AUTOLOGOUS CHONDROCYTE TRANSPLANTATION
IN THE KNEE

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COVERAGE RATIONALE

Autologous chondrocyte transplantation (ACT) is proven and medically necessary for treating patients with a single symptomatic full-thickness articular cartilage defect when ALL of the following criteria are met:

- Adult individuals younger than age 55;
- Defect is greater than 2 squared cm;
- Defect is caused by acute or repetitive trauma;
- Individual has defect in the articular cartilage of the femoral condyle (medial, lateral, or trochlea);
- Individual has had an inadequate response to a prior arthroscopic or other surgical repair procedure (e.g., debridement, microfracture, drilling/abrasion arthroplasty, or osteochondral allograft/autograft); and
- Individual has failed to respond to conservative treatment such as physical therapy, braces, and/or nonsteroidal anti-inflammatory drugs (NSAIDs)

ACT is unproven and not medically necessary for treating patients with the following indications due to insufficient evidence of efficacy:

- Individuals who have cartilage defects in locations other than the femoral condyle of the knee
- Individuals whose growth plates have not closed
- Individuals who have partial-thickness defects
- Individuals with history of multiple defects
- Individuals with history of defects of the patella
- Individuals who have osteochondritis dissecans
- Individuals who have had previous history of cancer in the bones, cartilage, fat or muscle of the treated limb
- Osteoarthritis
- Individuals with unstable knee,
- Total meniscectomy
- Inflammatory diseases of the joint

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this guideline does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.
Articular Cartilage Lesions
Normal articular cartilage is a complex tissue composed of matrix, chondrocytes and water. The chondrocytes are responsible for synthesizing the matrix, which is composed primarily of collagen fibers, hyaluronate, and sulfated proteoglycans. Damaged articular cartilage typically fails to heal on its own and can be associated with pain, loss of function and disability, and may lead to debilitating osteoarthritis over time. These manifestations can severely impair an individual's activities of daily living and adversely affect quality of life.

Treatment
Autologous chondrocyte transplantation (ACT), also referred to as autologous chondrocyte implantation (ACI), is a form of tissue engineering that creates a graft from a patient’s own cartilage cells to repair defects in the articular cartilage. For first-generation ACI, the process involves removal, expansion (culture), and reimplantation of the patient’s own chondrocytes under a piece of periosteal membrane that is excised from the tibia of the patient and sutured over the site of knee injury. With ACT, a region of healthy articular cartilage is identified and biopsied through arthroscopy. The tissue is sent to a facility licensed by the U.S. Food and Drug Administration (FDA) where it is minced and enzymatically digested, and the chondrocytes are separated by filtration. With the patient under general anesthesia, an arthrotomy is performed, and the chondral lesion is excised up to the normal surrounding cartilage. In second- and third-generation ACI, the cultured cells are injected under or grown attached to a synthetic membrane or scaffold that is sutured over or adhered to the knee lesion. (Camp et al. 2014)

Autologous Chondrocyte Transplantation
For individuals who have focal articular cartilage lesion(s) of the weight-bearing surface of the femoral condyles, trochlea, or patella who receive ACT, the evidence includes systematic reviews, randomized controlled trials (RCTs), and prospective observational studies. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, and quality of life. There is a large body of evidence on ACT for the treatment of focal articular cartilage lesions of the knee.

Kril et al. (2018) conducted a literature review to evaluate the treatment of autologous chondrocyte implantation (ACI) for knee cartilage defects. The authors note that the most common locations for chondral lesions in the knee in athletes are the patellofemoral joint (37%), including the trochlea (24%) and patella (13%), followed by the femoral condyle (25%) and the tibial plateau (25%). “The goal of cartilage-restoration procedures is to reconstitute the native articular surface with mature and organized hyaline or hyaline-like cartilage”. The application of chondrocytes within a matrix was created to improve cell delivery and allow for minimally invasive implantation in order to better replicate normal cartilage architecture, thus accelerating patient rehabilitation. The authors believe that ACI is an effective technique for the treatment of articular cartilage lesions in appropriately selected patients, and that ACI results are improved if the cartilage lesions are treated within 12 to 18 months after the initial onset of symptoms.

Oussedik et al (2015) performed a systematic review of the treatment of articular cartilage lesions of the knee by microfracture or ACI to determine the differences in patient outcomes after these procedures. These investigators searched PubMed/Medline, Embase, and The Cochrane Library databases in the period from January 10 through January 20, 2013, and included 34 articles in this qualitative analysis. All studies showed improvement in outcome scores in comparison with baseline values, regardless of the treatment modality. The authors concluded that microfracture appeared to be effective in smaller lesions and is usually associated with a greater proportion of fibrocartilage production, which may have an effect on durability and eventual failure. Autologous chondrocyte implantation is an effective treatment that may result in a greater proportion of hyaline-like tissue at the repair site.

Harris et al. (2010) conducted a systematic review to compare autologous chondrocyte implantation with other cartilage repair or restoration techniques. Thirteen studies (n = 917) were included. Patients underwent autologous chondrocyte implantation (n = 604), microfracture (n = 271), or osteochondral autograft (n = 42). Three of 7 studies showed better clinical outcomes after autologous chondrocyte implantation in comparison with microfracture after 1 to 3 years of follow-up, whereas 1 study showed better outcomes 2 years after microfracture and 3 other studies showed
no difference in these treatments after 1 to 5 years. Clinical outcomes after microfracture deteriorated after 18 to 24 months (in 3 of 7 studies). Autologous chondrocyte implantation and osteochondral autograft demonstrated equivalent short-term clinical outcomes, although there was more rapid improvement after osteochondral autograft (2 studies). A defect size of >4 cm² was the only factor predictive of better outcomes when autologous chondrocyte implantation was compared with a non-autologous chondrocyte implantation surgical technique. The authors concluded that all of the cartilage repair/restoration techniques provide short-term success.

A systematic review of 9 different trails (n=626) by Vasiiliadis et al. (2010) found that ACI is an effective treatment for full thickness chondral defects of the knee, providing an improvement of clinical outcomes. The authors note, however, that there is insufficient data to say whether ACI is superior to other treatment strategies in full thickness articular cartilage defects of the knee. Additional studies are needed before specific clinical recommendations can be made.

Vavken and Samartzis (2010) conducted a systematic review of 9 studies (n=526) to compare ACI to other methods of cartilage repair or placebo. The authors found that there was no clear recommendation concerning the efficacy of ACI compared to other treatment options such as microfracture or osteochondral grafts. There is, however, some evidence for better clinical outcomes for ACI compared with osteochondral grafts and equivalent outcomes compared with microfracture. Additional studies are needed to further assess the benefits of ACI compared to other treatments.

Saris et al. (2009) evaluated clinical outcome at 36 months after characterized chondrocyte implantation (CCI) versus microfracture (MF). Based on the results of the trial, the authors concluded that characterized chondrocyte implantation for the treatment of articular cartilage defects of the femoral condyles of the knee results in significantly better clinical outcome at 36 months in a randomized trial compared with MF. Time to treatment and chondrocyte quality were shown to affect outcome.

A case series by Peterson et al. (2010) evaluated the clinical outcomes of autologous chondrocyte implantation in 224 patients 10 to 20 years after implantation (mean = 12.8 years). The authors found that autologous chondrocyte implantation is an effective and durable solution for the treatment of large full-thickness cartilage and osteochondral lesions of the knee joint and clinical and functional outcomes remain high even 10 to 20 years after the implantation.

**ACI in Adolescents**

DiBartola et al. (2016) performed a systematic review of the use of autologous chondrocyte implantation in the adolescent knee. PubMed, MEDLINE, SCOPUS, CINAHL, and Cochrane Collaboration Library databases were searched systematically. Outcome scores recorded included the International Knee Documentation Committee score, the International Cartilage Repair Society score, the Knee Injury and Osteoarthritis Outcome Score, the visual analog scale, the Bentley Functional Rating Score, the Modified Cincinnati Rating System, Tegner activity Lysholm scores, and return athletics. Outcome scores were compared among studies based on proportion of adolescents achieving specific outcome quartiles at a minimum 1-year follow-up. The authors concluded that cartilage repair in adolescent knees using ACI provides success across different clinical outcomes measures. The only patient- or lesion-specific factor that influenced clinical outcome was the shorter duration of preoperative symptoms.

**ACI for Trochlear and Patellar Defects**

Ebert et al. (2015) conducted a prospective clinical and radiologic evaluation of patellofemoral matrix-induced autologous chondrocyte implantation. They prospectively evaluated the clinical and radiologic outcome of MACI in the patellofemoral joint. In 47 consecutive patients undergoing patellofemoral MACI, clinical (Knee injury and Osteoarthritis Outcome Score, 36-Item Short Form Health Survey, visual analog scale for pain, 6-minute walk test, knee range of motion, and strength assessment) and magnetic resonance imaging (MRI) assessments were undertaken before and 3, 12, and 24 months after surgery. The MRI was performed to assess graft infill and determine an overall MRI composite score. Results were analyzed according to (1) the patient sample overall and (2) after stratification into 4 subgroups per implant location (patella or trochlea) as well as whether or not adjacent tibial tubercle transfer for patellofemoral malalignment was required. The overall patient sample, as well as each of the 4 procedural subgroups, demonstrated clinically and statistically significant improvements over time for all clinical scores. Graft infill and the MRI composite score also demonstrated statistically significant improvements over time, with no evidence of a main effect for procedure group or interaction between procedure group and time. At 24 months after surgery, 40.4% of patients exhibited complete graft infill comparable with the adjacent native cartilage, with a further 6.4% demonstrating a hypertrophic graft. A further 31.9% of patients exhibited 50% to 100% tissue infill, and 17% demonstrated <50% tissue infill. Two patients (4.3%) demonstrated graft failure. At 24 months after surgery, 85% of patients were satisfied with the results of their MACI surgery. The authors concluded that these results demonstrate that MACI provides improved clinical and radiologic outcomes to 24 months in patients undergoing treatment specifically for articular cartilage defects on the patella or trochlea, with and without concurrent realignment of the extensor mechanism if required. The authors identify a number of limitations to this study; there is currently no agreement on a gold standard PRO measure for the evaluation of cartilage repair surgery; employed the 6-minute walk test as a basic measure of function, and while this test has been used in ACI patients it has not been validated; the MOCART scoring tool has not been validated against arthroscopic or histologic repair tissue findings.
Gomoll et al. (2014) conducted a multicenter study to show the repair of patellar cartilage defects with autologous chondrocyte implantation (ACI) can provide lasting improvements in pain and function. Patients were treated at 1 of 4 participating cartilage repair centers with ACI for cartilage defects in the patella; bipolar (patella + trochlea) defects were included as well. All patients were followed prospectively for at least 4 years with multiple patient-reported outcome instruments, including the International Knee Documentation Committee, Short Form-12, modified Cincinnati Rating Scale, Western Ontario and McMaster Universities Osteoarthritis Index, and Knee Society scores. Treatment failure was defined as structural failure of the graft combined with pain requiring revision surgery. A total of 110 patients were available for analysis. As a group, they experienced both statistically significant and clinically important improvements in pain and function in all physical outcome scales. The International Knee Documentation Committee improved from 40 ± 14 preoperatively to 69 ± 20 at the last follow-up; the Cincinnati Rating Scale, from 3.2 ± 1.2 to 6.2 ± 1.8; and the Western Ontario and McMaster Universities Osteoarthritis Index, from 50 ± 22 to 29 ± 22. Ninety-two percent of patients stated that they would choose to undergo ACI again, and 86% rated their knees as good or excellent at the time of final follow-up. Nine patients (8%) were considered treatment failures, and 16% reported that their knees were not improved. The authors concluded that while cartilage repair in the patellofemoral joint is arguably not without its challenges, and autologous chondrocyte implantation remains off-label in the patella, when performed with attention to patellofemoral biomechanics, self-rated subjective good and excellent outcomes can be achieved in more than 80% of patients treated with ACI, even in a patient population with large and frequently bipolar defects such as the one presented in this study. However, final functional scores, although significantly improved, still reflected residual disability in this challenging group of patients.

Niemeyer et al. (2008) reported the clinical results obtained in 70 patients treated with ACI for full-thickness defects of the patella. At a mean follow-up of 38.4 months, patients' subjective functional knee scores (IKDC, Lysholm) were analyzed, as were the results of objective examination (according to International Cartilage Research Society [ICRS]). The mean Lysholm score at the time of follow-up was 73.0 (+/-22.4) and the subjective IKDC score was 61.6 (+/-21.5); normal and nearly normal clinical results according to ICRS were achieved in 67.1% of the patients, while abnormal results were achieved in 20.0% of the patients and severely abnormal results, in 12.9% of the patients. The authors concluded that this study demonstrates that within a group of patients treated with ACI for retropatellar cartilage lesion there are significant differences in clinical outcome, which are important and should be taken into account of when a decision has to be made on whether or not ACI is indicated.

Published trials comparing ACT with other surgical repair procedures for defects in the knee included relatively few patients with trochlear or patellar defects. There are no adequate prospective clinical studies of the effectiveness of autologous chondrocyte implantation on defects of the patella or talus. Prospective, randomized clinical studies are needed to assess the impact on functional status, disability, and pain. In addition, studies need to compare the effectiveness of autologous chondrocyte implantation to established methods of treatment of patellar or talus defects.

**Additional Applications**

A review on “Surgical therapy of osteoarthritis” (Kalunian, 2014) states that “Replacing localized regions of degenerated cartilage with autologous chondrocyte grafts has not been studied in large groups of patients. It is unlikely that this technique will be helpful in patients with advanced joint degeneration because of the large surface area that needs grafting in this setting. Replacing localized regions of degenerated cartilage with autologous chondrocyte grafts may be beneficial for selected patients with less severe, localized articular cartilage defects, but it requires further study”. Additional research is needed to expand the knowledge of and develop guidelines for management of chondral injuries of the hip.

Jordan et al (2012) performed a systematic review of clinical outcomes following various treatments for chondral lesions of the hip and defined the techniques for the treatment of these cartilage defects. The full manuscripts of 15 studies were reviewed for this systematic review including case studies, case series, and clinical studies. A variety of techniques have been reported for the treatment of symptomatic chondral lesions in the hip. Although good results have been reported, most studies lacked both a control group and a large number of patients. The authors concluded that the findings in this article do provide a good foundation for treatments and stimulant for further study in an inherently difficult to treat young patient population with articular cartilage defects in the hip.

According to Hayes the results of the large body of overall low-quality evidence suggest that first-generation ACI may be an efficacious and reasonably safe treatment for symptomatic articular cartilage defects of the knee and may have similar outcomes as microfracture and mosaicplasty over short- and intermediate-term follow-up. While second- and third-generation ACI may provide greater benefit than first-generation ACI, some evidence was conflicting. Single studies found first-generation ACI more effective than cartilage debridement or abrasion, but debridement and abrasion seem to have been supplanted by microfracture in patients who are candidates for ACI. Additional well-designed studies involving larger study populations and long-term follow-up are needed to determine the clinical role of first-generation ACI relative to microfracture, mosaicplasty, and second- and third-generation ACI. (Hayes, 2017).
Zaslav et al. (2009) assessed the effectiveness of autologous chondrocyte implantation in a prospective clinical study of patients who failed prior treatments for articular cartilage defects of the knee. Follow-up was 48 months. One hundred twenty-six patients (82%) completed the study protocol. Seventy-six percent of patients were treatment successes at the end of the study and 24% were identified as treatment failures. Mean improvements were observed from baseline to all time points (P < .001) for all outcome measures. Preoperative to 48-month values, respectively, were as follows: On the Knee injury and Osteoarthritis Outcome Score subscales of pain: 48.7 to 72.2; other symptoms: 51.8 to 70.8; sports/recreation: 25.8 to 55.8; knee quality of life: 20.9 to 52.2; and activities of daily living: 58.6 to 81.0; on the Modified Cincinnati Overall Knee score: 3.3 to 6.3; on the visual analog scale: 28.8 to 69.9; and on the SF-36 Overall Physical Health: 33.0 to 44.4. Results did not differ between patients whose primary surgery had been a marrow-stimulating procedure and those whose primary procedure had been a debridement alone. The median difference in duration of benefit between autologous chondrocyte implantation and the failed non-autologous chondrocyte implantation procedure was at least 31 months (P < .001). Seventy-six patients (49%) had subsequent surgical procedure(s), predominantly arthroscopic. The investigators concluded that patients with moderate to large chondral lesions with failed prior cartilage treatments can expect sustained and clinically meaningful improvement in pain and function after autologous chondrocyte implantation. The subsequent surgical procedure rate observed in this study (49% overall; 40% related to autologous chondrocyte implantation) appears higher than generally reported after autologous chondrocyte implantation.

Matrix Guided Autologous Chondrocyte Transplantation

Devitt et al. (2017) conducted a systematic review of randomized controlled trials to provide updates on the most appropriate surgical procedures for knee cartilage defects. Two reviewers independently searched three databases for RCTs comparing at least two different treatment techniques for knee cartilage defects. Strict inclusion and exclusion criteria were used to identify studies with patients aged between 18 and 55 years with articular cartilage defects sized between one and 15cm. Risk of bias was performed using a Coleman Methodology Score. Data extracted included patient demographics, defect characteristics, clinical outcomes, and failure rates. Ten articles were included (861 patients). Eight studies compared microfracture to other treatment; four to autologous chondrocyte implantation (ACI) or matrix-induced ACI (MACI); three to osteochondral autologous transplantation (OAT); and one to BST. Two studies reported better results with OAT than with microfracture and one reported similar results. Two studies reported superior results with cartilage regenerative techniques than with microfracture, and two reported similar results. At 10 years significantly more failures occurred with microfracture compared to OAT and with OAT compared to ACI. Larger lesions (>4.5cm2) treated with cartilage regenerative techniques (ACI/MACI) had better outcomes than with microfracture. Based on the evidence from this systematic review, the authors concluded that no single treatment can be recommended for the treatment of knee cartilage defects, and this highlights the need for further RCTs, preferably patient-blinded, using an appropriate reference treatment or a placebo procedure.

Ebert et al. (2017) conducted a randomized controlled trial to investigate a 6-Week return to full weightbearing after matrix-induced autologous chondrocyte implantation. A total of 37 knees (n = 35 patients) were randomly allocated to either an 8-week return to full WB that the authors considered current best practice based on the existing literature (CR group; n = 19 knees) or an accelerated 6-week WB approach (AR group; n = 18 knees). Patients were evaluated preoperatively and at 1, 2, 3, 6, 12, and 24 months after surgery, using the Knee Injury and Osteoarthritis Outcome Score, 36-Item Short Form Health Survey, visual analog pain scale, 6-minute walk test, and active knee range of motion. Isokinetic dynamometry was used to assess peak knee extension and flexion strength and limb symmetry indices (LSIs) between the operated and non-operated limbs. Magnetic resonance imaging (MRI) was undertaken to evaluate the quality and quantity of repair tissue as well as to calculate an MRI composite score. The results showed significant improvements observed in all subjective scores, active knee flexion and extension, 6-minute capacity, peak knee extensor torque in the operated limb, and knee extensor LSI, although no group differences existed. Although knee flexor LSIs were above 100% for both groups at 12 and 24 months after surgery, LSIs for knee extensor torque at 24 months were 93.7% and 87.5% for the AR and CR groups, respectively. The MRI composite score and pertinent graft parameters significantly improved over time, with some superior in the AR group at 24 months. All patients in the AR group (100%) demonstrated good to excellent infill at 24 months, compared with 83% of patients in the CR group. Two cases of graft failure were observed, both in the CR group. At 24 months, 83% of patients in the CR group and 88% in the AR group were satisfied with the results of their MACI surgery. The authors concluded that patients in the AR group who reduced the length of time spent ambulating on crutches produced comparable outcomes up to 24 months, without compromising graft integrity.

Ebert et al. (2017) conducted a prospective clinical and radiological evaluation of the first 31 patients (15 male, 16 female) who underwent MACI via arthroscopic surgery to address symptomatic tibiofemoral chondral lesions. Clinical scores were administered preoperatively and at 3 and 6 months as well as 1, 2, and 5 years after surgery. These included the Knee injury and Osteoarthritis Outcome Score (KOOS), Lysholm knee scale (LKS), Tegner activity scale (TAS), visual analog scale for pain, Short Form-36 Health Survey (SF-36), active knee motion, and 6-minute walk test. Isokinetic dynamometry was used to assess peak knee extension and flexion strength and limb symmetry indices (LSIs) between the operated and non-operated limbs. High-resolution magnetic resonance imaging (MRI) was performed at 3 months and at 1, 2, and 5 years postoperatively to evaluate graft repair as well as calculate the MRI
composite score. The results showed there was a significant improvement in all KOOS subscale scores, LKS and TAS scores, the SF-36 physical component score, pain frequency and severity, active knee flexion and extension, and 6-minute walk distance. Isokinetic knee extension strength significantly improved, and all knee extension and flexion LSIs were above 90% (apart from peak knee extension strength at 1 year). At 5 years, 93% of patients were satisfied with MACI to relieve their pain, 90% were satisfied with improving their ability to undertake daily activities, and 80% were satisfied with the improvement in participating in sport. Graft infill and the MRI composite score significantly improved over time, with 90% of patients demonstrating good to excellent tissue infill at 5 years. There were 2 graft failures at 5 years after surgery. The authors concluded that arthroscopically performed MACI technique demonstrated good clinical and radiological outcomes up to 5 years, with high levels of patient satisfaction.

Schuette et al. (2017) completed a systematic review to investigate mid- to long-term clinical outcomes of Matrix-assisted autologous chondrocyte transplantation (MACT) in the patellofemoral (PF) and tibiofemoral (TF) joints. A systematic review was performed by searching PubMed, Embase, and the Cochrane Library to find studies evaluating minimum 5-year clinical outcomes of patients undergoing MACT in the knee joint. Patients were evaluated based on treatment failure rates, magnetic resonance imaging, and subjective outcome scores. Study methodology was assessed using the Modified Coleman Methodology Score (MCMS). The results included 10 studies and 587 patients (two level 1, one level 2, one level 3, and six level 4 evidence) that met inclusion and exclusion criteria, for a total of 442 TF patients and 136 PF patients. Treatment failure occurred in 9.7% of all patients, including 4.7% of PF patients and 12.4% of TF patients. Weighted averages of subjective outcome scores, including Knee injury and Osteoarthritis Outcome Score, Short Form-36 Health Survey, and Tegner scores, improved from baseline to latest follow-up in both TF and PF patients. The mean MCMS was found to be 57.4, with a standard deviation of 18.5. The authors concluded that patients undergoing MACT in the knee show favorable mid- to long-term clinical outcomes, with a significantly higher treatment failure rate found in patients undergoing MACT in the TF joint compared with the PF joint. The authors identified some limitations to this study; level 1 to 4 evidence studies were included; although 587 patients were included in this review, not all patients were evaluated using the same outcome measures, and therefore sample sizes were limited for particular outcomes; Of the defects compared, there was a significant disparity in defect numbers between those in the TF group (442) and those in the PF group; variation in different scaffold types, and overlapping of patients in studies with no mention of this in the individual studies.

Zhang et al. (2014) conducted a study aimed to evaluate whether MACI is a safe and efficacious cartilage repair treatment for patients with knee cartilage lesions. The primary outcomes were the Knee Injury and Osteoarthritis Outcome Score (KOOS) domains and magnetic resonance imaging (MRI) results, compared between baseline and postoperative months 3, 6, 12, and 24. A total of 15 patients (20 knees), with an average age of 33.9 years, had a mean defect size of 4.01 cm2. By 6-month follow-up, KOOS results demonstrated significant improvements in symptoms and knee-related quality of life. MRI showed significant improvements in four individual graft scoring parameters at 24 months postoperatively. At 24 months, 90% of MACI grafts had filled completely and 10% had good-to-excellent filling of the chondral defect. Most (95%) of the MACI grafts were isointense and 5% were slightly hypertense. Histologic evaluation at 15 and 24 months showed predominantly hyaline cartilage in newly generated tissue. There were no postoperative complications in any patients and no adverse events related to the MACI operation. This 2-year study has confirmed that MACI is safe and effective with the advantages of a simple technique and significant clinical improvements. Further functional and mechanistic studies with longer follow-up are needed to validate the efficacy and safety of MACI in patients with articular cartilage injuries. This study is limited by low number of participants and lack of randomization and control.

Basad et al. (2010) compared the clinical outcomes of patients with symptomatic cartilage defects treated with matrix-induced autologous chondrocyte implantation (MACI) or microfracture (MF). The 60 patients included were 18 to 50 years of age with symptomatic, post-traumatic, single, isolated chondral defects (4-10 cm2) and were randomized to receive MACI (40) or MF (20). Patients were followed up 8-12, 22-26 and 50-54 weeks postoperatively for efficacy and safety evaluation. The difference between baseline and 24 months post-operatively for both treatment groups was significant for the Lysholm, Tegner, patient ICRS and surgeon ICRS scores. However, MACI was significantly more effective over time (24 months versus baseline) than MF according to the Lysholm, Tegner, ICRS patient and ICRS surgeon scores. According to the authors, MACI is superior to MF in the treatment of articular defects over 2 years.

Zeifang et al. (2010) evaluated whether matrix-associated autologous chondrocyte implantation or the original periosteal flap technique provides superior outcomes in terms of clinical efficacy and safety. Twenty-one adult patients (mean age, 29.3 +/- 9.1 years) with symptomatic isolated full-thickness cartilage defects (mean 4.1 +/- 09 cm2) at the femoral condyle were randomized to matrix-associated autologous chondrocyte implantation or the original periosteal flap technique. The primary outcome parameter showed improvement of patients 1 year after autologous chondrocyte implantation, but there was no difference between the periosteal flap technique and matrix-associated ACI; 2 years after ACI, a similar result was found. The authors concluded that there was no difference in the efficacy between the original and the advanced ACI technique 12 and 24 months after surgery regarding International Knee
Documentation Committee, Tegner Activity Score, and Short Form-36; however, with respect to the Lysholm and Gillquist score, better efficacy was observed in the periosteal flap technique group.

According to a Hayes review of Matrix-Induced Autologous Chondrocyte Implantation Using MACI for Repair of Articular Cartilage of the Knee. Hayes concluded that there was insufficient published evidence to assess the safety and/or impact of the MACI implant on health outcomes or management in patients requiring articular cartilage repair. (Hayes 2018).

According to a Hayes review a large body of overall low-quality evidence suggests that second- and third-generation ACI are promising and reasonably safe treatments for articular cartilage defects of the knee over short- and intermediate-term follow up. Despite its large size, this body of evidence does not provide definitive conclusions concerning the efficacy and safety of second- and third-generation ACI relative to other procedures, including microfracture, mosaicplasty, and first-generation ACI, and additional high-quality studies are needed to confirm results of the available studies and to evaluate the long-term efficacy and safety of second-generation ACI and of all the different scaffold materials that have been used for third-generation ACI (Hayes 2018).

Professional Societies/Organizations

American Academy of Orthopaedic Surgeons (AAOS)

In a 2010 and 2012 clinical practice guideline on the diagnosis and treatment of osteochondritis dissecans (OCD), the American Academy of Orthopaedic Surgeons (AAOS) was unable to recommend for or against a specific cartilage repair technique in symptomatic skeletally immature or mature patients with an unsalvageable osteochondritis dissecans lesion. This recommendation of insufficient evidence was based on a systematic review that found four (4) level IV studies that addressed cartilage repair techniques for an unsalvageable OCD lesion. Because each of the level IV articles used different techniques, different outcome measures, and differing lengths of follow-up, the work group deemed that the evidence for any specific technique was inconclusive.

National Institute for Health and Clinical Excellence (NICE)

An updated NICE (2017) Guidance provided the following recommendations for Autologous chondrocyte implantation (ACI) of the knee:

Autologous chondrocyte implantation (ACI) is recommended as an option for treating symptomatic articular cartilage defects of the knee, only if:
- the person has not had previous surgery to repair articular cartilage defects
- 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)
- the defect is over 2 cm² and
- the procedure is done at a tertiary referral centre.

German Society of Orthopaedics and Trauma

In a 2016 guideline by the working group “Clinical Tissue Regeneration” of the German Society of Orthopaedics and Trauma entitled “Autologous chondrocyte implantation (ACI) for cartilage defects of the Knee” (Niemeyer et al. 2016) indications for ACI include:
- Defect stage: Full-thickness, symptomatic cartilage defect grades 3 and 4 as per ICRS and osteochondritis dissecans stages III and IV as per ICRS-OCD, possibly in combination with subchondral bone reconstruction
- Defect size: Minimum: 2.5 to 3 cm²; Maximum: no limit
- Defect localization: No limitation: Medial and lateral femoral condyle; Medial and lateral tibial plateau; Patellar bearing surface (trochlea); Patella
- Age: Typically up to about 55 years of age; higher age is however not a contraindication with relevant defect morphology and primarily intact joint conditions. Children and adolescents possible

Contraindications:
- Concomitant pathologies which cause it, which cannot be treated in parallel (e.g. misalignment)
- Advanced arthritis
- Subtotal resected meniscus in an impacted compartment
- Rheumatoid arthritis with relevant synovitis
- Hemophilia-associated arthropathy
REFERENCES


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**GUIDELINE HISTORY/REVISION INFORMATION**

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**INSTRUCTIONS FOR USE**

This Medical Management Guideline provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard benefit plan. In the event of a conflict, the member specific benefit plan document governs. Before using this guideline, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Management Guideline is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare West Medical Management Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Member benefit coverage and limitations may vary based on the member’s benefit plan Health Plan coverage provided by or through UnitedHealthcare of California, UnitedHealthcare Benefits Plan of California, UnitedHealthcare of Oklahoma, Inc., UnitedHealthcare of Oregon, Inc., UnitedHealthcare Benefits of Texas, Inc., or UnitedHealthcare of Washington, Inc.