerSR, Inc.). Discrepancies in study selection at the full-text level were adjudicated by a senior investigator or, in some cases, by consensus among the team.

Table 3. Population, Intervention, Comparator, Outcome, Timing, and Setting (PICOTS) for HTA on Treatment of Chondral Defects of the Knee

PICOTS	Include	Exclude
Population	• Individuals with damage to the articular cartilage of the knee—specifically of the femur, tibia, or patella surfaces • Any age (includes those with open or closed growth plates)	• Individuals with an articular cartilage defect in a joint other than the knee • Studies conducted in animals, in vitro, or in silico
Intervention	• Bone marrow stimulation procedures, specifically microfracture or drilling • Osteochondral autologous transplantation (OATS) • Osteochondral allograft transplantation (OCA) • Matrix-induced autologous chondrocyte implantation (MACI) • Procedures using materials that are FDA approved, have FDA Breakthrough Device designation, or are in Phase 3 clinical trials that fall under the categories above, including AMIC	• Autologous chondrocyte implantation (ACI) • Experimental treatments or other procedures not listed as included interventions • Procedures in which chondral defect repair is performed after a failed first-line (e.g., initial failed bone marrow stimulation procedure; MACI performed after failed first procedure)
Comparator	For microfracture or drilling: • Chondroplasty • Knee replacement (total or partial) • Sham surgery • Non-surgical interventions or conservative therapy (e.g., physical therapy, injections, oral analgesics) • Procedures using materials that are FDA approved, have FDA Breakthrough Device designation, or are in Phase 3 clinical trials that fall under the categories above, including AMIC For OATS, OCA: • Microfracture or drilling • MACI • Chondroplasty • Knee replacement (total or partial) • Sham surgery • Non-surgical interventions or conservative therapy (e.g., physical therapy, injections, oral analgesics) • Procedures using materials that are FDA approved, have FDA Breakthrough Device designation, or are in Phase 3 clinical trials that fall under the categories above, including AMIC	• Head-to-head comparisons of the same procedure with different techniques (e.g., MACI with scaffold A vs. MACI with scaffold B, OCA with cadaveric tissue vs. synthetic tissue) with the exceptions* • Waitlist control • No comparator **We included studies comparing first-line procedure with second-line procedure (e.g., first-line OCA vs. second-line OCA after failed microfracture) to inform the committee of benefits and harms of repeat cartilage repair procedures.*

PICOTS	Include	Exclude
	For MACI: • Microfracture or drilling • OATS • OCA • Chondroplasty • Knee replacement (total or partial) • Sham surgery • Non-surgical interventions or conservative therapy (e.g., physical therapy, injections, oral analgesics) • Procedures using materials that are FDA approved, have FDA Breakthrough Device designation, or are in Phase 3 clinical trials that fall under the categories above, including AMIC	
Outcomes	EQ: • Validated measures of knee symptoms and function • Activity levels: - Time to return to work - Time to return to sport - Rehabilitation time • Health-related quality of life • Response to treatment • Treatment failure • Reoperation • Avoidance of osteoarthritis and knee replacement SQ: • Serious adverse events (e.g., death, disability,) • Adverse events (e.g., infection, bleeding, nerve damage, tendonitis, joint swelling, or effusion) • CQ: (U.S.-based cost inputs only) • Cost-effectiveness • Cost-utility	• Intermediate outcomes (e.g., imaging outcomes, pathology findings) • Non-validated measurement tool • Non-U.S. cost inputs
Timing & Language	• No timing restrictions • English-language full-text articles	• No timing exclusions • Non–English language full-text articles
Study Design	• EQ: RCTs, NRSIs • SQ: RCTs, NRSIs • CQ: CEA, CUA, or CBA performed from the societal or payer perspective	• Editorial, commentaries, narrative reviews, or letters; conference abstracts; case reports or case series; case-control studies; other observational study designs without a comparator group • Relevant systematic reviews will be excluded but will be hand searched to identify potentially eligible primary studies
Setting	• Countries categorized as "very high human development" on the United Nations Development Programme's 2021 Human Development Index Report[10][a]	• Countries not categorized as "very high human development" according to the United Nations Development Programme's 2021 Human Development Index Report[a]

Notes: [a] Andorra, Argentina, Australia, Austria, Bahamas, Bahrain, Barbados, Belarus, Belgium, Brunei Darussalam, Bulgaria, Canada, Chile, Costa Rica, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hong Kong China (SAR), Hungary, Iceland, Ireland, Israel, Italy, Japan, Kazakhstan, Korea (Republic of), Kuwait, Latvia, Liechtenstein, Lithuania, Luxembourg, Malaysia, Malta, Mauritius, Montenegro, Netherlands, New Zealand, Norway, Oman, Palau, Panama, Poland, Portugal, Qatar, Romania, Russian Federation, Saudi Arabia, Serbia, Singapore, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, United Arab Emirates, United Kingdom, United States, Uruguay.

Abbreviations: ACI = autologous chondrocyte implantation; ACL = anterior cruciate ligament; AMIC = Autologous matrix-induced chondrogenesis; CBA = cost-benefit analysis; CEA = cost-effectiveness analysis; CQ = cost question; CUA = cost-utility analysis; EQ = efficacy question; FDA = Food and Drug Administration; MACI = matrix-induced autologous chondrocyte implantation; NRSI = nonrandomized studies of interventions; RCT = randomized controlled trial; SQ = safety question.

2.3.1 Population

We selected studies with individuals with a defect of the articular cartilage of the knee only. Studies could include individuals of any age. We excluded studies that assessed treatment of chondral defects in a joint other than the knee. We also looked for subgroup analyses based on age, sex or gender, race or ethnicity, disability, or additional subgroups that the study may have reported.

2.3.2 Intervention and Comparator

We selected studies that evaluated one of the eligible chondral defect repair surgeries for this HTA: bone marrow stimulation techniques, primarily microfracture (including drilling), OATS, OCA, or MACI. We also included studies of a procedure if it was FDA approved, had received FDA Breakthrough Device designation, or was in a phase 3 clinical trial. Studies with multiple intervention arms were included if an eligible control group was also included; only data from the comparisons between eligible intervention groups and eligible control groups were included in this HTA.

Comparators for microfracture included non-surgical interventions or conservative therapy, sham surgery, knee replacement, and chondroplasty. For OATS and OCA, microfracture was an additional eligible comparator. For MACI, OATS and OCA were additional eligible comparators. We excluded head-to-head comparisons of the same procedures with different techniques. However, we allowed comparisons between patients receiving a chondral restoration procedure for the first time (first-line procedure) to patients receiving the same procedure after a failed alternative procedure (second-line procedure), for example, OATS vs. OATS after failed microfracture, to inform the HTCC's decisions about coverage for repeat restoration procedures. Another exception was comparing 1 AMIC product with MF, as this AMIC product has Breakthrough Device status from FDA.

2.3.3 Outcomes

For the EQ, we selected studies with primary study outcomes of change in PROs of symptoms, function, or both. Only validated measures were included. Return to work and sport and rehabilitation time were eligible outcomes, as well as clinical response and treatment failure (e.g., generally based on a specified threshold for change in score on validated symptom scales), reoperation, and avoidance of osteoarthritis. We did not include studies that only reported a non-validated measure or intermediate outcomes (e.g., imaging results, appearance at arthroscopy, or pathologic specimens).

For the SQ, we selected studies that reported serious adverse events (SAEs), adverse events (AEs), or side effects including procedure-related complications. We did not require studies to report these types of outcomes based on any prespecified taxonomy or definitions.

For the CQ, we selected studies that reported on the cost-effectiveness of chondral defect repair surgery.

2.3.4 Settings

Studies in any care setting were eligible. For the EQ and SQ, we selected studies that were conducted in countries with a development rating designated as *very high* on the United Nations Human Development Index in August 2022 for selection because these countries (e.g., Canada, European countries, Australia, New Zealand, Japan, South Korea, Singapore, Hong Kong, and others) are like the United States with respect to standards of medical practice.[10] We excluded studies conducted in countries with a development rating designated as less than very high. For cost studies, we selected only studies conducted using U.S.-based cost inputs.

2.3.5 Study Design

For the EQ and SQ, we selected studies that used randomized controlled trials (RCTs), and nonrandomized studies of interventions (NRSIs) including controlled trials and observational cohort studies with a comparison group.

For both the EQ and SQ, we excluded case series, case reports, or other observational study designs without a comparison group; editorials; comments; letters to editor without original comparative data; conference abstracts; and narrative reviews. We did not include systematic reviews but did search their reference lists to identify relevant primary studies that our electronic database search may have missed.

For the CQ, we included cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis studies that were performed from the societal or payor perspective.

2.3.6 Time Period

We selected studies regardless of date of publication or years when the study was conducted.

2.3.7 What is Excluded From This HTA

This review did not include first- and second-generation ACI because this procedure has been superseded by the third-generation procedure MACI, which has fewer complications than first- and second-generation procedures and is less more to be used in current and future clinical practice.[9] Exclusion of ACI limits the review to procedures typically performed in contemporary clinical practice and allows the HTCC to make a coverage decision based on procedures that will not become obsolete in the near future. This review did not include studies published in languages other than English or conducted in countries that are not very highly developed based on the United Nations Human Development Index.[10] Further exclusion criteria are outlined in ***Table 3.***

2.4 Data Abstraction and Risk-of-Bias Assessment

One team member extracted relevant study data into a structured abstraction form in DistillerSR, and a senior investigator checked those data for accuracy. Two team members conducted independent risk-of-bias assessments on all included studies; discrepancies were resolved by

discussion. We used the Cochrane Risk of Bias (RoB 2) tool to assess the risk of bias for each included RCT.[11] Domains assessed with this tool included bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcomes data, bias in measurement of the outcomes, and bias in selection of the reported results. Risk of bias was assessed as "high," "some concerns," or "low" at the study level, unless different outcomes within a single study required outcome-level risk-of-bias ratings. We used the Risk Of Bias In Nonrandomized Studies of Interventions (ROBINS-I) to assess risk of bias of NRSIs.[12] The ROBINS-I tool assesses risk of bias as "critical," "serious," "moderate," and "low." We categorized the ratings used in ROBINS-I to align with the Cochrane RoB tool, such that a moderate rating was reported as "some concerns" and a rating of serious or critical was reported as "high." Relevant confounders we designated for use with this tool included age, body mass index (BMI), mechanism of injury, size of lesion/depth of lesion, location of lesion, pre-surgery treatment, previous same knee surgery, and concomitant knee conditions. We used the Quality of Health Economic Studies Instrument to assess the risk of bias of included cost analyses.[13] We considered studies with scores on this instrument of 90 or above to have low risk of bias, studies with scores between 60 and 89 to have some concerns for bias, and studies with scores below 60 to have high risk of bias.

2.5 Data Synthesis and Strength-of-Evidence Rating

We qualitatively synthesized study characteristics and results for each research question by clinical diagnosis category in tabular and narrative formats. To determine whether quantitative synthesis was appropriate, we assessed the number of studies and the clinical and methodological heterogeneity present based on established guidance.[14,15] We required a minimum of 3 studies to conduct meta-analyses. We also required at least 50% of studies for a condition with a similar intervention and comparator with the same outcome measured at approximately the same follow-up time point to calculate a pooled treatment effect for that comparison. For meta-analyses, we used random-effects models using the inverse variance method of DerSimonian and Laird to generate pooled mean differences (MDs) for continuous outcomes.[16] Statistical significance was assumed when 95% confidence intervals (CIs) of pooled results did not include the null effect (i.e., 1.0 for risk ratios [RRs], 0 for MDs). For all quantitative syntheses, the I^2 statistic was calculated to assess statistical heterogeneity in effects between studies.[70,71] An I^2 from 0% to 40% might not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity, and 75% or greater represents considerable heterogeneity.[70,71] All testing was two-sided. Stata version 17 (Stata Corp) was used to conduct all quantitative analyses.[17]

We graded the certainty of evidence (COE) for each procedure, category of outcomes, and study design type using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach[18]. We combined multiple outcome measures within the same outcome domain and graded COE for PROs, response, treatment failure, reoperation, AEs, and SAEs. COE can be graded as *very low*, *low*, *moderate*, or *high* and reflects our certainty in the findings; ***Table 4*** defines these levels. Bodies of evidence from NRSIs evaluated with the ROBINS-I tool and RCTs began with a *high* rating and were downgraded based on domains relating to study limitations (i.e., risk of bias), consistency, precision, directness, and reporting bias.[72] To assess

the consistency domain, we evaluated both the consistency in the direction and magnitude of the treatment effect. Single study bodies of evidence are not downgraded for consistency according to GRADE guidance. To assess the precision domain, we evaluated the width of the CI for pooled estimates; when pooled estimates were not available, we evaluated the overall sample size and variance of individual studies contributing to the evidence base for the comparison. When CIs were either not provided or could not exclude a meaningful benefit or harm, we downgraded for imprecision. Our study selection criteria only selected for outcomes and comparisons that we considered direct. We captured reporting bias as part of study limitations.

Table 4. COE Grades and Definitions

GRADE	Definition
High	We are **very confident** that the true effect lies close to the estimate of the effect.
Moderate	We are **moderately confident** in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our **confidence** in the effect estimate **is limited:** The true effect may be substantially different from the estimate of the effect
Very Low	We have **very little confidence** in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect.

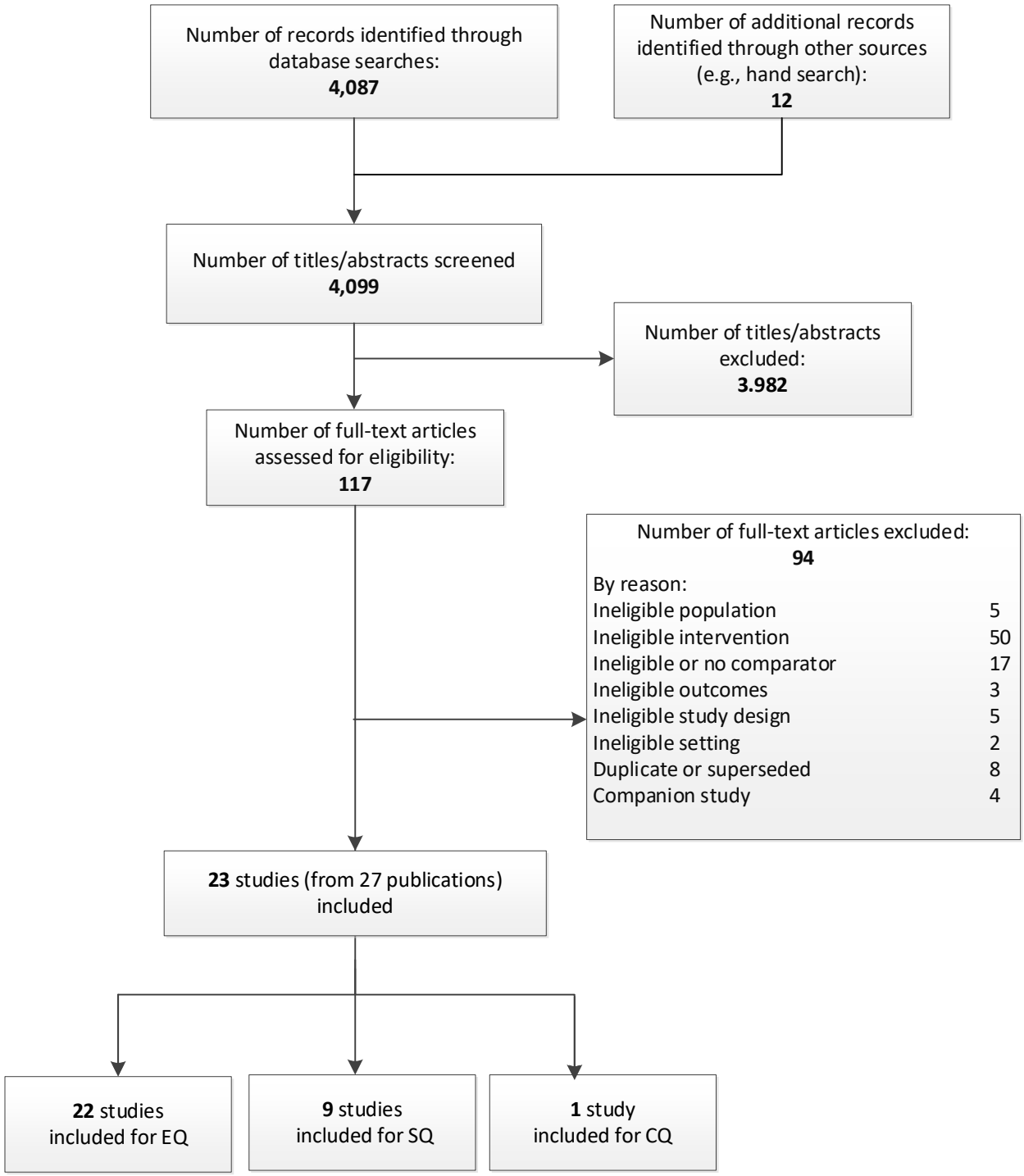
Notes: Adapted from GRADE Working Group et al. (2024).[18]

3. Results

3.1 Literature Search and Overview of Measures Reported

Figure 3 depicts the study flow diagram. We identified and screened 4,099 unique citations. We excluded 3,982 citations after title and abstract review. We reviewed the full text of 117 articles and included a total of 23 studies reported in 27 articles published between 2003 and 2023. Twenty-two studies were included for the EQ, 9 studies for the SQ, and 1 study for the CQ.

Figure 3. Study Flow Diagram for HTA on Treatment of Chondral Defects of the Knee



Abbreviations: CQ = cost question; EQ = efficacy question; HTA = health technology assessment; SQ = safety question.

Individual study and population characteristics and findings for all included studies are summarized in ***Appendix C***. The list of articles we screened at the full-text stage, but which we excluded, is provided in ***Appendix D***. Note that articles may have been excluded for more than 1 reason, but we report only 1 reason. We report our individual study risk-of-bias assessments for included studies in ***Appendix E. Table 5*** details the most commonly reported scales and indices used to report findings related to the EQ across the included studies. In the next section, we present results organized by procedure as follows:

- Matrix-associated autologous chondrocyte implantation compared to chondroplasty
- Matrix-associated chondrocyte implantation compared to microfracture
- Matrix-associated chondrocyte implantation compared to osteochondral autologous transplantation
- Osteochondral allograft transplantation compared to osteochondral autologous transplantation
- Osteochondral autologous transplantation compared to chondroplasty
- Osteochondral autologous transplantation compared to bone marrow stimulation procedures
- Cell-free implant compared to microfracture
- Autologous matrix-induced chondrogenesis compared to microfracture
- First-line procedures compared to second-line procedures

Table 5. Summary of Validated Measures Reported by Included Studies

Instrument	Description	Score Range; Directionality of Scale	Entity Completing Survey	Minimal Clinically Important Difference or Clinically Relevant Thresholds
Outcome Focus: Symptoms and Function				
Cincinnati Knee Rating System (CKRS)	8 questions in 3 domains measuring symptoms, function, and activities of daily living	0 to 100; higher scores indicate fewer symptoms and greater function	Patient	Unknown
Hospital for Special Surgery (HSS) Knee Rating Scale	Evaluates categories of pain, function, range of motion, muscle strength, flexion deformity, and instability	0 to 100; higher scores indicate fewer symptoms and greater function	Clinician	Excellent ≥ 85 Good = 70 to 84 Fair = 60 to 69 Poor ≤ 60[73]
International Knee Documentation Committee (IKDC) Subjective Score	Detects change in symptoms, function, and sports activities due to knee impairment	0 to 100; higher scores indicate fewer symptoms and greater function	Patient	Range: 6.3 to 16.7[74]
Knee Injury and Osteoarthritis Score (KOOS) Subscales	Rating of 5 domains: (1) pain; (2) knee symptoms; (3) performance of ADLs; (4) sports and recreational activities; (5) QOL	0 to 100; higher scores indicate fewer symptoms and greater function	Patient	Pain: 8.0 to 16.7 Symptoms: 2.5 to 10.0 ADL: 3.7 to 10.0 Sport:12.0 to 25.0 QOL: 3.7 to 9.3[75]
Lysholm score	Subscales for pain, instability, locking, swelling, limp, stair climbing, squatting, and need for support	0 to 100; higher scores indicate fewer symptoms and greater function	Patient	3.7 to 12.0[74,75] Categories[76] 95 to 100 = Excellent 84 to 94 = Good 65 to 83 = Fair < 65 points= Poor
Outcome Focus: Function				
Tegner Score[74]	Describes the level of work- and sports-based activity in which a patient can engage	0 to 10; higher scores indicate greater function	Patient	0: sick leave 5: return to work 7: return to recreational sports 10: return to high-impact sports

Abbreviations: ADL = activities of daily living; QOL = quality of life.

3.2 MACI Compared to Chondroplasty

We identified 1 NRSI comparing the effectiveness of MACI to chondroplasty.[19] The study did not specify the specific type of MACI used. For the rehabilitation protocol, all patients underwent rehabilitative physiotherapy, which involved the early mobilization of the joint followed by progressive weight-bearing exercises. Key findings are reported below.

- One year post-surgery, the percentage of participants who reported resuming normal sport and work activities was 71% and 60% for MACI and chondroplasty, respectively. COE in results were very low for comparative effectiveness.

The rest of this section provides detailed study characteristics and results.

3.2.1 Study Population and Characteristics

A summary of study characteristics is presented in ***Table 6***; detailed characteristics are in ***Appendix C, Tables C-1, C-2,*** and ***C-3***.

The study was conducted from 1998 to 2002. We assessed the study as having a high risk of bias for no attempt to control for confounding. The study was conducted in Italy and had a sample size of 62 patients; the two arms included in this comparison had a sample size of 47. Study sponsor was not reported.

The study included individuals from the ages of 19 to 45 years, with a mean age of 31 years; other demographic information was not reported. The study did not report on concurrent treatment of other knee injuries.

Table 6. Summary of Study Characteristics of Study Comparing MACI to Chondroplasty

Author, Year Country RoB	Study Design	Intervention and Comparator (N); Total Sample Size	Follow-up Timepoints; Mean Follow-up	Mean Age (SD); N (%) Female; Prior Knee Surgery	Location of Chondral Defect; Mean Defect Size; Number of Lesions
Macarini et al. (2003)[19] Italy High	NRSI	MACI (7) Chondroplasty (40) Total sample size: 47	6, 12 months (chondroplasty); 1 week, 3, 12 months (MACI); mean follow-up NR	Mean age (range): 31 (19 to 45) N (%) Female: NR Prior knee surgery: NR	Location of chondral defect: NR Mean defect size: NR Number of lesions: NR

Abbreviations: MACI = Matrix-associated cartilage implantation; N = number; NR = not reported; NRSI = nonrandomized study of intervention; RoB = risk of bias; SD = standard deviation.

3.2.2 Findings

This section provides detailed results for each category of outcome measure. A summary of findings and the COE are provided in ***Table 7***. Detailed findings are provided in ***Appendix C, Table C-4.***

Table 7. Summary of Findings and COE for MACI vs. Chondroplasty

No. Studies/No. Participants	Summary of Effect	Consistency	Precision	Directness	Study Limitations	Overall COE/ Direction
Return to sport or work at 1 year						
1 NRSI[19]/47	Similar percentage of individuals resumed normal sport and work activities, 1 year post-surgery for MACI and chondroplasty groups (71% vs. 60%, respectively; Calculated RR 1.2 (95% CI, 0.70 to 2.0))	Single study body of evidence	Imprecise	Direct	High	Very low for comparative effectiveness[a,b]

Notes:
[a] Downgrade 2 levels for imprecision for small sample size.
[b] Downgrade 2 level for study limitations.

Abbreviations: COE = certainty of evidence; MACI = Matrix-associated cartilage implantation; NRSI = nonrandomized study of intervention; RR = risk ratio.

Patient-reported Outcomes. One year post-surgery, the percentage of participants who reported resuming normal sport and work activities was 71% and 60% for MACI and chondroplasty, respectively.

Response, Treatment Failure, Reoperations. The study did not report on response, treatment failure, or reoperation.

Harms. The study did not report on safety outcomes.

Subgroups. The study did not report findings from any subgroup analyses.

3.3 MACI Compared to MF

We identified 5 studies comparing the effectiveness of MACI to MF, 3 of which were RCTs[20-22] and 2 were NRSIs.[23,24] Two of the studies used a porcine scaffold for MACI procedures,[20,22], 2 studies used an alternative scaffold,[21,23] and 1 study did not report the type used.[24] When the rehabilitation protocol was reported, it was the same for both MACI and MF groups, and, in general, allowed return to usual activity at 6 months and return to high-impact sports at 12 months. Four studies reported follow-up duration of 18 to 26 months,[21-24] and 1 study evaluated outcomes up to 5 years of follow-up.[20] Key findings are reported below.

- Three RCTs reported statistically and clinically significant improvements in PROs, with greater effectiveness of MACI compared with MF (moderate COE for RCTs). Two studies reported greater response to MACI compared to MF (moderate COE). The 1 NRSI reported similar results for PROs and response (very low COE).

- Few harms were reported across studies. In general, there were few or zero events reported or similar numbers of AEs in both groups (COE low for comparable harms).

The rest of this section provides detailed study characteristics and results by study design type.

3.3.1 Study and Population Characteristics

A summary of study characteristics is presented in ***Table 8***; detailed characteristics are in ***Appendix C***, ***Tables C-5***, ***C-6***, and ***C-7***.

RCTs

The 3 RCTs were conducted from 2000 to 2019 and were rated as low[20] or some concerns [21,22] of risk of bias. One study was a multicountry trial recruiting participants from 16 unspecified European countries.[20], 1 study was conducted in Germany,[22], and the other study in the United States.[21] Two of the 3 studies were funded entirely by industry,[20,21] and the remaining study did not report the study sponsor.[22] Study sample sizes ranged from 30 to 144 participants.

The RCTs enrolled patients from the age of 18 to mid-50s, and the mean age ranged from 33 to 46 years.[20-22] The percentages of female participants ranged from 17% to 30%. No study reported on race or ethnicity. Study inclusion criteria allowed a range of cartilage defect sizes from 1 cm^2 to 10 cm^2; however, actual defect size was generally in the range of 3 to 5 cm^2,[20,21] with the exception of 1 study that did not report mean defect size but included participants with defects ranging from 4 cm^2 to 10 cm^2.[22] The majority of study populations incurred cartilage injuries from acute trauma or sport (range 46% to 79%), followed by chronic degeneration (25% to 33%), and osteochondritis dissecans (range 6% to 17%). All but 1 study[21] allowed for concurrent treatment of other knee injuries.

NRSIs

The 2 NRSI studies[23,24] were rated as high risk of bias for not considering relevant confounders, missing data, and selective outcome reporting. One study was conducted in multiple countries,[23] and the other analyzed data from a health care claims data in Germany.[24] Study sample size ranged from 144 to 254 participants. The studies were conducted over the years 2012 to 2018, and both were entirely funded by industry; 1 study[23] was a matched-pair analysis using data from 2 trials in which the trials and the NRSI were funded by TETEC, [77]and the other[24] was sponsored by the company CO.DON GmbH,[78] both of which are tissue engineering companies. No study reported on race or ethnicity. Only 1 study reported eligibility criteria based on defect size (range 2 cm^2 to 12 cm^2), in which the mean defect size was 4.8 cm^2 for the MACI group and 3.4 cm^2 for the MF group. The other NRSI used claims data and only required that patients had an eligible procedure in the past 2 years.[24]

Table 8. Summary of Study Characteristics of Studies Comparing MACI to MF

Author, Year Country RoB	Study Design	Intervention and Comparator (N); Total Sample Size	Follow-up Timepoints; Mean Follow-up	Mean Age (SD); N (%) Female; Prior Knee Surgery	Location of Chondral Defect; Mean Defect Size; Number of Lesions
Basad et al. (2010)[22] Germany Some concerns	RCT	MACI (40) MF (20) Total sample size: 60	2-3 and 6 months, 1 to 2 years; follow-up reported at 3, 6, 12, 18 and 24 months; but not consistently at 3 months	Mean age (SD): MACI: 33.0 (NR) MF: 37.5 (NR) N (%) Female: 18 (30) Prior knee surgery: NR	Location of chondral defect: Condylar: 45 (75) Patellar-trochlear: 15 (25) Mean defect size: NR (entry criteria required 4 to 10 cm^2) Number of lesions: Participants had single, isolated, symptomatic chondral defects
Crawford et al. (2012)[21] United States Some concerns	RCT	MACI, NeoCart (21) MF (9) Total sample size: 30	3, 6, 12, 24 months; mean (SD) follow-up 26 (2) months	Mean age (SD): 40 (9) N (%) Female: 5 (17) Prior knee surgery: NR	Location of chondral defect: Medial or lateral femoral condyle, N (%): 30 (100) Mean (SD) defect size (cm^2): 2.8 (14) Number of lesions: Participants had 1 or 2 isolated articular cartilage lesions of the femoral condyle(s)
Saris et al. (2014)[20] Brittberg et al. (2018)[79] 16 European sites Low	RCT	MACI (72) MF (72) Total sample size: 144	1, 2, 3, 4, 5 years; mean follow-up NR	Mean age (SD): MACI: 34.8 (9.2) MF: 32.9 (8.8) N (%) Female MACI: 37.5 (27) MF: 33.3 (24) N (%) prior knee surgery: MACI: 65 (90.3) MF: 60 (83.3)	Location of chondral defect: Medial femoral condyle, N (%) MACI: 54 (75.0) MF: 53 (73.6) Lateral femoral condyle, N (%) MACI: 13 (18.1) MF: 15 (20.8) Trochlea, N (%) MACI: 5 (6.9) MF: 4 (5.6) Mean (SD) defect size (cm^2): MACI: 4.9 (2.8) MF: 4.7 (1.8) Number of lesions: Participants had 1 or more symtomatic cartilage defects

Author, Year Country RoB	Study Design	Intervention and Comparator (N); Total Sample Size	Follow-up Timepoints; Mean Follow-up	Mean Age (SD); N (%) Female; Prior Knee Surgery	Location of Chondral Defect; Mean Defect Size; Number of Lesions
Niemeyer et al. (2023)[23] Lithuania, Czech Republic, Hungary, Germany, Poland, France, Latvia, Switzerland, and the United Kingdom High	NRSI	MACI, NOVOCART (72) MF (72) Total sample size: 144	3, 6, 12, 18, 24 months; follow-up range: 3 - 24 months	Mean age (SD): MACI: 39.3 (12.1) MF: 39.3 (11.9) N (%) Female: MACI: 21 (29.2) MF: 21 (29.2) Prior knee surgery: Previous surgery in target knee N (%): MACI: 46 (63.9) MF: 45 (62.5) Meniscus removal MACI: 20 (27.8) MF: 26 (36.1) Ligament operation MACI: 12 (16.7) MF: 11 (15.3) Joint debridement MACI: 10 (13.9) MF: 11 (15.3) Arthroscopy MACI: 14 (19.4) MF: 14 (19.4)	Location of chondral defect N (%): Femur MACI: 82 (85.4) MF: 79 (100) Tibia MACI: 4 (4.2) MF: 0 (0) Patella MACI: 10 (10.4) MF: 0 (0) Mean (SD) defect size (cm^2): All lesions: MACI: 4.8 (1.7) MF: 3.4 (1.3) N (%) number of lesions: 1 lesion MACI: 48 (66.7) MF: 65 (90.3) 2 lesions MACI: 24 (33.3) MF: 7 (9.7)
Niemeyer et al. (2019)[24] Germany High	NRSI	MACI (N adjusted 127) MF (N adjusted 127) Total (adjusted sample size 254)	2 years	Mean age (SD): Unadjusted MACI: 36.0 (11.1) MF: 53.0 (14.0) After matching MACI: 36.8 (10.9) MF: 36.9 (10.9) N (%) Female: Unadjusted MACI: 60 (39.5) MF: 2,866 (45.7) Adjusted MACI: 52 (41.0) MF: 52 (40.9) Prior knee surgery: NR	Location of chondral defect: NR Mean defect size: NR Number of lesions: NR

Abbreviations: MACI = Matrix-associated cartilage implantation; MF = microfracture; N = number; NR = not reported; NRSI = nonrandomized study of intervention; RoB = risk of bias; RCT = randomized controlled trial; SD = standard deviation.

3.3.2 Findings

A summary of findings and the COE are provided in ***Table 9***. Detailed findings are provided in ***Appendix C***, ***Tables C-8*** and ***C-9.*** Compared to MF, MACI groups reported greater improvements than PROs and response to treatment groups, whereas treatment failure, reoperations, and harms were comparable between groups.

Table 9. Summary of Findings and COE for MACI vs. MF

No. Studies/No. Participants	Summary of Effect	Consistency	Precision	Directness	Study Limitations	Overall COE/ Direction
RCTs						
PROs, follow-up time 6 months to 5 years						
3 RCTs[20-22]/234	Changes in IKDC (MD 11.59 (95% CI 1.353 to 21.82)), Lysholm (MACI vs. MF: 92 vs. 69, respectively, *P*<0.01) and CKRS scores (MD 1.05, *P*=0.04) were greater for the MACI group compared to MF group in all studies. Similar results were reported for KOOS subscales in 2 studies (MD > 10 points) [20,21]; results for most outcomes across studies were clinically significant.	Consistent	Imprecise	Direct	Some concerns	Moderate for greater effectiveness of MACI[a]
Response, follow-up time 5 years						
2 RCTs[20,21]/174	Response was defined using different thresholds of different PROs for each study. Both studies reported more responders to therapy in the MACI group compared to MF. At 2 years, RR 1.3 (95% CI, 1.1 to 1.5) for 1 study,[20] and at 12 months, RR 3.4 (95% CI, 0.99 to 11.1) for the other.[80]	Consistent	Imprecise	Direct	Some concerns	Moderate for greater effectiveness of MACI[b]
Treatment failure defined as reoperation over 2 years						
1 RCT[20]/144	Small and similar number of reoperations (also defined as treatment failure) in each group with small number of events and no statistical testing.	Single study body of evidence	Imprecise	Direct	Low	Low for comparable effectiveness[c]

No. Studies/No. Participants	Summary of Effect	Consistency	Precision	Directness	Study Limitations	Overall COE/ Direction
Any adverse events, follow-up 2 to 5 years						
3 RCTs[20-22]/234	Mixed results; 1 study reported more AE in MF group; 1 study reported more AE in the MACI group; 1 study reported 0 events	Inconsistent	Imprecise	Direct	Some concerns	Low for comparable harms[c,e]
Any serious adverse events, follow-up 2 years						
2 RCTs[20,21]/174	Mixed results, but few or 0 events in MACI and MF groups for 1 study[20]; more events for MF group compared to MACI in another study though no statistical testing	Inconsistent	Imprecise	Direct	Some concerns	Very low for comparable harms[c,e]
NRSIs						
Patient-reported outcomes, follow-up time 2 years						
1 NRSI[23]/144 participants	Measures included IKDC (MD 7.4, *P*<0.03) and KOOS (MD 10.1; 95% CI, 3.6 to 16.5); both measures found statistically and clinically higher scores in the MACI group compared to MF group	Single study body of evidence	Imprecise	Direct	High	Very low for greater effective-ness of MACI[b,f]
Response, follow-up time 2 years						
1 NRSI[23]/144 participants	Response defined as > 10-point improvement from baseline KOOS score. Study reported greater response in the MACI group compared to MF (94% vs. 72%, calculated RR 1.3 [95% CI, 1.1 to 1.6])	Single study body of evidence	Precise	Direct	High	Low for greater effective-ness of MACI[f]
Treatment failure, follow-up time 2 years						
1 NRSI[23]/144 participants	Treatment failure defined as surgical reinterventions affecting the closed surface of the transplant area. No events were reported in either group	Single study body of evidence	Imprecise	Direct	High	Very low for comparable effective-ness[c,f]

No. Studies/No. Participants	Summary of Effect	Consistency	Precision	Directness	Study Limitations	Overall COE/ Direction
Reoperations, follow-up time 2 years						
2 NRSI[23,24]/398	Reoperation defined as any surgery after MACI or MF in 1 study with only 1 event overall but did not report group, and in 1 study as a claim for an ICD code for a second surgical procedure in the knee reporting a RRR of 43%, which was statistically significant	Single study body of evidence	Imprecise	Direct	High	Very low for greater effective-ness of MACI[d,f]
Any adverse events, follow-up time 2 years						
1 NRSI[23]/144 participants	1 study reporting only 1 event in the MACI group	Single study body of evidence	Imprecise	Direct	High	Very low for comparable harms[c,f]

Notes:
[a] Downgrade 1 level for imprecision for wide confidence intervals size and no reporting of absolute values or variance in 1 or more studies.
[b] Downgrade 1 level for imprecision for wide confidence intervals
[c] Downgrade 2 levels for imprecision for small sample size and no or small number of events.
[d] Downgrade 1 level for few events.
[e] Downgrade 1 level for inconsistency.
[f] Downgrade 2 levels for study limitations (high ROB in NRSI).

Abbreviations: CI = confidence interval; CKRS = Cincinnati Knee Rating System; COE = certainty of evidence; ICD = International Classification of Disease; IKDC = International Knee Documentation Committee Subjective Knee Form; KOOS = Knee Injury and Osteoarthritis Outcome Score; MACI = Matrix-associated cartilage implantation; MD = mean difference; MF = microfracture; NRSI = nonrandomized study of intervention; RCT = randomized controlled trial; ROB = risk of bias; RR = risk ratio; RRR = relative risk reduction

RCTs

Patient-reported Outcomes. All 3 RCTs reported measures including questions about knee symptoms and function. All studies reported statistically significant improvement in the MACI group compared to MF group for Cincinnati Knee Rating System (CKRS) over 5 years,[20] International Knee Documentation Committee (IKDC) over 2 years,[21] or Lysholm score over 2 years.[22] One of these studies also reported numerical improvements in IKDC favoring MACI, but these findings were not statistically significant.[20] Follow-up scores for Knee Injury and Osteoarthritis Outcome Score (KOOS) subscales of pain, symptoms quality of life, and return to sport were not reported, though authors did report statistically significant improvements in these subscales favoring MACI compared with MF.[20,21]

Response, Treatment Failure, Reoperations. Response to surgery was defined variably for the 2 studies reporting this outcome[20,22] (see ***Appendix C, Table C-8***). These studies reported statistically significant greater response in MACI compared with MF groups over 12 to 24

months. There were no significant differences observed for treatment failure, defined by reoperations within 2 years, in 1 study.[20]

Harms. All RCTs reported AEs. Results were mixed for 2 studies, such that a greater number of AEs occurred in the MF group for one study,[20] and in the MACI group for the other.[21] The remaining study reported only 1 event overall but did not report which group.[22] Common AEs included knee pain and joint swelling. SAEs were reported in 2 RCTs, with all reporting a small number of events (2 to 11 for the MACI group and 0 to 19 for the MF group).[21,22] SAEs reported included deep vein thrombosis, septic arthritis, and muscle atrophy.

Subgroups. In the 1 study reporting subgroup analyses, there were more responders in the MACI group than in the MF group in participants less than 34.5 years of age compared to older participants, participants with lesions larger than 4 cm^2 compared to smaller lesions, and in male participants compared to female participants.[20]

NRSIs

Patient-reported Outcomes. Only 1 study reported a PRO. In this study, the mean difference from baseline to 2 years for the total KOOS score and for the KOOS return to sport and quality of life subscales favored the MACI group by 10 to 14 points.[23] Authors reported similar findings for the IKDC score.[23]

Response, Treatment Failure, Reoperations. One study reported on response, which was measured as a 10 point or more improvement in KOOS total score from baseline.[23] Ninety-four percent of MACI patients responded to treatment at 2 years compared to 65% of MF patients ($P<0.01$).[23] Reoperations were less common in the MACI group than in the MF group in 1 study (12% vs. 22%, $P<0.05$)[24]. In the other study, unplanned surgeries after the initial treatment were numerically more common in the MACI group (6 participants, 8.3%) than in the MF group (3 participants, 4.2%), but no statistical significance testing was conducted.[23] There were no treatment failures in either group for 1 study.[23]

Harms. Neither study specifically reported AEs or SAEs. In 1 study, 1 of the unplanned surgeries was assessed as treatment related (compression syndrome caused by overtightened sutures).[23]

Subgroups. Neither NRSI reported findings from any subgroup analyses.

3.4 MACI Compared to OATS

We identified 2 NRSIs comparing MACI to OATS.[19,25] Key findings are as follows:

- Limited evidence supports a lower effectiveness of MACI compared to OATS (COE very low).

The rest of this section provides detailed study characteristics and results.

3.4.1 Study Population and Characteristics

A summary of study population and characteristics are presented in ***Table 10.*** Additional details are found in ***Appendix C***, ***Tables C-10***, ***C-11***, and ***C-12***.

The studies were rated as high risk of bias for no information on missing data,[25] and no control for confounding.[19] One study from a single site in Germany matched 9 MACI to 9 OATS patients on age, BMI, lesion localization, and postoperative interval; patients who underwent MACI had a defect size greater than 3 cm^2, and patients who underwent OATS had a defect size less than 3 cm^2.[25] The other study used data from a single site in Italy from 1998 to 2002.[19] Race and ethnicity were not reported. The mean follow-up time ranged from 41 to 42 months.

Table 10. Summary of Study Characteristics of Studies Comparing MACI to OATS

Author, Year Country RoB	Study Design	Intervention and Comparator (N); Total Sample Size	Follow-up Timepoints; Mean Follow-up	Mean Age (SD); N (%) Female; Prior Knee Surgery	Location of Chondral Defect; Mean Defect Size; Number of Lesions
Macarini et al. (2003)[19] Italy High	NRSI	MACI (7) OATS (15) Total sample size: 22	Mean (SD), range of follow-up: MACI: 42.0 (17.4) months, range 25 to 77 months OATS: 41.3 (16.5) months, range 23 to 75 months	Mean age (range): 31 (19 to 45) N (%) Female: NR Prior knee surgery: NR	Location of chondral defect: NR Mean defect size: NR Number of lesions: NR
Salzmann et al. (2009)[25] Germany High	NRSI	MACI, Verigen (9) OATS (9) Total sample size: 18	6, 12 months (OATS); 1 week, 3, 12 months (MACI)	Mean age (SD): MACI: 32.7 (7.2) OATS: 33.9 (7.5) N (%) Female: MACI: 1 (11.1) OATS: 1 (11.1) Prior knee surgery: NR	Location of chondral defect N (%): MACI Medial femoral condyle: 6 (66.7) Lateral femoral condyle: 1 (11.1) Patella: 2 (22.2) OATS Medial femoral condyle: 6 (66.7) Lateral femoral condyle: 1 (11.1) Patella: 2 (22.2) Mean (range) defect size (cm^2): MACI: 6.3 (range 3 to 12) OATS: 2.3 (range 0.9 to 2.6) Number of lesions: NR

Abbreviations: MACI = Matrix-associated cartilage implantation; N = number; NR = not reported; NRSI = nonrandomized study of intervention; OATS = osteochondral autologous transplantation; RoB = risk of bias; SD = standard deviation.

3.4.2 Findings

A summary of findings and the COE are provided in ***Table 11***. Detailed findings are provided in ***Appendix C***, ***Table C-13.*** This section provides detailed results for each category of outcome measure.

Table 11. Summary of Findings and COE for MACI compared to OATS

No. Studies/No. Participants	Summary of Effect	Consistency	Precision	Directness	Study Limitations	Overall COE/ Direction
Patient-reported outcomes, follow-up 3.5 years						
1 NRSI[25]/18	Outcomes of Lysholm, CKRS, and Tegner scores were higher in the MACI group compared to OATS group.	Consistent	Imprecise	Direct	High	Very low for greater effective-ness of MACI[a,b]
Return to sport or work at 1 year						
1 NRSI[19]/22	Smaller percentage of individuals resumed normal sport and work activities, 1 year post surgery for MACI compared to OATS groups (71% vs. 100%, respectively)	Consistent	Imprecise	Direct	High	Very low for greater effectiveness of OATS[a,b]

Notes:
[a] Downgrade 2 levels for imprecision for small sample size.
[b] Downgrade 2 levels for study limitations (high RoB in NRSI).

Abbreviations: CKRS = Cincinnati Knee Rating System; COE = certainty of evidence; MACI = Matrix-associated cartilage implantation; OATS = osteochondral autologous transplantation; NRSI = nonrandomized study of intervention; ROB = risk of bias.

Patient-reported Outcomes. For 1 study, after 42 months of follow-up, the mean difference of the Lysholm score between groups favored MACI over OATS (Lysholm score 77 vs. 67; 95% CI, -22.00 to 0.59), though absolute value was not reported. MDs for Tegner and CKRS scores also favored MACI over OATS, though results were not statistically significant.[25] For the other study, the percentage of participants who reported resuming normal sport and work activities at 1 year was 71% for MACI and 100% for OATS.[19]

Response, Treatment Failure, Reoperations. These outcomes were not reported.

Harms. No harms reported by the study.

Subgroups. No subgroup analyses were performed.

3.5 OCA Compared to OATS

We identified 2 NRSIs comparing the effectiveness of OCA to OATS.[26,27] One study conducted among patients age 21 or younger used data from the Pediatric Health Information System for patients undergoing OCA or OATS. Study follow-up ranged from 0.6 to 54.8 months.[26] The other used the PearlDiver Mariner database, which combines administrative data from private insurances and Medicare;[28] data from 2010 to 2018 were queried to identify individuals undergoing OCA or OATS.[27]

Key findings are reported below.

- Studies reported no statistically significant differences between OCA and OATS groups. (Low COE for comparable effectiveness.)
- No harms were reported for either study.

The rest of this section provides detailed study characteristics and results. A summary of study characteristics is presented in ***Table 12***; detailed findings are in ***Appendix C***, ***Tables C-14***, ***C-15***, and ***C-16***.

Table 12. Summary of Study Characteristics of Study Comparing OCA to OATS

Author, Year Country RoB	Study Design	Intervention and Comparator (N); Total Sample Size	Follow-up Timepoints; Mean Follow-up	Mean Age (SD); N (%) Female; Prior Knee Surgery	Location of Chondral Defect; Mean Defect Size; Number of Lesions
Hall et al. (2022)[26] United States High	NRSI	OCA (393) OATS (339) Total sample size: 732	Range: 0.6 to 54.8 months	Mean age (SD): 15.4 (2.4) N (%) Female: 318 (43.4) Prior knee surgery: NR	Location of chondral defect: NR Mean defect size: NR Number of lesions: NR
Burroughs et al. (2022)[27] United States High	NRSI	OCA (1,631) OATS (967) Total sample size: 2,598	10 years	Mean age (SD): OCA: 34.5 (12.1) OATS: 32.1 (12.9) N (%) Female: OCA: 842 (5.16) OATS: 493 51.0 Prior knee surgery: NR	Location of chondral defect: NR Mean defect size: NR Number of lesions: NR

Abbreviations: N = number; NR = not reported; NRSI = nonrandomized study of intervention; OATS = osteochondral autologous transplantation; OCA = osteochondral allograft transplantation; RoB = risk of bias; SD = standard deviation.

3.5.1 Study Population and Characteristics

NRSIs

We assessed both studies as having a high risk of bias for insufficient measurement, insufficient control for confounding, no information about missing outcome data, and no information to assess deviations from intended procedures since the analysis is entirely based on administrative data. Both studies were conducted in the United States and had sample sizes of 732 patients[26] and 2,598 patients.[27] Study sponsor was not reported for either study.

One study included patients younger than 21 years, with a mean age of 15.4 years.[26] The other study included patients age 10 to 59 years with a mean age range 32 to 35 years. Given administrative data were used, mean defect size of patients undergoing either procedure, location, size, and number of lesions were not available.

3.5.2 Findings

A summary of findings and the COE are provided in ***Table 13***. Detailed findings are provided in ***Appendix C***, ***Table C-17***. This section provides detailed results for each category of outcome measure.

Table 13. Summary of Findings and COE for OCA vs. OATS

No. Studies/No. Participants	Summary of Effect	Consistency	Precision	Directness	Study Limitations	Overall COE/ Direction
Reoperation, follow-up not reported or 10 years						
2 NRSI[26,27]/3,330	For any reoperation performed, similar rate of reoperation in both studies; 17% in the OCA group and 22% in the OATS group (*P*=0.08) for 1 study and 24% vs. 22% for the other study.	Consistent	Precise	Direct	High	Low for comparable effective-ness[a]

Notes:
[a] Downgrade 2 levels for study limitations (high RoB in NRSI).

Abbreviations: COE = certainty of evidence; NRSI = nonrandomized study of intervention; OATS = osteochondral autologous transplantation; OCA = osteochondral allograft transplantation; ROB = risk of bias.

NRSIs

Patient-reported Outcomes. Studies did not report any PROs.

Response, Treatment Failure, Reoperations. Both studies reported on reoperation and defined the outcome as any secondary surgery on knee. In both studies, the OATS and OCA groups had similar incidence of reoperation. In 1 study, 17% in the OCA group and 22% in the OATS group (*P*=0.08) had a reoperation,[26] and in the other study, the incidence was 24% (OCA) vs. 22% (OATS, *P*=0.25).[27] Survival analysis yielded similar rates of reoperation in both groups at 5 years for the latter study. Common secondary surgeries included repeat OCA, repeat OATS, chondroplasty, and ACI. Neither study reported response or treatment failure.

Harms. Studies did not report on safety outcomes.

Subgroups. One study reported predictors of reoperation based on a multivariate analysis. Patients undergoing open OATS had 1.7 (95% CI 1.1 to 2.8; *P*=0.04) times higher odds of reoperation than those undergoing open OCA. Multivariate analysis results examining differences by geographic region and insurance status were not statistically significant.[26]

3.6 OATS Compared to Chondroplasty

We identified 1 NRSI comparing the effectiveness of OATS to chondroplasty.[19] For the rehabilitation protocol, all patients underwent rehabilitative physiotherapy, which involved the early mobilization of the joint followed by progressive weight-bearing exercises. Key findings are reported below.

- One year post-surgery, the percentage of participants who reported resuming normal sport and work activities was 100% and 60% for OATS and chondroplasty, respectively (low COE for greater effectiveness of OATS).

The rest of this section provides detailed study characteristics and results.

3.2.1 Study Population and Characteristics

A summary of study characteristics is presented in ***Table 14***; detailed characteristics are in ***Appendix C***, ***Tables C-18***, ***C-19***, and ***C-20***.

The study was conducted from 1998 to 2002. We assessed the study as having a high risk of bias for inadequate control for confounding. The study was conducted in Italy, and the 2 eligible arms had a sample size of 55 patients. Study sponsor was not reported.

The study enrolled individuals with a mean age of participants or 31; other demographic information was not reported. The study did not report on concurrent treatment of other knee injuries.

Table 14. Summary of Study Characteristics of Study Comparing OATS to Chondroplasty

Author, Year Country RoB	Study Design	Intervention and Comparator (N); Total Sample Size	Follow-up Timepoints; Mean Follow-up	Mean Age (SD); N (%) Female; Prior Knee Surgery	Location of Chondral Defect; Mean Defect Size; Number of Lesions
Macarini et al. (2003)[19] Italy High	NRSI	OATS (15) Chondroplasty (40) Total sample size: 55	6, 12 months (chondroplasty); 1 week, 3, 12 months (OATS); mean follow-up NR	Mean age (range): 31 (19 to 45) N (%) Female: NR Prior knee surgery: NR	Location of chondral defect: NR Mean defect size: NR Number of lesions: NR

Abbreviations: N = number; NR = not reported; NRSI = nonrandomized study of intervention; OATS = osteochondral autologous transplantation; RoB = risk of bias; SD = standard deviation.

3.2.2 Findings

This section provides detailed results for each category of outcome measure. A summary of findings and the COE are provided in ***Table 15***. Detailed findings are provided in ***Appendix C***, ***Table C-21***.

Table 15. Summary of Findings and COE for OATS vs. Chondroplasty

No. Studies/No. Participants	Summary of Effect	Consistency	Precision	Directness	Study Limitations	Overall COE/ Direction
Return to sport or work at 1 year						
1 NRSI[19]/47	Greater percentage of individuals resumed normal sport and work activities, 1 year post-surgery for OATS compared to chondroplasty group (100% vs. 60%, respectively; calculated RR 1.6; 95% CI, 1.2 to 2.1)	Consistent	Precise	Direct	High	Low for greater effective-ness of OATS[a]

Notes:
[a] Downgrade 2 levels for study limitations (high RoB in NRSI).

Abbreviations: COE = certainty of evidence; NRSI = nonrandomized study of intervention; OATS = osteochondral autologous transplantation; RR = risk ratio.

Patient-reported Outcomes. One year post-surgery, the percentage of participants who reported resuming normal sport and work activities was 100% and 60% for OATS and chondroplasty, respectively.

Response, Treatment Failure, Reoperations. The study did not report on response, treatment failure, or reoperation.

Harms. The study did not report on safety outcomes.

Subgroups. The study did not report findings from any subgroup analyses.

3.7 OATS Compared to Bone Marrow Stimulation Procedures

We identified a total of 7 studies examining the comparative effectiveness of OATS with bone marrow stimulation procedures, including 5 RCTs comparing OATS to MF[29-33] and 2 NRSIs comparing OATS to MF or drilling.[34,35] Rehabilitation protocols were the same for both groups across all studies, with goals of recommended return to pre-operative activity levels at 6 months[30,35,36] and return to sport at 6[32,33] to 12 months[30] postoperatively for studies that reported this information. There was a wide range of mean follow-up durations: 1 study followed study participants for 2 years,[32] 4 studies from 3 to 10 years,[30,31,33,35] and 2 studies exceeding 10 years.[29,34] Key findings are as follows:

- Based on RCT and NRSI evidence, OATS and MF groups reported similar improvements in PROs (low COE for comparable effectiveness in RCT and NRSI study designs, respectively).
- One small RCT (N = 40) reported greater response to treatment for the OATS group compared to the MF group.[29] (low COE).
- Treatment failure was similar for both groups for 3 RCTs (low COE) and favored OATS for fewer treatment failures in 1 NRSI (moderate/low COE).
- Harms were similar for each procedure, though there were 0 or few events (very low COE for comparable harms).
- The 1 study of cost-effectiveness reported mixed results on whether OATS or MF was more cost-effective.[37] (low COE)

The rest of this section provides detailed study characteristics and results by study design type.

3.7.1 Study Population and Characteristics

A summary of study characteristics is presented in ***Table 16***; detailed findings are in ***Appendix C, Tables C-22, C-23,*** and ***C-24.***

RCTs

We rated the risk of bias for the 5 RCTs as some concerns[29,30,32,33] for lack of information on randomization and lack of reported protocol and 1 study as high risk of bias for not using an intent-to-treat analysis and no information on how missing data was managed.[31] All studies were conducted in countries outside of the United States: Norway,[29,30] Lithuania,[32,33] and South Korea.[31] Funding sources were not reported for any study. Sample sizes ranged from 25 to 109 participants.

For the 3 studies that included age as part of their eligibility criteria, 2 studies allowed patients between the ages of 18 to 50;[29,30] the other study was exclusively conducted in participants younger than 18 years with osteochondritis dissecans.[33] Study inclusion criteria allowed a range of defect size from 2 cm^2 to 6 cm^2 for 3 studies[29,30,33] and 1 cm^2 to 4 cm^2 for 2 studies.[31,32] Mean defect size ranged from 2.6 cm^2 to 3.6 cm^2. No study allowed for concurrent knee surgery. The most common mechanism of injury was trauma followed by osteochondritis dissecans.

NRSIs

The 2 NRSIs[34,35,81] evaluating OATS compared to MF and drilling were rated as high risk of bias for not considering relevant confounders and lack of reporting on how missing data was managed. One study was conducted in Norway[34,81] and the other in the United States.[35] Sample sizes ranged from 96 to 203 participants and each used data obtained from patients from a registry of a single institution, between 1999 to 2017 for 1 study[34,81] and from 1999 to an unknown follow-up time in the other study.[35] The source of funding was not reported for either

study. Participants aged 15 to less than 60 years were eligible for the 2 NRSIs. No study reported on race or ethnicity. Only 1 study used defect size as an eligibility criterion (1 to 6 cm^2).

Table 16. Summary of Study Characteristics of Included Studies Comparing OATS to MF

Author, Year Country RoB	Study Design	Intervention and Comparator (N); Total Sample Size	Follow-up Timepoints; Mean Follow-up	Mean Age (SD); N (%) Female; Prior Knee Surgery	Location of Chondral Defect; Mean Defect Size; Number of Lesions
Gudas et al. (2005)[32] Gudas et al., 2012[82] Gudas et al., 2006[83] Lithuania Some concerns	RCT	OATS (28) MF (29) Total sample size: 57	6, 12, 24, 36 months, mean follow-up 37.1 months	Mean age (SD): OATS: 24.6 (6.54) MF: 24.3 (6.80) N (%) Female: 22 (38.6) Prior knee surgery: NR	Location of chondral defect N (%): Medial femoral condyle: 48 (84) Lateral femoral condyle: 9 (16) Mean (SD) defect size (cm^2): OATS: 2.80 (0.65) MF: 2.77 (0.68) Number of lesions: Participants had a single symptomatic OCD or full-thickness articular cartilage lesion
Gudas et al. (2009)[33] Lithuania Some concerns	RCT	OATS (25) MF (25) Total sample size: 50	6 months, 1, 2, 3, 4 years; mean follow-up 4.2 years	Mean age (range): OATS: 14.6 (12 to 18) MF: 14.1 (12 to 18) N (%) Female: OATS: 10 (40) MF: 9 (41) Prior knee surgery: NR	Location of chondral defect: Medial femoral condyle, N (%) OATS: 21 (84) MF: 20 (91) Lateral femoral condyle, N (%) OATS: 4 (16) MF: 2 (9) Mean (SD) defect size (cm^2): OATS: 3.2 (0.34) MF: 3.2 (0.38) Number of lesions: Participants had a single symptomatic OCD lesion

Author, Year Country RoB	Study Design	Intervention and Comparator (N); Total Sample Size	Follow-up Timepoints; Mean Follow-up	Mean Age (SD); N (%) Female; Prior Knee Surgery	Location of Chondral Defect; Mean Defect Size; Number of Lesions
Lim et al. (2012)[31] South Korea High	RCT	OATS (22) MF (25) Total sample size: 109 (52 after post-randomization exclusions)	1, 6, 12, 24, 36 months, and last follow-up (minimum 3 years, mean 5.7 years, range 3-10.5 years); Follow-up mean (range) OATS: 5.8 years (3.2 to 7.5), MF: 6.7 years (3.5 to 10.5)	Mean age (range): OATS: 30.4 (20 to 39) MF: 32.9 (22 to 42) N (%) Female: OATS: 10 (45) MF: 12 (40) Prior knee surgery: Prior surgery not eligible	Location of chondral defect N (%) Medial femoral condyle OATS: 19 (86) MF: 23 (77) Lateral femoral condyle OATS: 3 (14) MF: 7 (23) Mean (range) defect size (cm^2): OATS: 2.8 (1.0 to 4.0) MF: 2.8 (1.2 to 3.6) Number of lesions: Participants had a single symptomatic articular cartilage lesion
Solheim et al. (2018)[29] Norway Some concerns	RCT	OATS (20) MF (20) Total sample size: 40	1, 5, 10, 15 years	Mean age (SD): OATS: 31 (7) MF: 35 (9) N (%) Female: OATS: 6 (30) MF: 6 (30) Prior knee surgery: Previous realignment surgery not eligible; other types of knee surgery were NR.	Location of chondral defect: All participants had lesions on femoral condyle or trochlea Mean (SD) defect size (cm^2): OATS: 3.4 (0.9) MF: 3.6 (0.8) N (%) number of lesions: 1 lesion OATS: 18 (90) MF: 18 (90) 2 lesions OATS: 2 (10) MF: 2 (10)

Author, Year Country RoB	Study Design	Intervention and Comparator (N); Total Sample Size	Follow-up Timepoints; Mean Follow-up	Mean Age (SD); N (%) Female; Prior Knee Surgery	Location of Chondral Defect; Mean Defect Size; Number of Lesions
Ulstein et al. (2014)[30] Norway Some concerns	RCT	OATS (14) MF (11) Total sample size: 25	10 years; Median follow-up (range) 9.8 years (4.9 to 11.4)	Mean age (SD): OATS: 32.7 (7.8) MF: 31.7 (8.0) N (%) Female: OATS: 6 (43) MF: 5 (45) Prior knee surgery: Previous cartilage surgery, N (%) OATS: 1 (7) MF: 3 (23)	Location of chondral defect N (%): Trochlea OATS: 2 (14) MF : 0 (0) Medial femoral condyle OATS: 10 (71) MF: 10 (91) Lateral femoral condyle OATS: 2 (14) MF: 1 (9) Median (range) defect size (cm^2): OATS: 3.0 (2.0–6.0) MF: 2.6 (2.0–5.2) Number of lesions: NR
Krych et al. (2012)[35] United States High	NRSI	OATS (46) Drilling (50) Total sample size: 96	1, 2, 3, 5 years; Mean follow-up years (range) OATS: 3.1 (2 to 10) MF: 4.4 (2 to 10)	Mean age (range): OATS: 29.7 (15 to 49) MF: 32.5 (15 to 46) N (%) Female: OATS: 16 (34.9) MF: 16 (34.9) Prior knee surgery: N (%) OATS: 16 (34.9) (prior microfracture) MF: 0 (0)	Location of chondral defect N (%): Medial femoral condyle OATS: 27 (58.7) MF: 27 (58.7) Lateral femoral condyle OATS: 16 (34.8) MF: 16 (34.8) Trochlea OATS: 5 (10.9) MF: 5 (10.9) Mean (range) defect size (cm^2): OATS: 2.65 (1.00 to 6.25) MF: 2.55 (1.00 to 6.25) Number of lesions: Participants had a single symptomatic cartilage lesion

Author, Year Country RoB	Study Design	Intervention and Comparator (N); Total Sample Size	Follow-up Timepoints; Mean Follow-up	Mean Age (SD); N (%) Female; Prior Knee Surgery	Location of Chondral Defect; Mean Defect Size; Number of Lesions
Solheim et al. (2020)[34] Solheim et al. (2017)[81] Norway High	NRSI	OATS (84) MF (119) Total sample size: 203	Follow-up conducted "several points after surgery, then at routine check-up for first few years, then every 2 to 3 years." Mean follow-up calculated from enrollment to 2017 (years): 14 to 19	Median age (range): 36 (15-60) N (%) Female: 85 (41.9) Prior knee surgery: Prior surgery not eligible	Location of chondral defect N (%): Medial femoral condyle: 118 (58) Lateral femoral condyle: 14 (7) Trochlea: 28 (14) Patella: 30 (15) Lateral tibial plateau: 12 (6) Median (range) defect size (mm^2): 350 (100 to 1700) Number of lesions: Participants could have 1 or multiple treated lesions

Abbreviations: MF = microfracture; N = number; NR = not reported; NRSI = nonrandomized study of intervention; OATS = osteochondral autologous transplantation; OCD = osteochondritis dissecans; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation.

3.7.2 Findings

A summary of findings and the COE are provided in ***Table 17***. Detailed findings are provided in ***Appendix C***, ***Tables C-25*** and ***C-26***.

Table 17. Summary of Findings and COE for OATS Compared to Bone Marrow Stimulation

No. Studies/No. Participants	Summary of Effect	Consistency	Precision	Directness	Study Limitations	Overall COE/ Direction
RCTs						
Patient-reported outcomes, follow-up time 6 months to 10 years						
4 RCTs[29-32]/231	Pooled estimate for change in Lysholm score based on 3 studies eligible for meta-analysis[29-31] was 3.60 (95% CI, -9.66 to 16.85), n = 112, I^2 = 84.6%. MCID on this measure ranges from 3.7 to 12.0.[74,75] 1 additional RCT[32] not included in the meta-analysis reported greater HSS scores in the OATS group compared to MF at 1 and 3 years that were statistically significant.	Consistent[a]	Imprecise	Direct	High	Low for comparable effective-ness[b,c]
Response over 1 year						
1 RCT[29]/40	Response was defined using threshold for good or excellent Lysholm score. 1 study showed response was higher in the OATS group compared with MF (60% vs. 20%, *P*=0.01).	Single study body of evidence	Imprecise	Direct	Some concerns	Low for greater effective-ness of OATS[d]
Treatment failure follow-up 2 years to 15 years						
3 RCTs[29,32,33]/147	Treatment failure definitions variable. All studies reported fewer failures in the OATS group, though few events in either group.	Consistent	Imprecise	Direct	High	Very low for comparable effective-ness[c,d]
Reoperation, follow-up 10 years						
3 RCTs[30-32]/134	Few events in all 3 studies (< 10); similar numbers of reoperations in each group.	Consistent	Imprecise	Direct	High	Very low for comparable effective-ness[c,d]

No. Studies/No. Participants	Summary of Effect	Consistency	Precision	Directness	Study Limitations	Overall COE/ Direction
Any adverse events, follow-up 1 to 15 years						
3 RCTs[29,32,33]/147	All studies with few events, 2 of which reported more events in the OATS group; the other study reported more events in the MF group.	Inconsistent	Imprecise	Direct	High	Very low for comparable harms[c,d,e]
NRSIs						
Patient-reported outcomes, follow-up time 2 years						
1 NRSI[35]/96	1 study reporting similar results for IKDC score and KOOS-ADL score, statistically nonsignificant.	Single study body of evidence	Imprecise	Direct	High	Very low for comparable effective-ness[d,f]
Treatment failure follow-up 15 years						
1 NRSI[34]/203	Fewer treatment failures in the OATS group (51%) compared to MF group (66%), *P*=0.011.	Single study body of evidence	Precise	Direct	High	Low favoring less treatment failure in OATS[f]

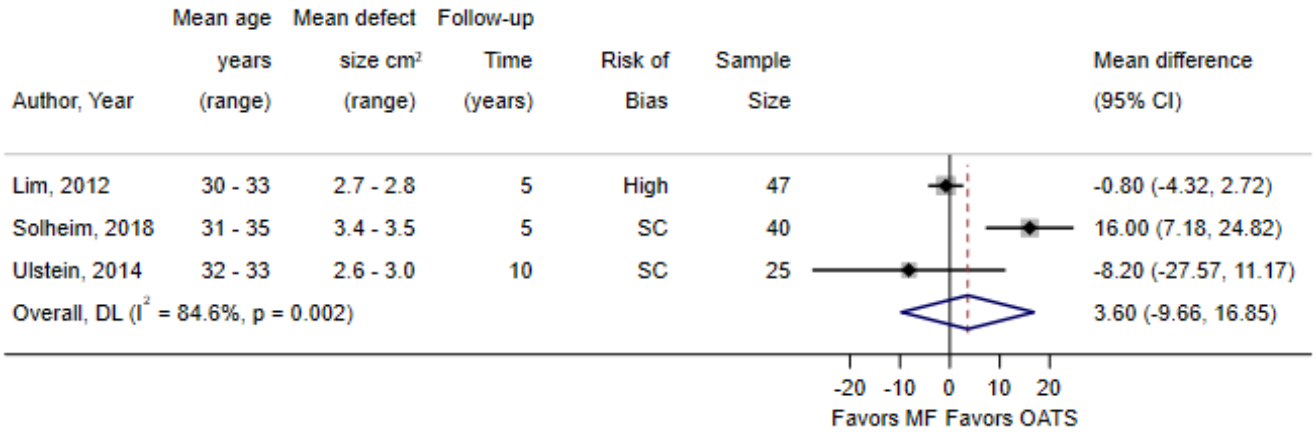
Notes:
[a] The consistency domain was not downgraded despite the high I^2, due to the following reasons that explain heterogeneity: differences in ROB, duration of symptoms, prior cartilage surgery, number of lesions treated.
[b] Downgrade 1 level for imprecision, wide confidence intervals that include clinically non-significant results.
[c] Downgrade 1 level for study limitations, at least 1 study with high ROB.
[d] Downgrade 2 levels for imprecision, small sample size and small number of events.
[e] Downgrade 1 level for inconsistency.
[f] Downgrade 2 levels for study limitations (high RoB in an NRSI).

Abbreviations: CI = confidence interval; COE = certainty of evidence; HSS = Hospital for Special Surgery; IKDC = International Knee Documentation Committee Subjective Knee Form; KOOS-ADL = Knee Injury and Osteoarthritis Outcome Score-Activities of Daily Living subscore; MCID = minimal clinically important difference; MF = microfracture; OATS = osteochondral autologous transplantation; NRSI = nonrandomized study of intervention; RCT = randomized controlled trial; RoB = risk of bias.

RCTs

PROs. A total of 4 RCTs included data on PROs.[29-32] Three studies[29-31] reported the Lysholm score and the pooled estimate for between group difference from meta-analysis was 3.60 (95% CI, -9.66 to 16.85), 112 participants, $I^2 = 84.6\%$ (***Figure 4***). One additional RCT[32] reported greater Hospital for Special Surgery scores in the OATS group compared to MF at 1 and 3 years that were statistically significant.

Figure 4. Meta-analysis of OATS Compared to MF Using Lysholm Score



Abbreviations: CI = confidence interval, DL= DerSimonian & Laird estimator for pooling estimates, MF=microfracture, OATS = osteochondral autologous transplantation; SC = some concerns.

Response, Treatment Failure, Reoperations

The 1 study reporting response, defined as Lysholm score greater than or equal to 80, found more participants undergoing OATS met response criteria compared to MF (60% vs. 20%, *P*=0.01).[29] Treatment failure was defined very differently across 3 studies (knee replacement, symptomatic after rehabilitation, and any revision surgery) and at follow-up times ranging from 2 years to 15 years.[29,32,33] All studies reporting treatment failure had few events in each group, with fewer failures in the OATS group. Reoperations were measured in 3 studies,[30-32] in which all studies reported few and similar number of events.

Harms

Among the 3 studies reporting any AEs, 2 reported few events.[29,32] The third study reported individual AEs including knee pain, joint swelling, and crepitation that were higher in the MF group.[33] No studies reported SAEs.

Subgroups

Two studies reported subgroup analyses, in which poorer results were found for larger lesion size in the MF group.[32,33]

NRSIs

PROs

One study reported the IKDC measure, which a captures symptom and function; scores were not statistically different at follow-up over 2 and 5 years[35] Authors observed similar results for the KOOS activities of daily living (ADL) subscore.

Response, Treatment Failure, Reoperations

No studies reported outcomes of response or reoperations. One study reported on treatment failures defined as Lysholm score less than 65 or ipsilateral knee replacement.[34] Treatment failures were greater in the MF groups compared to OATS group, as well as having a shorter mean time to failure (OATS 8.4 years vs. MF 4.0 years, *P*=0.011).[34]

Harms

Neither study reported AEs or SAEs.

Subgroups

One study reported improved results in the OATS group compared to the MF group for age younger than 51 and lesion size less than 5 cm^2.[34]

Cost Effectiveness

We identified one decision analysis conducted using U.S.-based cost inputs.[37] No study sponsorship was reported. We rated the study as some concerns of risk of bias. (***Appendix E, Table E-1)***. Study characteristics are summarized in ***Table 18***. (Details can be found in ***Appendix C, Table C-41***.) The study was a decision model comparing OATS to MF. Effectiveness data inputs (e.g., validated knee function/pain scores) were derived from 3 RCTs,[30,31,83] and costs were obtained from the investigators' academic institution. The study modeled the costs of the initial procedure and operating room procedures and staff, along with costs of failure, which included costs of return evaluation visits, repeat MRI imaging, and a second procedure. A cumulative failure rate of 28.6% and 12.5% for MF and OATS, respectively, were used to estimate costs associated with the evaluation and treatment with a second-line procedure.

Table 18. Study Characteristics and Findings for Studies Reporting Cost-Effectiveness for OATS vs. MF (CQ)

Author (Year) Country Risk of Bias Sponsor	Study Design	Population	Key Analysis Parameters	Outcomes
Miller et al. (2009)[37] United States Some concerns NR	Modeled cost-effectiveness	Healthy young adults with isolated cartilage lesions; outcomes modeled from data on participants in 3 trials[30,31,82] comparing OATS vs. MF among persons with isolated, focal cartilage defects of the distal femur; mean age 28.8 years; range of mean lesion size from 2.7 to 2.8 cm^2	*Follow-up:* 10 years with endpoints of no further procedures, early failure, or late failure *Costs:* 2013 U.S. dollars from investigators' institution's (academic medical/surgical center) actual costs including initial procedure cost and operating room fees, cost of failure; rehabilitation costs excluded. *Time Horizon: 1 year, 10 years* *Effectiveness measures:* Lysholm, Tegner, HSS, ICRS scores; return to play	Calculated incremental cost per point improvement for OATS vs. MF Lysholm score: $130 Tegner score: -$143 HSS: $95 ICRS score: -$98.29 Calculated incremental cost to return to play at 1 year for OATS vs. MF: -$5,525

Abbreviations: HSS = Hospital for Special Surgery Knee-Rating Scale; ICRS = International Cartilage Repair Society; MF = microfracture; NR = not reported; OATS = osteochondral autologous transplantation.

The difference in net cost between OATS and MF was $1,843 at 1 year and $996 at 10 years. Cost per point improvement on validated measures of knee pain and function varied based on effectiveness measure. OATS was less expensive per point improvement using the Tegner score and ICRS, whereas MF was less expensive per point improvement using the Lysholm score and HSS. However, the authors did not explicitly report the length of follow-up time over which these costs per point improvement were reported. The cost to return patients back to play at 1 year was $5,525 less for OATS compared with MF and remained lower at 3- and 10-year follow-ups. Sensitivity analyses evaluated how varying base assumptions would affect findings, including variance in costs, revision rate, and adding indirect costs for physical therapy and lost earnings due to missing work. For most sensitivity analyses, the total costs for OATS and MF were equivalent.

Table 19. Summary of Findings and COE for Cost-Effectiveness of OATS Compared to MF

No. Studies/No. Participants	Summary of Effect	Consistency	Precision	Directness	Study Limitations	Overall COE/ Direction
1 CUA[37]/70	Mixed results depending on which PRO used for effectiveness measure; MF lower cost per point improvement using Lysholm and HSS; OATS lower cost using Tegner and ICRS	Single study	Imprecise	Indirect	Some concerns	Low/Unable to determine[a,b]

Notes:
[a] Downgrade 1 level for no 95% CIs reported for estimates to determine variance around ICERs.
[b] Downgrade 1 level for decision model.

Abbreviations: CI = confidence interval; COE = certainty of evidence; CUA = cost-utility analysis; HSS = Hospital for Special Surgery Knee Score; ICER = incremental cost effectiveness ratio; ICRS = International Cartilage Repair Society; MF = microfracture; OATS = osteochondral autologous transplantation; PRO = patient-reported outcome.

3.8 Cell-free Implants Compared to MF/Chondroplasty

We identified 1 RCT comparing a cell-free aragonite implant (Agili-C) used to plug osteochondral lesions to a comparator group of MF or chondroplasty, described by the authors as surgical standard of care.[38] Key findings include:

- Greater improvement in PROs and in response to treatment in the cell-free implant group compared to MF/chondroplasty (moderate COE for greater effectiveness of cell-free implant).
- Any adverse events were lower in the cell-free implant group compared to microfracture/chondroplasty (moderate COE for fewer harms in the cell-free implant group).

3.8.1 Study Population and Characteristics

A summary of study characteristics is presented in ***Table 20***; detailed findings are in ***Appendix C, Table C-27, C-28,*** and ***C-29.*** The study was conducted in multiple countries and was funded entirely by industry between the years 2017 and 2019.[38] The sample size was 251 and enrolled patients were between ages 21 to 75 years. The study was rated with some concerns for ROB given lack of information in randomization domain and baseline differences in disease severity, though authors to control for baseline differences in analysis.

Table 20. Summary of Study Characteristics of Included Studies Comparing Cell-free Implant to MF/Chondroplasty

Author, Year Country RoB	Study Design	Intervention and Comparator (N); Total Sample Size	Follow-up Timepoints; Mean Follow-up	Mean Age (SD); N (%) Female; Prior Knee Surgery	Location of Chondral Defect; Mean Defect Size; Number of Lesions
Altschuler et al. (2023)[38] United States, Belgium, Israel, Hungary, Italy, Romania, Serbia High	RCT	Cell-free implant (167) MF or debridement (84) Total sample size: 251	2, 6, 12, 18, 24 months; mean follow-up NR (97% of participants completed 2-year study)	Mean age (SD): Cell-free implant: 42 (11.2) MF: 46 (11.2) N (%) Female: Cell-free implant: 60 (35.9) MF/Debridement: 33 (39.3) Prior knee surgery: History of ACL reconstruction, N (%) Cell-free implant: 13 (7.8) MF/Debridement: 7 (8.3) History of meniscectomy, N (%) Cell-free implant: 36 (21.6) MF/Debridement: 22 (26.2)	Location of chondral defect: NR N (%) defect size > 3 cm^2 Cell-free implant: 98 (58.7) MF/Debridement: 41 (48.8) N (%) number of lesions: Single lesion: Cell-free implant: 109 (65.3) MF: 58 (69) Multiple lesions: Cell-free implant: 58 (34.7) MF: 26 (31) Presence of up to 3 joint surface lesions allowed

Abbreviations: ACL = anterior cruciate ligament; MF = microfracture; N = number; NR = not reported; RCT = randomized controlled trial; SD = standard deviation.

3.8.2 Findings

A summary of findings and the COE are provided in ***Table 21***. Detailed findings are provided in ***Appendix C, Tables C-30*** and ***C-31***.

Table 21. Summary of Findings and COE for Cell-free Implant Compared to MF/Chondroplasty

No. Studies/No. Participants	Summary of Effect	Consistency	Precision	Directness	Study Limitations	Overall COE/ Direction
RCT						
Patient-reported outcomes, follow-up time 6 to 24 months						

No. Studies/No. Participants	Summary of Effect	Consistency	Precision	Directness	Study Limitations	Overall COE/ Direction
1 RCT[38]/251	PROs include KOOS total and subdomains of pain, ADLs, and QOL. Follow-up total KOOS scores increased from baseline to 6 and 24 months, greater in the cell-free implant group compared to MF (MD, 22.5 [95% CI, 17.0 to 28.0], *P*<0001 at all timepoints). Individual KOOS domains have similar results, but authors did not report specific values.	Single study body of evidence	Precise	Direct	Some concerns	Moderate for greater effective-ness of cell-free implant[a]
Response, follow-up time 24 months						
1 RCT[38]/251	Response, defined by an overall increase in KOOS score greater than 30, was significantly greater in the cell-free implant group, compared to MF. Calculated ARD 43.7% (95% CI, 31.7 to 55.7)	Single study body of evidence	Precise	Direct	Some concerns	Moderate for greater effective-ness of cell-free implant[a]
Treatment failure, follow-up time 24 months						
1 RCT[38]/251	Treatment failure, defined as any secondary procedure (surgical or injection) to the joint, was similar in both groups. (ARD -3.5%, 95% CI, -12.4% to 5.5%)	Single study body of evidence	Imprecise	Direct	Some concerns	Moderate for comparable effect[b]
Any adverse events, follow-up time 24 months						
1 RCT[38]/251	Smaller proportion of individuals experiencing at least 1 AE in the cell-free implant group compared to MF. Calculated ARD -17.8% (95% CI, -29.5 to -6.0)	Single study body of evidence	Imprecise	Direct	Some concerns	Moderate for lower harms of cell-free implant[b]
Any severe adverse events, follow-up time 24 months						
1 RCT[38]/251	Few events reported in either group.	Single study body of evidence	Imprecise	Direct	Some concerns	Low for comparable harms[c]

Notes:
[a] Downgrade 1 level for study limitations: study reports KOOS total score as primary outcome though the individual KOOS subdomains are not meant to be totaled.[74]
[b] Downgrade 1 levels for imprecision, wide confidence interval.
[c] Downgrade 2 levels for imprecision, few events.

Abbreviations: AE = adverse events; ARD = absolute risk difference; CI = confidence interval; KOOS = Knee Injury and Osteoarthritis Outcome Score; MF = microfracture; N = number; NR = not reported; RCT = randomized controlled trial; SD = standard deviation.

Patient-reported Outcomes. The RCT reported a KOOS total score (MD= 22.5 [95% CI, 17.0 to 28.0], *P*<0001 at all timepoints). KOOS subdomains of pain, ADL, and QOL were reported to

have a greater increase in all scores for the cell-free implant group compared to the MF group, though absolute values and statistical significance were not reported.

Response, Treatment Failure, Reoperations. Response, defined as an overall improvement in KOOS total score of 30 of more, was greater in the cell-free implant group compared to MF. The outcome of treatment failure (any secondary procedure, including joint injections) was comparable between groups. The authors did not report on reoperations.

Harms. Over 24 months, a lower percentage of individuals in the cell-free implant group experienced harms than the MF group (59% vs. 77%, $P<0.01$). Few SAEs related to either treatment were reported.

Subgroups. The RCT combined both groups and stratified by age, severity of lesions, and size of lesions, but did not report differences by intervention group.

3.9 AMIC vs. MF

We identified 1 RCT comparing the effectiveness of AMIC to MF.[39] The study used sutured and glued AMIC procedures with Chondro-Gide, a collagen type I/III matrix. The rehabilitation protocol was the same for the sutured AMIC, glued AMIC, and MF groups and allowed full weight-bearing after 8 weeks, jogging after 6 months, and contact sports at 18 months. The study evaluated outcomes through 5 years of follow-up. Key findings are reported below.

- CKRS improved at 1 year for AMIC and MF groups; at 5 years follow-up, improvements were sustained in the AMIC groups only while the MF group experienced a score degradation. AMIC had greater effectiveness for this outcome at both timepoints (low for greater effectiveness of AMIC).

- 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).

The rest of this section provides detailed study characteristics and results.

3.9.1 Study Population and Characteristics

A summary of study characteristics is presented in ***Table 22***; detailed findings are in ***Appendix C, Tables C-32, C-33,*** *and* ***C-34****.*

The RCT was published in 2017 (specific dates conducted were not reported). We assessed the study as having a high risk of bias for not using an intention to treat analysis, missing outcome data, and non-blinded assessment of the outcome, which may have been biased in the MF group by receipt of an older procedure. The study was conducted in Germany, was funded entirely by industry (Geistlich Pharma AG), and had a sample of 47 participants.

The study enrolled patients from the age of 18 to 50 years. Race and ethnicity were not reported. Study inclusion criteria allowed a range of cartilage defect sizes from 2 cm^2 to 10 cm^2; mean defect size was 3.6 cm^2. The study did not include concurrent treatment of other knee injuries.

Table 22. Summary of Study Characteristics of Included Studies for AMIC vs. MF

Author, Year Country RoB	Study Design	Intervention and Comparator (N); Total Sample Size	Follow-up Timepoints; Mean Follow-up	Mean Age (SD); N (%) Female; Prior Knee Surgery	Location of Chondral Defect; Mean Defect Size; Number of Lesions
Volz et al. (2017)[39] Germany High	RCT	Sutured AMIC (17) Glued AMIC (17) MF (13) Total sample size: 47	1, 2, 5 years	Mean age: (SD): 37 (10) N (%) Female: 10 (21) Prior knee surgery: Previous operation (specific operation not specified), N (%): 24 (51) Meniscus revision, N (%): 15 (32)	Location of chondral defect: Specific data NR. "Lesions were mostly located on the femoral condyles" Mean (SD) defect size (cm^2): 3.6 (1.6) Number of lesions: Participants had 1 or 2 isolated cartilage defects of the knee

Abbreviations: AMIC = autologous matrix-induced chondrogenesis; MF = microfracture; N = number; NR = not reported; RCT = randomized controlled trial; RoB = risk of bias; SD = standard deviation.

3.9.2 Findings

This section summarized results for each category of outcome measure. A summary of findings and the COE are provided in ***Table 23***. Detailed findings are provided in ***Appendix C***, ***Tables C-35*** and ***C-36***.

Table 23. Summary of Findings and COE for AMIC vs. MF

No. Studies/No. Participants	Summary of Effect	Consistency	Precision	Directness	Study Limitations	Overall COE/ Direction
Patient-reported outcomes, follow-up time 1 to 5 years						
1 RCT[39]/47	CKRS: 1-year follow-up results show within-group improvement across all groups (82 vs. 67, *P*<0.001 for AMIC and MF, respectively); 5-year follow-up results favor sutured and glued AMIC over MF, though values were not reported.	Single study body of evidence	Imprecise	Direct	High	Low for greater effectiveness of AMIC[a,b]
Reoperation, follow-up time 1 year						
1 RCT[39]/47	After 1 year, 1 patient treated with glued AMIC received a joint replacement, and 1 patient with MF received an ACI procedure.	Single study body of evidence	Imprecise	Direct	High	Very low for comparable effective-ness[b,c]

No. Studies/No. Participants	Summary of Effect	Consistency	Precision	Directness	Study Limitations	Overall COE/ Direction
Harms – adverse events, follow-up time 5 years						
1 RCT[39]/47	A small number of adverse events were reported for the total study sample, no information by group.	Single study body of evidence	Imprecise	Direct	High risk of bias study	Very low for comparable effective-ness[b,c]

Notes:
[a] Downgrade 1 level for imprecision due to small sample size.
[b] Downgrade 1 level for study limitations.
[c] Downgrade 2 levels for imprecision due to small number of events and small sample size.

Abbreviations: ACI = Autologous chondrocyte implantation; AMIC = autologous matrix-induced chondrogenesis; COE = certainty of evidence; MF = microfracture; NRSI = nonrandomized study of intervention; RCT = randomized controlled trial; ROB = risk of bias.

RCTs

Patient-reported Outcomes. The RCT reported one measure (CKRS) capturing function and symptoms. The study reported statistically significant improvements in the measure favoring AMIC compared with MF only at the 5-year follow-up timepoint. At 1 year follow-up, scores improved significantly within each group, but between group differences were not reported. At 5 years follow-up, improvements were sustained in the sutured and glued AMIC groups while the MF group experienced a score degradation; between group differences at 5 years were statistically significantly higher in AMIC groups compared to MF.

Response, Treatment Failure, Reoperations. The study reported on reoperation. One patient with MF received an ACI procedure after 1 year, and 1 patient treated with glued AMIC received a joint replacement after 1 year.

Harms. For the complete study population, 13 AEs were reported in 9 patients, but these events were not reported by group. No SAEs related to the treatment were reported.

Subgroups. The RCT did not report findings from any subgroup analyses.

3.10 First-line Procedures vs. Second-line Procedures (MACI and OCA)

We identified 4 studies comparing a first-line surgery with the same procedure performed as a second-line surgery after an earlier failed chondral restoration procedure. One NRSI compared first-line MACI to second-line MACI[40] and 3 NRSIs compared first-line OCA to second-line OCA, both second-line procedures performed after failed bone marrow stimulation.[41-43] Rehabilitation protocols for OCA allowed for return to sports within 6 to 8 months postoperatively, whereas those undergoing MACI were allowed to return to high-impact sports 12 months after surgery. The follow-up time for the MACI study was 6 to 36 months; follow-up duration for the OCA studies ranged from 3 to 11 years.

Key findings are reported below.

- There were more treatment failures and re-operations for second-line MACI and OCA procedures compared to first-line MACI and OCA procedures (COE Very Low for greater effectiveness of first-line procedures).

- First-line MACI procedures reported greater improvement in PROs compared to MF (COE very low for first-line MACI); PRO results for first-line and second-line OCA were similar (COE very low for comparable effectiveness).

The rest of this section provides detailed study characteristics and results by procedure comparisons.

3.10.1 Study Population and Characteristics

A summary of study characteristics is presented in ***Table 24***; detailed findings are in ***Appendix C***, ***Tables C-37***, ***C-38***, and ***C-39***.

First-line MACI vs. Second-line MACI

One study conducted in Germany matched patients undergoing first-line MACI to patients undergoing MACI after a failed bone marrow stimulation technique.[40] The study was rated as high risk of bias for only accounting for confounders of number and location of defects, not other participant characteristics such as age, BMI, or lesion depth, which could influence the outcome. Further, this analysis is a comparison of patient populations, not the actual MACI procedure. Forty patients were included in the study with a mean age of 32.9 years in the first-line MACI group and 39.1 years in the patients undergoing MACI as a second-line procedure after failed bone-marrow stimulation. Average defect size ranged from 4.8 cm^2 to 5.4 cm^2.

First-line OCA vs. Second-line OCA

All 3 NRSIs comparing first-line OCA to second-line OCA were conducted at single site centers in the United States.[41-43] For 2 studies, patients undergoing a second-line OCA procedures were matched to patients who had a first-line OCA procedure,[42,43] and 1 study matched patients receiving second-line OCA to a first-line procedure of either failed bone marrow stimulation[42,43] or ACI (no information if first- or third-generation procedure).[41] All 3 were rated as high risk of bias primarily for no or unclear management of missing follow-up data. The studies considered several relevant confounders but often did not include some additional variables that could impact the outcomes of procedures such as imbalance in baseline severity of knee disease. Further, this analysis is a comparison of patient populations, not the actual OCA procedure. A non-profit foundation supported 1 study,[43] and the others reported either no financial support[42] or no information.[41] Patient ages ranged from 26.2 to 36.2 years. No study reported race or ethnicity. Mean defect size ranged from 4.0 to 8.2 cm^2.

Table 24. Summary of Study Characteristics of Included Studies for First-line Compared to Second-line Procedures (MACI and OATS)

Author, Year Country RoB	Study Design	Intervention and Comparator (N); Total Sample Size	Follow-up Timepoints; Mean Follow-up	Mean Age (SD); N (%) Female; Prior Knee Surgery	Location of Chondral Defect; Mean Defect Size; Number of Lesions
First-line MACI vs. MACI after failed MF					
Müller, et al. (2020)[40] Germany High	NRSI	MACI NOVOCART 3D (20) MACI after failed MF (20) Total sample size: 40	6, 12, 24, 36 months; mean follow-up NR	Mean age (SD), (range) MACI (first-line): 32.9 (11.8), (16 to 55) MACI (second-line): 39.1 (10), (19 to 53) N (%) Female: MACI (first-line): 12 (60) MACI (second-line): 14 (70) Prior knee surgery: N (%) First-line MACI: NR Second-line MACI: 20 (100); inclusion criteria was prior failed BMS	Location of chondral defect N (%): Femoral: MACI (first-line): 11 (55) MACI (second-line): 10 (50) Patellar: MACI (first-line): 8 (40) MACI (second-line): 9 (45) Trochlear MACI (first-line): 1 (5) MACI (second-line): 1 (5) Mean (SD), (range) defect size (cm^2): MACI (first-line): 5.4 (2.6), (2 to 15) MACI (second-line): 4.8 (2.0), (2 to 10) Number of defects = 1, N (%) MACI (first-line): 16 (80) MACI (second-line): 16 (80) Number of defects = 2, N (%) MACI (first-line): 4 (20) MACI (second-line): 4 (20) N (%) number of lesions: 1 treated defect MACI (first-line): 16 (80) MACI (second-line): 16 (80) 2 treated defects MACI (first-line): 4 (20) MACI (second-line): 4 (20)

Author, Year Country RoB	Study Design	Intervention and Comparator (N); Total Sample Size	Follow-up Timepoints; Mean Follow-up	Mean Age (SD); N (%) Female; Prior Knee Surgery	Location of Chondral Defect; Mean Defect Size; Number of Lesions
First-line OCA vs. OCA after failed BMS or ACI					
Gracitelli et al. (2015)[43] United States High	NRSI	First-line OCA (46) Second-line OCA after failed first-line OCA. (46) Total sample size: 92	Mean (SD) follow-up, only for grafts that remained in situ First-line OCA: 7.8 (5.1) years, 41 knees Second-line OCA: 11.3 (6.6), 39 knees	Mean age (SD): First-line OCA: 27.5 (11.8) Second-line OCA: 26.2 (10.4) N (%) Female: First-line OCA: 18 (39) Second-line OCA: 18 (39) Prior knee surgery: NR	Location of chondral defect N (%): Femoral condyle First-line OCA: 42 (91) Second-line OCA: 44 (96) Patella First-line OCA: 1 (2) Second-line OCA: 1 (2) Trochlea First-line OCA: 3 (6) Second-line OCA: 1 (2) Mean (SD) defect size (cm^2): First-line OCA: 8.2 (3.6) Second-line OCA: 8.0 (3.2) Number of lesions: NR
Merkley et al. (2021)[41] United States High	NRSI	First-line OCA (13) after failed ACI (13) Total sample size: 13	Mean (SD) follow-up: 3.2 (1.5) years	Mean age (SD): First-line OCA: 36.2 (8.5) Second-line OCA: 36.2 (9.1) N (%) Female: First-line OCA: 8 (61.5) Second-line OCA: 8 (61.5) Prior knee surgery: N (%) Second-line OCA group all had prior ACI 13 (100) Other types of previous surgeries i in Second-line OCA group: Chondroplasty: 2 (16.8) Partial medial meniscectomy: 3 (25) Medial patellofemoral ligament reconstruction: 1 (8.3) ACL reconstruction: 2 (16.8) Internal fixation for OCD fragment: 3 (25) Microfracture: 2 (16.8) Prior surgery in the First-line OCA group was NR.	Location of chondral defect, N: First-line OCA Medial femoral condyle: 6 Lateral femoral condyle: 4 Patella: 4 Trochlea: 3 Medial tibial plateau: 0 Lateral tibial plateau: 0 Second-line OCA Medial femoral condyle: 11 Lateral femoral condyle: 1 Patella: 4 Trochlea: 1 Medial tibial plateau: 0 Lateral tibial plateau: 0 Mean (SD) defect size (cm^2): First-line OCA: 5.0 (2.5) Second-line OCA: 6.1 (2.9) Number of lesions: Participants had 1 or more full-thickness chondral or osteochondral defects

Author, Year Country RoB	Study Design	Intervention and Comparator (N); Total Sample Size	Follow-up Timepoints; Mean Follow-up	Mean Age (SD); N (%) Female; Prior Knee Surgery	Location of Chondral Defect; Mean Defect Size; Number of Lesions
Riff, et al. (2020)[42] United States High	NRSI	First-line OCA (79) OCA after failed MF or subchondral drilling (88) Total sample size: 167	2 years, > 5 years; mean (SD) follow-up: First-line OCA: 43.5 (20.9) months Second-line OCA: 44.4 (27.3) months	Mean age (SD): First-line OCA: 32.5 (10.4) Second-line OCA: 35.4 (10.7) N (%) Female: First-line OCA: 39 (49) Second-line OCA: 43 (49) Prior knee surgery: N (%) First-line OCA: NR Second-line OCA: 88 (100); participants selected based on failure of prior microfracture or drilling Other prior knee surgery NR	Location of chondral defect, N (%): First-line OCA Medial femoral condyle: 44 (55.7) Lateral femoral condyle: 32 (40.5) Both medial and lateral femoral condyle: 3 (3.8) Second-line OCA Medial femoral condyle: 61 (69.3) Lateral femoral condyle: 24 (27.3) Both medial and lateral femoral condyle: 3 (3.4) Mean (SD) defect size (mm^2): First-line OCA: 496 (NR) Second-line OCA: 396 (NR) Number of lesions: NR

Abbreviations: MACI = matrix-induced autologous chondrocyte implantation; MF = microfracture; N = number; NR = not reported; NRSI = nonrandomized study of intervention; OCA = osteochondral allograft transplantation; RoB = risk of bias; SD = standard deviation.

3.10.2 Findings

This section provides detailed results for each category of outcome measure. A summary of findings and the COE are provided in ***Table 25***. Detailed findings are provided in ***Appendix C***, ***Table C-40***.

First-line MACI vs. second-line MACI

PROs. The 1 NRSI reported the IKDC at follow-up times of 6, 12, and 24 points in which scores showed improvement in both groups at 6 and 12 months and were stable at the last reported time point. The difference between groups was statistically significant at all follow-up times, with changes within the range of minimally clinically significant difference for this measure (6.3 to 16.7) (***Table 5***).

Response, Treatment Failure, Reoperations. The study only reported treatment failure, defined as the need for revision surgery, in which there were few in one group or zero events in the other.

Harms

No harms were reported.

Subgroups

No subgroup analyses.

First-line OCA vs. Second-line OCA

A summary of findings and COE can be found in ***Table 26***.

PROs. Only 1 study reported an outcome measuring both knee symptom and function domains;[43] there was no statistical difference for within-group change in IKDC score between groups over an unspecified length of follow-up. Similarly, KOOS subscales reported few absolute values for results and non-statistical significance for follow-up scores or within-group changes between groups.

Response, Treatment Failure, Reoperations. Treatment failure, defined as reoperation due to graft failure, was reported by all 3 studies[41-43] and generally lower for first-line OCA though there were few events (e.g., 6 vs. 12 reoperations). Reoperation was more broadly defined as operations after graft failure or a knee procedure for any other reason. There were mixed results across the 3 studies, but there were a limited number of events and only 1 study reporting a statistically significant result, in which there were a greater number of reoperations among second-line MACI compared to first-line MACI participants.[43] No studies reported on the outcome of response.

Harms

No harms were reported.

Subgroups

No subgroup analyses.

Table 25. Summary of Findings and COE for First-line vs. Second-line MACI

No. Studies/No. Participants	Summary of Effect	Consistency	Precision	Directness	Study Limitations	Overall COE/ Direction
Patient-reported outcomes, follow-up 2 years						
1 NRSI[40]/40	IKDC improved more in the first-line MACI group than the second-line MACI group, by a clinically significant difference over 6 to 12 months[75] (6 mo: 57.8 vs. 44.3; 12 mo: 72.5 vs. 50.1, *P*<0.05) and remained stable at 24 months (77.7 vs. 48.6, *P*=0.001).	Single study body of evidence	Imprecise	Direct	High	Very low for greater effective-ness of first-line MACI[a,b]
Treatment failure, follow-up 2 years (Also Reoperation)						
1 NRSI[40]/40	Treatment failure defined as need for a revision surgery, which only occurred for patients in the second-line MACI group. Zero or few events.	Single study body of evidence	Imprecise	Direct	High	Very low for greater effective-ness of first-line MACI[b,c]

Notes:
[a] Downgrade 1 level for imprecision, small study sample.
[b] Downgrade 2 levels for study limitations; two different patient populations compared
[c] Downgrade 2 levels for imprecision, small sample size and few events.

Abbreviations: COE = certainty of evidence; IKDC = International Knee Documentation Committee Subjective Knee Form; KOOS-ADL = Knee Injury and Osteoarthritis Outcome Score; MACI = matrix-induced autologous chondrocyte implantation;

MF = microfracture; OATS = osteochondral autologous transplantation; NRSI = nonrandomized study of intervention; ROB = risk of bias.

Table 26. Summary of Findings and COE for First-line vs. Second-line OCA

No. Studies/No. Participants	Summary of Effect	Consistency	Precision	Directness	Study Limitations	Overall COE/ Direction
Patient-reported outcomes, follow-up						
1 NRSI[43]/92	One study reporting no statistically significant difference in IKDC or KOOS subscales	Single study body of evidence	Imprecise	Direct	High	Very low for comparable effective-ness[a,b]
Treatment failure, follow-up						
3 NRSIs[41-43]/285	Three studies all defining treatment failure as reoperation of a failed graft reported fewer events in the first-line groups compared to second-line group.	Consistent	Imprecise	Direct	High	Very low for comparable effective-ness[b,c]
Reoperations, follow-up						
3 NRSIs[41-43]/285	Reoperation was defined as any knee surgery; 1 study reported fewer re-operations in the first-line OCA group (calculated ARD, -19.6% [95% CI, -38.5 to -0.7%], *P*=0.04).[43] The other studies were not statistically significant	Consistent	Imprecise	Direct	High	Very low for fewer reoperations in the first-line OCA[b,d]

Notes: [a]Downgrade 1 level for imprecision, small study sample.
[b]Downgrade 2 level for study limitations (high RoB in a NRSI).
[c]Downgrade 2 level for imprecision, small study sample and few events.
[a]Downgrade 1 level for imprecision, wide confidence interval.

Abbreviations: ARD = absolute risk difference; COE = certainty of evidence, IKDC = International Knee Documentation Committee Subjective Knee Form, KOOS-ADL = Knee Injury and Osteoarthritis Outcome Score, MACI = Matrix-induced autologous chondrocyte implantation, OCA = osteochondral allograft transplantation, NRSI = nonrandomized study of intervention, ROB = risk of bias.

4. Discussion

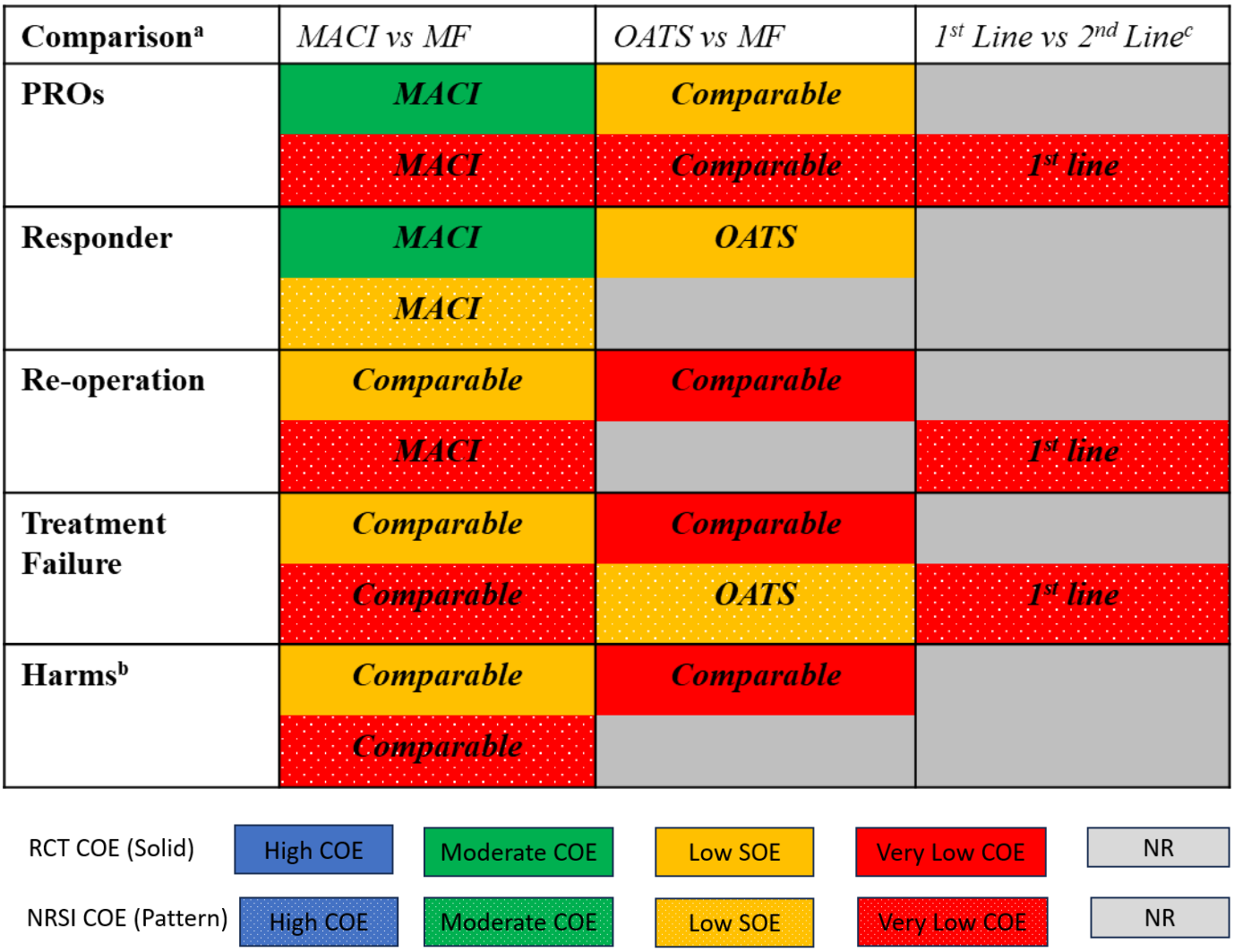
4.1 Summary of the Evidence

A summary of the COE ratings for comparisons with the largest bodies of evidence are provided in ***Figure 5***; detailed visual representation of COE ratings for all comparison are provided ***Appendix F***.

We identified the largest bodies of evidence for comparisons of MACI vs. MF and OATS vs. MF. MF is often considered first-line therapy due to being less technically difficult, limited morbidity, and low cost,[38,44] and is a clinically relevant comparator for the more involved procedures of MACI and OATS. For the MACI and MF comparison, we found moderate COE among RCTs for greater effectiveness of MACI compared to MF for PROs and response to treatment. NRSIs reported similar results, though with very low COE primarily driven by high

risk of bias and small study samples resulting in imprecision. Both RCTs and NRSIs reported comparable effectiveness of MACI and MF for treatment failure, reoperations, and harms.

Figure 5. Summary of COE Ratings for Selected Comparisons of Chondral Defect Procedures of the Knee Included in This HTA



Notes: Solid-colored cells indicate RCT study design. Speckled cells indicate NRSI study design. Gray cells indicate no evidence. Text inside cells indicates whether one of procedures has greater effectiveness or the procedures are of comparable effectiveness.
[a]Comparisons with a minimum of three studies were highlighted in this table. See ***Appendix F*** for figure of all comparisons.
[b]Includes harms for both AEs and SAEs. Color represents the highest COE of the two outcomes.
[c]Includes both MACI and OCA.

Abbreviations: AE = adverse events, MACI = matrix-induced autologous chondrocyte implantation, MF= microfracture, OATS = osteochondral autologous transplantation, PROs = patient-reported outcomes.

Outcomes from OATS and MF comparisons were similar for most outcomes with low to very low COE, with the exception of greater effectiveness of OATS for the outcome of response to treatment and reoperations (low COE). One NRSI also reported less treatment failure in the OATS group (low COE). The reasons for low COE were generally related to high risk of bias.

The 2011 State of Washington Health Care Authority HTA on OCA and OATS[45] determined evidence to be insufficient for the comparison of OATS to MF based on 2 studies that were also included in this present HTA, both of which were included in this review.[32,33] Studies in the last HTA that were excluded in this HTA related to a different scope to the prior review. The prior HTA had a key question related to validation of measures used to assess results of studies and included single arm studies and 1st and 2nd generation ACI. The scope of this HTA was limited to the knee, comparative studies, and 3rd generation ACI (MACI) Limiting the scope to comparative studies raises the robustness of our review. 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. Limiting our scope to the more modern MACI procedure, gives us a clearer picture of the comparative effectiveness of cell-based restoration to MF.

MF is the most common procedure performed to repair articular cartilage defects in clinical practice and is often used as a "standard of care" comparator for more technically involved procedures in comparative effectiveness research.[38] However, MF may not be appropriate for some lesions, based on size, depth, or location. Comparative effectiveness studies are not always based on lesion-specific characteristics (e.g., eligibility criteria allowing a wide range of lesion sizes) which does not represent clinical care. Our results should be interpreted in light of the different contexts of clinical care vs. clinical studies. In many cases, surgeons will pick a procedure based on lesion-specific characteristics, which may obviate consideration of another procedure.

Chondroplasty can be an option for patients with symptoms from chondral defects. In our HTA, we found only 1 small study (N = 47) reporting 1 outcome comparing MACI or OATS to chondroplasty, limiting our ability to make a judgment about the comparative effectiveness of these procedures compared to chondroplasty. This may reflect the practice community's assessment of chondroplasty as an inferior option, as it is not a reparative technique.

Given that treatment of cartilage defects is often a procedure for younger, active patients for whom arthroplasty is not the optimal choice, when a cartilage repair procedure fails to improve a patient's symptoms or function, a surgeon and patient may consider a second-line cartilage replacement (OATS or OCA) or restoration procedure (MACI). Among the studies comparing MACI to MF and OATS to MF, many studies reported few reoperations, limiting precision resulting in low COE for reoperation outcomes. A few NRSIs reported lower reoperations or treatment failure in the MACI group or OATS group compared with MF.[23,24,34] Studies comparing first-line MACI or OCA to second-line MACI or OATS after MF reported greater or comparable effectiveness of a first-line MACI or OCA procedure, reduced treatment failure for first-line MACI or OCA procedures, and similar harms, whether the MACI or OCA was performed as first- or second-line surgery.[40,43] This may signal that a second procedure may still have have significant benefits after a failed first procedure without additional harms. Additionally, first-line treatment with MACI compared to the more standard treatment of MF, may result in a reduced need to reoperate and could be considered as first-line treatment despite higher upfront costs.[46] One postulated mechanism is that though MF is generally used to treat surface lesions, the procedure may affect the underlying bone, making MACI less successful.[46]

MF is the most commonly performed cartilage repair procedure, with lower cost being 1 consideration.[47-49] We only identified 1 study evaluating the cost-effectiveness of OATS compared to MF.[37] The results from this decision analysis were mixed based on cost per point improvement on validated knee function and pain scores without a clear indication of which procedure is more cost-effective. However, based on return to play outcome, OATS appears to be more cost-effective at 1, 3 and 10 years of follow-up. This appears to be driven by higher failure rates for MF over time, which offsets the higher initial cost of OATS. However, this study is limited since costs were derived from a single institution. Further research on cost-effectiveness of all cartilage repair surgeries would provide more data for policy makers to consider in coverage decisions.

The other comparisons identified in this HTA included MACI vs. OATS, OCA vs. OATS, and AMIC vs. MF. For all of these comparisons, we identified a few NRSIs reporting few outcomes that we rated as low to very low COE. This limited amount of evidence may be related to the differential use of these procedures for different sized lesions and subchondral bone involvement (***Table 1***). For example, OCA is usually selected over OATS for patients with larger lesions and so studies directly comparing these procedures are less likely be conducted. We identified few studies evaluating OCA due to the size and depth of lesions treated and that the most appropriate comparator to OCA may be arthroplasty. Surgeons and patients may be trying to avoid arthroplasty due to young age and activity level and, clinically, the same surgeon may not have expertise in both articular cartilage repair and arthroplasty. OCA also requires a size and location matched donor and cadaveric tissue is only viable for a short amount of time, limiting the feasibility of this procedure, particularly in a study context.

We identified 1 RCT comparing a cell-free implant, similar to OCA, to MF or chondroplasty, in which patients receiving the cell-free implant had greater increases in PROs and higher response to therapy (moderate COE) and treatment failure and harms with comparable effectiveness (low COE). These results suggest that AEs in surgical products and techniques may yield superior results to procedures commonly performed in current clinical practice.

A limited number of studies reported harms, and when they were reported, the COE was low or very low due to few events and high risk of bias in the evidence base. More robust and systematic ascertainment of harms in future studies would facilitate pooling across studies and would likely increase the COE ratings that could be assigned to harm outcomes.

The inclusion and exclusion criteria of this systematic review varied significantly from prior reviews and the 2011 HTA on OATS.[45] Foremost, we excluded first- and second-generation ACI procedures, which use a periosteal patch rather than a porcine or synthetic scaffold on which to culture chondrocytes (MACI). MACI has fewer complications[9] and has largely replaced ACI in practice. We also excluded studies without a comparator group to limit the review to higher quality evidence for drawing causal inferences. We excluded intermediate outcomes, including imaging and pathologic findings, opting to focus on PROs and other outcomes more relevant to patients and policy makers.

4.2 Limitations of the Evidence Base

This HTA included many RCTs and NRSIs with high risk of bias due to lack of transparency about the randomization process, limited adjustments for confounders, and not reporting missing data and if analyses to limit bias from missing data were performed. Confounding in the NRSI evidence for this topic is particularly problematic because the selection of restoration procedure is often based on clinical characteristics and surgeon experience or preference, both of which may be related to the outcome. Many of the included studies had extended follow-up times, which is often associated with significant attrition, and many studies did not report the number of patients with follow-up data available at various timepoints. Studies with small sample sizes also resulted in imprecise effect estimates. Studies with more robust methodology are needed to increase the certainty of the evidence. Reducing the high risk of bias in NRSIs includes thorough consideration of confounding factors, reporting of missing data, and use of statistical methods to limit bias.

Almost no studies in this HTA reported on time to return to work or rehabilitation time, which is particularly important given many rehabilitation programs were reported to last 6 to 12 months with the goal of returning the individual to high-impact sports. The majority of PROs include questions about very specific knee symptoms or return to high-impact sports, the latter of which may not be as relevant to more general population compared to high-level athletes. Furthermore, with the exception of the Tegner score and KOOS-ADL domains, questions related to daily function are usually part of an overall score. Measuring time to pre-injury function and return to work would expand understanding of the effectiveness of cartilage repair and restoration procedures in a broader population, important factors in clinical and policy decisions. Finally, we only identified 1 eligible study on cost-effectiveness that compared OATS with MF with costs inputs derived from a single institution.

4.3 Clinical Practice Guidelines

Clinical practice guidelines and recommendations for chondral defect restoration are presented in ***Table 27***. We rated the quality of each guideline using the Appraisal of Guidelines for Research & Evaluation II (AGREE-II) instrument.[84] With this instrument, 6 domains are assessed and an overall score of 1 (lowest quality) to 7 (best quality) is assigned. We identified 3 organizations with treatment guidelines for chondral defect repair of the knee, 1 of which was related to rehabilitation after articular cartilage surgery.[50] United Kingdom guidelines addressed mosaicplasty, which includes OATS, and stated that evidence of harms and benefits were adequate to support the use of the procedure.[51] A guideline from the American Society of Pain and Neuroscience stated that mosaicplasty was an effective treatment with qualifications, while bone marrow stimulation techniques, OATS, and ACI were "neither recommended nor advisable."[52]

We searched the websites of several additional U.S. and international orthopedic surgery societies (listed in ***Appendix B***) and did not identify any additional clinical practice guidelines for the procedures of interest in this HTA.

Table 27. Clinical Practice Guidelines including Recommendations on the Use Chondral Defect Repair Procedures of the Knee

Title and Organization	Year	Procedure	AGREE Rating	Summary of Treatment Recommendation(s)
Knee Pain and Mobility Impairments: Meniscal and Articular Cartilage Lesions Revision 2018: Clinical Practice Guidelines Linked to the International Classification of Functioning, Disability and Health from the Orthopaedic Section of the **American Physical Therapy Association**[a][50]	2018	Articular cartilage lesions	4	Clinicians may use early progressive knee motion following knee meniscal and articular cartilage surgery. (C) Physicians may need to delay return to activity depending on the type of articular cartilage surgery. (E) Clinicians should use a stepwise progression of weight-bearing to reach full bearing by 6 to 8 weeks after MACI for articular cartilage lesions. (B) Clinicians should provide supervised, progressive, range-of-motion exercises; progressive strength training of the knee and hip muscles; and neuromuscular training to patients with knee meniscus tears and articular cartilage lesions and after meniscus or articular cartilage surgery. (B)
Consensus Guidelines on Interventional Therapies for Knee Pain (STEP Guidelines) from the **American Society of Pain and Neuroscience**[b][52]	2022	Marrow stimulation ACI Mosaicplasty OATS	4	• Marrow stimulation is an effective treatment for younger patients with small, isolated hyaline defects. (C) • ACI is an effective treatment for young patients with small, isolated cartilage lesions less than 2 cm^2 who have tried and failed conservative care. (C) • Mosaicplasty is an effective long-term treatment option for patients 18 to 50 years old with hyaline cartilage lesions 2 cm^2 to 5 cm^2. (A) OATS is an effective knee joint preservation technique. (C)
Mosaicplasty for symptomatic articular cartilage defects of the knee: **National Institute for Health and Care Excellence (NICE)**[51]	2018	Mosaicplasty (OATS)	4	Current evidence on the safety and efficacy of mosaicplasty for knee cartilage defects is adequate to support the use of this procedure provided that standard arrangements are in place for clinical governance, consent, and audit. The procedure should only be done by surgeons experienced in cartilage surgery and who have specific training in mosaicplasty for knee cartilage defects. Clinicians should enter data from all patients having the procedure onto the International Cartilage Regeneration and Joint Preservation Society Patient Registry.

Notes: [a] Recommended grade definitions for the American Physical Therapy Association are as follows: B – Moderate Evidence: single, high-quality randomized controlled trial or a preponderance of level II studies (e.g., prospective studies, trials with high risk of bias) support the recommendation; C – Weak Evidence: single level II study or a preponderance of level III and IV studies (e.g., case-control studies, case series), including statements of consensus by content experts, support the recommendation); E – Expert Opinion (best practices based on the clinical experience of the guidelines development team).
[b] Recommended grades for American Society of Pain and Neuroscience are as follows: Grade A – Extremely recommendable based on at least one randomized controlled trial (good evidence that the measure is effective and that benefits outweigh the harms); C – Neither recommendable nor in advisable based on cohort or case studies and well-designed controls (at least moderate evidence that the measure is effective, but benefits are similar to harms and a general recommendation cannot be justified).

Abbreviations: ACI = autologous chondrocyte implantation; MACI = matrix-induced autologous chondrocyte implantation; OATS = osteochondral autologous transplantation.

4.4 Selected Payer Coverage Policies

No Medicare national coverage determination or local coverage determinations for chondral defect restoration procedures were identified. We also conducted a scan of commercial payer coverage documents for chondral defect restoration (***Table 28***). Four payers had coverage policies for ACI or MACI, 3 payers had policies for OATS or OCA, and 1 payer had a policy for MF or drilling. The clinical criteria for coverage varied across the payers and procedures (***Table 29***). All policies required individuals with closed growth plates; some had specific requirements for full-thickness focal lesions and lesion size dependent on procedures (e.g., lesions < 4 cm^2 for MF). Other requirements also included failed conservative therapy, age too young to be considered for a total knee replacement (e.g., age < 55 years), and BMI less than 35.

Table 28. Select Overview of Payer Coverage Policies for Chondral Defect Repair of the Knee

Condition	Medicare	Cigna[85]	Kaiser Permanente	Premera Blue Cross[86,87]	Regence BlueShield[88]	UnitedHealth [89]
Microfracture	—	—	—	—	—	✓
Drilling	—	—	—	—	—	—
OATS	—	✓	—	✓	—	✓
OCA	—	✓	—	✓	—	✓
ACI/MACI	—	✓	—	✓	✓	✓

Notes: ✓ = covered; X = not covered; — = no policy identified.

Abbreviations: ACI = autologous chondrocyte implantation; MACI = matrix-induced autologous chondrocyte implantation; OATS = osteochondral autologous transplantation; OCA = osteochondral allograft transplantation.

Table 29. Chondral Defect Repair Coverage Policies for Selected Commercial Payers

Payer (Effective Date)	Coverage Policy
Cigna[85] (4/15/2024)	**MF/Drilling** No coverage policy for articular cartilage of the knee. **OATS, OCA, ACI/MACI** Each of the following procedures is considered experimental, investigational, or unproven for treatment of articular cartilage defects involving joints other than the distal femur and patellar articular cartilage within the knee (e.g., ankle, elbow, shoulder): • ACI (e.g., Carticel®, MACI® [Vericel Corporation, Cambridge, MA]) • Osteochondral allograft transplantation • Osteochondral autograft transplantation Articular cartilage repair using ANY of the following, for any joint, is considered experimental, investigational, or unproven: • Cartilage regeneration membrane (e.g., Chondro Gide®) • Xenograft implantation into the articular surface • Synthetic resorbable polymers (e.g., PolyGraft™ BGS, TruFit® [cylindrical plug], TruGraft™ [granules]) • Juvenile cartilage allograft tissue implantation, including minced cartilage (e.g., DeNovo® NT Natural Tissue Graft, DeNovo® ET™ Engineered Tissue Graft [ISTO Technologies, Inc., St. Louis, MO / Zimmer, Inc., Warsaw IN]; BioCartilage® [Arthrex, Naples, Florida]) • Decellularized osteochondral allograft implant (e.g., Chondrofix® Osteochondral Allograft [Zimmer Biomet, Warsaw, IN])

Payer (Effective Date)	Coverage Policy
Premera Blue Cross[86,87] (8/1/2023)	**MF/Drilling** None found. **OATS** Osteochondral autografting, using one or more cores of osteochondral tissue, may be considered medically necessary: • For the treatment of symptomatic, full-thickness cartilage defects of the knee caused by acute or repetitive trauma in individuals who have had an inadequate response to a prior surgical procedure, when all of the following have been met: - Adolescent individuals should be skeletally mature with documented closure of growth plates (e.g., ≥ 15 years). - Adult individuals should be too young to be considered an appropriate candidate for total knee arthroplasty or other reconstructive knee surgery (e.g., ≤ 55 years). - Focal, full-thickness (Grade III or IV) unipolar lesions on the weight-bearing surface of the femoral condyles, trochlea, or patella that are between 1.0 and 2.5 cm^2 in size. - Documented minimal to absent degenerative changes in the surrounding articular cartilage (Outerbridge Grade II or less) and normal-appearing hyaline cartilage surrounding the border of the defect. - Normal knee biomechanics or alignment and stability achieved concurrently with osteochondral grafting. • Large (area > 1.5 cm^2) or cystic (volume > 3.0 cm^3) osteochondral lesions of the talus. • Revision surgery after failed marrow stimulation for osteochondral lesion of the talus. **OCA** Fresh osteochondral (human cadaver tissue) allografting may be considered medically necessary as a technique to repair: • Full-thickness chondral defects of the knee caused by acute or repetitive trauma when other cartilage repair techniques (e.g., microfracture, osteochondral autografting or ACI) would be inadequate due to lesion size, location, or depth). • Large (area > 1.5 cm^2) or cystic (volume > 3.0 cm^3) osteochondral lesions of the talus when autografting would be inadequate due to lesion size, depth, or location. • Revision surgery after failed prior marrow stimulation for large (area > 1.5 cm^2) or cystic (volume > 3.0 cm^3) osteochondral lesions of the talus when autografting would be inadequate due to lesion size, depth, or location. *Additional information related to OATS and OCA*: • If debridement is the only prior surgical treatment, consideration should be given to marrow stimulating techniques before osteochondral grafting is performed, particularly for lesions less than 1.5 cm^2 in area or 3.0 cm^3 in volume. • Severe obesity (e.g., body mass index > 35 kg/m^2) may affect outcomes due to the increased stress on weight-bearing surfaces of the joint. • Misalignment and instability of the joint are contraindications. Therefore, additional procedures, such as repair of ligaments or tendons or creation of an osteotomy for realignment of the joint, may be performed at the same time. In addition, meniscal allograft transplantation may be performed in combination, either concurrently or sequentially, with osteochondral allografting or osteochondral autografting.

Payer (Effective Date)	Coverage Policy
Premera Blue Cross[86,87] (8/1/2023) (cont.)	**ACI/MACI** ACI of the knee may be considered medically necessary when ALL of the following criteria are met: • Severe disabling knee pain and loss of knee function caused by acute or repetitive trauma that interferes with activities of daily living or work ability is present. • Adolescent individuals should be skeletally mature with documented closure of growth plates (e.g., ≥ 15 years). • Adult individuals are too young to be considered an appropriate candidate for total knee arthroplasty or other reconstructive knee surgery (e.g., ≤ 55 years). • Focal, full-thickness (Grade III or IV Outerbridge scale) unipolar lesions of the weight-bearing surface of the femoral condyles, trochlea, or patella that are at least 1.5 cm^2 in size. • Documented minimal to absent degenerative changes in the surrounding articular cartilage (Outerbridge Grade II or less), and normal-appearing hyaline cartilage surrounding the border of the defect. • All of the following are present on exam: - Stable knee with intact or reconstructed ligaments (ACL or PCL) or repairs are planned with the procedure - Normal joint alignment **Normal joint space**
Regence Blue Shield[88] (9/1/2023)	**MF/Drilling** None found **OATS/OCA** None found **ACI/MACI** I. ACI may be considered medically necessary for the treatment of disabling full-thickness articular cartilage defects of the knee caused by acute or repetitive trauma, when all of the following criteria are met (A–E): • Adolescent patients should be skeletally mature with documented closure of growth plates (e.g., ≥ 15 years). Adult patients should be too young to be considered an appropriate candidate for total knee arthroplasty or other reconstructive knee surgery (e.g., ≤ 55 years). • Focal, full-thickness (Grade III or IV) unipolar lesions of the patella or on the weight-bearing surface of the femoral condyles or trochlea at least 1.5 cm^2 in size. • Documented Outerbridge Grade II or less degenerative changes in the surrounding articular cartilage and normal-appearing hyaline cartilage surrounding the border of the defect. • Normal knee mechanics, alignment, and stability are present before or are planned to be restored simultaneously with the ACI procedure. • Body mass index less than 35. II. ACI when Criterion I is not met and for all other joints, including talar, and any indications other than those listed above is considered investigational.

Payer (Effective Date)	Coverage Policy
United Health[89] (5/1/2023)	**MF** MF repair to treat full- and partial-thickness chondral defects of the knee is proven and medically necessary when all the following criteria are met. • Symptomatic focal cartilage defects of the weight-bearing femoral condyles, tibial plateau, trochlea, and patella • Defect has been identified by MRI, arthrogram, or arthroscopy • Outerbridge Grade III or IV cartilage lesions • Measure less than or equal to 4 cm^2 MF repair of the knee is unproven and not medically necessary with any of the following indications: • Misalignment of the knee • Osteoarthritis • Systemic immune-mediated disease, disease-induced arthritis, or cartilage disease • Unwilling or unable to participate in post-operative physical rehabilitation program **OATS/OCA** Osteochondral autograft and allograft transplantation is proven and medically necessary for treating individuals with cartilage defects of the knee. For medical necessity clinical coverage criteria for osteochondral autograft and allograft: • Transplantation, refer to the InterQual® Procedures[a] • Arthroscopy or Arthroscopically Assisted Surgery, Knee • Arthroscopy or Arthroscopically Assisted Surgery, Knee (Pediatric) • Arthrotomy, Knee Osteochondral autograft and allograft transplantation is unproven and not medically indicated for all other indications than those listed above. Articular cartilage repair is unproven and not medically necessary for treating individuals with any of the following due to insufficient evidence of efficacy: • Use of minced articular cartilage repair (whether synthetic, allograft, or autograft) for treating osteochondral defects of the knee • Use of Xenograft implantation into the articular surface of any joint • Use of cryopreserved viable Osteochondral Allograft products (e.g., Cartiform) **ACI/MACI** Autologous chondrocyte transplantation (ACT) is proven and medically necessary for treating individuals with symptomatic full-thickness articular cartilage defects when all the following criteria are met: • Each individual lesion is: - Greater than or equal to 2 cm^2 - A result of acute or repetitive trauma - Single or multiple full-thickness (Outerbridge Classification of Grade III or IV) articular cartilage defect of the femoral condyle (medial, lateral, or trochlea) and/or patella • Knee is stable with intact menisci and ligaments. • Normal joint space and alignment confirmed by X-ray. • No active inflammatory or other arthritis, clinically and by X-ray. • Failed non-surgical conservative management (e.g., physical therapy, braces, and/or nonsteroidal anti-inflammatory drugs). • Individual is less than 55 years of age.

Payer (Effective Date)	Coverage Policy
United Health[89] (5/1/2023) (cont.)	ACT is unproven and not medically necessary for treating individuals with the following indications due to insufficient evidence of efficacy: • Treatment of joints other than the knee • Growth plates have not closed • History of partial-thickness defects • Osteochondritis dissecans • Malignancy in the bone, cartilage, fat, or muscle of the treated limb • Active infection in the affected knee • Instability of the knee • History of total meniscectomy • Repeat ACT • Active inflammatory degenerative, rheumatoid, or osteoarthritis

Notes: [a] InterQual guidance not publicly available.

Abbreviations: ACI = autologous chondrocyte implantation; ACL = anterior cruciate ligament; MACI = matrix-induced autologous chondrocyte implantation; MF = microfracture; MRI = magnetic resonance imaging; OATS = osteochondral autologous transplantation; OCA = osteochondral allograft transplantation; PCL = posterior cruciate ligament.

4.5 Limitations of This HTA

This HTA was limited to peer-reviewed studies published in English. We did not include data or results presented solely in conference abstracts. We only included validated measures for disease specific PROs; we did not include general QOL outcomes. We did not include first- or second-generation ACI procedures given fewer complications of third-generation MACI and limiting this review to procedures in current practice. We included only comparative study designs, which raises the quality of effectiveness results but may not offer a comprehensive assessment of longer-term benefits and harms. Studies conducted in countries other than *very high* on the United Nations Human Development Index were also excluded from this review. Finally, we only included cost studies based on U.S. dollar inputs as this offers the most applicable results for HTCC decision making.

4.6 Ongoing and Future Research

We identified 2 ongoing trials that were relevant to the comparisons in this review. One trial focuses on MACI compared to MF in individuals ages 10 to 17 years, is funded by industry, and is expected to be completed in 2027. The other trial compares MACI to MF in adult patients and it also expected to be completed in 2027.

5. Conclusion

This HTA examined the comparative effectiveness, safety, and cost-effectiveness of treatments for chondral defects of the knee. MACI has low to moderate evidence for greater effectiveness compared to microfracture for PROs and response to treatment among RCTs, the highest level of COE identified in this HTA. OATS and MF were comparable for outcomes indicating similar benefit of these procedures. Both MACI and OATS had comparable harms to MF, though our COE was low. The rest of the evidence base was limited with respect to the other comparisons examined. Rigorous study design, consistent reporting of outcomes, particularly harms, would strengthen the evidence base for comparative effectiveness of these procedures.

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Appendix A. State of Washington Health Care Authority Utilization Data

The State of Washington Health Care Authority will provide data on utilization of the chondral defects included in this health technology assessment (HTA).

Appendix B. Search Strategy

Dates of Search: Inception through November 30, 2023

PubMed (Limits: English language)

Condition (knee AND cartilage)
#1 ("Knee Joint"[Mesh] OR "Knee Injuries"[Mesh] OR "knee"[tw] OR "knees"[tw] OR "knee lesion*"[tw] OR "patellofemoral lesion*"[tw] OR "trochlear defect*"[tw]) **AND** ("Cartilage, Articular/pathology"[Mesh] OR "Cartilage, Articular/physiopathology"[Mesh] OR "articular cartilage*"[tw] OR "cartilage lesion*"[tw] OR "cartilage defect*"[tw] OR "chondral defect*"[tw] OR "chondral lesion*"[tw] OR "condylar lesion*"[tw] OR "condyle lesion*"[tw] OR "osteochondral defect*"[tw]) Filters: English 13,303

Intervention (surgery)
#2 "Cartilage, Articular/surgery"[Mesh] OR "Cartilage, Articular/transplantation"[Mesh] OR "Cartilage Diseases/surgery"[Mesh] OR "Cartilage/surgery"[Mesh] OR "Cartilage/transplantation"[Mesh] OR "Chondrocytes"[Mesh] OR "Chondrocytes/transplantation"[Mesh] OR "Arthroplasty"[Mesh] OR "Arthroplasty, Subchondral"[Mesh] OR "Tissue Scaffolds"[Mesh] OR "chondroplasty"[tw] OR "articular cartilage repair*"[tw] OR "articular resurfacing"[tw] OR "abrasion arthroplasty"[tw] OR "microfracture*"[tw] OR "autologous chondrocyte implantation*"[tw] OR "ACI"[tw] OR "matrix-assisted chondrocyte implantation*"[tw] OR "matrix-assisted autologous chondrocyte implantation*"[tw] OR "matrix-assisted autologous chondrocyte transplantation*"[tw] OR "MACI"[tw] OR "mosaicplasty"[tw] OR "osteochondral autograft transfer system*"[tw] OR "OATS"[tw] OR "osteochondral cylinder transplantation*"[tw] OR "osteochondral cylinder*"[tw] OR "osteochondral allograft*"[tw] OR "cartilage repair*"[tw] OR "cartilage restoration*"[tw] OR "cartilage implantation*"[tw] OR "cartilage transplantation*"[tw] OR "marrow stimulation*"[tw] OR "osteochondral autografting"[tw] OR "osteochondral autograft*"[tw] Filters: English 159,205

Condition AND Intervention
#3 #1 **AND** #2 Filters: English 5,878
Exclusions - Publication Types
#4 #3 NOT ("Address"[pt] OR "Autobiography"[pt] OR "Bibliography"[pt] OR "Biography"[pt] OR "Book Illustrations"[pt] OR "Case Reports"[pt] OR "Clinical Conference"[pt] OR "Collected Work"[pt] OR "Comment"[pt] OR "Congress"[pt] OR "Consensus Development Conference"[pt] OR "Consensus Development Conference, NIH"[pt] OR "Dataset"[pt] OR "Dictionary"[pt] OR "Directory"[pt] OR "Editorial"[pt] OR "Ephemera"[pt] OR "Festschrift"[pt] OR "Government Publication"[pt] OR "Guideline"[pt] OR "Historical Article"[pt] OR "Interactive Tutorial"[pt] OR "Interview"[pt] OR "Lecture"[pt] OR "Legal Case"[pt] OR "Legislation"[pt] OR "Letter"[pt] OR "News"[pt] OR "Newspaper Article"[pt] OR "Patient Education Handout"[pt] OR "Periodical Index"[pt] OR "Personal Narrative"[pt] OR "Pictorial Work"[pt] OR "Popular Work"[pt] OR "Portrait"[pt] OR "Technical Report"[pt] OR "Video Audio Media"[pt] OR "Webcast"[pt] OR "case report*"[tiab]) Filters: English 5,533

Exclusions – Animal Studies
#5 #4 NOT ("Animals"[Mesh] NOT "Humans"[Mesh]) Filters: English **4,090**

Study Design – Trials

#6 #5 AND (“Controlled Clinical Trial”[pt] OR “Clinical Trial, Phase IV”[pt] OR “Clinical Trial, Phase III”[pt] OR “Meta-Analysis”[pt] OR “Comparative Study”[pt] OR “Randomized Controlled Trial”[pt] OR “Single-Blind Method”[Mesh] OR “Double-Blind Method”[Mesh] OR “Random Allocation”[Mesh] OR “Pragmatic Clinical Trial”[pt] OR “Clinical Trial”[pt] OR “randomized”[tiab] OR “ramdomised”[tiab] OR “trial”[tiab] OR “trials”[tiab]) Filters: English **771**

Study Design - Systematic Reviews including Meta-Analyses
#7 #5 AND (("Review"[pt] AND "systematic"[tiab]) OR "systematic review*"[tw] OR ("Review Literature as Topic"[Mesh] AND "systematic"[tiab]) OR "Meta-Analysis"[pt] OR "Meta-Analysis as Topic"[Mesh] OR "metaanaly*"[tw] OR "meta-analy*"[tw] OR "Systematic Review"[pt] OR "Systematic Reviews as Topic"[Mesh]) Filters: English **237**

Study Design – Observational
#8 #5 AND ("Observational Study"[pt] OR "Comparative Study"[pt] OR "Epidemiologic Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR "Cohort Studies"[Mesh] OR "Follow-up Studies"[Mesh] OR "observational"[tiab]) Filters: English **1,455**

Study Design – Cost Studies
#9 #5 AND ("Costs and Cost Analysis"[Mesh] OR "cost-benefit*"[tiab] OR "cost benefit*"[tiab] OR "cost-effective*"[tiab] OR "cost effective*"[tiab] OR "cost-utility"[tiab] OR "cost utility"[tiab] OR "cost-utilities"[tiab] OR "cost utilities"[tiab] OR "Insurance, Health, Reimbursement"[Mesh] OR "Prospective Payment System"[Mesh] OR "cost*"[tiab] OR "costs"[tiab]) Filters: English **128**

Cochrane Database of Systematic Reviews

Condition

Knee
#1 [mh "Knee Joint"] OR [mh "Knee Injuries"] OR ("knee" OR "knees" OR knee NEXT lesion* OR patellofemoral NEXT lesion* OR trochlear NEXT defect*):ti,ab,kw 40,399
Cartilage
#2 [mh "Cartilage, Articular"/PA] OR [mh "Cartilage, Articular"/PP] OR (articular NEXT cartilage* OR cartilage NEXT lesion* OR cartilage NEXT defect* OR chondral NEXT defect* OR chondral NEXT lesion* OR condylar NEXT lesion* OR condyle NEXT lesion* OR osteochondral NEXT defect*):ti,ab,kw 1,300
Knee AND Cartilage
#3 #1 AND #2 1,028

Intervention (surgery)
#4 [mh "Cartilage, Articular"/SU] OR [mh "Cartilage, Articular"/TR] OR [mh "Cartilage Diseases"/SU] OR [mh Cartilage/SU] OR [mh Cartilage/TR] OR [mh Chondrocytes] OR [mh Chondrocytes/TR] OR [mh Arthroplasty] OR [mh "Arthroplasty, Subchondral"] OR [mh "Tissue Scaffolds"] OR ("chondroplasty" OR "articular cartilage" NEXT repair* OR "articular resurfacing" OR "abrasion arthroplasty" OR microfracture* OR "autologous chondrocyte" NEXT implantation* OR "ACI" OR "matrix-assisted chondrocyte" NEXT implantation* OR "matrix-assisted autologous chondrocyte" NEXT implantation* OR "matrix-assisted autologous chondrocyte" NEXT transplantation* OR "MACI" OR "mosaicplasty" OR "osteochondral autograft transfer" NEXT system* OR "OATS" OR "osteochondral cylinder" NEXT transplantation* OR osteochondral NEXT cylinder* OR osteochondral NEXT allograft* OR cartilage NEXT repair* OR cartilage NEXT restoration* OR cartilage NEXT implantation* OR cartilage NEXT

transplantation* OR marrow NEXT stimulation* OR "osteochondral autografting" OR osteochondral NEXT autograft*):ti,ab,kw 8,918

Condition AND Intervention
#5 #3 AND #4 in Cochrane Database of Systematic Reviews **3 (0 unique overall, 1 added for SRs)**

Clinical Practice Guideline Search

Orthopedic surgery societies searched in the United States

- American Academy of Orthopedic Surgeons
- American Association of Hip and Knee Surgeons
- American College of Rheumatology
- American Orthopedic Association
- American Orthopedic Society of Sports Medicine
- International Cartilage Regeneration & Joint Preservation Society
- Osteoarthritis Research Society International
- The Clinical Orthopaedic Society

International organizations searched

- Canadian Agency for Drugs and Technologies in Health
- Ontario Health Technology Advisory Committee
- International Combined Orthopaedic Research Societies
- The New Zealand Guidelines Group

Appendix C. Evidence Tables

Table C-1. Study Characteristics for Included Nonrandomized Studies of MACI vs. Chondroplasty

Author (Year) Country Registry #	Years conducted	Sponsor	Recruitment Setting	Inclusion Criteria	Exclusion Criteria
Macarini et al. (2003)[19] Italy	1998 to 2002	NR	NR	Focal osteochondral lesions of grade II and III according to Noyes	NR

Abbreviations: MACI = matrix-induced autologous chondrocyte implantation; NR = not reported.

Table C-2. Intervention Characteristics for Included Nonrandomized Studies of MACI vs. Chondroplasty

Author (Year)	Sample Size	Intervention Group(s)	Control Group	Rehabilitation Protocol
Macarini et al. (2003)[19]	47	MACI (specific type NR) comprising 3 phases: 1. Small amount of cartilaginous tissue was harvested in arthroscopy from the damaged joint 2. Chondrocytes were cultivated in vitro until an adequate concentration was reached and then seeded on a type I/III collagen matrix 3. At least 6 weeks later under arthrotomy; osteochondral lesion was prepared, trimmed, and covered by the collagen matrix using fibrin glue Technique category N (%): Open, Arthrotomy: 7 (100)	Chondroplasty/debridement: Abrasion chondroplasty surgery, consisting of the removal of the detached cartilage and the successive abrasion with a motorized burr of the subchondral bone Technique category N (%): Arthroscopic: 40 (100)	All patients underwent rehabilitative physiotherapy which involved the early mobilization of the joint followed by progressive weight-bearing exercises

Abbreviations: MACI = matrix-induced autologous chondrocyte implantation; N = number; NR = not reported.

Table C-3. Population Characteristics for Included Nonrandomized Studies of MACI vs. Chondroplasty

Author (Year)	Prior Knee Surgery	Injury Mechanism; Severity; Duration of Symptoms Prior to Surgery	Location of Chondral Defect; Mean Defect Size; Number of Lesions	Mean Age (SD) N (%) Female N (%) Race/Ethnicity Mean BMI
Macarini et al. (2003)[19]	NR	Injury mechanism: NR Severity of injury N (%): Grade II and III according to Noyes: 47 (100) Duration of symptoms prior to surgery: NR	Location of chondral defect: NR Mean defect size: NR Number of lesions: NR	Mean age, (range) 31, (19 to 45) N (%) Female: NR N (%) Race/Ethnicity: NR Mean BMI: NR

Abbreviations: BMI = body mass index; MACI = matrix-induced autologous chondrocyte implantation; N = number; NR = not reported; SD = standard deviation.

Table C-4. Efficacy Outcomes for Included Nonrandomized Studies of MACI vs. Chondroplasty

Author (Year) Intervention(s) and Comparison Sample size	Results
Macarini et al. (2003)[19] Intervention: MACI (specific type NR) Comparator: Chondroplasty/ debridement Sample size: 47	**Composite Scores** **Resumed normal sport and work activities,** 1 year post-surgery, MACI: 7; Chondroplasty: 40, N (%) MACI: 5 (71) Chondroplasty: 24 (60) **KOOS Total, CKRS, IKDC Subjective Knee Evaluation Form, Lysholm score, Hospital for Special Surgery Score:** NR **Activity Scores** **Tegner Score, KOOS-ADL, KOOS-Sport:** NR **Symptom Scores** **KOOS-Pain, KOOS-Symptoms, KOOS-QOL:** NR **Responder, treatment failure, reoperation** **Responder, Treatment failure, Reoperation:** NR **Subgroup Analyses:** NR

Abbreviations: IKDC = International Knee Documentation Committee; KOOS = Knee Injury and Osteoarthritis Outcome Score; KOOS-ADL = Knee Injury and Osteoarthritis Outcome Score, Activities of Daily Living subscale; KOOS-QOL = Knee Injury and Osteoarthritis Outcome Score, Quality of Life subscale; MACI = matrix-induced autologous chondrocyte implantation; N = number; NR = not reported.

Table C-5. Study Characteristics for Included RCTs and Nonrandomized Studies of MACI vs. MF

Author (Year) Country Registry # Study Design	Years conducted	Sponsor	Recruitment Setting	Inclusion Criteria	Exclusion Criteria
Basad et al. (2010)[22] Germany RCT	2000 to 2005	NR	Single orthopedic clinic in Germany	Age ≥ 18 and ≤ 50 with posttraumatic, single, isolated, symptomatic chondral defects (4-10 cm^2) of the femoral condyle or patella Alignment criteria: Varus or vakgus abnormalities were excluded.	Chronic inflammatory arthritis, instability of the knee joint, prior or planned meniscectomy (> 30% of the meniscus), BMI > 30, varus or valgus abnormality, osteonecrosis, osteoarthritis and chondrocalcinosis.
Crawford et al. (2012)[21] United States NCT00548119 RCT	NR	Industry: Histogenics Corporation	NR	18-55 years; had a symptomatic ICRS grade III cartilage lesion of the femoral condyle; lesions 1-3cm; lesions with total area less than area of NeoCart (7-8cm^2) Alignment criteria: Excluded for malalignment > 3 degrees outside mechanical axis of other knee, or need for surgery to correct malalignment	Any previous surgical treatment of lesion other than debridement; BMI > 35; Joint space narrowing of less than a third compared with normal knee, or < 3 mm of joint space measured on radiographs, osteophytes, sclerosis, or degenerative conditions in treatment knee noted on radiographs; Other symptomatic pathology of contralateral knee; Surgery on contralateral knee within 8 weeks prior to scheduled arthroscopy; Inflammatory arthritis; Ankylosing spondylitis; Synovioma, hemangioma, pigmented villonodular synovitis, or neoplasms in knee; Subchondral bone loss; Patient requiring a concomitant procedure other than medial or lateral partial meniscectomy, removal of loose bodies, debridement of articular cartilage lesions other than that being treated and synovectomy; Untreated ACL and/or PCL deficiency or ligamentous instability in involved knee; Meniscus with rim < 50% of normal thickness; ICRS grade III or IV kissing lesion; More than slight anterior knee pain referable to patellofemoral joint and ICRS grade 2 (B), 3 (C), or 4 trochlear groove or patellar lesion
Saris et al. (2014)[20] Brittberg et al. (2018)[79]	2008 to 2015	Industry: Genzyme --> Sanofi Biosurger	NR	Age 18 to 55 years; ≥ 1 symptomatic cartilage defects; moderate to severe; Knee Injury and Osteoarthritis Outcome Score (KOOS) pain value	Any knee joint surgery within 6 months before screening; modified Outerbridge grade III or IV defects on the patella or tibia; symptomatic musculoskeletal condition in the lower limbs that

Author (Year) Country Registry # Study Design	Years conducted	Sponsor	Recruitment Setting	Inclusion Criteria	Exclusion Criteria
16 European sites Primary study NCT00719576, Extension study NCT01251588; EudraCT 2009-016970-33 RCT				< 55 at baseline were included; Outerbridge grade III or IV focal cartilage defects of MFC, LFC, and/or trochlea; ≥ 3 cm^2 in size; partial or intact meniscus (> 50%) stable knee; ligament reconstruction procedures allowed before or concurrently with study treatment, meniscal repair or resection allowed for intact or partial meniscus if ≥ 50% of the functional meniscus remained. Alignment criteria: NR	could impede efficacy measures in the target knee; total meniscectomy, meniscal allograft, or bucket-handle tear or displaced tear requiring > 50% removal of the meniscus in the target knee; malalignment requiring osteotomy to correct tibial-femoral or patella-femoral alignment; Kellgren-Lawrence grade 3 or 4 osteoarthritis; inflammatory disease or other condition affecting the joints; or septic arthritis within 1 year before screening.
Niemeyer et al. (2023)[23] Lithuania, Czech Republic, Hungary, Germany, Poland, France, Latvia, Switzerland, and the United Kingdom NCT03319797, NCT01656902 NRSI	NInject trial : October 2017 to February 2019 N3D trial: May 2013 to February 2018	Industry: TETEC–Tissue Engineering Technologies	Study arms from the NInject and N3D trials were compared indirectly; each trial recruited from several clinics throughout Europe	14-65 years with closed epiphyseal growth plate; 1 or 2 articular cartilage defects (ICRS grade 3 or 4); defects between 2 cm^2 and 6 cm^2 in N3D and between 4 cm^2 and 12 cm^2 in NInject; defects of the femoral condyle, trochlea, patella, or tibial plateau; stable knee joint or sufficiently reconstructed ligaments; no more than 50% resection of menisci; baseline KOOS score of < 60 (N3D) or < 65 (NInject).	BMI > 35 kg/m2; degenerative joint disease (Kellgren-Lawrence grade > 2); Joint space narrowing less than a third the target knee when compared with contralateral knee or < 3 mm joint space; prior surgical treatment using mosaicplasty, autologous chondrocyte transplantation and/or MFx. NInject Trial accepted prior surgical treatment if the previously treated defect is the same defect to be treated and procedures were performed > 24 months before screening; osteochondral defect (N3D) or subchondral defect > 2mm unless adjuvant defect filling performed (NInject).
Niemeyer et al. (2019)[24] Germany NRSI	2012 to 2015	Industry: CO.DON	Unclear; secondary analysis of data from a health care claims database.	Received at least one MACI or MF procedure in the 2 year index period.	NR

Abbreviations: ACL = anterior cruciate ligament; BMI = body mass index; ICRS = International Cartilage Repair Society; LFC = lateral femoral condyle; MACI = matrix-induced autologous chondrocyte implantation; MF = microfracture; MFC = medial femoral condyles; NR = not reported; NRSI = nonrandomized study of intervention; PCL = posterior cruciate ligament; RCT = randomized controlled trial.

Table C-6. Intervention Characteristics for Included RCTs and Nonrandomized Studies of MACI vs. MF

Author (Year) Study Design	Sample Size	Intervention Group(s)	Control Group	Rehabilitation Protocol
Basad et al. (2010)[22] RCT	60	MACI (Genzyme Biosurgery, Cambridge, MA) Technique category N (%): Both arthroscopic and open, 40 (100)	MF: Specific surgical technique was NR. Technique category N (%): Arthroscopic, 20 (100)	Patients in the MF group underwent rehabilitation in line with the recommendations made by Steadman et al. which include 6 weeks of partial weight-bearing (10 kg) on crutches, continuous passive motion (CPM) and physiotherapy. From 6 weeks postoperatively, patients progressed gradually to full weight-bearing. Rehabilitation for patients in the MACI group included a dorsal plaster cast (10 flexion) for 2 days postoperatively to prevent delamination of the graft, CPM and physiotherapy, followed by 8 weeks of partial weight-bearing (10 kg) on crutches.
Crawford et al. (2012)[21] RCT	30	MACI (NeoCart), Implantation was carried out during a second outpatient surgical procedure via miniarthrotomy, debridement, and preparation of the defect bed in a manner analogous to microfracture, without subchondral penetration. The NeoCart was secured without suture by using a proprietary collagenb-ased polymer (CT-3; Histogenics) to anneal the implant to the prepared condyle defect bed and adjacent tissue. Technique category N (%): Arthroscopic, 21 (100)	MF: Lesion debridement to a stable cartilage margin, removal of the calcified cartilage layer, and the homogeneous creation of subchondral osseous penetrations within the base of the cartilage defect with use of 2 to 4-mm awls Technique category N (%): Arthroscopic, 9 (100)	6 weeks of toe-touch weight-bearing, 6 to 8 hours of CPM daily beginning on postoperative day 1, and restriction of sports activity for 6 months. One patient began immediate unrestricted weight-bearing 10 days after NeoCart implantation in concurrence with the rehabilitation protocol, which allowed accelerated weight-bearing by individuals.

Author (Year) Study Design	Sample Size	Intervention Group(s)	Control Group	Rehabilitation Protocol
Saris et al. (2014)[20] Brittberg et al. (2018)[79] RCT	144	MACI (Vericel scaffold): Genzyme Biosurgery, Cambridge, Massachusetts Technique category N (%): Open and arthroscopic, 72 (100)	MF: Technique described by Steadman et al. Technique category N (%): Arthroscopic, 72 (100)	Standardized 4 phase rehabilitation program same for each group but individualized for each patient. Early protection phase (phase 1, weeks 0-6) restricted weight bearing; transition phase (phase 2, weeks 6-12) attain full passive flexion and extension and increase weight-bearing; remodeling phase (phase 3, weeks 12-26) reintroduce activities; maturation phase (phase 4, weeks 26-52) full unrestricted activity, low-impact sports 4-6 months, moderate impact sports 8 months, high-impact sports 12-18 months.
Niemeyer, 2023 et al. (2023)[23] NRSI	144	MACI (NOVOCART) MACI according to procedure described in Niemeyer et al, 2022. In the first step, osteochondral biopsies were harvested from patients during arthroscopic surgery from a non–weight-bearing area of the knee joint. In the second step, MACI was performed either arthroscopically or through a miniarthrotomy approach using NOVOCART Inject plus, a 2-component hydrogel-based MACI system, consisting of an autologous articular chondrocyte suspension (2-8 million cells per mL) and a crosslinker solution. Technique category N (%): Arthroscopic or miniarthrotomy approach: 100%	MF according to procedure by Steadman et al, 2003 Technique category N (%): NR	Defined rehabilitation protocol based on Hirschmueller et al. Limitations on weight-bearing for 6 weeks were recommended with stepwise increase to full weight-bearing between 7 and 8 weeks after surgery. Strength training, maximum sensorimotor stimulation, and low-impact sports from weeks 12-26. After week 26, return to sports allowed. Return to high-impact sports was recommended after 12 months at the earliest.

Author (Year) Study Design	Sample Size	Intervention Group(s)	Control Group	Rehabilitation Protocol
Niemeyer et al. (2019)[24] NRSI	Unadjusted: 6,425 Adjusted: 254	MACI (type unreported) Technique category N (%): NR	MF Technique category N (%): NR	NR

Abbreviations: CPM = continuous passive motion; MA = Massachusetts; MACI = matrix-induced autologous chondrocyte implantation; MF = microfracture; NR = not reported; NRSI = nonrandomized study of intervention; RCT = randomized controlled trial.

Table C-7. Population Characteristics for Included RCTs and Nonrandomized Studies of MACI vs. MF

Author (Year) Study Design	Prior Knee Surgery	Injury Mechanism; Severity; Duration of Symptoms Prior to Surgery	Location of Chondral Defect; Mean Defect Size; Number of Lesions	Mean Age N (%) Female N (%) Race/Ethnicity Mean BMI
Basad et al. (2010)[22] RCT	NR	Injury mechanism N (%): Accident: 11 (22) Sport: 27 (45) Work: 2 (3) Daily activities: 7 (12) Unknown: 13 (18) Severity of injury: NR Mean (SD) duration of symptoms prior to surgery: 2.3 (NR) years	Location of chondral defect: Condylar: 45 (75) Patellar-trochlear: 15 (25) Mean defect size: NR (entry criteria required 4 to 10 cm^2) Number of lesions: Participants had single, isolated, symptomatic chondral defects	Mean age (SD): MACI: 33.0 (NR) MF: 37.5 (NR) N (%) Female: 18 (30) N (%) Race/Ethnicity: NR Mean BMI (range): MACI: 25.3 (range 20–34) MF: 27.3 (range 24–35)
Crawford et al. (2012)[21] RCT	NR	Injury mechanism: NR Severity of injury: IKDC score, mean (SD) 47 (13) Mean (SD) duration of symptoms prior to surgery: 3 (5) years	Location of chondral defect: Medial or lateral femoral condyle, N (%): 30 (100) Mean (SD) defect size (cm^2): 2.8 (14) Number of lesions: Participants had 1 or 2 isolated articular cartilage lesions of the femoral condyle(s)	Mean age (SD): 40 (9) N (%) Female: 5 (17) N (%) Race/Ethnicity: NR Mean (SD) BMI: 28 (4)
Saris et al. (2014)[20] Brittberg et al. (2018)[79] RCT	N (%) MACI: 65 (90.3) MF: 60 (83.3)	Injury mechanism N (%): Acute trauma MACI: 33 (45.8) MF: 53 (73.6) Chronic degeneration MACI: 18 (25.0) MF: 9 (12.5) Osteochondritis dissecans MACI: 8 (11.1) MF: 12 (16.7)	Location of chondral defect: Medial femoral condyle, N (%) MACI: 54 (75.0) MF: 53 (73.6) Lateral femoral condyle, N (%) MACI: 13 (18.1) MF: 15 (20.8) Trochlea, N (%)	Mean age (SD): MACI: 34.8 (9.2) MF: 32.9 (8.8) N (%) Female MACI: 37.5 (27) MF: 33.3 (24) N (%) Race/Ethnicity: NR Mean BMI (SD)

Author (Year) Study Design	Prior Knee Surgery	Injury Mechanism; Severity; Duration of Symptoms Prior to Surgery	Location of Chondral Defect; Mean Defect Size; Number of Lesions	Mean Age N (%) Female N (%) Race/Ethnicity Mean BMI
		Unknown MACI: 9 (12.5) MF: 6 (8.3) Other MACI: 4 (5.6) MF: 0 (0) Severity of injury: Outerbridge grade, N (%) MACI: 21 (29.2) MF: 15 (20.8) Outerbridge grade, N (%) MACI: 51 (70.8) MF: 57 (79.2) Mean (range) duration of symptoms prior to surgery: MACI: 5.8 years (0.05 -28.0) MF: 3.7 years (0.1 - 15.4)	MACI: 5 (6.9) MF: 4 (5.6) Mean (SD) defect size (cm^2): MACI: 4.9 (2.8) MF: 4.7 (1.8) Number of lesions: Participants had 1 or more symtomatic cartilage defects	MACI: 26.2 (4.3) MF: 26.4 (4.0)
Niemeyer et al. (2023)[23] NRSI	Previous surgery in target knee N (%): MACI: 46 (63.9) MF: 45 (62.5) Meniscus removal MACI: 20 (27.8) MF: 26 (36.1) Ligament operation MACI: 12 (16.7) MF: 11 (15.3) Joint debridement MACI: 10 (13.9) MF: 11 (15.3) Arthroscopy MACI: 14 (19.4) MF: 14 (19.4)	Injury mechanism N (%): Traumatic: MACI: 58 (60.4) MF: 62 (78.5) Osteochondritis dissecans: MACI: 6 (6.3) MF: 0 (0) Degenerative: MACI: 32 (33.3) MF: 5 (6.3) Other: MACI: 0 (0) MF: 12 (15.2) Severity of injury N (%): ICRS grade III MACI: 72 (75)	Location of chondral defect N (%): Femur MACI: 82 (85.4) MF: 79 (100) Tibia MACI: 4 (4.2) MF: 0 (0) Patella MACI: 10 (10.4) MF: 0 (0) Mean (SD) defect size (cm^2): All lesions: MACI: 4.8 (1.7) MF: 3.4 (1.3)	Mean age (SD): MACI: 39.3 (12.1) MF: 39.3 (11.9) N (%) Female: MACI: 21 (29.2) MF: 21 (29.2) N (%) Race/Ethnicity: NR Mean BMI (SD): MACI: 27.1 (4.1) MF: 27.4 (3.9)

Author (Year) Study Design	Prior Knee Surgery	Injury Mechanism; Severity; Duration of Symptoms Prior to Surgery	Location of Chondral Defect; Mean Defect Size; Number of Lesions	Mean Age N (%) Female N (%) Race/Ethnicity Mean BMI
		MF: 41 (51.9) ICRS grade IV MACI: 24 (25) MF: 38 (48.1) Duration of symptoms prior to surgery, mean (SD): MACI: 18.5 (20.1) months MF: 16.3 (19.5) months	N (%) number of lesions: 1 lesion MACI: 48 (66.7) MF: 65 (90.3) 2 lesions MACI: 24 (33.3) MF: 7 (9.7)	
Niemeyer et al. (2019)[24] NRSI	NR	Injury mechanism: NR Severity of injury: NR Duration of symptoms prior to surgery: NR	Location of chondral defect: NR Mean defect size: NR Number of lesions: NR	Mean age (SD): Unadjusted MACI: 36.0 (11.1) MF: 53.0 (14.0) After matching MACI: 36.8 (10.9) MF: 36.9 (10.9) N (%) Female: Unadjusted MACI: 60 (39.5) MF: 2,866 (45.7) Adjusted MACI: 52 (41.0) MF: 52 (40.9) N (%) Race/Ethnicity: NR Mean BMI: NR

Abbreviations: BMI = body mass index; ICRS = International Cartilage Repair Society; MACI = matrix-induced autologous chondrocyte implantation; MF = microfracture; NR = not reported; NRSI = nonrandomized study of intervention; RCT = randomized controlled trial; SD = standard deviation.

Table C-8. Efficacy Outcomes for Included RCTs and Nonrandomized Studies of MACI vs. MF

Author (Year) Intervention(s) and Comparison Sample size Study Design	Results
Basad et al. (2010)[22] Intervention: MACI (Collagen scaffold) Comparator: MF Sample size: 60 RCT	***Composite Scores*** **Lysholm score:** Lysholm score, Baseline, mITT (MACI = 39, MF = 17), Mean (SD) MACI: 52 (26) MF: 55 (25) Lysholm score, 6 months, mITT (MACI = 39, MF = 17), Mean (SD) MACI: 87 (17) MF: 82 (18) Lysholm score, 2 years, mITT (MACI = 33, MF = 15), Mean (SD) MACI: 92 (9) MF: 69(26) *P*=0.005 for treatment X time interaction over 2 years between groups. **KOOS Total, CKRS, IKDC Subjective Knee Evaluation Form, Hospital for Special Surgery Score:** NR ***Activity Scores*** **Tegner Score:** Tegner Score, Baseline, unclear (MACI = 39, MF = 20), Median MACI: 2 MF: 2 Tegner Score, 6 months, unclear(MACI = 39, MF = 18), Median MACI: 3 MF: 3 Tegner Score, 24 months, unclear (MACI = 37, MF = 17), Median MACI: 4 MF: 3 *P*=0.04 for time X treatment interaction over 2 years between groups. **KOOS-ADL, KOOS-Sport:** NR ***Symptom Scores*** **KOOS-Pain, KOOS-Symptoms, KOOS-QOL:** NR ***Responder, treatment failure, reoperation*** **Responder, Treatment failure, Reoperation:** NR ***Subgroup Analyses:*** NR

Author (Year) Intervention(s) and Comparison Sample size Study Design	Results
Crawford et al. (2012)[21] Intervention: MACI (NeoCart) Comparator: MF Sample size: 30 RCT	***Composite Scores*** **KOOS Total:** KOOS, Improvement from baseline to 6 months, ITT (MACI = 21; MF = 9) MACI: values NR, *P*=significant for improvement compared to baseline MF: values NR, *P*=NS for improvement compared to baseline KOOS, Improvement from baseline to 24 months, ITT (MACI = 21; MF = 9) MACI: values NR, *P*=significant for improvement compared to baseline MF: values NR, *P*=NS for improvement compared to baseline No reporting of P values for between group differences in change in scores at any timepoint. **IKDC Subjective Knee Evaluation Form:** IKDC, Baseline, ITT (MACI = 21; MF = 9), mean (SD) MACI: 44 (13) MF: 52 (12) *P*=NS IKDC, 6 months, ITT (MACI = 21; MF = 9), mean change MACI: value NR, only presented in figure MF: value NR, only presented in figure Between group *P*=NS IKDC, 24 months, ITT (MACI = 21; MF = 9), mean change MACI: value NR, only presented in figure MF: value NR, only presented in figure Between group *P*<0.05 IKDC Subjective, 24 months, ITT (MACI = 21; MF = 9), Mean difference MACI vs. MF: 11.59 (95% CI, 1.353 to 21.82) **CKRS, Lysholm score, Hospital for Special Surgery Score:** NR ***Activity Scores*** **KOOS-ADL:** KOOS-ADL, Improvement from baseline to 6 months, ITT (MACI = 21; MF = 9) MACI: values NR, *P*=significant for improvement compared to baseline MF: values NR, *P*=NS for improvement compared to baseline KOOS-ADL, Improvement from baseline to 24 months, ITT (MACI = 21; MF = 9) MACI: values NR, *P*=significant for improvement compared to baseline MF: values NR, *P*=significant for improvement compared to baseline

Author (Year) Intervention(s) and Comparison Sample size Study Design	Results
	Between group difference *P*=NS **KOOS-Sport:** KOOS-SR, Improvement from baseline to 6 months, ITT (MACI = 21; MF = 9) MACI: values NR, *P*=significant for improvement compared to baseline MF: values NR, *P*=NS for improvement compared to baseline KOOS-SR, Improvement from baseline to 24 months, ITT (MACI = 21; MF = 9) MACI: values NR, *P*=significant for improvement compared to baseline MF: values NR, *P*=significant for improvement compared to baseline *P*<0.05 for difference between groups at 12 and 24 months **Tegner Score:** NR ***Symptom Scores*** **KOOS-Pain:** KOOS-P, Baseline, ITT (MACI = 21; MF = 9), mean (SD) MACI: 65 (12) MF: 73 (16) *P*=NS KOOS-P, 3 months, ITT (MACI = 21; MF = 9), mean MACI: value NR, only presented in figure MF: value NR, only presented in figure *P*=NS KOOS-P, 24 months, ITT (MACI = 19; MF = 9), mean MACI: value NR, only presented in figure MF: value NR, only presented in figure *P*=NS Mean change in KOOS-P, 3 months, ITT (MACI = 21; MF = 9), mean change MACI: value NR, only presented in figure MF: value NR, only presented in figure *P*=NS KOOS-P, 24 months, ITT (MACI = 21; MF = 9), Mean difference MACI - MF: 12.06 (95% CI, 2.39 to 21.74) Mean change in KOOS-P, 24 months, ITT (MACI = 19; MF = 9), mean change MACI: value NR, only presented in figure MF: value NR, only presented in figure

Author (Year) Intervention(s) and Comparison Sample size Study Design	Results
	P<0.05 favoring MACI (Between group differences also significant and favoring MACI at 6 and 12 months) ANCOVA for change in scores from baseline to 12 mos, *P*=0.016 favoring MACI **KOOS-Symptoms:** KOOS-S, Improvement from baseline to 6 months, ITT (MACI = 21; MF = 9) MACI: values NR, *P*=significant for improvement compared to baseline MF: values NR, *P*=NS for improvement compared to baseline KOOS-S, Improvement from baseline to 24 months, ITT (MACI = 21; MF = 9) MACI: values NR, *P*=significant for improvement compared to baseline MF: values NR, *P*=NS for improvement compared to baseline Between group differences significant but *P*=NR **KOOS-QOL:** KOOS-QOL, Improvement from baseline to 6 months, ITT (MACI = 21; MF = 9) MACI: values NR, *P*=significant for improvement compared to baseline MF: values NR, *P*=NS for improvement compared to baseline KOOS-QOL, Improvement from baseline to 24 months, ITT (MACI = 21; MF = 9) MACI: values NR, *P*=significant for improvement compared to baseline MF: values NR, *P*=NS for improvement compared to baseline *P*<0.05 for difference between groups at 24 months only ***Responder, treatment failure, reoperation*** **Responder:** Improvement in the IKDC score of ≥ 20 points and the KOOS-Pain score of ≥ 12 points, N (%), 6 months MACI: 9/21 (43) MF: 2/8 (25) *P*=0.0125 N (%), 12 months MACI: 16/21 (76) MF: 2/9 (22) *P*=0.0125 N (%), 24 months MACI: 15/19 (79) MF: 4/9 (44) *P*=0.097

Author (Year) Intervention(s) and Comparison Sample size Study Design	Results
	N (%), 25.6 months MACI: 17/21 (81) MF: 4/9 (44) **Treatment failure, Reoperation:** NR ***Subgroup Analyses:*** NR
Saris et al. (2014)[20] Brittberg et al. (2018)[79] Intervention: MACI (Vericel scaffold) Comparator: MF Sample size: 144 RCT	***Composite Scores*** **CKRS:** CKRS, baseline (MACI = 72; MF = 72), mean (SD), P value MACI: 3.0 (1.2) MF: 3.0 (1.2) CKRS, year 2 (MACI = 72; MF = 71), mean (SD), P value MACI: 6.4 (2.1) MF: 5.4 (2.2) CKRS, year 5 (MACI = 65; MF = 59), mean (SD), P value MACI: 59.8 (24.6) MF: 52.4 (26.6) *P*=NR CKRS, baseline to 2 years, ITT (MACI = 72; MF = 72), difference in mean change (SD), P value MACI vs. MF: 1.05 (NR), *P*=0.002 CKRS, baseline to 5 years, ITT, (MACI = 72, MF = 72), difference in mean change, mean (SD), P value MACI vs. MF: NR (NR), *P*=0.035 **IKDC Subjective Knee Evaluation Form:** IKDC subjective knee evaluation, baseline (MACI = 71; MF = 72), mean (SD) MACI: 32.9 (13.3) MF: 29.3 (13.4) IKDC subjective knee evaluation, baseline to 2 years, ITT (MACI = 72; MF = 71), mean (SD), estimated mean difference, P value MACI: 65.7 (18.5) MF: 58.8 (22.3) Estimated mean difference: 5.94, *P*=0.069 IKDC subjective knee evaluation, baseline to 5 years, ITT (MACI = 65; MF = 59), mean (SD), P value[79] MACI: 68.5 (21.2) MF: 61.8 (21.5) *P*=0.113

Author (Year) Intervention(s) and Comparison Sample size Study Design	Results
	KOOS Total, Lysholm score, Hospital for Special Surgery Score: NR ***Activity Scores*** **KOOS-ADL:** KOOS-ADL, baseline (MACI = 72; MF = 72), mean (SD), P value MACI: 43.5 (18.2) MF: 42.6 (19.6) *P*=NR KOOS-ADL, year 2 (MACI = 72; MF = 71), mean (SD), P value MACI: 87.2 (16.5) MF: 78.8 (24.2) *P*=NR KOOS-ADL, year 5 (MACI = 65; MF = 59), mean (SD), P value MACI: 86.4 (17.6) MF: 80.0 (21.2) *P*=0.007 KOOS-ADL, baseline to 2 years, ITT (MACI = 72; MF = 72), mean difference (SD), P value MACI vs. MF: 12.01 (NR), *P*<0.001 **KOOS-Sport:** KOOS-SR, baseline (MACI = 72; MF = 71), mean (SD) MACI: 14.9 (13.5) MF: 12.6 (16.7) KOOS-SR, year 2 (MACI = 72; MF = 70), mean (SD) MACI: 60.9 (27.8) MF: 48.7 (30.3) KOOS-SR year 5 (MACI = 65; MF = 59), mean (SD) MACI: 61.9 (30.9) MF: 50.3 (32.3) *P*=0.022 KOOS-SR, baseline to 5 years, mITT (MACI = 64; MF = 59), mean change (SD), P value MACI: 47.2 (32.2) MF: 37.6 (33.6) *P*=NR KOOS-SR, baseline to 2 years, ITT (MACI = 72; MF = 72), difference in mean change (SD), P value

Author (Year) Intervention(s) and Comparison Sample size Study Design	Results
	MACI vs. MF: 11.41 (NR), *P*=0.001 P value is for co-primary endpoint (KOOS-P and KOOS-S), Wilks gamma test statistic for difference between means for change from baseline to year 2. **Tegner Score:** NR ***Symptom Scores*** **KOOS-Pain:** KOOS-P, baseline (MACI = 72; MF = 71), mean (SD), P value MACI: 37.0 (3.5) MF: 35.5 (12.1) *P*=NR KOOS-P, year 2 (MACI = 71; MF = 70), mean (SD), P value MACI: 82.5 (6.2) MF: 70.9 (24.2) *P*=NR KOOS-P, year 5 (MACI = 65; MF = 59), mean (SD), P value MACI: 82.5 (20.1) MF: 74.8 (21.7) *P*=0.022 KOOS-P, baseline to 5 years, mITT (MACI = 64; MF = 59), mean change (SD), P value MACI: 45.2 (21.6) MF: 38.4 (23.6) *P*=NR KOOS-P, baseline to 2 years, ITT (MACI = 72; MF = 72), mean difference in change (SD), P value MACI vs. MF: 11.76 (NR), P=0.001 P value is for co-primary endpoint (KOOS-P and KOOS-S), Wilks gamma test statistic for difference between means for change from baseline to year 2. **KOOS-Symptoms:** KOOS-S, baseline (MACI = 72; MF = 72), mean (SD), P value MACI: 48.3 (16.9) MF: 44.4 (18.6) *P*=NR KOOS-S, year 2 (MACI = 72; MF = 71), mean (SD), P value MACI: 83.7 (14.0)

Author (Year) Intervention(s) and Comparison Sample size Study Design	Results
	MF: 72.2 (19.5) *P*=NR KOOS-S, year 5 (MACI = 65; MF = 59), mean (SD), P value MACI: 80.9 (18.0) MF: 74.8 (18.5) *P*=0.078 KOOS-S, baseline to 2 years, ITT (MACI = 72; MF = 72), mean difference in change (SD), P value MACI vs. MF: 11.61 (NR), ≤ 0.001 **KOOS-QOL:** KOOS-QOL, baseline (MACI = 72; MF = 72), mean (SD), P value MACI: 18.8 (14.7) MF: 17.2 (14.1) KOOS-QOL, year 2 (MACI = 72; MF = 71), mean (SD), P value MACI: 56.2 (23.9) MF: 47.3 (27.0) KOOS-QOL, year 5 (MACI = 65; MF = 59), mean (SD), P value MACI: 59.8 (24.6) MF: 52.4 (26.6) *P*=0.007 KOOS-QOL, baseline to 2 years, ITT (MACI = 72; MF=72), difference in mean change (SD), P value MACI vs. MF: 8.98 (NR), *P*=0.029 ***Responder, treatment failure, reoperation*** **Responder:** KOOS-P and KOOS-SR ≥ 10-point improvement on both subscales, Responder, Year 2, (MACI = 72, MF = 72) N calculated (%), P value MACI: 63 (87.5) MF: 49 (68.1) *P*=0.016 Responder, Year 5, (MACI = 65, MF= 59) N calculated (%), P value MACI: 51 (78) MF: 43 (73) *P*=NR (calculated NS) **Reoperation:** At least one subsequent surgical procedure, Year 2, (MACI = 72; MF = 72), N (%)

Author (Year) Intervention(s) and Comparison Sample size Study Design	Results
	MACI: 6 (8.3) MF: 7 (9.7) At least one subsequent surgical procedure, Year 2, (MACI = 65; MF = 59), N calculated (%) MACI: 7 (10.8) MF: 6 (9.5), NR **Treatment failure:** NR ***Subgroup Analyses*** 2 year follow-up Significant differences: MACI greater number of responders vs. MF: male patients, median age < 34.5 years, only 1 lesions, lesions resulting from acute trauma, 1 prior surgery, duration of symptoms > 3 years, lesions > 4 cm^2, lesions located on MFC. Non-significant differences: MACI and MF similar responder rate for patients with and without prior cartilage surgeries. 5-year follow-up: Improvements in KOOS Pain and Function scores were greater in each subgroup of lesion location (MFC, LFC, trochlea) in MACI compared with microfracture patients
Niemeyer, 2023 et al. (2023)[23] Intervention: MACI – SB (NOVOCART) Comparator: MF Sample size: 144 NRSI	**Composite Scores** **KOOS Total:** KOOS, Baseline, MACI = 72; MF = 72, mean (SD) MACI: 41.7 (13.1) MF: 43.1 (14.5) KOOS, 3 months, MACI = 69; MF = 69, mean (SD) MACI: 67.7 (15.5) MF: 60.3 (17.4) Between group difference in change from baseline: 6.8 (SE 2.8); 95% CI, 1.28 to 12.28); *P*=0.0161 [favor MACI] KOOS, 12 months, MACI = 71; MF = 64, mean (SD) MACI: 79.9 (14.9) MF: 72.1 (16.3) Between group difference in change from baseline: 8.7 (SE 2.8); 95% CI, 3.1 to 14.3); *P*=0.0027 KOOS, 24 months, MACI = 72; MF = 60, mean (SD) MACI: 81.8 (16.8) MF: 73.1 (20.6) Between group difference in change from baseline: 10.1 (SE 3.3); 95% CI, 3.6 to 16.5); *P*=0.0026 Sensitivity analyses using imputation for missing data found results were robust. **IKDC Subjective Knee Evaluation Form:**

Author (Year) Intervention(s) and Comparison Sample size Study Design	Results
	IKDC, Baseline, MACI = 72; MF = 60, mean (SD) MACI: 36.3 (NR) MF: 35.5 (NR) IKDC, 24 months, MACI = 72; MF = 60, mean (SD) MACI: 75.4 (NR) MF: 68.8 (NR) Between group difference in change from baseline: 7.4 (SD NR; 95% CI, NR; *P*=0.0334) Participants achieving > 20.5 point improvement in IKDC, 24 months, MACI = NR, MF = NR, N (%) MACI: NR (83.3) MF: NR (61.1) *P*=0.0126 **CKRS, Lysholm score, Hospital for Special Surgery Score:** NR **Activity Scores** **KOOS-Sport:** KOOS-Sports/Rec, 24 months, MACI = 72; MF = 60, mean (SD) MACI: NR MF: NR Between group differences in change from baseline: 14.1 (95% CI, 5.2 to 22.9) [favor MACI] Participants achieving 30-point improvement in KOOS-SR, 24 months, MACI = NR, MF = NR, N (%) MACI: NR (84.7) MF: NR (56.9) P NR **Tegner Score, KOOS-ADL:** NR **Symptom Scores** **KOOS-QOL:** KOOS-QOL, 24 months, MACI = 72; MF = 60, mean (SD) MACI: NR MF: NR Between group differences in change from baseline: 11.4 (95% CI, 2.5 to 20.2) [favor MACI] Participants achieving 37.5-point improvement in KOOS-QoL, 24 months, MACI = NR, MF = NR, N (%) MACI: NR (72.2) MF: NR (44.4) P NR

Author (Year) Intervention(s) and Comparison Sample size Study Design	Results
	KOOS-Pain, KOOS-Symptoms: NR **Responder, treatment failure, reoperation** **Responder:** ≥ 10-point improvement from baseline in KOOS score, N (%), baseline to 3 months MACI (n = NR): NR (73.6) MF (n = NR): NR (65.3) P not tested N (%), baseline to 12 months MACI (n = NR): NR (94.4) MF (n = NR): NR (72.2) *P*=not tested N (%), baseline to 24 months MACI (n = NR): NR (94.4) MF (n = NR): NR (65.3) *P*<0.0001 **Treatment failure:** Surgical reinterventions affecting the closed surface of the transplant area, No treatment failures reported in either group. **Reoperation:** N (%) MACI: 6 (8.3); 1 was considered treatment related MF: 3 (4.2); 0 were considered treatment related, Meniscus removal; joint dislocation reduction, adhesiolysis; arthrolysis, chondroplasty, ligament operation, meniscus operation, osteosynthesis, osteotomy **Subgroup Analyses:** NR
Niemeyer et al. (2019)[24] Intervention: MACI (type scaffold NR) Comparator: MF Sample size: Unadjusted: 6,425 Adjusted: 254 NRSI	**Composite Scores** **KOOS Total, CKRS, IKDC Subjective Knee Evaluation Form, Lysholm score, Hospital for Special Surgery Score:** NR **Activity Scores** **Tegner Score, KOOS-ADL, KOOS-Sport:** NR **Symptom Scores** **KOOS-Pain, KOOS-Symptoms, KOOS-QOL:** NR **Responder, treatment failure, reoperation**

Author (Year) Intervention(s) and Comparison Sample size Study Design	Results
	Reoperation: Follow-up from index surgery to 2 years (Adjusted results) MACI: 16 (12.6) MF: 28 (22.0) Relative risk reduction: 43% (95% CI, 0% to 67.5%); this is equivalent to an RR of 0.57 Difference in time to event, 2 years from index surgery NR by group but *P*=0.0498, favoring MACI Reoperations (more than 1 per patient was possible) MACI Knee Joint: 11 (8.7) Meniscus and cartilage: 11 (8.7) Patella: < 5 Knee replacement: < 5 MF Knee Joint: 12 (9.4) Meniscus and cartilage: 22 (17.3) Patella: < 5 Knee replacement: <5 **Responder, Treatment failure:** NR **Subgroup Analyses:** NR

Abbreviations: CI = confidence interval; CKRS = Cincinnati Knee Rating System; IKDC = International Knee Documentation Committee; ITT = intention to treat; KOOS = Knee Injury and Osteoarthritis Outcome Score; KOOS-ADL = Knee Injury and Osteoarthritis Outcome Score, Activities of Daily Living subscale; KOOS-P= Knee Injury and Osteoarthritis Outcome Score, Pain subscale; KOOS-QOL = Knee Injury and Osteoarthritis Outcome Score, Quality of Life subscale; KOOS-SR = Knee Injury and Osteoarthritis Outcome Score, Sport and Recreation subscale; MACI = matrix-induced autologous chondrocyte implantation; MF = microfracture; NR = not reported; NS = not significant; NRSI = nonrandomized study of intervention; RCT = randomized controlled trial; SD = standard deviation; SE = standard error.

Table C-9. Safety Outcomes for Included RCTs and Nonrandomized Studies of MACI vs. MF

Author (Year) Study Design	Any Adverse Effects	Serious Adverse Effects
Basad et al. (2010)[22] RCT	"No treatment-related safety issues during the study." However, authors also report 1 patient with persistent pain after 12 months related to subchondral edema that required retrograde bone grafting.	NR
Crawford et al. (2012)[21] RCT	Total number adverse events MACI: 62 MF: 24 Events included a repeat arthroscopic biopsy; an arthroscopic microfracture of a lesion in the ipsilateral knee; an ACL reconstruction of the contralateral knee after the patient had returned to full activity; and postoperative pain, stiffness, swelling, back pain, arm pain, and peri-incisional numbness. Adverse events considered related to the study interventions were consistent with those associated with routine outpatient arthroscopy or mini-knee arthrotomy, with the exception of the repeat biopsy.	SAEs as defined by US DHHS ORP NeoCart: 2 events in 1 patient (septic arthritis in contralateral knee after meniscectomy and subsequent total knee arthroplasty) Microfracture: cancer gynecologic origin None of these events were considered to be related to the treatment of the cartilage defect
Saris et al. (2014)[20] Brittberg et al. (2018)[79] RCT	Any TEAE, Year 2, MACI = 72; MF = 72, N (%) MACI: 55 (76.4) MF: 60 (83.3) Arthralgia, Year 2, MACI = 72; MF = 72, N (%) MACI: 37 (51.4) MF: 46 (63.9) Headache, Year 2, MACI = 72; MF = 72, N (%) MACI:13 (18.1) MF: 21 (29.2) Nasopharyngitis, Year 2, MACI = 72; MF = 72, N (%) MACI: 10 (13.9) MF: 7 (9.7) Back pain, Year 2, MACI = 72; MF = 72, N (%) MACI: 8 (11.1) MF: 7 (9.7) Joint swelling, Year 2, MACI = 72; MF = 72, N (%) MACI: 7 (9.7) MF: 4 (5.6) Joint effusion, Year 2, MACI = 72; MF = 72, N (%) MACI: 5 (6.9) MF: 4 (5.6)	SAE, Year 2, MACI = 72; MF = 72, N (%) MACI: 11 (15.3) MF: 19 (26.4) Most common: treatment failure, arthralgia, joint swelling (NR by group). Subsequent surgical procedures classified as SAE

Author (Year) Study Design	Any Adverse Effects	Serious Adverse Effects
	Influenza, Year 2, MACI = 72; MF = 72, N (%) MACI: 4 (5.6) MF: 5 (6.9) Pyrexia, Year 2, MACI = 72; MF = 72, N (%) MACI: 4 (5.6) MF: 2 (2.8) Cartilage injury, Year 2, MACI = 72; MF = 72, N (%) MACI: 3 (4.2) MF: 9 (12.5) Procedural pain, Year 2, MACI = 72; MF = 72, N (%) MACI: 3 (4.2) MF: 4 (5.6) Ligament sprain, Year 2, MACI = 72; MF = 72, N (%) MACI: 2 (2.8) MF: 4 (5.6) Abdominal pain, Year 2, MACI = 72; MF = 72, N (%) MACI: 0 (0) MF: 5 (6.9) Any TAE, Year 5, MACI = 65, MF = 59, N (%) "Similar frequency as 2 years" Specific values NR	
Niemeyer, 2023 et al. (2023)[23] NRSI	In the MACI group, 1 patient experienced a surgery-related lateral patellar compression syndrome possibly caused by overtightened sutures of the knee joint capsule during transplantation surgery	NR
Niemeyer et al. (2019)[24] NRSI	NR	NR

Abbreviations: ACL = anterior cruciate ligament; ; = International Cartilage Repair Society; MACI = matrix-induced autologous chondrocyte implantation; MF = microfracture; NR = not reported; NRSI = nonrandomized study of intervention; RCT = randomized controlled trial; SAE = serious adverse event; TEAE = treatment-emergent adverse events; US DHHS ORP = U.S. Department of Health and Human Services Office for Human Research Protections.

Table C-10. Study Characteristics for Included Nonrandomized Studies of MACI vs. OATS

Author (Year) Country Registry #	Years conducted	Sponsor	Recruitment Setting	Inclusion Criteria	Exclusion Criteria
Macarini et al. (2003)[19] Italy	1998 to 2002	NR	NR	Focal osteochondral lesions of grade II and III according to Noyes	NR
Salzmann et al. (2009)[25] Germany	NR	NR	NR	MACI: Patients with ICRS 3 to 4a lesions and lesion size more than 3 cm^2 OATS: Patients with ICRS 4a or 4b lesions and a defect size less than 3 cm^2	Obesity (BMI > 35), osteoarthritis (> grade 1 according to the Kellgren and Lawrence classification), rheumatoid arthritis, absence or extensive meniscal loss, ligamentous instability, active local or systemic infections, inflammatory arthropathy, varus or valgus deformity of more than 2 degrees and limited range of motion with active knee flexion below 120 degrees or an extension deficiency exceeding 15 degrees

Abbreviations: BMI = body mass index; ICRS = International Cartilage Repair Society; MACI = matrix-induced autologous chondrocyte implantation; NR = not reported; OATS = osteochondral autologous transplantation.

Table C-11. Intervention Characteristics for Included Nonrandomized Studies of MACI vs. OATS

Author (Year) Sample Size	Sample Size	Intervention Group(s)	Control Group	Rehabilitation Protocol
Macarini et al. (2003)[19]	22	MACI (specific type NR) comprising 3 phases: 1. Small amount of cartilaginous tissue was harvested in arthroscopy from the damaged joint 2. Chondrocytes were cultivated in vitro until an adequate concentration was reached and then seeded on a type I/III collagen matrix 3. At least 6 weeks later under arthrotomy; osteochondral lesion was prepared, trimmed, and covered by the collagen matrix using fibrin glue Technique category N (%): Open, Arthrotomy: 7 (100)	OATS performed under arthrotomy in 2 phases: 1. Osteochondral fragment was harvested from a donor site in a non–weight-bearing area, external surface of the lateral femoral condyle of the knee 2. During the same session, the harvested osteochondral fragment was positioned in the lesion after being shaped to fit precisely into the site of the lesion and restore the physiological curve of the articular surface Technique category N (%): Open, Arthrotomy: 15 (100)	All patients underwent rehabilitative physiotherapy which involved the early mobilization of the joint followed by progressive weight-bearing exercises
Salzmann et al. (2009)[25]	18	MACI – P (Vericel scaffold): Verigen, Leverkusen, Germany, according to procedure by Cherubino et al.[90] Technique category N (%): Open, 9 (100)	OATS (Arthrex, Naples, FL) with 10 mm cylinders; mean (SD) number of transplanted cylinders: 1.5 (1.0) Technique category N (%): Open, 9 (100)	NR

Abbreviations: FL = Florida; MACI = matrix-induced autologous chondrocyte implantation; N = number; NR = not reported; OATS = osteochondral autologous transplantation; SD = standard deviation.

Table C-12. Population Characteristics for Included Nonrandomized Studies of MACI vs. OATS

Author (Year)	Prior Knee Surgery	Injury Mechanism; Severity; Duration of Symptoms Prior to Surgery	Location of Chondral Defect; Mean Defect Size; Number of Lesions	Mean Age N (%) Female N (%) Race/Ethnicity Mean BMI
Macarini et al. (2003)[19]	NR	Injury mechanism: NR Severity of injury N (%): Grade II and III according to Noyes: 22 (100) Duration of symptoms prior to surgery: NR	Location of chondral defect: NR Mean defect size: NR Number of lesions: NR	Mean age, (range) 31, (19 to 45) N (%) Female: NR N (%) Race/Ethnicity: NR Mean BMI: NR
Salzmann et al. (2009)[25]	NR	Injury mechanism N (%): Traumatic event MACI: 7 (77.8) OATS: 2 (22.2) Subtle symptom improvement: MACI: 2 (22.2) OATS: 3 (33.3) Osteochondrosis dissecans: MACI: 0 (0) OATS: 3 (33.3) Patellar flake fracture: MACI: 0 (0) OATS: 1 (11.1) Severity of injury N (%): Grade III MACI: 4 (44.4) OATS: 0 (0) Grade IV MACI: 5 (55.6) OATS: 9 (100) Duration of symptoms prior to surgery: NR	Location of chondral defect N (%): MACI Medial femoral condyle: 6 (66.7) Lateral femoral condyle: 1 (11.1) Patella: 2 (22.2) OATS Medial femoral condyle: 6 (66.7) Lateral femoral condyle: 1 (11.1) Patella: 2 (22.2) Mean (range) defect size (cm^2): MACI: 6.3 (range 3 to 12) OATS: 2.3 (range 0.9 to 2.6) Number of lesions: NR	Mean age (SD): MACI: 32.7 (7.2) OATS: 33.9 (7.5) N (%) Female: MACI: 1 (11.1) OATS: 1 (11.1) N (%) Race/Ethnicity: NR Mean BMI (SD): MACI: 26.9 (4.7) OATS: 26.9 (4.6)

Abbreviations: BMI = body mass index; MACI = matrix-induced autologous chondrocyte implantation; NR = not reported; OATS = osteochondral autologous transplantation; SD = standard deviation.

Table C-13. Efficacy Outcomes for Included Nonrandomized Studies of MACI vs. OATS

Author (Year) Intervention(s) and Comparison Sample size	Results
Macarini et al. (2003)[19] Intervention: MACI (specific type NR) Comparator: OATS Sample size: 22	**Composite Scores** **Resumed normal sport and work activities,** 1 year post-surgery, MACI: 7; OATS: 1, N (%) MACI: 5 (71) OATS: 15 (100) **KOOS Total, CKRS, IKDC Subjective Knee Evaluation Form, Lysholm score, Hospital for Special Surgery Score:** NR **Activity Scores** **Tegner Score, KOOS-ADL, KOOS-Sport:** NR **Symptom Scores** **KOOS-Pain, KOOS-Symptoms, KOOS-QOL:** NR **Responder, treatment failure, reoperation** **Responder, Treatment failure, Reoperation:** NR **Subgroup Analyses:** NR
Salzmann et al. (2009)[25] Intervention: MACI (Vericel) Comparator: OATS Sample size: 18	**Composite Scores** **CKRS:** CKRS, average 41.6 months follow-up, MACI = 9; OATS = 9, mean (SD), 95% CI MACI: 74.3 (16.2) OATS: 68.3 (18.3) Mean difference (95% CI): NR (-21.5 to 3.6); *P*=0.12 (adjusted for matching variables age and BMI) **Lysholm score:** Lysholm score, average 41.6 months follow-up, MACI = 9; OATS = 9, mean (SD), 95% CI MACI: 77 (9.9) OATS: 66.8 (9.9) Mean difference (95% CI): NR (-22 to 0.59); *P*=0.04 (adjusted for matching variables age and BMI) **IKDC Subjective Knee Evaluation Form, KOOS Total, Hospital for Special Surgery Score:** NR **Activity Scores** **Tegner Score:** Tegner score, average 41.6 months follow-up, MACI = 9; OATS = 9, mean (SD), 95% CI MACI: 5.4 (1.9)

Author (Year) Intervention(s) and Comparison Sample size	Results
	OATS: 5.0 (2.1) Mean difference (95% CI): NR (-2.6 to 1.8); *P*=0.69 (adjusted for matching variables age and BMI) **KOOS-ADL, KOOS-Sport:** NR **Symptom Scores** **KOOS-Pain, KOOS-Symptoms, KOOS-QOL:** NR **Responder, treatment failure, reoperation** **Responder, Treatment failure, Reoperation:** NR **Subgroup Analyses**: NR

Abbreviations: BMI = body mass index; CI = confidence interval; HSS = hospital for special surgery score; IKDC = International Knee Documentation Committee; KOOS = Knee Injury and Osteoarthritis Outcome Score; KOOS-ADL = Knee Injury and Osteoarthritis Outcome Score, Activities of Daily Living subscale; KOOS-QOL = Knee Injury and Osteoarthritis Outcome Score, Quality of Life subscale; MACI = matrix-induced autologous chondrocyte implantation; N = number; NR = not reported; OATS = osteochondral autologous transplantation; SD = standard deviation.

Table C-14. Study Characteristics for Included Nonrandomized Studies of OCA vs. OATS

Author (Year) Country Registry #	Years conducted	Sponsor	Recruitment Setting	Inclusion Criteria	Exclusion Criteria
Hall et al. (2022)[26] United States	2012 to 2018	NR	Administrative data from the Pediatric Health Information System; a national database of 49 children's hospitals associated with the Children's Hospital Association.	All patients younger than 21 years who underwent open or arthroscopic OATS or OCA in the Pediatric Health Information System	NR
Burroughs et al. (2022)[27] United States	2010 to 2018	NR	PearlDiver Mariner database which combines administrative data from private insurances and Medicare	Patients aged 10 to 59 years who underwent OCA or OATS in the PearlDiver Mariner database	NR

Abbreviations: NR = not reported; OATS = osteochondral autologous transplantation; OCA = osteochondral allograft transplantation.

Table C-15. Intervention Characteristics for Included Nonrandomized Studies of OCA vs. OATS

Author (Year) Sample Size	Sample Size	Intervention Group(s)	Control Group	Rehabilitation Protocol
Hall et al. (2022)[26]	732	OCA Technique category N (%) Open: 273 (69) Arthroscopic: 120 (31)	OATS Technique category N (%): Open: 137 (40.4) Arthroscopic: 202 (59.6)	NR
Burroughs et al. (2022)[27]	2,598	OCA Technique category N (%) Open: 1,067 (65.4) Arthroscopic: 564 (34.6)	OATS Technique category N (%) Open: 398 (41.2) Arthroscopic: 569 (58.8)	NR

Abbreviations: NR = not reported; OATS = osteochondral autologous transplantation; OCA = osteochondral allograft transplantation.

Table C-16. Population Characteristics for Included Nonrandomized Studies of OCA vs. OATS

Author (Year)	Prior Knee Surgery	Injury Mechanism; Severity; Duration of Symptoms Prior to Surgery	Location of Chondral Defect; Mean Defect Size; Number of Lesions	Mean Age (SD) N (%) Female N (%) Race/Ethnicity BMI
Hall et al. (2022)[26]	NR	Injury mechanism, N (%): OCD: 336 (45.9) Cruciate ligament injury: 120 (16.4) Patellar instability: 92 (12.6) Severity of injury: NR Duration of symptoms prior to surgery: NR	Location of chondral defect: NR Mean defect size: NR Number of lesions: NR	Mean age (SD): 15.4 (2.4) N (%) Female: 318 (43.4) N (%) Race/Ethnicity: OCA Black: 68 (17) Unknown: 77 (20) White: 248 (63) OATS Black: 60 (18) Unknown: 66 (19) White: 213 (63) BMI: NR
Burroughs et al. (2022)[27]	NR	Injury mechanism, N (%): NR Severity of injury: NR Duration of symptoms prior to surgery: NR	Location of chondral defect: NR Mean defect size: NR Number of lesions: NR	Mean age (SD): OCA: 34.5 (12.1) OATS: 32.1 (12.9) N (%) Female: OCA: 842 (5.16) OATS: 493 51.0 N (%) Race/Ethnicity: NR

Abbreviations: BMI = body mass index; N = number; NR = not reported; OATS = osteochondral autologous transplantation; OCA = osteochondral allograft transplantation; OCD = osteochondritis dissecans; SD = standard deviation.

Table C-17. Efficacy Outcomes for Included Nonrandomized Studies of OCA vs. OATS

Author (Year) Intervention(s) and Comparison Sample size	Results
Hall et al. (2022)[26] Intervention: OCA Comparator: OATS Sample size: 732	**Composite Scores** **KOOS Total, CKRS, IKDC Subjective Knee Evaluation Form, Lysholm score, HSS:** NR **Activity Scores** **Tegner Score, KOOS-ADL, KOOS-Sport:** NR **Symptom Scores** **KOOS-Pain, KOOS-Symptoms, KOOS-QOL:** NR **Responder, treatment failure, reoperation** **Reoperation:** N (%) OCA (n = 393): 68 (17.3) OATS (n = 339): 76 (22.4) *P*=0.08, Revision cartilage procedures performed N (%) OCA (n = 10) Revision with OATS: 1 (10) Revision with OCA: 7 (70) Revision with ACI: 2 (20) OATS (n = 8) Revision with OATS: 4 (50) Revision with OCA: 1 (12.5) Revision with ACI: 3 (37.5) Reoperations performed (not reported by initial treatment group and unclear whether includes the procedures listed above) Implant removal (37); loose body removal (13); extraarticular ligament reconstruction (8); chondroplasty (7); microfracture (7); lysis of adhesions/manipulation under anesthesia (7); meniscectomy (7); patellar stabilization (6); meniscus repair (5); open OCA (4); arthroscopic synovectomy (4); OCD drilling and fixation (4); ACL reconstruction (4); ACI (3); Open OATS (3); diagnostic arthroscopy (3); other (22) **Responder, Treatment failure:** NR **Subgroup Analyses** Predictors of reoperation in multivariate analysis Open OATS vs. open OCA: (OR 1.7; 95% CI, 1.1 to 2.8; *P*=0.04) Geographic region vs. west Northeast: (OR 1.6; 95% CI, 0.7 to 3.4; *P*=0.25)

Author (Year) Intervention(s) and Comparison Sample size	Results
	Midwest: (OR 1.6; 95% CI, 0.7 to 3.5; *P*=0.29) South: (OR 1.7; 95% CI, 0.8 to 3.7; *P*=0.20) Insurance, private vs. government vs. other: (OR 0.4; 95% CI, 0.04 to 4.42; *P*=0.44)
Burroughs et al. (2022)[27] Intervention: OCA Comparator: OATS Sample size: 2,598	**Composite Scores** **KOOS Total, CKRS, IKDC Subjective Knee Evaluation Form, Lysholm score, Hospital for Special Surgery Score:** NR **Activity Scores** **Tegner Score, KOOS-ADL, KOOS-Sport:** NR **Symptom Scores** **KOOS-Pain, KOOS-Symptoms, KOOS-QOL:** NR **Responder, treatment failure, reoperation** **Reoperation:** N (%) secondary surgery rates OCA: 390 (23.9) OATS: 212 (21.9) *P*=0.249 **Responder, Treatment failure:** NR **Subgroup Analyses:** NR

Abbreviations: ACI = autologous chondrocyte implantation; ACL = anterior cruciate ligament; CI = confidence interval; HSS = hospital for special surgery score; IKDC = International Knee Documentation Committee; KOOS = Knee Injury and Osteoarthritis Outcome Score; KOOS-ADL = Knee Injury and Osteoarthritis Outcome Score, Activities of Daily Living subscale; KOOS-QOL = Knee Injury and Osteoarthritis Outcome Score, Quality of Life subscale; N = number; NR = not reported; OATS = osteochondral autologous transplantation; OCA = osteochondral allograft transplantation; OCD = osteochondritis dissecans; OR = odds ratio.

Table C-18. Study Characteristics for Included Nonrandomized Studies of OATS vs. Chondroplasty

Author (Year) Country Registry #	Years conducted	Sponsor	Recruitment Setting	Inclusion Criteria	Exclusion Criteria
Macarini et al. (2003)[19] Italy	1998 to 2002	NR	NR	Focal osteochondral lesions of grade II and III according to Noyes	NR

Abbreviations: NR = not reported; OATS = osteochondral autologous transplantation.

Table C-19. Intervention Characteristics for Included Nonrandomized Studies of OATS vs. Chondroplasty

Author (Year)	Sample Size	Intervention Group(s)	Control Group	Rehabilitation Protocol
Macarini et al. (2003)[19]	55	OATS performed under arthrotomy in 2 phases: 1. Osteochondral fragment was harvested from a donor site in a non–weight-bearing area, external surface of the lateral femoral condyle of the knee 2. During the same session, the harvested osteochondral fragment was positioned in the lesion after being shaped to fit precisely into the site of the lesion and restore the physiological curve of the articular surface Technique category N (%): Open, Arthrotomy: 15 (100)	Chondroplasty/debridement: Abrasion chondroplasty surgery, consisting of the removal of the detached cartilage and the successive abrasion with a motorized burr of the subchondral bone Technique category N (%): Arthroscopic: 40 (100)	All patients underwent rehabilitative physiotherapy which involved the early mobilization of the joint followed by progressive weight-bearing exercises

Abbreviations: N = number; OATS = osteochondral autologous transplantation.

Table C-20. Population Characteristics for Included Nonrandomized Studies of OATS vs. Chondroplasty

Author (Year)	Prior Knee Surgery	Injury Mechanism; Severity; Duration of Symptoms Prior to Surgery	Location of Chondral Defect; Mean Defect Size; Number of Lesions	Mean Age (SD) N (%) Female N (%) Race/Ethnicity Mean BMI
Macarini et al. (2003)[19]	NR	Injury mechanism: NR Severity of injury N (%): Grade II and III according to Noyes: 55 (100) Duration of symptoms prior to surgery: NR	Location of chondral defect: NR Mean defect size: NR Number of lesions: NR	Mean age, (range) 31, (19 to 45) N (%) Female: NR N (%) Race/Ethnicity: NR Mean BMI: NR

Abbreviations: BMI = body mass index; N = number; NR = not reported; OATS = osteochondral autologous transplantation; SD = standard deviation.

Table C-21. Efficacy Outcomes for Included Nonrandomized Studies of OATS vs. Chondroplasty

Author (Year) Intervention(s) and Comparison Sample size	Results
Macarini et al. (2003)[19] Intervention: OATS Comparator: Chondroplasty/debridement Sample size: 55	**Composite Scores** **Resumed normal sport and work activities,** 1 year post-surgery, OATS: 15; Chondroplasty: 40, N (%) OATS: 15 (100) Chondroplasty: 24 (60) **KOOS Total, CKRS, IKDC Subjective Knee Evaluation Form, Lysholm score, HSS:** NR **Activity Scores** **Tegner Score, KOOS-ADL, KOOS-Sport:** NR **Symptom Scores** **KOOS-Pain, KOOS-Symptoms, KOOS-QOL:** NR **Responder, treatment failure, reoperation** **Responder, Treatment failure, Reoperation:** NR **Subgroup Analyses:** NR

Abbreviations: HSS = hospital for special surgery score; IKDC = International Knee Documentation Committee; KOOS = Knee Injury and Osteoarthritis Outcome Score; KOOS-ADL = Knee Injury and Osteoarthritis Outcome Score, Activities of Daily Living subscale; KOOS-QOL = Knee Injury and Osteoarthritis Outcome Score, Quality of Life subscale; N = number; NR = not reported; OATS = osteochondral autologous transplantation; SD = standard deviation.

Table C-22. Study Characteristics for Included RCTs and Nonrandomized Studies of OATS vs. MF

Author (Year) Country Registry # Study Design	Years conducted	Sponsor	Recruitment Setting	Inclusion Criteria	Exclusion Criteria
Gudas et al. (2005)[32] Gudas et al., 2012[82] Gudas et al., 2006[83] Lithuania RCT	1998 to 2002	NR	Recruited from outpatient clinic at the University of Lithuania	Age < 40 years; competitive or well-trained athletes before injuries (regional or national-level); articular cartilage defects of the medial or lateral femoral condyle; Grade 3 and 4 lesions (according to ICRS); defects between 1 cm^2 and 4 cm^2 diameter Alignment criteria: NR	Lesions larger than 4 cm^2; patients with ligament deficient knees; generalized chondromalacia or osteoarthritis; malalignment with valgus or varus compared with normal; patellofemoral instability; and overweight patients
Gudas et al. (2009)[33] Lithuania RCT	2001 to 2005	NR	NR	Children < 18 years; single grade 3 or 4 osteochondritis dissecans lesion of the medial or lateral femoral condyle; defects between 2 cm^2 and 4 cm^2; failed 6 months of conservative treatment. Alignment criteria: NR	Patients with a preference for type of treatment were excluded
Lim et al. (2012)[31] South Korea RCT	2000 to 2008	NR	Patients who lived in Seoul or who were referred through another hospital	Focal cartilage defects of the medial and lateral femoral condyle with a stable knee and without any concomitant disease; symptomatic and isolated cartilage defects; grades 3 and 4 lesions according to modified Outerbridge grades; defects between 1 cm^2 and 4cm^2 Alignment criteria: NR	Patients who had a second arthroscopic procedure on the same knee for trauma or other diseases (e.g., ligament injuries, meniscal tears, intraarticular infections)

Author (Year) Country Registry # Study Design	Years conducted	Sponsor	Recruitment Setting	Inclusion Criteria	Exclusion Criteria
Solheim et al. (2018)[29] Norway RCT	2000 to 2002	NR	Recruited from department of orthopedics at a single university hospital	Age 18 to 50 years; 1 or 2 symptomatic focal full-thickness articular chondral defects (ICRS Grade 3-4) on the femoral condyles or trochlea, with a total size 2 cm^2 to 6 cm^2 Alignment criteria: > 5 degrees varus or valgus malalignment were excluded	Joint space narrowing (to a space < 4 mm), > 5 degrees varus or valgus malalignment, previous or concurrent realignment surgery, ligament instabilities, or the inability to follow the rehabilitation protocol.
Ulstein et al. (2014)[30] Norway RCT	2000 to 2006	NR	Orthopedic cartilage repair centers	Age 18 to 50 years; arthroscopically verified chondral or osteochondral lesion (ICRS) grade 3 or 4; located on the femoral condyle or trochlea; area between 2 cm^2 and 6 cm^2 and depth < 10 mm; Lysholm score < 80; Tegner score < 6 Alignment criteria: major malalignment; major ligament injury or instability, extension deficit > 3; flexion deficit > 5	Radiographic osteoarthritis (OA); major malalignment; major ligament injury or instability, extension deficit > 3; flexion deficit > 5; chondral lesion(s) of ICRS grade 3 or 4 on the tibial plateau or patella; contralateral impaired knee function that might influence the ability to follow the rehabilitation protocol.
Krych et al. (2012)[35] United States NRSI	1999 to end date NR	No external funding reported in methods; in disclosure statement: "One or more of the authors received payments or services, either directly or indirectly (i.e., via his or her institution), from a third party in	A prospective registry tracking of patient outcomes after articular cartilage repair and reconstruction procedures.	Age 15 to 50, skeletal maturity, single symptomatic lesion of the medial condyle, lateral condyle, or trochlea of the femur that classified as Outerbridge grade III or IV at the time of the initial arthroscopy and did not involve substantial bone loss, lesion area of 1 to 6 cm2, minimum of 2 years follow-up data available.	Generalized osteoarthritis, osteonecrosis, lower extremity malalignment, ligamentous instability or concomitant stabilization procedures involving more than one ligament, inflammatory arthritis, and an age of less than 15 years or more than 50 years.

Author (Year) Country Registry # Study Design	Years conducted	Sponsor	Recruitment Setting	Inclusion Criteria	Exclusion Criteria
		support of an aspect of this work."			
Solheim et al. (2020)[34] Solheim et al. (2017)[81] Norway NRSI	1998 to 2017	None	Single center, other details NR	Age ≤ 60 years; 1 to 3 symptomatic focal full-thickness chondral defect of the knee, verified by arthroscopic evaluation; treated with either MF or OATS.	Joint space narrowing (< 4mm) on AP films; applied at the time of surgery; ≥ 5 degrees varus or valgus malalignment; previous or concurrent surgery; ligament instabilities

Abbreviations: AP = anteroposterior; ICRS = International Cartilage Repair Society; MF = microfracture; NRSI = nonrandomized study of intervention; OATS = osteochondral autologous transplantation; RCT = randomized controlled trial.

Table C-23. Intervention Characteristics for Included RCTs and Nonrandomized Studies of OATS vs. MF

Author (Year) Study Design	Sample Size	Intervention Group(s)	Control Group	Rehabilitation Protocol
Gudas et al. (2005)[32] Gudas et al., 2012[82] Gudas et al. (2006)[83] RCT	57	OATS: The donor transplant was harvested with a larger (0.1mm) cylinder, and the lesion was carved out with a smaller cylinder, so that a press-fit transplantation of the ostechondral cylinder could be achieved. All plugs were placed at the same level with the healthy cartilage. There was an average of 4.3 osteochondral plugs (range from 3 to 6 plugs) used per operation Technique category N (%): Arthroscopic: 28 (100)	MF: According to procedure by Steadman et al, 1990 Technique category N (%): Arthroscopic: 29 (100)	Rehabilitation program same for both groups: non–weight-bearing for 4 weeks, partial weight bearing for next 4 weeks, progress to full weight-bearing after 8 weeks, return to sport 4 to 6 months.
Gudas et al. (2009)[33] RCT	50	OATS: Used 5 and 6mm plugs from the lateral or/and medial margin of the femoral trochlea. All plugs were placed at the same level as the healthy cartilage, as close to each other as possible. There were an average of 4.7 osteochondral plugs (range from 3 to 7 plugs) Technique category N (%): Arthroscopic, 25 (100)	MF: The exposed bone was debrided of all the remaining unstable and necrotic bone with a handheld curved curette or a full radius resector. The fibrotic cartilage from the defect was always removed. After the preparation of the lesion, an arthroscopic awl made multiple holes, or MFs, in the exposed subchondral bone plate. This technique resulted in MF holes approximately 2 to 4 mm wide. Technique category N (%): Arthroscopic, 25 (100)	Weight-bearing prevented for 4 weeks. On the second postoperative day, self-assisted mobilization of the knee was recommended until 90 degree of flexion was attained. In the third or fourth week weight touchdown with crutches was allowed, and was usually completed within 6 to 8 weeks after surgery. Most the patients achieved full weight-bearing by 6 weeks. At 3 to 4 months after surgery, the rehabilitation goal was to return to a correct running pathway through proprioceptive, strength, and endurance exercises and aerobic training. Return to sports was allowed n earlier than 6 months after surgery.

Author (Year) Study Design	Sample Size	Intervention Group(s)	Control Group	Rehabilitation Protocol
Lim et al. (2012)[31] RCT	109 (52 after post-randomization exclusions)	OATS: Plugs of 4, 6, and 8 mm in diameter. Each donor transplant was harvested with a larger (0.1-mm) cylinder, and the lesion was carved out with a smaller cylinder so that a press-fit transplantation of the osteochondral cylinder could be achieved. All plugs were placed at the same level with the healthy cartilage. Technique category N (%): Arthroscopic, 22 (100)	MF: Performed using specialized tapered awls. Cartilaginous remnants on the subchondral bone were debrided fully with an arthroscopic curette and shaver. Conical holes of 0.5 mm to 1 mm in diameter and 4 mm deep were punched throughout the defect at a distance of 3 mm to 4 mm apart with awls. Holes were created in the defective lesion by using instruments from appropriate angles. Creation of the holes was started from the periphery to the center of them lesion at the demarcation line of the intact cartilage. Technique category N (%): Arthroscopic, 25 (100)	Patients told to perform certain rehabilitative exercises using a continuous passive motion (CPM) device 2 to 4 hours per day for 6 to 8 weeks. Allowed to bear weight partially on their tiptoes for 6 to 8 weeks. After 8 weeks, full weight-bearing was permitted and the patient returned to work. Normal activities of daily living were resumed 4 to 6 months after treatment.
Solheim et al. (2018)[29] RCT	40	OATS: The mosaicplasty procedure (Smith & Nephew Inc) was performed as described by Hangody et al. Technique category N (%): Arthroscopic, 20 (100)	MF: Procedure as described by Steadman et al. Technique category N (%): Arthroscopic, 20 (100)	CPM for 4 to 7 days; Foot-touch weight-bearing for 6 weeks with crutches; then, full weight-bearing. Physiotherapy starting before discharge and continuing after, though length of time not specified. Initial exercises included stretching, straight-leg raise exercise, and progressing though active closed-kinetic chain exercises, including stationary bicycling to dynamic weight training.
Ulstein et al. (2014)[30] RCT	25	OATS: Debridement was done similar to that described for MF; OATS mosaicplasty procedure was performed as described by Hangody et al. Technique category N (%): Open, 14 (100)	MF: Technique by Steadman et al Technique category N (%): Arthroscopic, 11 (100)	Similar for both groups; initial 6 weeks maximum load of 15–20 kg weight; gradual discontinuation of crutches and progressive weight-bearing up to 8 weeks; return to full activity by 6 months; return to competitive contact sports at 12 months.

Author (Year) Study Design	Sample Size	Intervention Group(s)	Control Group	Rehabilitation Protocol
Krych et al. (2012)[35] NRSI	96	OATS procedure described by Hangody et al. Technique category N (%): Open, 46 (100)	Drilling: Procedure described by Steadman et al and Mithoefer et al. Technique category N (%): Arthroscopic, N (%) NR	Patients in both groups had the same postoperative rehabilitation scheduled; weight-bearing was permitted after 6 weeks; return to regular activities was generally achieved in both groups at 6 to 8 months postoperatively
Solheim et al. (2020)[34] Solheim et al. (2017)[81] NRSI	203	OATS performed as described by Hangody et al. 2004 Technique category N (%): Both open and arthroscopic, 84 (100)	MF according to procedure by Steadman et al, 1990 Technique category N (%): NR	CPM 4 to 7 days, partial weight-bearing for 6 weeks, gradual increase in closed-chain exercises such as stationary bike to dynamic weight-bearing. Total rehabilitation time not reported.

Abbreviations: AMIC = autologous matrix-induced chondrogenesis; CPM = continuous passive motion; MF = microfracture; N = number; NR = not reported; NRSI = nonrandomized study of intervention; OATS = osteochondral autologous transplantation; RCT = randomized controlled trial.

Table C-24. Population Characteristics for Included RCTs and Nonrandomized Studies of OATS vs. MF or AMIC

Author (Year) Study Design	Prior Knee Surgery	Injury Mechanism; Severity; Duration of Symptoms Prior to Surgery	Location of Chondral Defect; Mean Defect Size; Number of Lesions	Mean Age N (%) Female N (%) Race/Ethnicity Mean BMI
Gudas et al. (2005)[32] Gudas et al., 2012[82] Gudas et al. (2006)[83] RCT	NR	Injury mechanism N (%): Posttraumatic symptomatic full-thickness articular cartilage lesions: 32 (56) Osteochondritis dissecans defects: 25 (44) Severity of injury: Specific values not reported; all patients had ICRS grade 3 or 4. ICRS scores of the patients were comparable between the 2 groups Duration of symptoms prior to surgery, mean (SD): 21.32 (5.57) months	Location of chondral defect N (%): Medial femoral condyle: 48 (84) Lateral femoral condyle: 9 (16) Mean (SD) defect size (cm^2): OATS: 2.80 (0.65) MF: 2.77 (0.68) Number of lesions: Participants had a single symptomatic OCD or full-thickness articular cartilage lesion	Mean age (SD): OATS: 24.6 (6.54) MF: 24.3 (6.80) N (%) Female: 22 (38.6) N (%) Race/Ethnicity: NR BMI: Specific values not reported; BMI was normal in both groups and there was no statistical difference between the groups (*P*=0.80)
Gudas et al. (2009)[33] RCT	NR	Injury mechanism N (%): Osteochondritis Dessicans: 50 (100) Severity of injury: ICRS score mean OATS: 51 MF: 51 Duration of symptoms prior to surgery, mean (SD): 23.5 (4.2) months	Location of chondral defect: Medial femoral condyle, N (%) OATS: 21 (84) MF: 20 (91) Lateral femoral condyle, N (%) OATS: 4 (16) MF: 2 (9) Mean (SD) defect size (cm^2): OATS: 3.2 (0.34) MF: 3.2 (0.38) Number of lesions: Participants had a single symptomatic OCD lesion	Mean age (range): OATS: 14.6 (12 to 18) MF: 14.1 (12 to 18) N (%) Female: OATS: 10 (40) MF: 9 (41) N (%) Race/Ethnicity: NR BMI: BMI was reported as normal in both groups and there was no statistical difference between the groups (*P*=0.3)
Lim et al. (2012)[31] RCT	Prior surgery not eligible	Injury mechanism: NR Severity of injury N (%): Outerbridge grades 3 and 4: 52 (100) Duration of symptoms prior to surgery: NR	Location of chondral defect N (%) Medial femoral condyle OATS: 19 (86) MF: 23 (77) Lateral femoral condyle OATS: 3 (14) MF: 7 (23)	Mean age (range): OATS: 30.4 (20 to 39) MF: 32.9 (22 to 42) N (%) Female: OATS: 10 (45) MF: 12 (40)

Author (Year) Study Design	Prior Knee Surgery	Injury Mechanism; Severity; Duration of Symptoms Prior to Surgery	Location of Chondral Defect; Mean Defect Size; Number of Lesions	Mean Age N (%) Female N (%) Race/Ethnicity Mean BMI
			Mean (range) defect size (cm^2): OATS: 2.8 (1.0 to 4.0) MF: 2.8 (1.2 to 3.6) Number of lesions: Participants had a single symptomatic articular cartilage lesion	Race/Ethnicity: NR BMI: NR
Solheim et al. (2018)[29] RCT	Previous realignment surgery not eligible; other types of knee surgery were NR.	Injury mechanism: NR Severity of injury: all participants had Grade III or IV full-thickness lesions. Duration of symptoms prior to surgery, mean (SD): OATS: 52 (60) months MF: 58 (48) months	Location of chondral defect: All participants had lesions on femoral condyle or trochlea Mean (SD) defect size (cm^2): OATS: 3.4 (0.9) MF: 3.6 (0.8) N (%) number of lesions: 1 lesion OATS: 18 (90) MF: 18 (90) 2 lesions OATS: 2 (10) MF: 2 (10)	Mean age (SD): OATS: 31 (7) MF: 35 (9) N (%) Female: OATS: 6 (30) MF: 6 (30) Race/Ethnicity: NR BMI: NR
Ulstein et al. (2014)[30] RCT	Previous cartilage surgery, N (%) OATS: 1 (7) MF: 3 (23)	Injury mechanism N (%): Gradual onset OATS: 4 (29) MF : 0 (0) Trauma/acute onset OATS: 6 (43) MF : 5 (45) Osteochondritis dissecans OATS: 4 (29) MF : 6 (55) Severity of injury, mean (SD): ICRS grade III: OATS: 8 (57)	Location of chondral defect N (%): Trochlea OATS: 2 (14) MF : 0 (0) Medial femoral condyle OATS: 10 (71) MF: 10 (91) Lateral femoral condyle OATS: 2 (14) MF: 1 (9) Median (range) defect size (cm^2): OATS: 3.0 (2.0–6.0) MF: 2.6 (2.0–5.2)	Mean age (SD): OATS: 32.7 (7.8) MF: 31.7 (8.0) N (%) Female: OATS: 6 (43) MF: 5 (45) N (%) Race/Ethnicity: NR BMI: NR

Author (Year) Study Design	Prior Knee Surgery	Injury Mechanism; Severity; Duration of Symptoms Prior to Surgery	Location of Chondral Defect; Mean Defect Size; Number of Lesions	Mean Age N (%) Female N (%) Race/Ethnicity Mean BMI
		MF: 4 (36) ICRS grade IV: OATS: 6 (43) MF: 7 (63) Duration of symptoms prior to surgery, mean (SD): OATS: 75.8 (73.5) months MF: 111.0 (77.3) months	Number of lesions: NR	
Krych et al. (2012)[35] NRSI	N (%) OATS: 16 (34.9) (prior microfracture) MF: 0 (0)	Injury mechanism N (%): Chronic OATS: 13 (28.3) MF: 23 (50) Traumatic OATS: 20 (43.5) MF: 22 (47.8) Osteochondritis dissecans OATS: 15 (32.6) MF: 3 (0.07) Severity of injury: NR Duration of symptoms prior to surgery: NR	Location of chondral defect N (%): Medial femoral condyle OATS: 27 (58.7) MF: 27 (58.7) Lateral femoral condyle OATS: 16 (34.8) MF: 16 (34.8) Trochlea OATS: 5 (10.9) MF: 5 (10.9) Mean (range) defect size (cm^2): OATS: 2.65 (1.00 to 6.25) MF: 2.55 (1.00 to 6.25) Nmber of lesions: Participants had a single symptomatic cartilage lesion	Mean age (range): OATS: 29.7 (15 to 49) MF: 32.5 (15 to 46) N (%) Female: OATS: 16 (34.9) MF: 16 (34.9) N (%) Race/Ethnicity: NR Mean BMI kg/m^2 (range): OATS: 25.2 (18 to 36) MF: 25.5 (21 to 31)
Solheim et al. (2020)[34] Solheim et al. (2017)[81] NRSI	Prior surgery not eligible	Injury mechanism: NR Severity of injury: NR Duration of symptoms prior to surgery, median (range): 60 months (1 to 360)	Location of chondral defect N (%): Medial femoral condyle: 118 (58) Lateral femoral condyle: 14 (7) Trochlea: 28 (14) Patella: 30 (15) Lateral tibial plateau: 12 (6) Median (range) defect size (mm^2): 350 (100 to 1700)	Median age (range): 36 (15-60) N (%) Female: 85 (41.9) N (%) Race/Ethnicity: NR BMI: NR

Author (Year) Study Design	Prior Knee Surgery	Injury Mechanism; Severity; Duration of Symptoms Prior to Surgery	Location of Chondral Defect; Mean Defect Size; Number of Lesions	Mean Age N (%) Female N (%) Race/Ethnicity Mean BMI
			Number of lesions: Participants could have 1 or multiple treated lesions	

Abbreviations: AMIC = autologous matrix-induced chondrogenesis; BMI = body mass index; ICRS = International Cartilage Repair Society; MF = microfracture; N = number; NR = not reported; NRSI = nonrandomized study of intervention; OATS = osteochondral autologous transplantation; OCD = osteochondritis dissecans; RCT = randomized controlled trial; SD = standard deviation.

Table C-25. Efficacy Outcomes for Included RCTs and Nonrandomized Studies of OATS vs. MF

Author (Year) Intervention(s) and Comparison Sample size Study Design	Results
Gudas et al. (2005)[32] Gudas et al., 2012[82] Gudas et al. (2006)[83] Intervention: OATS Comparator: MF Sample size: 57 RCT	**Composite Scores** **KOOS Total, CKRS, IKDC Subjective Knee Evaluation Form, Lysholm score:** NR **HSS:** HSS score, Baseline, NR (OATS = 28; MF = 29), mean (SD) OATS: 77.88 (6.23) MF: 77.22 (8.12) Modified HSS score, 12 months, NR (OATS = NR, MF = NR), mean (SD) OATS: 88 (NR) MF: 83 (NR) *P*<0.01 Modified HSS score, 36 months, NR (OATS = NR, MF = NR), mean (SD) OATS: 91 **Activity Scores** **Tegner Score, KOOS-ADL, KOOS-Sport:** NR **Symptom Scores** **KOOS-Pain, KOOS-Symptoms, KOOS-QOL:** NR **Responder, treatment failure, reoperation** **Treatment failure:** Symptomatic after postoperative rehabilitation and unable to return to pre-sports level activity, Treatment failure, 24 months (OATS = NR, MF = NR), N (%) OATS: 1 (NR) MF: 9 (NR) *P*=NR **Reoperation:** Reoperation, NR (OATS = NR, MF = NR), N (%) OATS: 1 (NR) MF: 9 (NR) *P*=NR, MFX: debridement, OATS OATS: OATS revision

Author (Year) Intervention(s) and Comparison Sample size Study Design	Results
	Responder: NR **Subgroup Analyses** No differences by the following subgroups: location of lesions, cartilage grade, age, gender, BMI, duration of symptoms. (No specific values reported) Significant differences by: lesion size, mechanism of injury (trauma vs. osteochondritits dessicans)
Gudas et al. (2009)[33] Intervention: OATS Comparator: MF Sample size: 50 RCT	**Composite Scores** **KOOS Total, CKRS, IKDC Subjective Knee Evaluation Form, Lysholm score, HSS:** NR **Activity Scores** **Tegner Score, KOOS-ADL, KOOS-Sport:** NR **Symptom Scores** **KOOS-Pain, KOOS-Symptoms, KOOS-QOL**: NR **Responder, treatment failure, reoperation** **Responder:** Not eligible, based on appearance at second-look arthroscopy and not available for all participants. **Treatment failure:** Treatment failure definition NR, N (%): OAT: 0 (0) MF: 9 (41) **Reoperation:** Second-look arthroscopies for persistent symptoms at a mean of 20.3 months post-surgery OAT: 5/25 (20) MF: 16/22 (73) **Subgroup Analyses** Significant difference found by lesions size on MF group, but not OATS group. No significant differences by: patients younger than 14 vs. patients 14 years and older.
Lim et al. (2012)[31] Intervention: OATS Comparator: MF	**Composite Scores** **Lysholm score:** Lysholm score, Baseline, Completer (OATS = 22; MF = 25), mean (SD) OATS: 53.2 (7.2)

Author (Year) Intervention(s) and Comparison Sample size Study Design	Results
Sample size: 109 (52 after post-randomization exclusions) RCT	MF: 51.2 (6.2) Lysholm score, 5 years, Completer (OATS = 22; MF = 25), mean (SD) OATS: 84.8 (5.5) MF: 85.6 (6.8) *P*=0.432 (including comparison with ACI group, which was not eligible) **HSS** HSS Score, Baseline, Completer (OATS = 22; MF = 25), mean (SD) OATS: 78.7 (7.2) MF: 78.2 (9.1) HSS Score, 5 years, Completer (OATS = 22; MF = 25), mean (SD) OATS: 88.1 (4.2) MF: 87.6 (4.6) *P*=0.516 (including comparison with ACI group, which was not eligible) **KOOS Total, CKRS, IKDC Subjective Knee Evaluation Form:** NR **Activity Scores** **Tegner Score:** Tegner Score, Baseline, Completer (OATS = 22; MF = 25), mean (SD) OATS: 2.7 (1.5) MF: 2.8 (1.4) Tegner Score, 5 years, Completer (OATS = 22; MF = 25), mean (SD) OATS: 5.3 (1.2) MF: 5.1 (1.5) *P*=0.213 (including comparison with ACI group, which was not eligible) **KOOS-ADL, KOOS-Sport:** NR **Symptom Scores** **KOOS-Pain, KOOS-Symptoms, KOOS-QOL:** NR **Responder, treatment failure, reoperation** **Reoperation:** Reoperation (reoperation definition NR) OATS: 1/NR (NR)

Author (Year) Intervention(s) and Comparison Sample size Study Design	Results
	MF: 3/NR (NR), MR: 2 arthroscopies due to recurrent knee pain, 1 also required arthrolysis OATS: 1 arthroscopy because of knee problems **Responder:** Not eligible; assessed based on MRI or repeat arthroscopy **Treatment failure:** NR **Subgroup Analyses:** NR
Solheim et al. (2018)[29] Intervention: OATS Comparator: MF Sample size: 40 RCT	**Composite Scores** **Lysholm score:** Lysholm, Baseline, ITT (OATS = 30, MF = 20), mean (SD) score OATS: 56 (15) MF: 50 (16) *P*=0.2 Lysholm, 1-year post-op, ITT (OATS = 20, MF = 20), mean (SD) score OATS: 85 (12) MF: 72 (22) *P*=0.015 Lysholm, 15 years post-op, ITT (OATS = 20, MF = 20), mean (SD) score OATS: 77 (17) MF: 61 (22) *P*=0.011 **KOOS Total, HSS, CKRS, IKDC Subjective Knee Evaluation Form:** NR **Activity Scores** **Tegner Score, KOOS-ADL, KOOS-Sport:** NR **Symptom Scores** **KOOS-Pain, KOOS-Symptoms, KOOS-QOL:** NR **Responder, treatment failure, reoperation** **Responder:** Lysholm score good/excellent (≥ 80), N (%) OATS: 12 (60) MF: 4 (20)

Author (Year) Intervention(s) and Comparison Sample size Study Design	Results
	P=0.010 **Treatment failure:** Knee Replacement at 15 years, N (%) OATS: 1 (5) MF: 3 (15) *P*=0.292 **Reoperation:** NR **Subgroup Analyses**: NR
Ulstein et al. (2014)[30] Intervention: OATS Comparator: MF Sample size: 25 RCT	**Composite Scores** **Lysholm score:** Lysholm score, Baseline (OATS = 14; MF = 11), mean (95% CI) OATS: 49.2 (43.0 to 55.4) MF: 48.2 (38.2 to 58.2) Lysholm score, Follow-up (median 9.8 years), (OATS = 14; MF = 11), mean (95% CI) OATS: 62.6 (52.6 to 72.6) MF: 69.7 (55.1 to 84.4) Lysholm score, change from baseline to year 10, ITT (OATS = 14; MF = 11), mean change (95% CI) OATS: 13.4 (0.9 to 25.8) MF: 21.6 (3.7 to 39.4) Lysholm score, change over time, ITT (OATS = 14; MF = 11), mean difference (95% CI), P value OATS vs. MF: -8.8 (-28.1 to 11.7), *P*>0.05 **KOOS Total, CKRS, IKDC Subjective Knee Evaluation Form, HSS:** NR **Activity Scores** **KOOS-ADL:** KOOS-ADL change from baseline to year 10, ITT (OATS = 14; MF = 11), mean change (95% CI) OATS: 7.5 (-4.3 to 19.3) MF: 13.0 (-3.8 to 29.8) KOOS-ADL, change over time, ITT (OATS = 14; MF = 11), mean difference (95% CI), P value OATS vs. MF: -5.5 (-24.4 to 13.4), *P*>0.05 **KOOS-Sport:**

Author (Year) Intervention(s) and Comparison Sample size Study Design	Results
	KOOS-SR, change from baseline to year 10, ITT (OATS = 14; MF = 11), mean change (95% CI) OATS: 41.3 (23.7 to 58.9) MF: 32.4 (13.3 to 51.6) KOOS-SR, change over time, ITT (OATS = 14; MF = 11), mean difference (95% CI), P value OATS vs. MF: 8.9 (-15.7 to 33.4), *P*>0.05 **Tegner Score:** NR **Symptom Scores** **KOOS-Pain:** KOOS-P, change from baseline to follow-up (median 9.8 years), ITT (OATS = 14; MF = 11), mean change (95% CI) OATS: 11.8 (-2.8 to 26.4) MF: 20.6 (2.8 to 38.3) KOOS-P, change over time, ITT (OATS = 14; MF = 11), mean difference (95% CI), P value OATS vs. MF: -8.8 (-30.3 to 12.7), *P*>0.05 **KOOS-Symptoms:** KOOS-S change from baseline to to follow-up (median 9.8 years), ITT (OATS = 14; MF = 11), mean change (95% CI) OATS: 8.5 (-3.5 to 20.6) MF: 17.4 (2.6 to 32.2) KOOS-S, change over time, ITT (OATS = 14; MF = 11), mean difference (95% CI), P value OATS vs. MF: -8.9 (-26.7 to 8.9), *P*>0.05 **KOOS-QOL:** KOOS-QOL, change from baseline to year 10, ITT (OATS = 14; MF = 11), mean change (95% CI) OATS: 25.0 (10.6 to 39.3) MF: 34.6 (15.1 to 54.0) KOOS-QOL, change over time, ITT (OATS = 14; MF = 11), mean difference (95% CI), P value OATS vs. MF: -9.6 (-31.9 to 12.7), *P*>0.05 **Responder, treatment failure, reoperation** **Reoperation:** OATS (n = 14): 5 (36) MF (n = 11): 6 (55), ACI; OAT mosaicplasty; open wedge osteotomy; removal of loose body; diagnostic arthroscopy/debridement; scheduled to TKA. All knees that underwent a second cartilage repair (n = 3) or TKA (n = 1) were in the MF group.

Author (Year) Intervention(s) and Comparison Sample size Study Design	Results
	ACI, N (%) OATS: 0 (0) MF: 2 () OATS, N (%) OATS: 0 (0) MF: 1 (18) Open wedge osteotomy, N (%) OATS: 1 (7) MF: 0 (0) Removal of loose body, N (%) OATS: 0 (0) MF: 1 (9) Diagnostic arthroscopy/ debridement, N (%) OATS: 4 (29) MF: 1 (9) TKA, N (%) OATS: 0 (0) MF: 1 (9) **Responder, Treatment failure:** NR **Subgroup Analyses**: NR
Krych et al. (2012)[35] Intervention: OATS Comparator: Drilling Sample size: 96 NRSI	**Composite Scores** **IKDC Subjective Knee Evaluation Form:** IKDC, Baseline, OATSv= 48; MF = 48, mean (SD) OATS: 43.7 (15.8) MF: 49.7 (15.8) *P*=0.15 IKDC, 2 years, OATS = 48; MF = 48, mean (SD) OATS: 75.2 (NR) MF: 69.2 (NR) *P*=NS IKDC, 5 years, OATS = NR; MF = NR, mean (SD) OATS: 79.0 (NR)

Author (Year) Intervention(s) and Comparison Sample size Study Design	Results
	MF: 72.4 (NR) *P*=NS **KOOS Total, CKRS, Lysholm score, HSS:** NR **Activity Scores** **KOOS-ADL:** KOOS-ADL, Baseline, OATS = 48; MF = 48, mean (SD) OATS: 63.6 (NR) MF: 64.1 (NR) *P*=NS KOOS-ADL, 2 years, OATS = 48; MF = 48, mean (SD) OATS: 85.8 (NR) MF: 79.1 (NR) *P*=NS KOOS-ADL, 5 years, OATS = NR; MF = NR, mean (SD) OATS: 83.1 (NR) MF: 84.4 (NR) *P*=NS **Tegner Score, KOOS-Sport:** NR **Symptom Scores** **KOOS-Pain, KOOS-Symptoms, KOOS-QOL:** NR **Responder, treatment failure, reoperation:** NR **Subgroup Analyses** NR
Solheim et al. (2020)[34] Solheim et al. (2017)[81] Intervention: OATS Comparator: MF Sample size: 203	**Composite Scores** **Lysholm score:** Lysholm Total, Baseline, OATS = 84; MF = 119, mean (SD) OATS: 47 (16) MF: 47 (18) Follow-up scores NR

Author (Year) Intervention(s) and Comparison Sample size Study Design	Results
NRSI	**KOOS Total, CKRS, IKDC Subjective Knee Evaluation Form, HSS:** NR **Activity Scores** **Tegner Score, KOOS-ADL, KOOS-Sport:** NR **Symptom Scores** **KOOS-Pain, KOOS-Symptoms, KOOS-QOL:** NR **Responder, treatment failure, reoperation** **Treatment failure:** Lysholm score < 65 points (1 year follow-up or later) or ipsilateral knee replacement procedure., Total failures at median, 15 years (range 1-18), N calculated (%) OATS: 43 (51) MF: 79 (66) *P*=0.011 Mean time to failure, N years (SD) OATS: 8.4 (4.8) MF: 4.0 (4.1) *P*<0.001 **Responder, Reoperation:** NR **Subgroup Analyses** Authors managed confounders by doing a subgroup analysis for variables with significant differences at baseline (age, size of treated area). Similar survival outcomes for subgroup of patients (n = 134) for ages < 51 years and treated lesions size < 500 mm^2.

Notes: [a] Results categorized using the modified Cinncinnati rating system as excellent (> 80 points), good (55 to 79), fair (30 to 54) or poor (< 30 points).

Abbreviations: ACI = autologous chondrocyte implantation; AMIC = autologous matrix-induced chondrogenesis; CI = confidence interval; HSS = Hospital for Special Surgery; IKDC = International Knee Documentation Committee; ITT = intention to treat; KOOS = Knee Injury and Osteoarthritis Outcome Score; KOOS-ADL = Knee Injury and Osteoarthritis Outcome Score, Activities of Daily Living subscale; KOOS-P = Knee Injury and Osteoarthritis Outcome Score, Pain subscale KOOS-QOL = Knee Injury and Osteoarthritis Outcome Score, Quality of Life subscale; KOOS-SR = Knee Injury and Osteoarthritis Outcome Score, Sport and Recreation subscale; MF = microfracture; N = number; NR = not reported; NRSI = nonrandomized study of intervention; OATS = osteochondral autologous transplantation; OCD = osteochondritis dissecans; RCT = randomized controlled trial; SD = standard deviation; TKA = total knee arthroplasty.

Table C-26. Safety Outcomes for Included RCTs and Nonrandomized Studies of OATS vs. MF

Author (Year) Study Design	Any Adverse Effects	Serious Adverse Effects
Gudas et al. (2005)[32] Gudas et al., 2012[82] Gudas et al. (2006)[83] RCT	Any AE, 24 months (OATS = NR, MF = NR), N (%) OATS: 2 (NR) MF: 0 (0) OATS Superficial infection 2 (NR)	NR
Gudas et al. (2009)[33] RCT	Knee pain OATS: 9/25 (36%) MF: 13/22 (59%) P NR Joint swelling between 14 and 34 days after operation OATS: 2/25 (8) MF: 10/22 (45) *P*=0.0032 Knee joint crepitation OATS: 10/25 (40) MF: 4/22 (18) *P*=0.043 1 case of superficial infection in OATS group	NR
Lim et al. (2012)[31] RCT	NR	NR
Solheim et al. (2018)[29] RCT	N (%) with early complications OATS: 3 (15) [wound rupture with superficial infection; deep infection, DVT] MF: 0 (0)	NR
Ulstein et al. (2014)[30] RCT	NR	NR
Krych et al. (2012)[35] NRSI	NR	NR

Author (Year) Study Design	Any Adverse Effects	Serious Adverse Effects
Solheim et al. (2020)[34] Solheim et al. (2017)[81] NRSI	NR	NR

Abbreviations: AE = adverse event; AMIC = autologous matrix-induced chondrogenesis; MF = microfracture; N = number; NR = not reported; NRSI = nonrandomized study of intervention; OATS = osteochondral autologous transplantation; RCT = randomized controlled trial.

Table C-27. Study Characteristics for Included RCTs Cell-free Implants vs. MF/Chondroplasty

Author (Year) Country Registry # Study Design	Years conducted	Sponsor	Recruitment Setting	Inclusion Criteria	Exclusion Criteria
Altschuler et al. (2023)[38] United States, Belgium, Israel, Hungary, Italy, Romania, Serbia NCT03299959 RCT	2017 to 2019	Industry: Cartiheal, Ltd	26 medical centers; no additional details reported.	Age 21 to 75 years; presence of up to 3 ICRS grade 3a or above lesions on the femoral condyles or trochlea; total treatable area of 1 to 7 cm^2; nonresponsive to physical therapy for at least 3 to 4 weeks. Alignment criteria: > 8 degrees varus or > 8 degrees valgus malalignment according to standing radiogragh	KOOS-Pain subscale score at baseline < 20 or > 65; defect depth > 8 mm; lesions in the tibia or the patella ICRS grade 4a or above; severe OA of the index knee (Grade 4 according to KL score); significant instability of the index knee (grade C or D according to IKDC Form 2000); lack of functional remaining meniscus, > 5 mm rim at the end of the procedure; history of intraarticular or osseous infection of the index knee; lack of vital bone wall > 2 mm thick completely surrounding the lesion; inability to position the implant 2 mm recessed relative to the articular surface.

Abbreviations: ICRS = International Cartilage Repair Society; KL = Kellgren-Lawrence; KOOS = Knee Injury and Osteoarthritis Outcome Score; MF = microfracture; N = number; NR = not reported; OA = osteoarthritis; RCT = randomized controlled trial.

Table C-28. Intervention Characteristics for Included RCTs Cell-free Implants vs. MF/Chondroplasty

Author (Year) Study Design	Sample Size	Intervention Group(s)	Control Group	Rehabilitation Protocol
Altschuler et al. (2023)[38] RCT	251	Aragonite-based biphasic implant (Agili-C) Technique category N (%): Open, 167 (100)	MF or debridement: Participants with focal chondral defects and KL scores 0 or 1 received MF, those with mild to moderate OA (KL 2 or 3) received debridement. Technique category N (%): Arthroscopic, 84 (100)	Total rehabilitation time 12 months. Partial weight-bearing for 4 weeks; isometric exercises and return to full range of motion weeks 5-12; muscle strengthening months 4-6; return to activity 6 months; return to impact activities 12 months.

Abbreviations: KL = Kellgren-Lawrence; KOOS = Knee Injury and Osteoarthritis Outcome Score; MF = microfracture; N = number; OA = osteoarthritis; RCT = randomized controlled trial.

Table C-29. Population Characteristics for Included RCTs Cell-free Implants vs. MF/Chondroplasty

Author (Year) Study Design	Prior Knee Surgery	Injury Mechanism; Severity; Duration of Symptoms Prior to Surgery	Location of Chondral Defect; Mean Defect Size; Number of Lesions	Mean Age N (%) Female N (%) Race/Ethnicity Mean BMI
Altschuler et al. (2023)[38] RCT	History of ACL reconstruction, N (%) Cell-free implant: 13 (7.8) MF/Debridement: 7 (8.3) History of meniscectomy, N (%) Cell-free implant: 36 (21.6) MF/Debridement: 22 (26.2)	Injury mechanism: NR N (%) severity of injury: ICRS grade III and IVa Cell-free implant: 104 (62.3) MF/Debridement: 68 (81) ICRS grade IVb: Cell-free implant: 63 (37.7) MF/Debridement: 16 (19) Duration of symptoms prior to surgery: NR	Location of chondral defect: NR N (%) defect size > 3 cm^2 Cell-free implant: 98 (58.7) MF/Debridement: 41 (48.8) N (%) number of lesions: Single lesion: Cell-free implant: 109 (65.3) MF: 58 (69) Multiple lesions: Cell-free implant: 58 (34.7) MF: 26 (31) Presence of up to 3 joint surface lesions allowed	Mean age (SD): Cell-free implant: 42 (11.2) MF: 46 (11.2) N (%) Female: Cell-free implant: 60 (35.9) MF/Debridement: 33 (39.3) N (%) Race/Ethnicity: NR BMI, N (%) ≥ 30: Cell-free implant: 37 (22.2) MF/Debridement: 27 (32.1)

Abbreviations: ACL = anterior cruciate ligament; BMI = body mass index; ICRS = International Cartilage Repair Society; MF = microfracture; N = number; NR = not reported; RCT = randomized controlled trial; SD = standard deviation.

Table C-30. Efficacy Outcomes for Included RCTs Cell-free Implants vs. MF/Chondroplasty

Author (Year) Intervention(s) and Comparison Sample size Study Design	Results
Altschuler et al. (2023)[38] Intervention: Cell-free implant Comparator: MF/Debridement Sample size: 251 RCT	***Composite Scores*** **KOOS Total:** KOOS Total, mITT (Cell-free implant = 54; MF/Debridement = 40), MD (95% CI) baseline to 6 months 8.2 (3.3 to 13.0) KOOS Total, mITT (Cell-free implant = 54; MF/Debridement = 40), MD (95% CI) baseline to 24 months 22.5 (17.0 to 28.0) *P*<0.0001 at all timepoints (6, 12, 18, 24 months) **CKRS, IKDC Subjective Knee Evaluation Form, Lysholm score, HSS:** NR ***Activity Scores*** **KOOS-ADL:** NR (Figure only, no specific values reported); **Tegner Score, KOOS-Sport:** NR ***Symptom Scores*** **KOOS-Pain, KOOS-QOL:** NR (Figure only, no specific values reported); **KOOS-Symptoms:** NR ***Responder, treatment failure, reoperation*** **Responder:** Improvement in overall KOOS score ≥ 30, N (%) Baseline to 24 months Cell-free implant (n = 164): 77.8 MF/Debridement (n = 83): 33.6 *P*=0.0001 **Treatment failure:** Any secondary intervention in the treated joint (e.g., surgical or arthroscopic procedure) or intraarticular joint injection, Cell-free implant (n = 164): 18 (21.4) MF/Debridement (n = 83): 12 (7.2) *P*=0.002 **Reoperation:** NR ***Subgroup Analyses*** Age, presence of OA by KL grade, and lesion size. No difference by OA KL grade or age. Significantly larger treatment effect in larger lesions

Table C-31. Safety Outcomes for Included RCTs Cell-free Implants vs. MF/Chondroplasty

Author (Year) Study Design	Any Adverse Effects	Serious Adverse Effects
Altschuler et al. (2023)[38] RCT	N (%) experiencing ≥ 1 adverse event, 24 months Cell-free implant (n = 167): 98 (58.7) MF (n = 84): 65 (77.4) Common AE (N calculated by abstractor), 24 months Transient knee pain: Cell-free implant (n = 167): 25 (15.0) MF/Debridement (n = 84): 33 (39.3) Swelling or effusion: Cell-free implant (n = 167): 9 (5.4) MF/Debridement (n = 84): 4 (4.8)	Deep vein thrombosis, 24 months Cell-free implant (n = 167): 1 (0.6) MF/Debridement (n = 84): 1 (1.2) Wound complications, 24 months Cell-free implant (n = 167): 2 (1.2) MF/Debridement (n = 84): 1 (1.2) Septic arthritis, MACI (n=167): Cell-free implant (n = 167): 1 (0.6) MF/Debridement (n = 84): 0 (0) Decreased range of motion from baseline, 24 months Cell-free implant (n = 167): 2 (1.2) MF/Debridement (n = 84): 0 (0) Persistent muscle atrophy, 24 months Cell-free implant (n = 167): 2 (1.2) MF/Debridement (n = 84): 0 (0) OA progression leading to revision surgery, 24 months Cell-free implant (n = 167): 0 (0) MF/Debridement (n = 84): 4 (4.8)

Abbreviations: CI = confidence interval; KL = Kellgren-Lawrence; KOOS = Knee Injury and Osteoarthritis Outcome Score; KOOS-ADL = Knee Injury and Osteoarthritis Outcome Score, Activities of Daily Living subscale; KOOS-QOL = Knee Injury and Osteoarthritis Outcome Score, Quality of Life subscale; MD = mean difference; MF = microfracture; N = number; NR = not reported; OA = osteoarthritis; RCT = randomized controlled trial.

Table C-32. Study Characteristics for Included RCTs of AMIC vs. MF

Author (Year) Country	Years conducted	Sponsor	Recruitment Setting	Inclusion Criteria	Exclusion Criteria
Volz et al. (2017)[39] Germany	NR	Industry: Geistlich Pharma AG	Initially recruited from 5 centers, but due to poor enrollment, only data from patients recruited from 2 centers were used.	Between 18 and 50 years of age with 1 or 2 cartilage defects of grade III or IV according to the Outerbridge classification, located either on the medial or lateral femoral condyle, trochlea or patella, and a defect size between 2 cm^2 and 10 cm^2 Alignment criteria: Patients with any malalignment were excluded.	Patients with more than 2 defects, 2 corresponding defects or defects on both knees; signs of osteoarthrosis; bone lesion > 0.7 cm; uncorrected knee instability; rheumatoid arthritis; parainfectious or infectious diseases; chronic heart, endocrine, metabolic or autoimmune disease; varus or valgus deformation; previous complete meniscus resection or mosaicplasty; treatment with cartilage specific medication (e.g. hyaluronic acid); chondropathia patellae or dysplasia of the patella

Abbreviations: AMIC = autologous matrix-induced chondrogenesis; MF = microfracture; RCT = randomized controlled trial.

Table C-33. Intervention Characteristics for Included RCTs of AMIC vs. MF

Author (Year) Sample Size	Sample Size	Intervention Group(s)	Control Group	Rehabilitation Protocol
Volz et al. (2017)[39]	47	Sutured AMIC: A collagen type I/III matrix (Chondro-Gide, Geistlich Pharma AG, Wolhusen, Switzerland) was added to cover the microfractured defect area. Chondro-Gide was placed with the porous layer facing the bone surface and fixed using sutures (PDS 5.0, Ethicon, Norderstedt, Germany; sutured AMIC) Technique category N (%): Open, Miniarthrotomy: 17 (100) Glued AMIC: A collagen type I/III matrix (Chondro-Gide, Geistlich Pharma AG, Wolhusen, Switzerland) added to cover microfractured defect area. Chondro-Gide placed with the porous layer facing the bone surface and fixed by gluing the matrix onto the bone surface (Tissucol, Baxter, Germany). Technique category N (%): Open, Miniarthrotomy: 17 (100)	MF: MF according to procedure by Steadman et al, 1999 Technique category N (%): Arthroscopic: 13 (100)	All patients assigned to same rehabilitation protocol. Consisted of foot sole contact for 6 weeks using crutches building up full weight-bearing after 8 weeks. Range of motion was restricted to 0/0/30° in defects of the patella or trochlea and 0/0/60° of the femoral condyle for the first 10 days postoperatively and to 0/0/90° for 6 weeks for both groups. Mobilization exercises including continuous passive motion, electrotherapy of leg muscles and proprioception training were provided. Jogging was allowed after 6 months and contact sports were restricted for 18 months

Abbreviations: AMIC = autologous matrix-induced chondrogenesis; MF = microfracture; N = number; PDS = polydioxanone suture; RCT = randomized controlled trial.

Table C-34. Population Characteristics for Included RCTs of AMIC vs. MF

Author (Year)	Prior Knee Surgery	Injury Mechanism; Severity; Duration of Symptoms Prior to Surgery	Location of Chondral Defect; Mean Defect Size; Number of Lesions	Mean Age N (%) Female N (%) Race/Ethnicity Mean BMI
Volz et al. (2017)[39]	Previous operation (specific operation not specified), N (%): 24 (51) Meniscus revision, N (%): 15 (32)	Injury mechanism: NR Severity of injury, N (%): Grade III or IV: 47 (100) Duration of symptoms prior to surgery: NR	Location of chondral defect: Specific data NR. "Lesions were mostly located on the femoral condyles" Mean (SD) defect size (cm^2): 3.6 (1.6) Number of lesions: Participants had 1 or 2 isolated cartilage defects of the knee	Mean age: (SD): 37 (10) N (%) Female: 10 (21) N (%) Race/Ethnicity: NR Mean BMI (SD): 26.8 (3.9)

Abbreviations: AMIC = autologous matrix-induced chondrogenesis; BMI = body mass index; MF = microfracture; N = number; NR = not reported; RCT = randomized controlled trial; SD = standard deviation.

Table C-35. Efficacy Outcomes for Included RCTs of AMIC vs. MF

Author (Year) Intervention(s) and Comparison Sample size	Results
Volz et al. (2017)[39] Interventions: Sutured AMIC, Glued AMIC Comparator: MF Sample size: 47	**Composite Scores** **CKRS:** Modified CKRS, Baseline, completers (sutured AMICv= 17; glued AMIC = 17; MF = 13), mean (SD) Sutured AMIC: 45 (19) Glued AMIC: 48 (15) MF: 38 (19) Modified CKRS, 1 year follow-up, completers (sutured AMIC = 13; glued AMIC = 15; MF = 11), mean (SD), P value for difference from baseline to year 1 Sutured AMIC: 82 (15), *P*<0.001 Glued AMIC: 67 (26), *P*=0.028 MF: 72 (18), *P*<0.001 Modified CKRS, 5 year follow-up, completers (sutured AMIC = 16; glued AMIC = 14; MF = 9), P value for score compared to MF Sutured AMIC: values NR (figure only), *P*=0.01 Glued AMIC: values NR (figure only), *P*=0.002 **KOOS Total, IKDC Subjective Knee Evaluation Form, Lysholm score, HSS:** NR **Activity Scores** **Tegner Score, KOOS-ADL, KOOS-Sport:** NR **Symptom Scores** **KOOS-Pain, KOOS-Symptoms, KOOS-QOL:** NR **Responder, treatment failure, reoperation** **Reoperation:** One patient with MF received an ACI procedure after one year and one patient treated with glued AMIC received a joint replacement after one year Reoperation, completers analysis, from baseline to 5 years follow-up AMIC-glued (n = 14): 1 (7) AMIC-sutured (n = 16): 0 (0) MF (n = 9): 1 (11) **Responder, Treatment failure:** NR **Subgroup Analyses**: NR

Abbreviations: ACI = autologous chondrocyte implantation; AMIC = autologous matrix-induced chondrogenesis; IKDC = International Knee Documentation Committee; KOOS = Knee Injury and Osteoarthritis Outcome Score; KOOS-ADL = Knee Injury and Osteoarthritis Outcome Score, Activities of Daily Living subscale; KOOS-QOL = Knee Injury and Osteoarthritis Outcome Score, Quality of Life subscale; MF = microfracture; N = number; NR = not reported; RCT = randomized controlled trial; SD = standard deviation.

Table C-36. Safety Outcomes for Included RCTs of AMIC vs. MF

Author (Year)	Any Adverse Effects	Serious Adverse Effects
Volz et al. (2017)[39]	For the complete study population, 13 adverse events were reported in 9 patients	No serious adverse event related to the treatment was reported for any patient

Abbreviations: AMIC = autologous matrix-induced chondrogenesis; MF = microfracture; RCT = randomized controlled trial.

Table C-37. Study Characteristics for Included Nonrandomized Studies of First-line vs. Second-line Interventions

Author (Year) Country Registry # Procedures	Years conducted	Sponsor	Recruitment Setting	Inclusion Criteria	Exclusion Criteria
Müller, et al. (2020)[40] Germany First-line vs. Second-line MACI	NR	No financial support received	NR	Cartilage defects of knee classified as grades 3 to 4 according to the International Cartilage Repair Society (ICRS)	NR
Gracitelli et al. (2015)[43] United States First-line vs. Second-line OCA	1983 to 2011	Joint Restoration Foundation, Scripps Clinical Medical Group: Joint Restoration Foundation, Scripps Clinical Medical Group	Single clinic, details NR	Isolated osteochondral lesions, ICRS grades 3 and 4, failed prior surgical or non-surgical interventions, patients wishing to avoid arthroplasty.	Less than 2 years of follow-up
Merkley et al. (2021)[41] United States First-line vs. Second-line OCA	September 2012 to February 2016	No financial support received	Setting NR; but all patients were seen by a single surgeon suggesting a single site.	One or more full-thickness chondral or osteochondral defects of the knee with symptoms matching the defect location. Surgery was indicated in patients who were resistant to nonoperative therapies. Patients were evaluated through a physical examination, radiography, MRI, and arthroscopic surgery before treatment with OCA was considered	Inflammatory joint disease, unresolved or recent septic arthritis, metabolic or crystal disorders, or deficient soft tissue coverage
Riff, et al. (2020)[42] United States First-line vs. Second-line OCA	1998 to 2014	NR	Recruited from one medical center	Patients with the presence of symptomatic, full-thickness (grade IV) chondral defect involving the patella, trochlea, or femoral condyles; patients with and without a prior marrow stimulation technique, including either subchondral drilling or microfracture	NR

Abbreviations: ACI = autologous chondrocyte implantation; ICRS = International Cartilage Repair Society; MACI = matrix-induced autologous chondrocyte implantation; MF = microfracture; MRI = magnetic resonance imaging; OCA = osteochondral allograft transplantation; N = number; NR = not reported.

Table C-38. Intervention Characteristics for Included Nonrandomized Studies of First-line vs. Second-line Interventions

Author (Year) Sample Size Procedures	Sample Size	Intervention Group(s)	Control Group	Rehabilitation Protocol
Müller et al. (2020)[40] First-line vs. Second-line MACI	40	MACI – SB (Other scaffold): NOVOCART 3D, first-line procedure Technique category N (%): Both open and arthroscopic, 20 (100); step 1 was arthroscopic; step 2 was open	MACI as second-line procedure after failed MF Technique category N (%): Both,open and arthroscopic 20 (100); step 1 was arthroscopic; step 2 was open	24 hours of bedrest with continuous passive motion (CPM), first 6 weeks partial loading up to 20 kg, full weight-bearing after wound healing, moderate physical activity at 3 months, high-impact sports at 12 months after surgery
Gracitelli et al. (2015)[43] First-line vs. Second-line OCA	92	First-line OCA Technique category N (%): Open, 46 (100)	Second-line OCA Technique category N (%): Open, 46 (100)	For femoral condyle OCA, full active range of motion with no weight-bearing for 8 to 12 weeks. For patella and trochlear OCA, weight-bearing allowed at 3 to 4 weeks. All patients were allowed to participate in recreation and sports after 6 months.
Merkley et al. (2021)[41] First-line vs. Second-line OCA	26	OCA as described in McCulloch et al, 2007 and Cotter et al, 2018 Technique category N (%): Open, N (%) NR	Revision to OCA after prior failed ACI; OCA technique as described in McCulloch et al, 2007 and Cotter et al, 2018 Technique category N (%): Open, N (%) NR	Protected weight-bearing with knee brace was applied for 4 to 6 weeks, followed by progression to full weight-bearing as tolerated. Stationary bicycle permitted at 4 weeks. Strengthening added at 6 weeks and was increased over the next 2 to 3 months. Patients progressed to sport-specific activities by 4 to 6 months after surgery for isolated OCA and by 8 to 12 months for those undergoing concomitant procedures.
Riff et al. (2020)[42] First-line vs. Second-line OCA	167	First-line OCA; a small vastus-sparing medial or lateral arthrotomy was used for lesions involving the medial or lateral femoral condyle. Surgical technique described in Dhollander et al. (2016), Gracitelli et al. (2015), and Gudas et al. (2005). Technique category N (%): Open, N (%) NR	Second-line OCA after failed microfracture or subchondral drilling; same technique as the other group. Technique category N (%): Open, N (%) NR	Hinged knee brace locked in full extension for the first 2 weeks; continuous passive motion machine for 4 to 6 hours daily. For grafts to the patellofemoral joint, immediate full weight-bearing was permitted with the brace in full extension (unless a tibial tubercle osteotomy was performed). For grafts to the femoral condyles, non–weight-bearing for 6 weeks and AEanced to full weight-bearing by 8 weeks. At 8 weeks, core strengthening, balance training, unilateral stance activities, and closed-kinetic chain exercises. At 12 weeks, elliptical, bike, or pool activities. Return to impact and sport-specific activity around postoperative 8 months.

Abbreviations: ACI = autologous chondrocyte implantation; ICRS = International Cartilage Repair Society; MACI = matrix-induced autologous chondrocyte implantation; MF = microfracture; OCA = osteochondral allograft transplantation; N = number; NR = not reported.

Table C-39. Population Characteristics for Included Nonrandomized Studies of First-line vs. Second-line Interventions

Author (Year) Procedures	Prior Knee Surgery	Injury Mechanism; Severity; Duration of Symptoms Prior to Surgery	Location of Chondral Defect; Mean Defect Size; Number of Lesions	Mean Age N (%) Female N (%) Race/Ethnicity BMI
Müller et al. (2020)[40] First-line vs. Second-line MACI	Prior knee surgery, N (%) First-line MACI: NR Second-line MACI: 20 (100); inclusion criteria was prior failed BMS	Injury mechanism N (%): Osteochondritis dissecans First-line MACI: 4 (20) Second-line MACI: 2 (10) Old trauma > 12 months First-line MACI: 3 (15) Second-line MACI: 3 (15) Chonic/degenerative First-line MACI: 13 (65) Second-line MACI: 15 (75) Severity of injury: NR Duration of symptoms prior to surgery: NR	Location of chondral defect N (%): Femoral: First-line MACI: 11 (55) Second-line MACI: 10 (50) Patellar: First-line MACI: 8 (40) Second-line MACI: 9 (45) Trochlear First-line MACI: 1 (5) Second-line MACI: 1 (5) Mean (SD), (range) defect size (cm^2): First-line MACI: 5.4 (2.6), (2 to 15) Second-line MACI: 4.8 (2.0), (2 to 10) Number of defects: 1, N (%) First-line MACI: 16 (80) Second-line MACI: 16 (80) Number of defects: 2, N (%) First-line MACI: 4 (20) Second-line MACI: 4 (20) N (%) number of lesions: 1 treated defect First-line MACI: 16 (80) Second-line MACI: 16 (80) 2 treated defects First-line MACI: 4 (20) Second-line MACI: 4 (20)	Mean age (SD), (range) First-line MACI: 32.9 (11.8), (16 to 55) Second-line MACI: 39.1 (10), (19 to 53) N (%) Female: First-line MACI: 12 (60) Second-line MACI: 14 (70) N (%) Race/Ethnicity: NR Mean BMI (SD), (range): First-line MACI: 26.8 (4.9), (19.2 to 34.4) Second-line MACI: 26.5 (3.6), (20.0 to 34.0)
Gracitelli et al. (2015)[43] First-line vs. Secon-line OCA	NR	Injury mechanism N (%): Avascular necrosis/osteochondritis dessiccans First-line OCA: 42 (91)	Location of chondral defect N (%): Femoral condyle First-line OCA: 42 (91) Second-line OCA: 44 (96) Patella	Mean age (SD): First-line OCA: 27.5 (11.8) Second-line OCA: 26.2 (10.4) N (%) Female: First-line OCA: 18 (39)

Author (Year) Procedures	Prior Knee Surgery	Injury Mechanism; Severity; Duration of Symptoms Prior to Surgery	Location of Chondral Defect; Mean Defect Size; Number of Lesions	Mean Age N (%) Female N (%) Race/Ethnicity BMI
		Second-line OCA: 42 (91) Degenerative chondral lesions First-line OCA: 1 (2.2) Second-line OCA: 1 (2.2) Traumatic chondral injury First-line OCA: 3 (6.5) Second-line OCA: 3 (6.5) Severity of injury: NR Duration of symptoms prior to surgery: NR	First-line OCA: 1 (2) Second-line OCA: 1 (2) Trochlea First-line OCA: 3 (6) Second-line OCA: 1 (2) Mean (SD) defect size (cm^2): First-line OCA: 8.2 (3.6) Second-line OCA: 8.0 (3.2) Number of lesions: NR	Second-line OCA: 18 (39) N (%) Race/Ethnicity: NR Mean BMI (SD): First-line OCA: 25.0 (5.1) Second-line OCA: 25.2 (5.0)
Merkley et al. (2021)[41] First-line vs. Second-line OCA	N (%) prior knee surgery: Second-line OCA group all had prior ACI 13 (100) Other types of previous surgeries i in Second-line OCA group: Chondroplasty: 2 (16.8) Partial medial meniscectomy: 3 (25) Medial patellofemoral ligament reconstruction: 1 (8.3) ACL reconstruction: 2 (16.8)	Injury mechanism: NR Severity of injury: NR Duration of symptoms prior to surgery: NR	Location of chondral defect, N: First-line OCA Medial femoral condyle: 6 Lateral femoral condyle: 4 Patella: 4 Trochlea: 3 Medial tibial plateau: 0 Lateral tibial plateau: 0 Second-line OCA Medial femoral condyle: 11 Lateral femoral condyle: 1 Patella: 4 Trochlea: 1 Medial tibial plateau: 0 Lateral tibial plateau: 0 Mean (SD) defect size (cm^2): First-line OCA: 5.0 (2.5) Second-line OCA: 6.1 (2.9) Number of lesions: Participants had 1 or more full-thickness chondral or osteochondral defects	Mean age (SD): First-line OCA: 36.2 (8.5) Second-line OCA: 36.2 (9.1) N (%) Female: First-line OCA: 8 (61.5) Second-line OCA: 8 (61.5) N (%) Race/Ethnicity: NR Mean BMI (SD): First-line OCA: 26.6 (3.2) Second-line OCA: 27.1 (4.3)

Author (Year) Procedures	Prior Knee Surgery	Injury Mechanism; Severity; Duration of Symptoms Prior to Surgery	Location of Chondral Defect; Mean Defect Size; Number of Lesions	Mean Age N (%) Female N (%) Race/Ethnicity BMI
	Internal fixation for OCD fragment: 3 (25) Microfracture: 2 (16.8) Prior surgery in the First-line OCA group was NR.			
Riff et al. (2020)[42] First-line vs. Second-line OCA	Prior knee surgery, N (%) First-line OCA: NR Second-line OCA: 88 (100); participants selected based on failure of prior microfracture or drilling Other prior knee surgery NR	Injury mechanism: NR Severity of injury: Inclusion criteria for Second-line OCA (n = 88) was full-thickness (grade IV) chondral defect Duration of symptoms prior to surgery: Mean (SD) duration from microfracture or drilling to Second-line OCA was 30 (46.3) months (range, 3 to 288 months)	Location of chondral defect, N (%): First-line OCA Medial femoral condyle: 44 (55.7) Lateral femoral condyle: 32 (40.5) Both medial and lateral femoral condyle: 3 (3.8) Second-line OCA Medial femoral condyle: 61 (69.3) Lateral femoral condyle: 24 (27.3) Both medial and lateral femoral condyle: 3 (3.4) Mean (SD) defect size (mm^2): First-line OCA: 496 (NR) Second-line OCA: 396 (NR) Number of lesions: NR	Mean age (SD): First-line OCA: 32.5 (10.4) Second-line OCA: 35.4 (10.7) N (%) Female: First-line OCA: 39 (49) Second-line OCA: 43 (49) N (%) Race/Ethnicity: NR Mean BMI (SD): First-line OCA: 26.1 (5.8) Second-line OCA: 27.0 (4.7)

Abbreviations: ACI = autologous chondrocyte implantation; ACL = anterior cruciate ligament; BMI = body mass index; BMS = bone marrow stimulation; MACI = matrix-induced autologous chondrocyte implantation; OCA = osteochondral allograft transplantation; OCD = osteochondritis dissecans; N = number; NR = not reported; SD = standard deviation.

Table C-40. Efficacy Outcomes for Included Nonrandomized Studies of First-line vs. Second-line Interventions

Author (Year) Intervention(s) and Comparison Sample size	Results
Müller et al. (2020)[40] Intervention: First-line MACI (NOVOCART 3D) Comparator: MACI as second-line procedure after failed MF Sample size: 40	**Composite Scores** **IKDC Subjective Knee Evaluation Form:** IKDC score, baseline, First-line MACI = 20; Second-line MACI = 20, mean (SD) First-line MACI: 37.0 (13.7) Second-line MACI: 29.9 (17.0) *P*=NR IKDC score, 6 months, First-line MACI = 20; Second-line MACI = 20, mean (SD) First-line MACI: 57.6 (14.3) Second-line MACI: 44.3 (19.5) *P*=0.015 IKDC score, 12 months, First-line MACI = 20; Second-line MACI = 20, mean (SD) First-line MACI: 72.5 (14.8) Second-line MACI: 50.1 (20.4) *P*=0.001 IKDC score, 24 months, First-line MACI = 20; Second-line MACI = 20, mean (SD) First-line MACI: 77.7 (19.7) Second-line MACI: 48.6 (21.8) *P*=0.001 IKDC score, 36 months, First-line MACI = 20; Second-line MACI = 20, mean (SD) First-line MACI: 74.7 (22.6) Second-line MACI: 49.1 (21.2) *P*=0.011 **KOOS Total, CKRS, Lysholm score, HSS:** NR **Activity Scores** **Tegner Score, KOOS-ADL, KOOS-Sport:** NR **Symptom Scores** **KOOS-Pain, KOOS-Symptoms, KOOS-QOL:** NR **Responder, treatment failure, reoperation** **Treatment failure:** Need for another revision surgery, First-line MACI: 0 (0) Second-line MACI: 6 (20)

Author (Year) Intervention(s) and Comparison Sample size	Results
	Reoperation: First-line MACI: 0 (0) Second-line MACI: 6 (20), First-line MACI: None Second-line MACI MF: 3 (15) High tibial osteotomy: 1 (5) Knee arthroplasty: 1 (5) Drilling: 1 (5) **Responder:** NR **Subgroup Analyses** NR
Gracitelli et al. (2015)[43] Intervention: First-line OCA Comparator: Second-line OCA Sample size: 92	**Composite Scores** **IKDC Subjective Knee Evaluation Form:** IKDC-Total, Baseline, First-line OCA = 46, Second-line OCA = 46, mean (SD) First-line OCA: 68.9 (NR) Second-line OCA:68.2 (NR) IKDC-Total, follow-up time unspecified, First-line OCA = 46 Second-line OCA = 46, mean (SD) First-line OCA: 78.2 (NR) Second-line OCA: 78.8 (NR) IKDC-Total, change from baseline to follow-up, First-line OCA = 46, Second-line OCA = 46, mean (SD) First-line OCA: 45.6 (NR) Second-line OCA: 38.3 (NR) Between group difference *P*=0.29 IKDC-Pain, Baseline, First-line OCA = 46, Second-line OCA = 46, mean (SD) First-line OCA: 6.2 (NR) Second-line OCA: 5.4 (NR) IKDC-Pain, follow-up time unspecified, First-line OCA = 46 Second-line OCA = 46, mean (SD) First-line OCA: 2.4 (NR) Second-line OCA: 2.6 (NR) IKDC-Pain, change from baseline to follow-up, First-line OCA = NR, Second-line OCA = NR, mean (SD) First-line OCA: -4.2 (NR) Second-line OCA: -3.2 (NR) Between group difference *P*=0.09 IKDC-Function, Baseline, First-line OCA = 46, Second-line OCA = 46, mean (SD)

Author (Year) Intervention(s) and Comparison Sample size	Results
	First-line OCA: 2.9 (NR) Second-line OCA: 3.5 (NR) IKDC-Function, follow-up time, First-line OCA = 46, Second-line OCA = 46), mean (SD) First-line OCA: 7.8 (NR) Second-line OCA: 7.5 (NR) IKDC-Function, change from baseline to follow-up, First-line OCA = 46, Second-line OCA = 46, mean (SD) First-line OCA: 5.1 (NR) Second-line OCA: 4.4 (NR) Between group difference *P*=0.34 **KOOS Total, CKRS, Lysholm score, HSS:** NR **Activity Scores** **KOOS-ADL:** KOOS-ADL, Baseline, First-line OCA = 46, Second-line OCA = 46, mean (SD) First-line OCA: 72.0 (NR) Second-line OCA: 70.9 (NR) KOOS-ADL, follow-up time unspecified, First-line OCA = NR, Second-line OCA = NR, mean (SD) First-line OCA: 94.5 (NR) Second-line OCA: 87.1 (NR) KOOS-ADL, change from baseline to follow-up, First-line OCA = NR, Second-line OCA = NR, mean (SD) First-line OCA: 29.3 (NR) Second-line OCA: 14.0 (NR) Between group difference *P*=0.11 **KOOS-Sport:** KOOS-SR, Baseline, First-line OCA = 46, Second-line OCA = 46, mean (SD) First-line OCA: 37.5 (NR) Second-line OCA: 30.6 (NR) KOOS-SR, follow-up time unspecified, First-line OCA = NR, Second-line OCA = NR, mean (SD) First-line OCA: 72.7 (NR) Second-line OCA: 70.7 (NR) KOOS-SR, change from baseline to follow-up, First-line OCA = NR, Second-line OCA = NR, mean (SD) First-line OCA: 40.6 (NR) Second-line OCA: 43.3 (NR) Between group difference *P*=0.41

Author (Year) Intervention(s) and Comparison Sample size	Results
	Tegner Score: NR **Symptom Scores** **KOOS-Pain:** KOOS-P, Baseline, First-line OCA = 46, Second-line OCA = 46, mean (SD) First-line OCA: 65.6 (NR) Second-line OCA: 64.3(NR) KOOS-P, follow-up time unspecified, First-line OCA = NR, Second-line OCA = NR, mean (SD) First-line OCA: 89.9 (NR) Second-line OCA: 82.1(NR) KOOS-P, change from baseline to follow-up, First-line OCA = NR, Second-line OCA = NR, mean (SD) First-line OCA: 31.2 (NR) Second-line OCA: 10.0 (NR) Between group difference *P*=0.06 **KOOS-Symptoms:** KOOS-S, Baseline, First-line OCA = 46, Second-line OCA = 46, mean (SD) First-line OCA: 57.8 (NR) Second-line OCA: 53.0 (NR) KOOS-S, follow-up time unspecified, First-line OCA = NR, Second-line OCA = NR, mean (SD) First-line OCA: 87.8 (NR) Second-line OCA: 79.8 (NR) KOOS-S, change from baseline to follow-up, First-line OCA = NR, Second-line OCA = NR, mean (SD) First-line OCA: 27.5 (NR) Second-line OCA: 31.2 (NR) Between group difference *P*=0.81 **KOOS-QOL:** KOOS-QOL, Baseline, First-line OCA = 46, Second-line OCA = 46, mean (SD) First-line OCA: 28.2 (NR) Second-line OCA: 25.0 (NR) KOOS-QOL, follow-up time unspecified, First-line OCA = NR, Second-line OCA = NR, mean (SD) First-line OCA: 69.5 (NR) Second-line OCA: 64.6 (NR) KOOS-QOL change from baseline to follow-up, First-line OCA = NR, Second-line OCA = NR, mean (SD) First-line OCA: 45.5 (NR)

Author (Year) Intervention(s) and Comparison Sample size	Results
	Second-line OCA: 47.0 (NR) Between group difference *P*=0.92 **Responder, treatment failure, reoperation** **Treatment failure:** Reoperation defined as allograft failure, Allograft failure, First-line OCA = 46, Second-line OCA = 46), N (%) First-line OCA: 5 (NR) Second-line OCA: 7 (NR) *P*=0.53 **Reoperation:** Reoperation, First-line OCA = 46, Second-line OCA = 46), N (%), range of number of surgeries: First-line OCA: 11 (24), 1-2 surgeries Second-line OCA: 20 (46), 1-4 surgeries *P*=0.04, Revision of allograft, First-line OCA = 46, Second-line OCA = 46, N (%) First-line OCA: 2 (NR) Second-line OCA: 3 (NR) Total knee replacement, First-line OCA = NR, Second-line OCA = NR, N (%) of 46 knees First-line OCA: 3 (NR) Second-line OCA: 4 (NR) Arthroscopic debridement, diagnosis, or loose body removal First-line OCA: 6 (NR) Second-line OCA: 15 (NR) Meniscectomy First-line OCA: 0 (NR) Second-line OCA: 3 (NR) Meniscal repair First-line OCA: 1 (NR) Second-line OCA: 3 (NR) Extensor mechanism realignment First-line OCA: 0 (NR) Second-line OCA: 1 (NR) Lateral retinacular release First-line OCA: 1 (NR) Second-line OCA: 2 (NR) Hardware removal

Author (Year) Intervention(s) and Comparison Sample size	Results
	First-line OCA: 0 (NR) Second-line OCA: 3 (NR) Osteotomy First-line OCA: 0 (NR) Second-line OCA: 1 (NR) **Responder:** NR **Subgroup Analyses:** NR
Merkley et al. (2021)[41] Intervention: First-line OCA Comparator: Second-line OCA Sample size: 26	**Composite Scores** **Lysholm score:** Baseline and postoperative results provided in figure only, *P*=NS; results do not appear to be adjusted for baseline differences and were only reported for patients with an intact graft (22 of 26) **KOOS Total, CKRS, IKDC Subjective Knee Evaluation Form, HSS:** NR **Activity Scores** **KOOS-ADL:** Baseline and postoperative results provided in figure only, *P*=NS; results do not appear to be adjusted for baseline differences and were only reported for patients with an intact graft (22 of 26) **KOOS-Sport:** Baseline and postoperative results provided in figure only, *P*=NS; results do not appear to be adjusted for baseline differences and were only reported for patients with an intact graft (22 of 26) **Tegner Score:** NR **Symptom Scores** **KOOS-Pain:** KOOS-P, Baseline, First-line OCA = 13; Second-line OCA = 13, mean (SD) First-line OCA: 48.5 (15.6) Second-line OCA: 61.6 (14.4) *P*=0.042 KOOS-P, Postoperative, First-line OCA = 12; Second-line OCA = 10, mean (SD) First-line OCA: NR (results provided in figure only) Second-line OCA: NR (results provided in figure only) *P*=NS

Author (Year) Intervention(s) and Comparison Sample size	Results
	KOOS-Symptoms: Baseline and postoperative results provided in figure only, *P*=NS; results do not appear to be adjusted for baseline differences and were only reported for patients with an intact graft (22 of 26) **KOOS-QOL:** Baseline and postoperative results provided in figure only, *P*=NS; results do not appear to be adjusted for baseline differences and were only reported for patients with an intact graft (22 of 26) **Responder, treatment failure, reoperation** **Treatment failure:** Reoperation due to failure of the graft, Reoperation due to graft failure First-line OCA: 1 (7.7) Second-line OCA: 3 (23.1) *P*=0.593 **Reoperation:** Total reoperations: First-line OCA: 4 (31%) Second-line OCA: 8 (62%) P NR Reoperation with intact OCA graft Total First-line OCA: 3 (23.1) Second-line OCA: 5 (38.5) *P*=0.673 Reoperation due to graft failure Total First-line OCA: 1 (7.7) Second-line OCA: 3 (23.1) *P*=0.593, Reoperations with intact OCA graft First-line OCA: lysis of adhesions, chondroplasty, hardware removal Second-line OCA: lysis of adhesions, chondroplasty, hardware removal Reoperations due to graft failure First-line OCA: marrow stimulation technique Second-line OCA: OAT, OCA, Total knee arthroplasty **Responder:** NR

Author (Year) Intervention(s) and Comparison Sample size	Results
	Subgroup Analyses NR
Riff et al. (2020)[42] Intervention: First-line OCA Comparator: Second-line OCA after failed microfracture or subchondral drilling Sample size: 167	**Composite Scores** **IKDC Subjective Knee Evaluation Form:** IKDC score, minimum 2 year follow-up, First-line OCA = NR; Second-line OCA = NR, score First-line OCA: value NR (figure only) Second-line OCA: value NR (figure only) *P*=0.20 for difference between groups post operation, favoring First-line OCA **Lysholm score:** Lysholm score, minimum 2 year follow-up, First-line OCA = NR; Second-line OCA = NR, score First-line OCA: value NR (figure only) Second-line OCA: value NR (figure only) *P*=0.40 for difference between groups post operation, favoring First-line OCA **KOOS Total, CKRS, HSS:** NR **Activity Scores** **Tegner Score:** Tegner score, minimum 2 year follow-up, First-line OCA = NR; Second-line OCA = NR, score First-line OCA: value NR (figure only) Second-line OCA: value NR (figure only) *P*=0.09 for difference between groups post operation, favoring First-line OCA **KOOS-ADL:** KOOS-ADL, minimum 2 year follow-up, First-line OCA = NR; Second-line OCA = NR, score First-line OCA: value NR (figure only) Second-line OCA: value NR (figure only) *P*=0.82 for difference between groups post operation favoring First-line OCA **KOOS-Sport:** KOOS-Sport, minimum 2 year follow-up, First-line OCA = NR; Second-line OCA = NR, score First-line OCA: value NR (figure only) Second-line OCA: value NR (figure only) *P*=0.26 for difference between groups post operation, favoring First-line OCA **Symptom Scores** **KOOS-Pain:**

Author (Year) Intervention(s) and Comparison Sample size	Results
	KOOS-Pain, minimum 2 year follow-up, First-line OCA = NR; Second-line OCA = NR, score First-line OCA: value NR (figure only) Second-line OCA: value NR (figure only) *P*=0.21 for difference between groups post operation, favoring First-line OCA **KOOS-Symptoms:** KOOS-Symptoms, minimum 2 year follow-up, First-line OCA = NR; Second-line OCA = NR, score First-line OCA: value NR (figure only) Second-line OCA: value NR (figure only) *P*=0.90 for difference between groups post operation favoring Second-line OCA **KOOS-QOL:** KOOS-QOL, minimum 2 year follow-up, First-line OCA = NR; Second-line OCA = NR, score First-line OCA: value NR (figure only) Second-line OCA: value NR (figure only) *P*=0.11 for difference between groups post operation, favoring First-line OCA **Responder, treatment failure, reoperation** **Treatment failure:** Persistent or recurrent symptoms and evidence of graft delamination or grade IV chondrosis involving a significant portion of the graft site on second-look arthroscopy, a revision cartilage restoration procedure, or a prosthetic replacement., First-line OCA (n = 70): 6 (9) Second-line OCA (n = 79): 12 (15) *P*=0.34 **Reoperation:** First-line OCA: 26 (33) Second-line OCA: 19 (27) *P*=0.44, Arthroplasty, chondral debridement, revision OCA, debridement (meniscal, plica), lysis of adhesions **Responder:** NR **Subgroup Analyses** NR

Abbreviations: HSS = hospital for special surgery score; IKDC = International Knee Documentation Committee; KOOS = Knee Injury and Osteoarthritis Outcome Score; KOOS-ADL = Knee Injury and Osteoarthritis Outcome Score, Activities of Daily Living subscale; KOOS-P = Knee Injury and Osteoarthritis Outcome Score, Pain subscale; KOOS-QOL = Knee Injury and Osteoarthritis Outcome Score, Quality of Life subscale; KOOS-SR = Knee Injury and Osteoarthritis Outcome Score, Sport and Recreation subscale; MACI = matrix-induced autologous chondrocyte implantation; MF = microfracture; OCA = osteochondral allograft transplantation; N = number; NR = not reported; NS = not significant; SD = standard deviation.

Table C-41. Study Characteristics and Findings Related to Cost Outcomes

Author (Year) Country; Sponsor	Intervention; Comparator	Study Methods	Results
Miller et al. (2015)[37] United States Sponsor NR	OATS MF	Study design: Cost effectiveness analysis Study population: Year/unit of currency reported: 2013/U.S. Dollar Discount rate: NR Perspective: NR Time horizon: NR Costs included: Total costs based on actual costs from the investigators' institution (academic medical/surgical center), including initial procedure cost and operating room fees; if participants failed the first-line procedure, the cost of return visit, MRI, and secondary procedure costs. Sensitivity analysis: Varied base assumptions including assessing for both groups (1) variance in cost (11.5% reduction in costs for OATS, 13.5% increase in costs for MF); (2) the rates of revision surgery (increase 37.1% for MF, decrease 1.8% for OSTS); (3) adding indirect costs, such as PT and decreased earnings due to time lost from work (Increase $5,000/group, $10,000/group, or $16,500/group) Key assumptions: Mean (SD) age in years: 30.5 (12.3) % Female: 51 Mean (range) size lesion in cm^2, OAT:2.8 (1.0-6.0) Mean (range) size lesion in cm^2, MF:2.7 (1.2 to 5.2) Cumulative failure rate (%), OATS: 12.5 Cumulative failure rate (%), MF: 28.6 Pre-operative to post-operative difference in *specified* PRO: *Lysholm:* OATS: 24.5 MF: 30.9 *Tegner:* OATS: 2.6 MF: 2.4 *HSS:* OATS: 9.46 MF: 9.38	Total Net costs *1 year* Difference between OATS and MF: $1843 *5 year* Difference between OATS and MF: $996 Cost per Point Improvement: *Lysholm:* OATS: $469 MF: $339 *Tegner Score:* OATS: $4415 MF: $4558 *HSS:* OATS: $1213 MF: $1118 *ICRS:* OATS: $308.50 MF: $406.79 Return to play (1 year): OATS: $11,428 MF: $16,953 Return to play (3 years): OATS: $12,856 MF: $38,000 Return to play (10 years): OATS: $32,141 MF: $60,799 Calculated incremental cost per point improvement for OATS vs. MF Lysholm score: $130 Tegner score: -$143 HSS: $95 ICRS score: -$98.29

Author (Year) Country; Sponsor	Intervention; Comparator	Study Methods	Results
		ICRS: OATS: 37.2 MF: 25.8 Cost estimates: *Primary cost estimates:* OATS – arthroscopic: $10,320 OATS – open: $10,210 MF: $7220 Chondroplasty: $6540 Total knee replacement: $45,900 High tibial osteotomy: $20,600 *Secondary cost estimates:* OATS – arthroscopic: $11,220 OATS – open: $11,020 MF: $8120 Chondroplasty: $7440 Total knee replacement: $47,800 High tibial osteotomy: $51,200	Calculated incremental cost to return to play at 1 year for OATS vs. MF: $-5,525

Abbreviations: HSS = Hospital for Special Surgery knee-rating scale; ICER = incremental cost-effectiveness ratio, ICRS = International Cartilage Repair Society; MF = microfracture; NR = not reported; OATS = osteochondral autologous transplantation; PRO = patient-reported outcome.

Appendix D. Excluded Articles

1. Aae TF, Randsborg PH, Lurås H, et al. Microfracture is more cost-effective than autologous chondrocyte implantation: a review of level 1 and level 2 studies with 5 year follow-up. *Knee Surg Sports Traumatol Arthrosc*. 2018 Apr;26(4):1044-52. doi: 10.1007/s00167-017-4802-5. PMID: 29128878. Exclusion Code: X2.
2. Ackermann J, Duerr RA, Barbieri Mestriner A, et al. Effect of graft-host interference fit on graft integration after osteochondral allograft transplantation: a comparative MRI analysis of two instrumentation sets. *Cartilage*. 2021 Dec;13(1_suppl):920s-7s. doi: 10.1177/1947603519865314. PMID: 31375032. Exclusion Code: X3.
3. Ackermann J, Merkely G, Arango D, et al. The effect of mechanical leg alignment on cartilage restoration with and without concomitant high tibial osteotomy. *Arthroscopy*. 2020 Aug;36(8):2204-14. doi: 10.1016/j.arthro.2020.04.019. PMID: 32353621. Exclusion Code: X3.
4. Anders S, Volz M, Frick H, Gellissen J. A randomized, controlled trial comparing Autologous Matrix-Induced Chondrogenesis (AMIC®) to microfracture: analysis of 1- and 2-year follow-up data of 2 centers. *Open Orthop J*. 2013;7:133-43. doi: 10.2174/1874325001307010133. PMID: 23730377. Exclusion Code: X7.
5. Banitalebi H, Owesen C, Årøen A, et al. Is T2 mapping reliable in evaluation of native and repair cartilage tissue of the knee? *J Exp Orthop*. 2021 Apr 28;8(1):34. doi: 10.1186/s40634-021-00350-1. PMID: 33913035. Exclusion Code: X4.
6. Beck A, Wood D, Vertullo CJ, et al. Morphological assessment of MACI grafts in patients with revision surgery and total joint arthroplasty. *Cartilage*. 2021 Dec;13(1_suppl):526s-39s. doi: 10.1177/1947603519890754. PMID: 31793330. Exclusion Code: X4.
7. Bentley G, Biant LC, Carrington RW, et al. A prospective, randomised comparison of autologous chondrocyte implantation versus mosaicplasty for osteochondral defects in the knee. *J Bone Joint Surg Br*. 2003 Mar;85(2):223-30. doi: 10.1302/0301-620x.85b2.13543. PMID: 12678357. Exclusion Code: X2.
8. Bentley G, Biant LC, Vijayan S, et al. Minimum ten-year results of a prospective randomised study of autologous chondrocyte implantation versus mosaicplasty for symptomatic articular cartilage lesions of the knee. *J Bone Joint Surg Br*. 2012 Apr;94(4):504-9. doi: 10.1302/0301-620x.94b4.27495. PMID: 22434467. Exclusion Code: X2.
9. Bouwmeester PS, Kuijer R, Homminga GN, et al. A retrospective analysis of two independent prospective cartilage repair studies: autogenous perichondrial grafting versus subchondral drilling 10 years post-surgery. *J Orthop Res*. 2002 Mar;20(2):267-73. doi: 10.1016/s0736-0266(01)00099-7. PMID: 11924645. Exclusion Code: X2.
10. Brittberg M, Recker D, Ilgenfritz J, Saris DBF. Matrix-applied characterized autologous cultured chondrocytes versus microfracture: five-year follow-up of a prospective randomized trial. *Am J Sports Med*. 2018 May;46(6):1343-51. doi: 10.1177/0363546518756976. PMID: 29565642. Exclusion Code: X8.
11. Cepero S, Ullot R, Sastre S. Osteochondritis of the femoral condyles

in children and adolescents: our experience over the last 28 years. *J Pediatr Orthop B*. 2005 Jan;14(1):24-9. doi: 10.1097/01202412-200501000-00004. PMID: 15577303. Exclusion Code: X3.
12. Chung JY, Lee DH, Kim TH, et al. Cartilage extra-cellular matrix biomembrane for the enhancement of microfractured defects. *Knee Surg Sports Traumatol Arthrosc*. 2014 Jun;22(6):1249-59. doi: 10.1007/s00167-013-2716-4. PMID: 24258020. Exclusion Code: X2.
13. Chung K, Jung M, Jang KM, et al. Particulated costal allocartilage with microfracture versus microfracture alone for knee cartilage defects: a multicenter, prospective, randomized, participant- and rater-blinded study. *Orthop J Sports Med*. 2023 Jul;11(7):23259671231185570. doi: 10.1177/23259671231185570. PMID: 37457043. Exclusion Code: X3.
14. Clavé A, Potel JF, Servien E, et al. Third-generation autologous chondrocyte implantation versus mosaicplasty for knee cartilage injury: 2-year randomized trial. *J Orthop Res*. 2016 Apr;34(4):658-65. doi: 10.1002/jor.23152. PMID: 26742454. Exclusion Code: X2.
15. Coleman SH, Malizia R, Macgillivray J, Warren RF. Treatment of isolated articular cartilage lesions of the medial femoral condyle. A clinical nad MR comparison of autologous chondrocyte implantation vs. microfracture. *Ortop Traumatol Rehabil*. 2001 Apr 30;3(2):224-6. PMID: 17986989. Exclusion Code: X5.
16. Dozin B, Malpeli M, Cancedda R, et al. Comparative evaluation of autologous chondrocyte implantation and mosaicplasty: a multicentered randomized clinical trial. *Clin J Sport Med*. 2005 Jul;15(4):220-6. doi: 10.1097/01.jsm.0000171882.66432.80. PMID: 16003035. Exclusion Code: X2.
17. Frank RM, Della Valle CJ, Plummer DR, et al. Does prior cartilage restoration impact outcomes following knee arthroplasty? *Orthop Clin North Am*. 2017 Jul;48(3):265-73. doi: 10.1016/j.ocl.2017.03.001. PMID: 28577776. Exclusion Code: X2.
18. Fu FH, Zurakowski D, Browne JE, et al. Autologous chondrocyte implantation versus debridement for treatment of full-thickness chondral defects of the knee: an observational cohort study with 3-year follow-up. *Am J Sports Med*. 2005 Nov;33(11):1658-66. doi: 10.1177/0363546505275148. PMID: 16093543. Exclusion Code: X2.
19. Gaweda K, Walawski J, Węgłowski R, et al. Early results of one-stage knee extensor realignment and autologous osteochondral grafting. *Int Orthop*. 2006 Feb;30(1):39-42. doi: 10.1007/s00264-005-0020-8. PMID: 16235082. Exclusion Code: X1.
20. Gobbi A, Chaurasia S, Karnatzikos G, Nakamura N. Matrix-induced autologous chondrocyte implantation versus multipotent stem cells for the treatment of large patellofemoral chondral lesions: a nonrandomized prospective trial. *Cartilage*. 2015 Apr;6(2):82-97. doi: 10.1177/1947603514563597. PMID: 26069711. Exclusion Code: X2.
21. Gomoll AH, Ambra LF, Phan A, et al. Cell-seeded autologous chondrocyte implantation: a simplified implantation technique that maintains high clinical outcomes. *Am J Sports Med*. 2017 Apr;45(5):1028-36. doi: 10.1177/0363546516681000. PMID: 28056183. Exclusion Code: X3.
22. Gudas R, Gudaitė A, Kalesinskas RJ, et al. Clinical results after one-stage

articular cartilage and anterior cruciate ligament reconstruction procedures. *Osteoarthritis Cartilage*. 2014 2014/04/01/;22:S467. doi: https://doi.org/10.1016/j.joca.2014.02.889. Exclusion Code: X5.
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Appendix E. Individual Study Risk-of-Bias Assessment

Table E-1. Risk-of Bias Ratings for Randomized Controlled Trials—Randomization process

Author (Year)	Was the allocation sequence random?	Was allocation sequence concealed until participants were recruited and assigned to interventions?	Did baseline differences between intervention groups suggest a problem with the randomization process?	Risk of bias arising from the randomization process
Altschuler et al. (2023)[38]	No information	No information	Probably yes	High
Basad et al. (2010)[22]	Yes	No information	Probably no	Some concerns
Crawford et al. (2012)[21]	Yes	Yes	Probably no	Low
Gudas et al. (2005)[32]	No information	Yes	Probably no	Low
Gudas et al. (2009)[33]	Yes	No information	Probably no	Some concerns
Lim et al. (2012)[31]	Yes	Yes	No	Low
Saris et al. (2014)[20]	Yes	Yes	No	Low
Solheim et al. (2017)[29]	No information	Yes	Probably no	Some concerns
Ulstein et al. (2014)[30]	Yes	Yes	Probably yes	Low
Volz et al. (2017)[39]	Yes	Yes	No	Low

Table E-2. Risk-of Bias Ratings for Randomized Controlled Trials—Deviations from intended interventions

Author (Year)	Were the participants aware of their assigned intervention during the trial?	Were carers and people delivering the interventions aware of participants' assigned intervention during the trials?	Were there deviations from the intended intervention that arose because of the experimental process?	Were these deviations from intended intervention balanced between groups?	Were these deviations likely to have affected the outcome?	Was an appropriate analysis used to estimate the effect of assignment to intervention?	Was there potential for a substantial impact of the failure to analyze participants in the group to which they were randomized?	Risk of bias arising from deviations from intended interventions
Altschuler et al. (2023)[38]	Yes	Yes	Probably no	Not applicable	Not applicable	Yes	Not applicable	Low
Basad et al. (2010)[22]	Probably yes	Yes	No information	No information	No information	Yes	Probably no	Some concerns
Crawford et al. (2012)[21]	Yes	Yes	Probably no	Not applicable	Not applicable	Yes	Not applicable	Low
Gudas et al. (2005)[32]	Yes	Yes	Probably no	Not applicable	Not applicable	Probably yes	Not applicable	Low
Gudas et al. (2009)[33]	Yes	Yes	Probably no	Not applicable	Not applicable	Probably yes	Not applicable	Low
Lim et al. (2012)[31]	Yes	Yes	Probably no	Not applicable	Not applicable	No	No information	High
Saris et al. (2014)[20]	Yes	Yes	No	Not applicable	Not applicable	Yes	Not applicable	Low
Solheim et al. (2017)[29]	Yes	Yes	Probably no	Not applicable	Not applicable	Yes	Not applicable	Low
Ulstein et al. (2014)[30]	Yes	Yes	No	Not applicable	Not applicable	Yes	Not applicable	Low
Volz et al. (2017)[39]	Yes	Yes	Probably no	Not applicable	Not applicable	No	Probably yes	High

Table E-3. Risk-of Bias Ratings for Randomized Controlled Trials—Missing outcome data

Author (Year)	Were outcome data available for all, or nearly all, participants randomized?	Is there evidence that result was not biased by missing outcome data?	Could missingness in the outcome depend on its true value?	Is it likely that missingness in the outcome depended on its true value?	Risk of bias arising from missing outcome data
Altschuler et al. (2023)[38]	No	Yes	Not applicable	Not applicable	Low
Basad et al. (2010)[22]	No	Probably no	Probably no	Not applicable	Low
Crawford et al. (2012)[21]	No	Probably no	Not applicable	Not applicable	Low
Gudas et al. (2005)[32]	No information	No information	No information	No information	Some concerns
Gudas et al. (2009)[33]	No	Not applicable	Not applicable	Not applicable	Low
Lim et al. (2012)[31]	No	No	Probably yes	Probably yes	High
Saris et al. (2014)[20]	No	Yes	Not applicable	Not applicable	Low
Solheim et al. (2017)[29]	Yes	Not applicable	Not applicable	Not applicable	Low
Ulstein et al. (2014)[30]	Yes	Not applicable	Not applicable	Not applicable	Low
Volz et al. (2017)[39]	No	Probably no	Probably yes	Probably yes	High

Table E-4. Risk-of Bias Ratings for Randomized Controlled Trials—Measurement of the Outcome

Author (Year)	Was the method of measuring the outcome inappropriate?	Could measurement or ascertainment of the outcome have differed between intervention groups?	Were outcome assessors aware of the intervention received by study participants?	Could assessment of the outcome have been influenced by knowledge of intervention received?	Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	Risk of bias arising from measurement of the outcome
Altschuler et al. (2023)[38]	No	No	Yes	Probably no	Not applicable	Low
Basad et al. (2010)[22]	Probably no	Probably no	Probably yes	Probably no	Not applicable	Low
Crawford et al. (2012)[21]	No	No	Probably yes	Probably no	Not applicable	Low
Gudas et al. (2005)[32]	No	PN	Probably yes	Probably no	Not applicable	Low
Gudas et al. (2009)[33]	No	No	Yes	Probably no	Not applicable	Low
Lim et al. (2012)[31]	No	No	Yes	Probably no	Not applicable	Low
Saris et al. (2014)[20]	No	No	Yes	Probably no	Not applicable	Low
Solheim et al. (2017)[29]	No	No	Probably yes	Probably no	Not applicable	Low
Ulstein et al. (2014)[30]	No	No	Probably yes	Probably no	Not applicable	Low
Volz et al. (2017)[39]	No	No	Yes	Probably yes	Probably yes	High

Table E-5. Risk-of Bias Ratings for Randomized Controlled Trials—Selection of the reported result and overall risk of bias rating

Author (Year)	Was the trial analyzed in accordance with a prespecified plan that was finalized before unblinded outcome data were available for analysis?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g., scales, definitions, timepoints) within the outcome domain?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	Risk of bias arising from selection of reported results	Overall Rating	Rationale/Comments
Altschuler et al. (2023)[38]	Probably yes	Probably no	Probably no	Low	High	For no information about randomization process and baseline imbalance in disease severity.
Basad et al. (2010)[22]	No information	Probably no	Probably no	Some concerns	Some concerns	For lack of protocol or trial registration.
Crawford et al. (2012)[21]	Probably yes	Probably yes	Probably yes	Some concerns	Some concerns	Some concerns for selective reporting not consistent no registered trial protocol.
Gudas et al. (2005)[32]	No information	No information	No information	Some concerns	Some concerns	No information on how missing outcome data managed though low attrition reported.
Gudas et al. (2009)[33]	No information	No	No	Some concerns	Some concerns	No information on allocation concealment and no published trial registry or protocol.
Lim et al. (2012)[31]	No information	No	No	Some concerns	High	High risk of bias due to completers analysis, missing outcome data for 36% of those randomized, and no published protocol or trial registry
Saris et al. (2014)[20]	Yes	No	Probably no	Low	Low	Low for 2 year follow-up Some concerns for 5 year follow-up

Author (Year)	Was the trial analyzed in accordance with a prespecified plan that was finalized before unblinded outcome data were available for analysis?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g., scales, definitions, timepoints) within the outcome domain?	Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	Risk of bias arising from selection of reported results	Overall Rating	Rationale/Comments
Solheim et al. (2017)[29]	No information	No	No	Some concerns	Some concerns	Some concerns for bias because method of randomization not reported and some risk for publication bias because no published protocol or trial registry.
Ulstein et al. (2014)[30]	No information	Probably no	Probably no	Some concerns	Some concerns	For lack of protocol
Volz et al. (2017)[39]	No information	Probably no	Probably no	Some concerns	High	High for completers analysis, missing outcome domain, and assessment of outcome (signals that traditional MF group may have dropped out due to receiving an older procedure as well as completed surveys about PROs biased by receipt of older procedure).

Table E-6. Risk of bias ratings for nonrandomized studies of interventions—Confounding

Author (Year)	Is there potential for confounding of the effect of intervention in this study?	Was the analysis based on splitting participants' follow-up time according to intervention received?	Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Did the authors control for any post-intervention variables that could have been affected by the intervention?	Did the authors use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding?	Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?	Risk of bias arising from confounding
Burroughs et al. (2022)[27]	Yes	No	No information	No	Not applicable	No	Not applicable	Not applicable	High
Gracitelli (2015)[43]	Yes	Probably no	Not applicable	Probably yes	Probably yes	Probably no	Not applicable	Not applicable	High
Hall et al. (2022)[26]	Yes	No	No information	No information	Probably yes	Probably no	Not applicable	No information	High
Krych (2012)[35]	Probably Yes	Probably no	Not applicable	Probably no	Not applicable	No	Not applicable	Not applicable	High
Marcarini (2003)[19]	Yes	No	Probably no	No	Not applicable	Not applicable	Not applicable	Not applicable	High
Merkley (2021)[41]	Yes	Not applicable	Not applicable	No	Not applicable	Not applicable	Not applicable	Not applicable	High
Müller (2020)[40]	Yes	No	Not applicable	Probably no	Probably yes	Probably no	Not applicable	Not applicable	High

Author (Year)	Is there potential for confounding of the effect of intervention in this study?	Was the analysis based on splitting participants' follow-up time according to intervention received?	Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Did the authors control for any post-intervention variables that could have been affected by the intervention?	Did the authors use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding?	Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?	Risk of bias arising from confounding
Niemeyer et al. (2023)[23]	Yes	Not applicable	Not applicable	Probably yes	Probably yes	Probably no	Probably yes	Probably yes	High
Niemeyer (2019)[24]	Yes	Probably no	Not applicable	Probably no	Probably yes	No	Not applicable	Not applicable	High
Riff (2020)[42]	Yes	No	Not applicable	Probably no	Not applicable	Not applicable	Not applicable	Not applicable	High
Salzmann (2009)[25]	Yes	Not applicable	Not applicable	No	Not applicable	Probably no	Not applicable	Not applicable	Some concerns
Solheim (2020)[34]	Yes	No	Not applicable	Probably no	Not applicable	No	Probably no	Not applicable	High

Table E-7. Risk of bias ratings for nonrandomized studies of interventions—Selection of Participants into the Study

Author (Year)	Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	Were the post-intervention variables that influenced selection likely to be associated with intervention?	Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Do start of follow-up and start of intervention coincide for most participants?	Were adjustment techniques used that are likely to correct for the presence of selection biases?	Risk of bias arising from selection of participants into the study
Burroughs et al. (2022)[27]	Yes	Probably no	No information	Yes	No	High
Gracitelli et al. (2015)[43]	Probably no	Not applicable	Not applicable	Probably yes	Not applicable	Low
Hall et al. (2022)[26]	Probably no	Not applicable	Not applicable	Probably yes	No information	High
Krych et al. (2012)[35]	Probably no	Not applicable	Not applicable	Yes	Not applicable	Low
Marcarini et al. (2003)[19]	No	Not applicable	Not applicable	Probably yes	No	High
Merkley et al. (2021)[41]	No	Not applicable	Not applicable	Yes	Not applicable	Low
Müller et al. (2020)[40]	No	Not applicable	Not applicable	Yes	Not applicable	Low
Niemeyer et al. (2023)[23]	Probably no	Not applicable	Not applicable	Yes	Not applicable	Low
Niemeyer et al. (2019)[24]	No	Not applicable	Not applicable	Yes	Not applicable	Low
Riff et al. (2020)[42]	Probably no	Not applicable	Not applicable	Yes	Not applicable	Low
Salzmann et al. (2009)[25]	Probably no	Not applicable	Not applicable	Probably yes	Not applicable	Low
Solheim et al. (2020)[34]	Probably no	Not applicable	Not applicable	Yes	Not applicable	Low

Table E-8. Risk of bias ratings for nonrandomized studies of interventions— Classification of Interventions

Author (Year)	Were intervention groups clearly defined?	Was the information used to define intervention groups recorded at the start of the intervention?	Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Risk of bias arising from classification of interventions
Burroughs et al. (2022)[27]	Yes	Yes	Not	Low
Gracitelli et al. (2015)[43]	Yes	Yes	No	Low
Hall et al. (2022)[26]	Yes	Yes	No	Low
Krych et al. (2012)[35]	Yes	Yes	Probably yes	High
Marcarini et al. (2003)[19]	Yes	Yes	No	Low
Merkley et al. (2021)[41]	Probably no	Probably yes	Probably no	Some concerns
Müller et al. (2020)[40]	Yes	Yes	Probably no	Low
Niemeyer et al. (2023)[23]	Yes	Yes	No	Low
Niemeyer et al. (2019)[24]	Yes	Yes	Probably no	Low
Riff et al. (2020)[42]	Probably yes	Probably yes	Probably no	Some concerns
Salzmann et al. (2009)[25]	Yes	Probably yes	Probably no	Low
Solheim et al. (2020)[34]	Yes	Yes	No	Low

Table E-9. Risk of bias ratings for nonrandomized studies of interventions—Deviations from Intended Interventions

Author (Year)	Were there deviations from the intended intervention beyond what would be expected in usual practice?	Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Were important co-interventions balanced across intervention groups?	Was the intervention implemented successfully for most participants?	Did study participants adhere to the assigned intervention regimen?	Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Risk of bias arising from deviations from intended interventions
Burroughs et al. (2022)[27]	No information	Not applicable	No information	Probably yes	Yes	No information	High
Gracitelli et al. (2015)[43]	Probably no	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Low
Hall et al. (2022)[26]	No information	Not applicable	No information	Probably yes	Yes	No information	High
Krych et al. (2012)[35]	Probably no	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Low
Marcarini et al. (2003)[19]	Probably no	Not applicable	Not applicable	Probably yes	Yes	Not applicable	Low
Merkley et al. (2021)[41]	Probably no	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Low
Müller et al. (2020)[40]	Probably no	Not applicable	No information	Probably yes	Yes	Not applicable	Some concerns
Niemeyer et al. (2023)[23]	Probably no	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	No information
Niemeyer et al. (2019)[24]	Probably no	Probably no	No information	No information	Probably yes	Not applicable	Some concerns
Riff et al. (2020)[42]	Probably no	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Low
Salzmann et al. (2009)[25]	Probably no	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Low
Solheim et al. (2020)[34]	Probably no	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Low

Table E-10. Risk of bias ratings for nonrandomized studies of interventions—Missing Data

Author (Year)	Were outcome data available for all, or nearly all, participants?	Were participants excluded due to missing data on intervention status?	Were participants excluded due to missing data on other variables needed for the analysis?	Are the proportion of participants and reasons for missing data similar across interventions?	Is there evidence that results were robust to the presence of missing data?	Risk of bias arising from missing data
Burroughs et al. (2022)[27]	Probably no	Probably no	Probably yes	No information	No information	High
Gracitelli et al. (2015)[43]	No	No information	Yes	No information	No information	High
Hall et al. (2022)[26]	No information	Probably no	Probably yes	No information	Not applicable	High
Krych et al. (2012)[35]	Probably no	Probably yes	No information	No information	No information	High
Marcarini et al. (2003)[19]	Probably yes	Not applicable	Not applicable	Not applicable	Not applicable	Low
Merkley et al. (2021)[41]	Probably no	Probably no	No information	No information	No information	High
Müller et al. (2020)[40]	Yes	No information	No information	No information	Not applicable	Low
Niemeyer et al. (2023)[23]	Probably yes	Probably no	Probably no	No information	Probably yes	Low
Niemeyer et al. (2019)[24]	Probably no	Probably no	No information	No information	No information	High
Riff et al. (2020)[42]	No	No information	No information	No information	No information	High
Salzmann et al. (2009)[25]	Probably no	No information	No information	No information	No information	Some concerns
Solheim et al. (2020)[34]	Yes	Probably no	No information	No information	No information	Some concerns

Table E-11. Risk of bias ratings for nonrandomized studies of interventions—Measurement of outcomes

Author (Year)	Could the outcome measure have been influenced by knowledge of the intervention received?	Were outcome assessors aware of the intervention received by study participants?	Were the methods of outcome assessment comparable across intervention groups?	Were any systematic errors in measurement of the outcome related to intervention received?	Risk of bias arising from deviations from measurement of outcomes
Burroughs et al. (2022)[27]	No	Yes	Yes	No	Low
Gracitelli et al. (2015)[43]	Probably yes	Probably yes	Yes	No	Some concerns
Hall et al. (2022)[26]	No	Probably yes	Yes	Probably no	Low
Krych et al. (2012)[35]	Probably yes	Probably yes	Probably yes	Probably no	Some concerns
Marcarini et al. (2003)[19]	Probably yes	Probably yes	Yes	Probably no	Low
Merkley et al. (2021)[41]	Probably yes	Probably yes	Probably yes	Probably no	High
Müller et al. (2020)[40]	Probably yes	Probably yes	Yes	Probably no	Some concerns
Niemeyer et al. (2023)[23]	Probably yes	No information	Probably yes	Probably no	Some concerns
Niemeyer et al. (2019)[24]	Probably no	Yes	Yes	Probably no	Low
Riff et al. (2020)[42]	Probably yes	Probably yes	Probably yes	Probably no	High
Salzmann et al. (2009)[25]	Probably yes	Probably yes	Probably yes	Probably no	Some concerns
Solheim et al. (2020)[34]	Probably yes	Yes	Yes	No	Some concerns

Table E-12. Risk of bias ratings for nonrandomized studies of interventions—Selection of Reported Result and Overall Risk of Bias Judgment

Author (Year)	Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Risk of bias arising from selection of reported results	Overall risk of bias judgment
Burroughs et al. (2022)[27]	Probably no	Probably no	Probably no	Low	High Insufficient measurement and control for confounding is a critical bias; insufficient measurement, no information about missing outcome data, and no information to assess deviations from intended procedures
Gracitelli et al. (2015)[43]	Probably no	Probably no	No	Some concerns	High High risk of bias due to confounding and missing data, no prespecified analysis plan.
Hall et al. (2022)[26]	Probably no	Probably no	Probably no	Low	High Insufficient measurement and control for confounding is a critical bias; some concerns related to no information about missing outcome or data on confounders, lack of prespecified analysis, and no information to assess deviations from intended procedures since analysis entirely based on administrative data.
Krych et al. (2012)[35]	Probably no	Probably no	Probably no	Some concerns	High High risk of bias due to confounding, and missing data.
Marcarini et al. (2003)[19]	Probably no	Probably no	Probably no	Probably no	High Does not appear to be any attempt to control for confounding or selection bias

Author (Year)	Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Risk of bias arising from selection of reported results	Overall risk of bias judgment
Merkley et al. (2021)[41]	Probably no	Probably no	Probably no	Some concerns	High Critical risk due to confounding: patient groups differed because secondary procedure all had failed ACI; patients were matched per age, gender, BMI, and defect size but no other variables appear to have been considered; 2 / 15 participants excluded and 4 others with non-intact grafts did not have knee function/pain measured; no information on deviations from the intended intervention, outcome assessment, or on registration or prespecification of analysis.
Müller et al. (2020)[40]	No information	No information	No information	Some concerns	High Serious concerns for confounding; these are not comparable populations by design. One has already failed surgery. This is not a comparison of different procedures, but rather a comparison of outcomes from the same procedure in 2 different populations.
Niemeyer et al. (2023)[23]	Probably yes	No	No information	Some concerns	High Some concerns related to confounding, no information on outcome assessment masking, and selective outcome reporting.
Niemeyer et al. (2019)[24]	Probably no	Probably no	No	Some concerns	High Serious concerns for bias due to confounding and missing data; moderate to low concerns in other domains.

Author (Year)	Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Risk of bias arising from selection of reported results	Overall risk of bias judgment
Riff et al. (2020)[42]	Probably no	Probably no	Probably no	Some concerns	High Serious risk due to confounding: patient groups differed because secondary procedure all had failed subchondral drilling or microfracture. Patients were matched only per age, sex, and BMI. Follow-up data available for a mean 74% and 96% across all surveys for the second-line and first-line OCA groups, respectively. No information on deviations from intended interventions, masking in outcome assessment, or on prespecification of analysis.
Salzmann et al. (2009)[25]	Probably no	Probably no	Probably no	Some concerns	High Serious risk from confounding; matched participants on gender, age, BMI, cartilage defect localization, and postoperative interval but did not appear to consider other confounders. Group had significantly different sized lesions. No information on missing data or evidence that authors attempted to assess impact of missing data. No information on masking patients or prespecified protocol or analysis plan.
Solheim et al. (2020)[34]	Probably no	Probably no	Probably no	Some concerns	High Serious risk from confounding, baseline differences in groups and no information about how surgeons selected which procedure to use.

Table E-13. Quality of Health Economic Studies—Part I

Author (Year)	Was the study objective presented in a clear, specific, and measurable manner?	Were the perspective of the analysis (societal, third-party payer, and so on) and reasons for its selection stated?	Were variable estimates used in the analysis from the best available source (i.e., randomized control trial-best, expert opinion-worst)?	If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?	Was uncertainty handled by (i) statistical analysis to address random events; (ii) sensitivity analysis to cover a range of assumptions?	Was incremental analysis performed between alternatives for resources and costs?	Was the methodology for data abstraction (including value health states and other benefits) stated?
Miller et al. (2015)[37]	Yes	No	Yes	NA	No	No	Yes

Abbreviations: NA = not applicable.

Table E-14. Quality of Health Economic Studies—Part 2

Author (Year)	Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 yr. discounted (3–5%) and justification given for the discount rate?	Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	Was the primary outcome measure(s) for the economic evaluation clearly stated and were the major short-term, long-term, and negative outcomes included?	Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear transparent manner?	Were the choice of economic model, main assumptions and limitations of the study stated and justified?
Miller et al. (2015)[37]	No	Yes	No	Yes	No	Yes

Table E-15. Quality of Health Economic Studies—Part 3

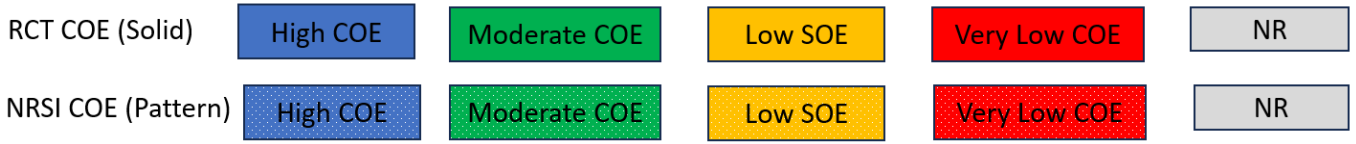
Author (Year)	Did the author(s) explicitly discuss direction and magnitude of potential biases?	Were the conclusions/recommendations of the study justified and based on the study results?	Was there a statement disclosing the source of funding for the study?	Total Score[a]/Total Modified Score
Miller et al. (2015)[37]	No	Yes	No	61

Notes: [a] Based on scale of 0 (worst quality) to 100 (best quality).

Appendix F. Summary of COE Ratings

Figure F-1. Summary of COE Ratings

Comparison	*MACI vs Chondroplasty*	*MACI vs MF*	*MACI vs OATS*	*OATS vs OCA*	*OATS vs Chondroplasty*	*OATS vs MF*	*Cell-free implant vs MF/ Chondroplasty*	*AMIC vs MF*	*1st Line vs 2nd Line*[b]
PROs		***MACI***				***Comparable***	***Cell-free implant***	***AMIC***	
	Comparable	***MACI***	***MACI***		***OATS***	***Comparable***			***1st line***
Responder		***MACI***				***OATS***	***Cell-free implant***		
		MACI							
Re-operation		***Comparable***				***Comparable***		***Comparable***	
		MACI		***Comparable***					***1st line***
Treatment Failure		***Comparable***				***Comparable***	***Comparable***		
		Comparable				***OATS***			***1st line***
Harms[a]		***Comparable***				***Comparable***	***Cell-free implant***[d]	***Comparable***	
		Comparable							



Notes: Solid colored cells indicate RCT study design. Speckled cells indicate NRSI study design. Gray cells indicates no evidence. Text inside cells indicates whether one of procedures has greater effectiveness or the procedures are of comparable effectiveness.
[a] Includes both AEs and SAEs. Color represents the highest COE of the two outcomes.
[b] Includes MACI and OCA
[c] PRO is return to sport or work
[d] Cell-free implant preferred for any adverse events, comparable for severe adverse events
Abbreviations: MACI = matrix-induced autologous chondrocyte implantation, MF= microfracture, OATS = osteochondral autologous transplantation, PROs = patient-reported outcomes.