Autologous Chondrocyte Implantation

Policy MP-075

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Disclaimer:

1. Policies are subject to change in accordance with State and Federal notice requirements.
2. Policies outline coverage determinations for U of U Health Plans Commercial and Healthy U (Medicaid) plans. Refer to the "Policy" section for more information.
3. This Medical Policy does not guarantee coverage or payment of the service. The service must be a benefit in the member's plan and the member must be eligible for coverage at the time of service. Additional payment guidelines may be applied that are not included in this policy.

Description:

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 intra-articular 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 (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 defect do not always produce significant symptoms, they can become full-thickness defects and be a predisposition to osteoarthritis.

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 new tissue graft 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 four 4 steps:

1. Initial arthroscopy for diagnosing/sizing defect, securing a chondral biopsy, harvesting of hyaline cartilage;

2. 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);
3. An arthroscopy or 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;
4. Postoperative rehabilitation.

Policy Statement and Criteria

1. Commercial Plans

U of U Health Plans considers Autologous Chondrocyte Implantation (ACI) 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. Failure of conservative treatment for a minimum of 2 months which includes physical therapy and may also include orthopedic bracing or nonsteroidal anti-inflammatory drugs

B. Disabling pain and/or knee locking which limits activities of daily living (ADLs)

C. Member's body mass index (BMI) is less than or equal to 35

D. Member has one of the following defects:

   i. Focal articular cartilage defect down to but not through the subchondral bone on a load bearing surface of the femoral condyle (medial, lateral, trochlear) or the patella, with intact menisci and ligaments

   ii. Focal, full-thickness (grade III or IV) unipolar lesions of the patella or the weight bearing surface of the femoral condyles or trochlea at least 1.5 cm^2 in size

E. The size of defect(s) are on average 5 cm^2 to as large as 15 cm^2

F. For smaller lesions (e.g., <4 cm2), if debridement is the only prior surgical treatment, then consideration should be given to marrow-stimulating techniques before autologous chondrocyte implantation is performed

G. Documented minimal to absent degenerative changes in the surrounding articular cartilage (e.g., Kellgren-Lawrence Grade II or less, Outerbridge Grade II or less), and normal-appearing hyaline cartilage surrounding the border of the defect

H. Normal knee biomechanics, alignment, joint space, and stability achieved concurrently with autologous chondrocyte implantation, with no active

inflammatory osteoarthritis or other arthritis, clinically documented or by x-ray
Have one of the appropriate age related characteristics:

i. Adolescent patients should be skeletally mature with documented closure of growth plates (e.g., 15 years or older)

ii. Adult patients should be too young to be considered an appropriate candidate for total knee arthroplasty or other reconstructive knee surgery (e.g., younger than 55 years).

When Autologous Chondrocyte Transplantation is **NOT** covered:

U of U Health Plans does NOT cover Autologous Chondrocyte Transplantation for any other joints besides the knee or any other indications not met in the above criteria as it is considered experimental/investigational, including but not limited to (may not be an all-inclusive list):

A. Treatment of joints other than the knee, including but not limited to ankle/talar, hip or shoulder joint lesions;

B. For individuals with a prior total meniscectomy;

C. Osteochondritis dissecans lesions;

D. Instability of the knee;

E. Osteoarthritis, active rheumatoid arthritis, active infection, or other inflammatory disease of the joint (where an osteoarthritic or inflammatory process significantly and adversely affects the quality of the perilesional cartilage);

F. Kissing lesions;

G. Previous cancer in the bones, cartilage, fat, or muscle of the treated limb;

H. Combined meniscal allograft and autologous chondrocyte implantation of the knee;

I. Combined autologous chondrocyte implantation and osteochondral autograft transfer system for surgical repair of cartilage defects of the knee;

J. Repeat autologous chondrocyte transplantation in the same area;

K. Patients with sensitivities to materials of a bovine origin;

L. Patients with a known history of an allergy to the antibiotic gentamicin.

2. Medicaid Plans

Coverage is determined by the State of Utah Medicaid program; if Utah State Medicaid has no published coverage position and InterQual criteria are not available, the U of U Health Plans Commercial criteria will apply. For the most up-to-date Medicaid policies and coverage, please visit their website at:

http://health.utah.gov/medicaid/manuals/directory.php or the Utah Medicaid code Look-Up tool

CPT/HCPCS codes covered by Utah State Medicaid may still require further evaluation to determine medical necessity for coverage.

Clinical Rationale

Numerous studies and reviews have been published supporting the clinical efficacy of autologous chondrocyte implantation. Systematic Reviews completed in 2016, included a systematic review by DiBartola et al that reported on 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 RCTs 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%). The authors found limitations of this review to include the fact that no RCT's or comparative studies were included in this review, and all of the studies were considered to be of fair, not good quality in terms of their methodology.

Also in 2016, DiBartola et al published a systematic review with meta-analysis on the use of different surgical treatments for cartilage lesions of the knee, focusing on histological outcomes including the degree of defect repair, integration to boarder zone, and macroscopic appearance (to calculate the IRCS score), as well as histological appearance such as hyaline-like cartilage, fibrocartilage, fibrous tissue, or mixed fibrocartilage and hyaline-like cartilage. Grades included normal/excellent (ICRS score = 12), nearly normal/good (IRCS score = 8 to 11), abnormal/fair (ICRS score = 7–4), or severely abnormal/poor (ICRS score = 1 to 3). Thirty-three small case series and RCTs (N=1511 patients) were included. Thirty evaluated ACI or one of its subtypes, six evaluated microfracture (MF), and seven evaluated osteochondral autografting (OATS). No significant difference was found cartilage quality using ICRS grading criteria among OATS, ACI-C, MACI, and ACI-P (ranging from 8.8 to 9.59 – nearly normal/good), however, ICRS scores for microfracture were significantly poorer compared to other treatments. Interestingly, the reviewers were unable to correlate histological outcomes with clinical outcomes, regardless of the method used.

Finally in 2016 (Andrade et al) completed a review which analyzed the surgical outcomes from articular cartilage and/or osteochondral lesions in the knees of soccer players. Five studies were included that met inclusion criteria, one of which was a small case series that used ACI as treatment and one small nonrandomized study that compared matrix-induced ACI (MACI) to microfracture. The other included studies were small case series using mosaicplasty, microfracture and chondral debridement as surgical treatments. The reviewers reported that ACI treatment provided the slowest return to competition and slower clinical and functional results compared to all other treatments reviewed. However, ACI and MACI procedures appeared to enhance longstanding clinical and functional results. The authors concluded that chondral debridement was the surgical technique that yielded the most positive results for all outcomes measured.

In2019 a couple of other systematic reviews were published. These included a systematic review (Andrade et al) reported on the surgical outcomes of patellofemoral cartilage restoration surgeries, including ACI. Forty-two studies were included in the review (N= 1,311 knees and 1,309 patellofemoral

defects). The mean follow-up evaluated was 59.2 months. Among the restoration techniques included in the review, 56% were ACI. Significant improvement in at least one outcome was observed in almost all studies and these surpassed the MCID threshold. The authors concluded, however, that no definitive conclusions could be made regarding the best surgical technique across all evaluated given the lack of comparative studies.

Another review in 2019 (Coughlin et al) studied outcomes of cartilage restoration techniques for grades I IV cartilage defects in the adolescent knee, including ACI. Eleven studies (N=307) were included in the review, with 98 of these subjects having had ACI (mean age 16.0), which was the most common procedure included in the review. The authors found that ACI was among the procedures observed to have the most positive postoperative functional outcomes and lowest complication rates.

A 2019 meta-analysis (Jones et al) reviewed the effectiveness of cartilage repair procedures including ACI for the treatment of symptomatic knee chondral defects. Weighted mean improvements in International Knee Documentation Committee (IKDC), Lysholm, and visual analog scale for pain (VAS pain) scores were calculated from preoperative to short- (1-4 years), mid- (5-9 years), and long-term (≥10 years) postoperative follow-up. The meta-analysis included a total of 89 studies with 3894 unique patients. All cartilage repair procedures met minimal clinically important difference (MCID) values at short- and midterm follow-up for IKDC and Lysholm scores; ACI/MACI additionally met minimal clinically important difference values at the long-term follow-up. It was concluded, the procedure provided extended maintenance of clinical benefits for patients undergoing these surgical interventions as compared with microfracture.

In a 2020 systematic review, Migliorini et al examined the clinical outcomes of ACI and Mesenchymal Stem Cell (MSC) injections for the treatment of focal chondral defects of the knee. Forty-three publications were included in the analysis of which 11 were RCTs and 32 were cohort studies, and pooled analyses were conducted in data from 3340 procedures. ACI procedures were analyzed as either first-generation (p-ACI) in which a periosteal patch is harvested from the proximal tibia is utilized, second-generation (c-ACI) in which a graft containing type I/III collagen membrane is utilized, or third generation (m-ACI), in which autologous chondrocytes are seeded and cultured on type I and III collagen membranes is utilized. Twelve studies reported on p-ACI procedure, eight studies reported on c-ACI procedures, and 13 studies reported on m-ACI procedures. In the p-ACI group (987 knees), the Cincinnati Score improved by 18.94% (p=0.1), VAS by 38% (p=0.01), Tegner score by 19.11% (p=0.03), Lysholm score by 22.40% (p=0.01), IKDC by 27.36% (p=0.003). In the c-ACI group (444 knees), the Cincinnati Score improved by 23.80% (p=0.08), KOOS by 23.48% (p=0.03), VAS by 33.2% (p=0.005), IKDC by 33.30% (p=0.005). In the MACI group (599 knees), the Cincinnati Score improved by 26.80% (p=0.08), KOOS by 31.59% (p=0.1), VAS by 30.43% (p=0.4), Tegner score by 23.1% (p=0.002), Lysholm score by 31.14% (p=0.004), IKCD by 30.57% (p<0.001). The review concluded that ACI techniques are considered a concrete solution to treat focal chondral defects of the knee, along with observing significant improvements from the first- to third-generation techniques.

In 2021, another systematic review by Su assessed long-term (at least two years post-treatment) clinical and radiographic outcomes of patients receiving cartilage restoration procedures including ACI and matrix-induced ACI (MACI) for the treatment of patellar chondral defects. The analysis included 10 studies (N= 293) that provided patient-reported functional outcome data, six of which also provided postoperative MRI with a mean time to postoperative time to MRI of 19 months (range 8-28.8 months). All studies were retrospective, and the mean sample size was 29 (range 10-49). Four studies evaluated ACI with or without TTO procedures, one evaluated ACI alone. Among the five studies on ACI, the range of defect size was 2.92 to 6.4 cm2 (one study did not report defect size). Two studies evaluated the MACI procedure with or without TTO for cartilage defects of the patella, and among these studies, the

mean defect size was 3.75 cm2. The authors concluded that all studies on ACI and MACI found statistically significant improvements in functional outcomes at least two years post-procedure. With respect to MRI findings, moderate-to complete infill of patellar cartilage lesions was seen in the majority of patients regardless of treatment type. However, reoperation was common, with rates ranging from 40% to 60% in studies reporting this variable after ACI. Study limitations included the retrospective study design, small sample size, and considerable variability in the outcomes reported, which precluded pooled analysis.

A 2022 systematic review (Colombini et al) evaluated mid- and long-term efficacy of ACI and MACI in patients with knee cartilage defects in the presence of osteoarthritis (OA). Inclusion criteria were; clear presence of osteoarthritis (KL >/= 1), ACI or MACI to treat knee cartilage defects, and minimum follow-up of 36 months. Data from five studies met inclusion/exclusion criteria (two on ACI and three on MACI) for a total of 235 patients (161 ACI, 74 MACI). The authors found stable clinical improvements following ACI and MACI at up to 11 and 15 years, respectively. A failure rate, defined as revision with re-operation or arthroplasty, of 8% for ACI and 10% for MACI was observed at three and four years, respectively. Long-term failure rates of 9.6% at 9 years was found for ACI. The study with the longest follow-up reported a failure rate of 58.5% after 15 years for MACI. A variety of limitations included the available data noted by the review authors, small sample size of studies and lack of biological details such as cell isolation, preservation, expansion, number and implantation techniques.

Abraamyan et al published a meta-analysis that reviewed cartilage repair techniques, including microfracture, augmented microfracture, and ACI/MACI in 2022. The authors included a total of 14 RCTs (N=775), and changes from baseline in the five Knee injury and Osteoarthritis Outcome Score (KOOS) subscales, including KOOS Sport, KOOS Quality of Life, KOOS Symptoms, KOOS Pain, and KOOS Activities of Daily Living, were measured. Only in the KOOS Sport subscale was statistically significant benefit with ACI/MACI procedures found compared to microfracture (p=0.02). The mean delta KOOS Sport after ACI/MACI procedures was 9.9 points greater than after microfracture and 11.7 points greater than after augmented microfracture. The authors concluded that comparisons between surgical techniques for the other subscales did not reach statistical significance.

Other published studies on autologous chondrocyte implantation include Knutsen, et al. who reported results of a randomized multicenter trial comparing autologous chondrocyte implantation (ACI) with microfracture and long-term follow up at 14 to 15 year 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.

Sacolick et al analyzed the patient-reported outcomes, complication rates, and failure rates of ACI and MACI for osteochondritis dissecans in adults (2019). Nine clinical studies were assessed (type not specified), with 179 (>200 lesions) patients aged 18-49 years (mean=27.6 y). Follow-up ranged from 6.5 months to 10 years. Results of patient-reported outcomes showed that 85% of patients reported excellent or good outcomes. Statistically significant improvements from preoperative to final follow-up

were reported for all patient reported outcome measures used across the studies including the IKDC, Lysholm Knee Questionnaire, EuroQol Visual Analog Scale, Cincinnati Rating System, and the Tegner Activity Scale. Of the studies that reported complication and failure rates for ACI/MACI, 23 (15.7%) of 146 patients reported complications, and failure rate was 8.2%. Unplanned reoperations were necessary for 20.5% of patients. The authors found that ACI/MACI had the best outcomes for active young males with small lesions. Older adults and less active individuals, as well as those with lesions >6 cm2, did not fare as well. However, one limitation of this review was the lack of randomized trials with controls to compare to ACI/MACI.

In 2020, Gou et al, reported on the clinical outcomes among patients with fractures of knee cartilage who were treated with ACI (n=332) or microfracture (n=327) from 12 RCTs. Patient age ranged from 25 to 41 years, with the majority of patients male. Treatment follow-up ranged from 1.5 to 15 years. There were diverse types of autologous chondrocyte implantation performed among the studies including MACI®, NeoCart, ACI with periosteum, and ChondroCelect. Outcomes included an overall clinical score, Knee Injury and Osteoarthritis Outcome Score subdomains of activities of daily living and function, quality of life, pain relief score, and failure/operation rate. No significant difference was found between the interventions in improvement in International Knee Documentation Committee and Lysholm scores or overall Knee Injury and Osteoarthritis Outcome Score measures at one, two, or five years of follow-up. There was also no difference in failure rate between the groups at two, three, or five years. ACI was associated with significant improvements in activities of daily living up to five years follow-up compared to microfracture as well as greater improvement in quality of life and pain relief at five and two-year follow-up examinations, respectively. Major limitations of this report include the small number of eligible RCTs in the final analysis and heterogeneity in ACI techniques, scales and scores for outcome measures, and lesion sizes. Blinding of the patients or surgeons was difficult to perform given the two-step procedure of autologous chondrocyte implantation.

Dhillon et al (2022) reviewed randomized controlled trials (RCTs) comparing clinical outcomes of microfracture to third generation ACI (cells cultured within a collagen membrane, MACI) for the treatment of focal chondral defects of the knee. Six studies (5 Level I, 1 Level II) met inclusion criteria, including a total of 238 patients undergoing microfracture and 274 undergoing MACI, however, two studies had an overlapping cohort and therefore the study with longer follow-up was used in all analyses. Average follow-up time ranged from 2.0 years to 6.0 years and lesion size ranged from 1.8 cm2 to 5.0 cm2. Treatment failure ranged from 0% to 1.8% in the MACI group and 2.5% to 8.3% in the microfracture group. The authors found significantly greater improvement in multiple knee Injury and Osteoarthritis Outcome Score sub-scores in the MACI group compared with microfracture in 4 studies. Limitations included no reports for pooled analyses or long-term outcomes.

In 2020, Hayes performed a technology assessment for matrix-induced autologous chondrocyte implantation (MACI) procedure for repair of articular cartilage of the knee. The authors concluded that "A large, moderate-quality body of evidence suggests that MACI is associated with improved symptoms, function, QOL, and ability to perform normal ADL for young and middle-aged and typically non-obese adults with symptomatic articular cartilage defects of the knee. Evidence also suggests that benefits may be durable beyond follow-up periods of 5 years. The evidence consistently favors MACI over MFX, and more limited evidence suggests that MACI and older-generation ACI procedures have similar clinical benefit. Evidence comparing MACI with other surgical procedures was too limited to draw conclusions. Although the majority of studies reported few safety concerns, additional studies are needed to further evaluate the comparative safety of MACI. There remains uncertainty as to when MACI is optimally prescribed in the chondral defect treatment hierarchy, and definitive patient selection criteria have not been clearly elucidated."

UpToDate published an overview of surgical therapy of knee and hip osteoarthritis. “Total joint arthroplasty (replacement) is reserved for patients with severe symptomatic osteoarthritis (OA) who have failed to respond to nonpharmacologic and pharmacologic management and who have clinically important impairment in their quality of life due to OA. Alternatives to total knee arthroplasty for selected patients with knee OA include unicompartmental knee arthroplasty and knee osteotomy. Alternatives to total hip arthroplasty for selected patients with hip OA include hemiarthroplasty, hip osteotomy, and perhaps, for a very specific group, hip resurfacing”. The authors found that “procedures that have no role for the treatment of knee or hip OA include joint irrigation/lavage, arthroscopic debridement, arthroscopic abrasion arthroplasty, arthroscopic synovectomy, or *autologous chondrocyte implantation*”.

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 osteochondritis dissecans 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. 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 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 cm2.

Applicable Coding

CPT Codes

27412	Autologous chondrocyte implantation, knee
29870	Arthroscopy, knee, diagnostic, with or without synovial biopsy (separate procedure)

HCPCS Codes

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

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Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

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