AUTOLOGOUS CHONDROCYTE TRANSPLANTATION IN THE KNEE

Policy Number: 2017T00300

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Community Plan Policy

• Autologous Chondrocyte Transplantation in the Knee

INSTRUCTIONS FOR USE

This Medical Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Medical Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Medical Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Medical Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Medical Policy 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. The MCG™ Care 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.

BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

Essential Health Benefits for Individual and Small Group

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits (“EHBs”). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

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 patient younger than age 55;
• Defect is greater than 2 squared cm;
• Defect is caused by acute or repetitive trauma;
Defect is in the articular cartilage of the femoral condyle (medial, lateral, or trochlea); Patient 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 Patient has failed to respond to conservative treatment such as physical therapy, braces, and/or nonsteroidal anti-inflammatory drugs (NSAIDs).

**Autologous chondrocyte transplantation is considered unproven and not medically necessary for treating patients with the following indications:**
- Patients who have cartilage defects in locations other than the femoral condyle of the knee
- Patients whose growth plates have not closed
- Patients who have partial-thickness defects
- Patients with history of multiple defects
- Patients with history of defects of the patella
- Patients who have osteochondritis dissecans
- Patients who have had previous history of cancer in the bones, cartilage, fat or muscle of the treated limb
- Osteoarthritis
- Patients with unstable knee
- Total meniscectomy
- Inflammatory diseases of the joint

There is insufficient evidence to conclude that ACT is beneficial for health outcomes in patients with osteochondritis dissecans, osteoarthritis, or for cartilage defects.

**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 policy 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 Coverage Determination Guidelines may apply.

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**DESCRIPTION OF SERVICES**

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. Articular cartilage damaged through acute or chronic trauma or osteochondritis dissecans, has limited ability to regenerate, leading to the symptoms of pain, restricted mobility and locking. When a full-thickness cartilage injury occurs, the articular surface does not usually regenerate on its own. Surgical treatment options include autologous chondrocyte transplantation.

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. 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.

**CLINICAL EVIDENCE**

**Autologous Chondrocyte Transplantation**

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
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 cm(2) 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.

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.

**ACT in Adolescents**

Some experts believe the use of ACT in children is not reasonable, since regenerative capacities are so much greater than in adults and due to potential interference epiphysis closure (Vanlauwe et al., 2007). However, other authors have seen the potential for faster healing to be a good reason to try ACT in athletes. A review of 37 adolescent (age 11-17) ACT procedures listed in the Cartilage Repair Registry showed an 88% rate of good/excellent outcomes (Micheli et al., 2006).

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.

**ACT 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 adjunct 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 (all P < .0001). 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.

Published trials comparing ACT with other surgical repair procedures for defects in the knee included relatively few patients with trochlear or patellar defects. A review of 40 Cartilage Repair Registry patients who underwent ACT for trochlear cartilage defects reported positive outcomes (Mandelbaum et al., 2007). In most cases, ACT followed previous attempts at surgical repair, often marrow stimulation. Defects were generally large (mean 4.5 cm2). A longitudinal study separately analyzed results for 45 patients who underwent ACT for defects on the patella, trochlea, patella plus trochlea, weight bearing condyle plus patella, weight bearing condyle plus trochlea, or weight bearing condyle plus patella plus trochlea (Minas and Bryant, 2005). Affected patellar surface averaged 4.86 cm2, and affected trochlear surface averaged 5.22 cm2. Most (71%) patients reported a good or excellent overall outcome. However, the rate of graft failure was rather high (18%).

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.

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.

Current evidence regarding ACI largely examines cartilage restoration of the knee joint. However, two small studies and one case report were identified in the literature that evaluated the use of ACT in other joints. Investigators assessed the use of autologous chondrocytes in osteochondral lesions of the ankle joint and osteochondrosis dissecans of the ankle joint (n=8; n=8). In the first study, at 2 years of follow-up, both subjective and objective clinical improvement was observed in all patients. (Giannini, 2001) Arthroscopy and histological analysis revealed cartilaginous tissue covering the lesion area, although cell numbers were increased compared with normal cartilage.

Koulalis et al. (2002) reported good to excellent results in the postoperative evaluation scores, with no complications. Arthroscopic examinations in 3 patients revealed the existence of cartilage-like tissue with complete coverage of the chondral effect. Romeo et al. (2002) reported on the use of ACT in the repair of an articular defect in the humeral head of a young patient. After 12 weeks, the patient demonstrated full range of painless motion with no complaints of rest pain or weather-related pain. Despite these early clinical results, the available scientific evidence does not allow definitive conclusions regarding the safety and efficacy of ACT in treating focal defects of joints other than the knee, such as ankle, hip, wrist, or shoulder.

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).

In a prospective cohort study, Kon et al. (2009) compared the clinical outcome of patients treated with second-generation Hyalograph C autologous chondrocyte implantation implants (n=40) with those treated with the microfracture repair (n=40). All patients had grade III to IV cartilage lesions of the femoral condyles or trochlea. Both groups demonstrated statistically significant improvement of all clinical scores from preoperative interval to 5-year follow-up. When comparing the groups, better improvement of the International Knee Documentation Committee objective (P < .001) and subjective (P = .003) scores was observed in the Hyalograph C group at 5-year follow-up. The return to sports at 2 years was similar in both groups and remained stable after 5 years in the Hyalograph C group; it worsened in the microfracture group. The investigators concluded that better clinical results and sport activity resumption were demonstrated in the group treated with second-generation autologous chondrocyte transplantation.

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 66.0. 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 prior 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 (MALT) 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 97.4, 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 hyperintense. 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 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 2017).

**Professional Societies/Organizations**

**American Academy of Orthopaedic Surgeons (AAOS)**

In a 2010 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.
National Institute for Health and Clinical Excellence (NICE)
Current NICE Guidance recommends against ACI for the treatment of articular cartilage defects of the knee joint, except in the context of ongoing or new clinical studies that are designed to generate robust and relevant outcome data, including the measurement of health-related quality of life and long-term follow-up (NICE, 2008).

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

U.S. FOOD AND DRUG ADMINISTRATION (FDA)
See the following website for more information regarding products used for Autologous Chondrocyte Transplantation and search by product name in device name section: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmncfpmn.cfm. (Accessed August 8, 2017)

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)
Medicare does not have a National Coverage Determination (NCD) for autologous chondrocyte transplantation (ACT) in the knee. Local Coverage Determinations (LCDs) do not exist at this time. (Accessed August 8, 2017)

REFERENCES


Kalunica KC. Surgical therapy of osteoarthritis. Last reviewed December 2014. UpToDate Inc., Waltham, MA.


**POLICY HISTORY/REVISION INFORMATION**

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| 10/01/2017| • Updated supporting information to reflect the most current description of services, clinical evidence, FDA and CMS information, and references; no change to coverage rationale or lists of applicable codes  
|           | • Archived previous policy version 2016T0030N                                       |