Molina Clinical Policy
Autologous Chondrocyte Implantation for Knee Cartilage Lesions: Policy No. 347

Last Approval: 10/13/2021
Next Review Due By: October 2022

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members.[1] References included were accurate at the time of policy approval and publication.

OVERVIEW

Autologous chondrocyte implantation (ACI) or matrix-induced autologous chondrocyte transplantation (ACT) is a form of tissue engineering that creates a graft from a patient's cartilage cells to repair defects in articular cartilage. The procedure involves the collection of cartilage cells (grown in a laboratory to create new tissue). The new tissue is then implanted into the defect with the goal of improving the quality of cartilage repair. MACI® is a next-generation matrix-induced ACI that is the only FDA-approved ACT therapy – it involves two stages and four 4 steps:[2-7]

- Initial arthroscopy for diagnosing/sizing defect, securing a chondral biopsy, harvesting of hyaline cartilage.
- Seeding of the cultivated autologous chondrocytes on an absorbable collagen membrane at a density of 500,000 to 1 million cells per square centimeter. (Process may take several weeks).
- An open arthrotomy is conducted to prepare the defect site, appropriately size and shape the implant, and attach the implant to the site of the lesion.
- Postoperative rehabilitation.

A variety of procedures are being developed to resurface articular cartilage defects. Damaged articular cartilage typically fails to heal on its own and eventually leads to pain in surrounding tissue as well as swelling, locking, and/or giving way. These physical issues can be associated with pain, loss of function, disability and may lead to debilitating osteoarthritis. There is no standard approach to the treatment of hyaline cartilage defects in the knee. Non-surgical treatments for pain relief include weight reduction, physical therapy, braces and orthotics, nonsteroidal anti-inflammatory drugs, and/or intraarticular injection of hyaluronic acid derivatives. When therapies are not sufficient, arthroscopic lavage with saline and/or debridement of loose tissue and unstable cartilage fragments may be performed. Cartilage defects can be classified as chondral (cartilage loss) or osteochondral (OC) (cartilage plus bone loss) fractures. Chondral defects are categorized further into partial thickness or full thickness, the latter of which extends to, but not into, the subchondral bone. Although partial-thickness defects do not always produce significant symptoms, they can become full-thickness defects and be a predisposition to osteoarthritis.[2-6]

COVERAGE POLICY

Autologous chondrocyte implantation (ACI) or autologous chondrocyte transplantation (ACT) using the MACI® implant for the treatment of knee articular cartilage lesions **may be considered medically necessary** when **ALL** of the following clinical criteria are met:

1. Diagnosis of **ONE** of the following:
   a. Symptomatic single or multiple full-thickness cartilage defects of the distal femoral articular surface (e.g., medial condyle, lateral condyle or trochlea); **OR**
   b. Patella caused by acute or repetitive trauma.

AND

2. Body Mass Index (BMI) of ≤ 35 or less; **AND**

3. Member is age 15-55 (e.g., adolescents who are skeletally mature with documented closure of growth plates; or adults who are not a candidate for total knee arthroplasty or other reconstructive knee surgery); **AND**

4. Member is experiencing function-limiting pain including, but not limited to, loss of knee function which interferes with activities of daily living; **AND**

5. Physical examination findings include **ALL** of the following:
   a. A stable knee with intact or reconstructed ligaments (ACL or PCL); **AND**
   b. Normal tibial-femoral and/or patella-femoral alignment; **OR**
   c. History of malalignment for deformity of the tibial femoral joint and/or patella maltracking that has been corrected and fixed.

AND

6. Failure of non-surgical medical management for at least three (3) months, as appropriate (e.g., weight reduction, physical therapy, braces and orthotics, intraarticular injection of hyaluronic acid derivatives, and nonsteroidal anti-inflammatory agents); **AND**

7. Focal, full-thickness (Grade III or IV) unipolar lesions of **ONE** of the following that is at least 1.5 centimeters squared in size as identified by MRI or CT arthrogram or during an arthroscopy:
   a. Patella; **OR**
   b. On the weight-bearing surface of the femoral condyles; **OR**
   c. Trochlea.

AND

8. 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; **AND**

9. Absence of osteoarthritis, generalized tibial chondromalacia, and inflammatory arthritis or other systemic disease affecting the joints.

Limitations and Exclusions

The following **are considered experimental, investigational and unproven** based on insufficient evidence.

1. Procedure is not for the treatment of degenerative arthritis (osteoarthritis); Talar (ankle) lesions, or lesions of other joints (e.g., hip and shoulder).
2. ACI as an initial or first line of surgical therapy.
3. Members who have had a previous total meniscectomy.
4. Members with a cartilaginous defect (related to osteoarthritis, rheumatoid arthritis or inflammatory diseases) or where an osteoarthritic or inflammatory process unfavorably affects peri lesional cartilage quality.
5. Members with an identified history of anaphylaxis to gentamicin or sensitivities to materials of bovine origin.
6. Meniscal allograft and ACI of the knee as evidence of efficacy has not been proven.
7. A combination of ACI and osteochondral autograft transfer system for repair of cartilage defects of the knee.
8. Combined ACI and meniscus reconstruction for large chondral defect due to discoid lateral meniscus tear as long-term outcomes have not been established.
9. Combined ACI and osteochondral autograft transfer for large knee osteochondral lesion as long-term outcomes have not been established.
10. Autologous matrix-induced chondrogenesis (AMIC) for articular cartilage defects of the talus, patella-femoral lesions and other osteochondral defects / lesions due to a lack of established evidence.
11. Two-stage bone and meniscus allograft and ACI for the treatment of unicompartmental osteoarthritis of the knee as efficacy has not been proven.
12. For any indications other than those listed above.

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

A large body of evidence suggests that ACI may be an efficacious and a reasonably safe treatment for symptomatic articular cartilage defects of the knee. Treatment may improve symptoms in some patients over short- and intermediate-term follow-up.

Ebert, et al. reported two-year outcomes of a randomized trial investigating a 6-week return to full weight bearing after matrix-induced ACI. A total of 35 patients were randomly allocated to either an 8-week return to full weight bearing or an accelerated 6-week weight bearing approach. Evaluation occurred preoperatively and at 1, 2, 3, 6, 12, and 24 months after surgery. Magnetic resonance imaging (MRI) was undertaken to evaluate the quality and quantity of repair tissue and to calculate an MRI composite score. Results showed significant improvements in all subjective scores, active knee flexion and extension, 6-minute capacity, peak knee extensor torque in the operated limb, and knee extensor (no group differences existed). It was concluded that patients who reduced the length of time spent ambulating on crutches produced comparable outcomes up to 24 months, without compromising graft integrity.[8]

Knutsen, et al. reported results of a randomized multicenter trial comparing ACI with microfracture and long-term follow up at 14 to 15 years of eighty patients with a single symptomatic chronic cartilage defect on the femoral condyle without general osteoarthritis. At the long-term follow-up evaluation, no significant differences between the treatment groups were detected with respect to the results on the clinical scoring systems. At the 15-year evaluation, there were 17 failures in the ACI group compared with 13 in the microfracture group. We observed that more total knee replacements were needed in the ACI group than in the microfracture group (6 compared with 3). The surviving patients in both groups (e.g., those who had not had a failure, had significant improvement in the clinical scores compared with baseline). Of the surviving patients 57% in the ACI group and 48% of patients in the microfracture group had radiographic evidence of early osteoarthritis (a Kellgren and Lawrence grade of≥2); the difference was not significant. Survivors in both groups improved their clinical scores in the short, medium, and long-term evaluations, and no significant difference between the groups was found at the long-term follow-up.[9]

Clavé, et al. reported results of a multicenter randomized controlled trial that compared 2-year functional outcomes (IKDC score) after Cartipatch® versus mosaicplasty in patients with isolated symptomatic femoral chondral defects (ICRS III and IV) measuring 2.5-7.5 cm(2). Of the 55 patients, 30 were allocated randomly to Cartipatch® and 25 to mosaicplasty. After 2 years, eight patients were lost to follow-up (six in the Cartipatch® group and two in the mosaicplasty group). The baseline characteristics of the two groups were not significantly different. The mean IKDC score and score improvement after 2 years were respectively 73.7±20.1 and 31.8±20.8 with Cartipatch® and 81.5±16.4 and 44.4±15.2 with mosaicplasty. The 12.6-point absolute difference in favor of mosaicplasty is statistically significant. Twelve adverse events were recorded in the Cartipatch® group against six in the mosaicplasty group. After 2 years, functional outcomes were significantly worse after Cartipatch® treatment compared to mosaicplasty for isolated focal osteochondral defects of the femur.[10]

Bentley, et al. reported ten-year results of a prospective randomized study of ACI versus mosaicplasty for symptomatic articular cartilage lesions of the knee. The study represents the first long-term randomized comparison of the two techniques with 100 patients at a minimum follow-up of ten years. The mean age of patients at the time of surgery was 31.3 years (range = 16 to 49); the mean duration of symptoms pre-operatively was 7.2 years (9 months to 20 years). Lesions were large with the mean size for the ACI group being 440.9 mm(2) (100 to 1050) and the mosaicplasty group being 399.6 mm(2) (100 to 2000). Patients had a mean of 1.5 previous operations (0 to 4) to the articular cartilage defect. Patients were assessed using the modified Cincinnati knee score and the Stanmore-Bentley Functional Rating system. The number of patients whose repair had failed at ten years was ten of 58 (17%) in the ACI group and 23 of 42 (55%) in the mosaicplasty group ($p < 0.001$). The functional outcome of those patients with a surviving graft was significantly better in patients who underwent ACI compared with mosaicplasty ($p = 0.02$).[11]

Zeifang, et al. reported results of a randomized controlled trial of 21 patients who were followed for 2 years; they found that first-generation ACI gave a statistically significant improvement in Lysholm and Gillquist score relative to third-generation ACI, but there were no significant differences in 2 other measures of knee outcomes.[12]

One new clinical trial was found during the 2021 review of this policy regarding autologous chondrocyte implantation (ACI). A phase 3 clinical trial examines the use of a second generation ACI by comparing it to standard of care therapy (microfracture) for the treatment of traumatic cartilage defects of the knee. NOVOCART 3D was the focus of the trial – it is a biphasic biological scaffold which contains cultivated chondrocytes derived from the patient in a previous tissue harvest procedure. The trial includes knee surgery (e.g., arthroscopy, or mini-arthrotomically for implantation surgery) as well as blood withdrawal during year one of treatment. Initial imaging is also completed (baseline); optional MRI imaging and biomarker collection is completed as sub-study at specific sites only.[20]

Marrow stimulation (MST) surgery (including microfracture, subchondral drilling, and abrasion arthroplasty, and autologous chondrocyte implantation [ACI]) are two surgical options to treat articular cartilage lesions in the knee joint. Recent studies suggest inferior outcomes when ACI is used after failed MST. Seven studies (2 level 2 studies, 5 level 3 studies) were identified which met inclusion criteria for a total of 1335 patients (Group A: n = 838; Group B: n = 497). The average age in all studies was 34.2 years and the average lesion size was 5.43 cm2. Treatment failure was found in 14% of Group A and in 27.6% of Group B. Four studies reported patient reported outcomes (PROs). Patient-reported improvement can be expected in patients undergoing primary or secondary ACI of the knee joint. However, those undergoing secondary ACI have a significantly higher risk of treatment failure and may have worse subjective outcomes compared with patients undergoing primary ACI. [21]

Hu, et al. conducted a meta-analysis to report various effects of ACI on osteochondral defects of the talus; this included 23 case series studies (458 patients) with osteochondral defects of the talus. It was observed that overall, following ACI for patients with osteochondral defects of the talus the incidence of success rate was 89%. For patients with osteochondral defects of the talus, after ACI the AOFAS score was 86.33. An analysis of the subgroup found that the AOFAS score after ACI was significantly different when stratified by the mean age of the patients. The study concluded that the use of ACI could provide a relatively high success rate and improve the AOFAS score for those with osteochondral defects of the talus and is recommended in clinical practice.[22]

Systematic Reviews

Kraeutler, et al. conducted a review to compare the midterm to long-term clinical outcomes of Microfracture (MFx) versus (ACI) for focal chondral defects of the knee. A total of 210 patients (211 lesions) undergoing MFx and 189 patients (189 lesions) undergoing ACI were reviewed. The average follow-up among all studies was 7.0 years. Four studies utilized first-generation, periosteum-based ACI (P-ACI), and 1 study utilized third-generation, matrix-associated ACI (M-ACI). Treatment failure occurred in 18.5% of patients undergoing ACI and 17.1% of patients undergoing MFx. Lysholm and KOOS scores were found to improve for both groups across studies, without a significant difference in improvement between the groups. The only significant difference in patient-reported outcome scores was found in the 1 study using M-ACI in which Tegner scores improved to a significantly greater extent in the ACI group compared with the MFx group. The authors found that patients undergoing MFx or first or third generation ACI for articular cartilage lesions in the knee can be expected to experience improvement in clinical outcomes at midterm to long-term follow-up without any significant difference between the groups.[13]

The National Institute for Health Research (NIHR) reported on a systematic review assessing the clinical effectiveness ACI in the knee. The NIHR review focused on reports from previous systematic reviews including adults with symptomatic articular cartilage defects in the knee published between 2004 and 2014. Twelve systematic reviews including 19 studies (11 RCTs) were selected. The main comparator of interest was microfracture and 4 trials (n=712) were identified that compared second- and third generation ACI with microfracture. One of the trials (ACTIVE, N=390) shared selected results with the NIHR reviewers but no results have been published. In summary, both MACI and ChondroCelect were more clinically effective than microfracture for the outcomes of reductions in pain and improvements in function on the Knee injury and Osteoarthritis Outcome Score (KOOS) over 2 to 5 years. Limited long-term data were available on the failure rates of both ACI and microfracture after 5 years; data were available from 6 observational studies. The conclusions regarding follow-up after 5 years were primarily based on one of the observational studies judged to be the highest quality. For ACI, failure rates were lower in patients who

had no previous knee repair and in people with minimal evidence of osteoarthritis. Larger defect size was not associated with poorer outcomes in these patients.[14-16]

A systematic review by Schuette, et al. was conducted to review mid to long-term clinical outcomes of Matrix-assisted autologous chondrocyte transplantation (MACT) in the patellofemoral (PF) and tibiofemoral (TF) joints. A total of 442 TF patients and 136 PF patients were reviewed. Treatment failure occurred in 9.7% of all patients, including 4.7% of PF patients and 12.4% of TF patients. The authors concluded that patients undergoing MACT in the knee show favorable mid- to long-term clinical outcomes. A significantly higher treatment failure rate was found in patients undergoing MACT in the TF joint compared with the PF joint.[17]

DiBartola, et al. reported a systematic review of clinical outcomes after ACI in the knees of adolescents ranging from 11 to 21 years (mean age 16.2), including five case series (N=115). No RCT's or comparative studies were included in this review. Overall, 99 patients (83%) underwent ACI with periosteal cover, six (5%) with type I/type III collagen cover, and 14 (12%) with matrix induced ACI. Follow-up ranged from 12 to 74 months (mean, 52.3 months). Mean defect size was 5.3 cm2 (range, 0.96 to 14 cm2). All studies reported significant improvement in clinical outcomes scores. Graft hypertrophy was the most common complication (7.0%). The overall percentage increase in clinical outcome scores was 35.7% (SD, 14.2%).[18,19]

National and Specialty Organizations

The **American Academy of Orthopaedic Surgeons (AAOS)** published the *Appropriate Use Criteria for Management of Osteochondritis Dissecans of the Femoral Condyle* which indicates that patients with OCD that have pain, mechanical symptoms (catching or locking), effusion, with closed growth plates, stable, and unsalvageable; that ACI may be appropriate. This recommendation was given a rating of 7 out of 9 total points. All other clinical conditions including no mechanical symptoms did not recommend ACI.[23,24]

Guidelines published by the **National Institute for Health and Care Excellence (NICE)** state that ACI is recommended for treating symptomatic articular cartilage defects of the knee if:[25,26]

- The person has not had previous surgery to repair articular cartilage defects; or
- There is minimal osteoarthritic damage to the knee (as assessed by clinicians experienced in investigating knee cartilage damage using a validated measure for knee osteoarthritis); or
- The defect is over 2 cm^2.

SUPPLEMENTAL INFORMATION

None.

CODING & BILLING INFORMATION

CPT Code

CPT	Description
27412	Autologous chondrocyte implantation, knee

HCPCS Codes

HCPCS	Description
J7330	Autologous cultured chondrocytes, implant
S2112	Arthroscopy, knee, surgical for harvesting of cartilage (chondrocyte cells)

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

10/13/2021	Policy reviewed, no changes to coverage criteria, updated Limitations & Exclusions, added 2021 literature review updates.
9/16/2020	Policy reviewed, no changes, updated references.
9/18/2019	New policy.

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APPENDIX

Reserved for State specific information (to be provided by the individual States, not Corporate). Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.

Washington

27412, J7330 are non-covered benefits as per the Medicaid Provider Guide: Physician-Related Serves/Professional Healthcare Services & Professional Administered Drug Fee Schedules.