Corporate Medical Policy
Autologous Chondrocyte Transplantation or Implantation

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Description
Autologous chondrocyte implantation (ACI) is a method of resurfacing articular cartilage defects. The procedure involves harvesting chondrocytes from healthy tissue, expanding the cells in vitro, and implanting the expanded cells into the chondral defect.

Background
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. Conventional treatment options include debridement, subchondral drilling, microfracture, and abrasion arthroplasty. Debridement involves the removal of synovial membrane, osteophytes, loose articular debris, and diseased cartilage, and is capable of producing symptomatic relief. Subchondral drilling, microfracture, and abrasion arthroplasty attempt to restore the articular surface by inducing the growth of fibrocartilage into the chondral defect. Compared to the original hyaline cartilage, fibrocartilage has less capability to withstand shock or shearing force and can degenerate over time, often resulting in the return of clinical symptoms. Osteochondral grafts and ACI attempt to regenerate hyaline-like cartilage and thereby restore durable function.

With autologous chondrocyte implantation, 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. The isolated chondrocytes are cultured for 11–21 days to expand the cell population, tested, and then shipped back for implantation. With the patient under general anesthesia, an arthrotomy is performed, and the chondral lesion is excised up to the normal surrounding cartilage. A periosteal flap is removed from the proximal medial tibia and sutured to the surrounding rim of normal cartilage. The cultured chondrocytes are then injected beneath the periosteal flap. ACI may be considered more effective for larger lesions than microfracture or osteochondral grafts, but it is technically difficult, requiring two procedures and harvesting of periosteum. In addition, use of the FDA-indicated periosteal cover may result in hypertrophy as well as donor site morbidity.

Methods to improve the ACI procedure are being investigated, including the use of a scaffold or matrix-induced ACI (MACI) composed of biocompatible carbohydrates, protein polymers, or synthetics. Desired features of articular cartilage repair procedures are the ability to 1) be implanted easily, 2) reduce surgical morbidity, 3) not require harvesting of other tissues, 4) enhance cell proliferation and maturation, 5) maintain the phenotype, and 6) integrate with the
surrounding articular tissue. In addition to the potential to improve the formation and distribution of hyaline cartilage, use of a scaffold with MACI eliminates the need for harvesting and suture of a periosteal patch. A scaffold without cells may also support chondrocyte growth.

**Regulatory Status**

The culturing of chondrocytes is considered by the FDA to fall into the category of manipulated autologous structural cells (MAS), which are subject to a biologic licensing requirement. At the present time, only Carticel™ (Genzyme) has received FDA approval for the culturing of chondrocytes through a biologics license. In 1997, Carticel received FDA approval for the repair of clinically significant, “…symptomatic cartilaginous defects of the femoral condyle (medial, lateral or trochlear) caused by acute or repetitive trauma…. “ The labeled indication was revised in October 1999 to read as follows:

“Carticel is indicated for the repair of symptomatic cartilaginous defects of the femoral condyle (medial, lateral, or trochlear), caused by acute or repetitive trauma, in patients who have had an inadequate response to a prior arthroscopic or other surgical repair procedure.” Thus the revised labeling suggests a more restricted use of autologous chondrocytes, i.e., as a second-line therapy after failure of initial arthroscopic or surgical repair.

“Carticel is not indicated for the treatment of cartilage damage associated with osteoarthritis. Carticel should only be used in conjunction with debridement, placement of a periosteal flap and rehabilitation. The independent contributions of the autologous cultured chondrocytes and other components of the therapy to outcome are unknown. Data regarding functional outcomes beyond 3 years of autologous cultured chondrocyte treatment are limited.”

A number of second generation methods for implanting cultured autologous chondrocytes in a biodegradable matrix are currently in development/testing. These include Chondroselect (characterized chondrocyte implantation, TiGenex, Phase III trial), BioCart II (ProChon Biotech, Phase II trial), Cartiliix (polymer hydrogel, Cartiliix), MACI® (matrix-induced ACI, Verigen, available outside of the United States), Cartipatch (solid scaffold with an agarose-alginate matrix, TBF Tissue Engineering, Phase III trial), NeoCart (ACI with a 3-dimensional chondromatrix, Histogenics, Phase II trial), Hyalograft C (ACI with a hyaluronic acid-based scaffold, Fidia Advanced Polymers), and CAIS (Cartilage Autograft Implantation System, which harvests cartilage and disperses chondrocytes on a scaffold in a single stage treatment, Johnson and Johnson). Although clinical use of these second-generation ACI products has been reported in Europe, none are approved for use in the United States at this time.

**Policy**

Benefits are subject to all terms, limitations and conditions of the subscriber contract.

Prior approval is required for all lines of business.

New England Health Plan members need an approved referral authorization for all inpatient hospital services and all outpatient surgery.

Federal Employee Program (FEP) members may have different benefits that apply. For further information please contact FEP customer service.

**When service or procedure is covered**

Autologous chondrocyte implantation may be considered medically necessary for the treatment of disabling full-thickness articular cartilage defects (grade III or IV) of the weight
bearing surface of the knee (medial or lateral femoral condyles or trochlear region) caused by acute or repetitive trauma, in patients who have had an inadequate response to a prior surgical procedure, when all of the following criteria are met:

- Adolescent patients should be skeletally mature with documented closure of growth plates (e.g., 15 years or older). 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);
- Focal, full-thickness (grade III or IV) unipolar lesions on the weight bearing surface of the femoral condyles or trochlea at least 1.5 cm² in size;
- Documented minimal to absent degenerative changes in the surrounding articular cartilage (Outerbridge Grade II or less), and normal-appearing hyaline cartilage surrounding the border of the defect;
- Normal knee biomechanics, or alignment and stability achieved concurrently with autologous chondrocyte implantation Absence of meniscal pathology
- BMI of 30.

When service or procedure may not be covered

When the criteria above are not met.

Autologous chondrocyte implantation for all other joints, including patellar and talar, and any indications other than those listed above is considered investigational.

Matrix-induced autologous chondrocyte implantation is considered investigational.

Policy Guidelines

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

The average defect size reported in the literature is about 5 cm²; many studies treated lesions as large as 15 cm².

Severe obesity, e.g., body mass index (BMI) greater than 35 kg/m², may affect outcomes due to the increased stress on weight bearing surfaces of the joint.

Misalignment and instability of the joint are contraindications. Therefore additional procedures, such as repair of ligaments or tendons or creation of an osteotomy for realignment of the joint, may be performed at the same time. The charges for the culturing component of the procedure are submitted as part of the hospital bill.

The entire autologous chondrocyte implantation (ACI) procedure consists of four steps: 1) the initial arthroscopy and biopsy of normal cartilage, 2) culturing of chondrocytes, 3) a separate arthrotomy to create a periosteal flap and implant the chondrocytes, and 4) post-surgical rehabilitation. The initial arthroscopy may be scheduled as a diagnostic procedure; as part of this procedure, a cartilage defect may be identified, prompting biopsy of normal cartilage in anticipation of a possible chondrocyte transplant. The biopsied material is then sent for culturing and returned to the hospital when the implantation procedure (i.e., arthrotomy) is scheduled.

There is a specific CPT category I code for ACI of the knee:

27412: Autologous chondrocyte implantation, knee

Arthroscopic harvesting of chondrocytes from the knee is reported using CPT code 29870. There is a HCPCS code for the autologous cultured chondrocyte implant - J7330.
Information required

The request must be accompanied by supporting documentation of medical necessity, which includes; member’s name and age, symptoms and duration, previous conservative treatments and outcomes, results of prior arthroscopic or surgical repairs including photographs of the defect (may be obtained at time of chondrocyte harvesting), grade level of the defect, size of the cartilage defect, patient’s ability to comply with post-surgical rehabilitation.

Rationale

This policy was based on a 2003 TEC Assessment of autologous chondrocyte implantation (ACI), which updates earlier 1996, 1997, and 2000 TEC Assessments on the same subject. (1-4) The 2003 TEC Assessment separately evaluated the data regarding ACI when performed as either a first-line or second-line therapy in various subgroups of patients. (4)

The published clinical data on autologous chondrocyte transplantation of the knee were largely derived from two patient cohorts: the Swedish series and the Cartilage Repair Registry. Abstract reports of several studies comparing ACI with an alternative treatment were also available. The body of evidence had improved in several regards since the policy was originally created: more of the original data had been published; the reported data contained more complete follow-up; outcome results were available at longer follow-up; and although results were not yet published outside of abstract reports, some comparative studies were being conducted. Nevertheless, the primary deficiency in the available evidence remained unchanged in that there were no published controlled studies that compared the outcomes of ACI with the outcomes of other treatments or even with the natural progression of the disease. The 2003 TEC Assessment concluded that evidence was insufficient to permit conclusions concerning the health outcomes associated with ACI.

Subsequent literature searches, conducted between 2003 and September 2009, identified the following published studies:

Results from the Study of the Treatment of Articular Repair (STAR) trial have been published; these were previously available in the Carticel package insert and from a meeting presentation in July 2007. (5-7) STAR was a prospective, open-label 4-year study in 154 patients (mean age: 35 years; 69% male) from 29 clinical centers. Each patient served as his or her own control, undergoing ACI after having failed or experienced an inadequate response to a prior cartilage repair procedure (for example, 78% underwent debridement, 29% microfracture, 12% subchondral drilling) on a distal femur index lesion (109 medial femoral condyle, 32 lateral femoral condyle, 46 trochlea). The median lesion size was 4.6 cm² (range of 1-30 cm²), with 26% involving osteochondritis dissecans. Fifty patients (32%) had multiple lesions in the reference knee and 29 (19%) received multiple cellular implants. Prior treatment inadequacy was defined as both patient and surgeon agreement that the patient’s symptoms or function required surgical retreatment of the defect and a patient’s rating of overall condition of the knee was a score of 5 or less, using the Modified Cincinnati Knee Rating System (MCKRS). In this group, the median time to meet the failure criteria was 3.4 months for the prior index procedure, with more than 90% of patients having failed within 10.3 months. Patients who met these criteria were treated with ACI and assessed every 6 months for up to 4 years.

The primary outcome, treatment failure for ACI, was defined as any of the following: 1) a patient underwent surgical retreatment that violated the subchondral bone or repeated ACI for the same index defect; 2) complete delamination or removal of the graft; or 3) a patient’s rating of the overall condition of the knee was a score of 5 or less, using the Modified Cincinnati Knee Rating System (MCKRS). In this group, the median time to meet the failure criteria was 3.4 months for the prior index procedure, with more than 90% of patients having failed within 10.3 months. Patients who met these criteria were treated with ACI and assessed every 6 months for up to 4 years.

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The mean overall MCKRS for the entire patient population at baseline was 3.3 (n=154), and 126 (82%) completed 4-year follow-up. Thirty-seven patients (24%) were considered failures; 11 failed based on the surgical failure criterion and 26 failed based on the MCKRS criterion. Most of the 37 failures (92%) occurred within 30 months. At 48 months, three fourths of all patients in the study (76%) showed good to excellent results with a
mean MCKRS score of 6.3 (n=115). Secondary outcome measures also showed improvement, including pain, symptoms, sports and recreation, knee-related quality of life, and activities of daily living. There was no relationship between the size of the lesion at baseline and treatment outcomes with ACI.

Over half of the population (54%) experienced at least one serious adverse event secondary to ACI, and 40% of patients underwent subsequent surgical procedures on the index knee related to ACI. Adverse events included arthrofibrosis (16%), graft overgrowth (15%), chondromalacia or chondrosis (12%), graft complications (i.e., fraying or fibrillation, 10%), graft delamination (6%), and joint adhesion (5%). Subsequent surgical procedures (regardless of relationship to ACI) included debridement of cartilage lesion (31%), lysis of adhesions (14%), other debridement (10%), meniscectomy (6%), loose body removal (5%), microfracture of the index lesion (5%), and scar tissue removal (5%). The most common cause for a subsequent surgical procedure was periosteal patch hypertrophy. A majority (61%) of patients who had a subsequent surgical procedure went on to have successful results, while 39% were eventually considered treatment failures. The results of the STAR trial suggest that ACI may improve knee symptoms and function in some patients with severe, debilitating, previously treated cartilage lesions of the distal femur for at least 4 years after the procedure. Additional surgical procedures may be expected.

**Systematic Reviews**

Three systematic reviews on ACI for chondral defects of the knee were identified. (8-10) The reviews concur that existing randomized clinical trials show some promising results for ACI in the treatment of focal cartilage lesions, but additional study of this technique is warranted to establish its place among cartilage restoration approaches. A 2008 systematic review by Magnussen et al assessed whether “advanced” cartilage repair techniques (osteochondral transplantation or autologous chondrocyte transplantation) showed superior outcomes in comparison with traditional abrasive techniques for the treatment of isolated articular cartilage defects. (10) Finding a total of 5 randomized controlled trials and 1 prospective comparative trial that met their selection criteria, Magnussen and colleagues concluded that no one technique had been shown to produce superior clinical results for treatment of articular cartilage defects with the available follow-up. They stated that, “any differences in outcome based on the formation of articular rather than fibrocartilage in the defect may be quite subtle and only reveal themselves after many years of follow-up.” Efficacy of the microfracture technique alone was examined in a 2009 systematic review. (11) Twenty-eight studies describing 3,122 patients were included in the review; 6 of the studies were randomized controlled trials. Microfracture was found to improve knee function in all studies during the first 24 months after the procedure, but the reports on durability were conflicting.

**ACI versus Marrow Stimulating Techniques**

In a randomized controlled trial (RCT) of 80 patients randomized to either ACI or microfracture of the knee (an arthroscopic marrow stimulation procedure), Knutsen and colleagues reported no significant differences in the treatment groups at 2-year follow-up in macroscopic and histologic findings. (12) The Lysholm and pain scores were also not significantly different at 1 and 2 years. The physical component score of the SF-36 was worse in the ACI group, which the authors suggest may be related to the greater surgical involvement. Five-year follow-up on all 80 patients revealed 9 failures (23%) for both groups. (13) There was a trend (p=0.10) for earlier failure in the ACI group (26 vs. 38 months) with no difference in subjective measures of pain or function between the ACI and microfracture groups. Thus, the more invasive ACI open surgical procedure was not associated with any added clinical benefit.

Saris et al published a multicenter randomized trial of characterized chondrocyte implantation (n=57) versus microfracture (n=61); the average lesion size was 2.8 cm². (14) Chondrocytes were isolated from a cartilage biopsy specimen and expanded ex vivo (ChondroCelect, TiGenix, Belgium). ChondroCelect is not approved for use in the United States. Each batch of chondrocytes was graded based on the quantitative gene expression of a selection of positive
and negative markers for hyaline cartilage formation. Chondrocytes that were predicted to form stable hyaline cartilage in vivo were implanted by arthrotomy approximately 27 days after chondrocyte harvest. Surgical and rehabilitation procedures were standardized, and evaluation of a biopsy specimen at 12 months was conducted by an independent evaluator. Histological analysis showed better results with ACI for some measures of structural repair such as cartilage surface area, safranin O and collagen II ratio, and cell morphology. However, measures of integration (e.g., subchondral bone abnormalities, basal integration, vascularization) and surface architecture were not improved relative to the microfracture group. Self-assessed pain and function with the KOOS questionnaire were similar following ACI or microfracture at 12 or 18 months’ follow-up. Joint swelling and joint crepititation were greater in the ACI group, particularly following the arthrotomy. Thus, although histological results were somewhat improved, in this study characterized chondrocyte implantation did not improve health outcomes in comparison with microfracture at short-term follow-up.

In Visna et al, 50 patients with full-thickness, moderate to large chondral defects of 2.0–10.0 cm² of the femoral condyle, trochlea, or patella (43 cases due to injury) were randomized to either Johnson abrasion techniques or ACI of the knee using a preparation of autologous chondrocytes using a fibrin tissue glue rather than a periosteal patch to seal the implanted chondrocytes. (15) The study reported improvements after 12 months in the Lysholm, International Knee Documentation Committee, and Tegner activity scores that were significantly better among the 25 ACI patients compared with the 25 patients in the abrasion group. Additional procedures (28 in the ACI group and 20 in the abrasion group) included anterior cruciate ligament replacement, meniscectomy, and lateral release.

**ACI versus Osteochondral Autografts**

Horas and colleagues reported 2-year follow-up on a study of 40 patients (between 18 and 42 years of age) with an articular lesion of the femoral condyle (range of 3.2 to 5.6 cm²) who were randomly assigned to undergo either autologous chondrocyte transplant or osteochondral autografting. (16) Eleven (28%) had received prior surgical treatment. The authors reported that both treatments resulted in an improvement in symptoms (85% of each group), although those in the osteochondral autografting group responded more quickly. Histomorphological evaluation of 5 biopsy specimens at 2 years or less after transplantation indicated that the osteochondral cylinders had retained their hyaline character, although the investigators noted a persistent interface between the transplant and the surrounding original cartilage. Evaluation of autologous chondrocyte implants indicated a rigid, elastic tissue, with partial roughening and the presence of fibrocartilage.

Bentley and colleagues randomized 100 consecutive patients with symptomatic lesions of the knee (average 4.7 cm², range of 1 to 12 cm²) to ACI or mosaicplasty. (17) Seventy-four percent of lesions were on the femoral condyle, and 25% of lesions were on the patella. Ninety-four patients had undergone previous surgical interventions, and the average duration of symptoms before surgery was 7 years. Clinical assessment at 1 year showed excellent or good results in 98% of the ACI patients and in 69% of the mosaicplasty patients. The mosaicplasty plugs showed incomplete healing of the spaces between the grafts, fibrillation of the repair tissue, and disintegration of the grafts in some patients. This finding may be related to the unusual prominent placement of the plugs in this study, which was intended to allow contact with the opposite articular surface. Arthroscopy at 1 year showed filling of the defects following ACI, but soft tissue was observed in 50% of patients. Biopsy specimens taken from 19 ACI patients revealed a mixture of hyaline and fibrocartilage.

Dozin et al reported results from a multicenter randomized clinical trial in which ACI was compared to osteochondral autografting. (18) Forty-four individuals (61% male, 39% female) aged 16-40 years (mean 28.7 ± 7.8), who had a focal, symptomatic chondral injury of Outerbridge grade III or IV with no previous surgical treatment, were randomly assigned to ACI or mosaicplasty 6 months after undergoing arthroscopic debridement. The average lesion size was 1.9 cm. Only 12 of 22 (54%) in the ACI group and 11 of 22 (50%) of the mosaicplasty group actually underwent the assigned procedure. Dropouts comprised 14 patients (32%) who
reported spontaneous improvement following arthroscopy and did not undergo subsequent surgery, 5 who did not show up at the presurgery examination and could not be further traced, and 2 who refused surgery for personal reasons. Because of the substantial dropout rate, the original primary outcome measure, the mean Lysholm Knee Scoring Scale (LKSS) assessed 12 months post-surgery was converted into a scale in which improvement was categorized by proportions of responders (LKSS < 60, LKSS 60–90, LKSS 90-100). With this scale, and including 10 patients who were cured by debridement (intention-to-treat analysis) the percentages of patients who achieved complete success were 89% (16 of 18 evaluable cases) in the mosaicplasty arm versus 68% (13 of 19 evaluable cases) in the ACI arm (test for trend p = 0.093). The high rate of spontaneous improvement after simple debridement raises questions about the appropriateness of additional surgical intervention in patients similar to those included in this trial. These results are not sufficient to permit conclusions regarding the effect of ACI on health outcomes in comparison with mosaicplasty or to demonstrate an independent effect of the use of ACI versus debridement and exercise rehabilitation.

Other Randomized Trials

Gooding and colleagues randomized 68 patients with osteochondral defects (mean 4.5 cm², range 1–12 cm²) of the femoral condyle (54%), trochlea (6%), or patella (40%) to ACI with either a periosteal or collagen cover. (19) At 2 years, 74% of the patients with the collagen cover had good to excellent results compared with 67% of the patients with the periosteal cover. Hypertrophy required shaving in 36% of patients treated with the periosteal cover. None of the collagen covers required shaving.

Observational Studies

Browne et al published 5-year outcomes from 87 of the first 100 patients (40 centers, 87% follow-up) treated with ACI for lesions on the distal femur from the FDA-regulated Carticel safety registry maintained by Genzyme Biosurgery. (20) Patients were an average of 37 years old, with a mean lesion size of 4.9 cm² (range of 0.8 to 23.5 cm²). Seventy percent of the patients had failed at least one previous cartilage procedure, and the average self-rated overall condition was 3.2 (poor to fair). At 5 years following the index procedure, the average follow-up score was 5.8 (fair to good), a 2.6-point improvement on the 10-point scale. Sixty-two patients (71%) reported improvement, 25 (29%) reported no change or worsening. Thirty-seven patients (42%) had 51 operations after ACI. The most common findings were adhesions (n=6), hypertrophic changes of the graft (n=5), loose bodies (n=4), loose or delaminated periosteal patch (n=4), and meniscal tears (n=4). Factors associated with failure in 6 patients were non-compliance with the postoperative protocol, additional injury, and uncorrected malalignment. Defect size was not found to be significantly associated with outcome; self-reported outcomes were associated with workers’ compensation claims.

Rosenberger et al reported average 4.7 years’ follow-up (range 2–11 years) on a cohort of 56 patients (45 to 60 years of age) with lesions of the femoral condyle (49%), trochlea (29%), or patella (22%). (21) Results were generally similar to those observed in younger patients, with 72% rating themselves as good or excellent but 43% requiring additional arthroscopic procedures for periosteal-related problems and adhesion. A European group reported complications in 309 consecutive patients, 52 of whom (17%) had undergone revision surgery for persistent clinical problems. (22) Three different ACI techniques had been used, periosteum-covered, membrane-covered (Chondrogide Geistlich Biomaterials, Switzerland), and 3-dimensional matrix (BioSeed-C, Biotissue Technologies, Germany). Follow-up at a mean of 4.5 years showed that the highest rate of revision surgery was in patients with periosteum-covered ACI (27%) in comparison with membrane-covered or matrix-induced ACI (12% and 15%, respectively). There was a trend (p = 0.09) for a higher incidence of hypertrophy with patellar defects in comparison with the femoral condyles or trochlea.

ACI for patellar cartilage defects is typically reported as less effective than ACI for lesions of the femoral condyles, and some studies have reported biomechanical alignment procedures and unloading to improve outcomes for retropatellar ACI. (23, 24) A 2008 study from Europe
described clinical results from 70 of 95 patients (74%) treated with ACI or matrix-induced ACI (MACI) for full-thickness defects of the patella. (25) The average defect was 4.4 cm². Depending on surgeon preference, patients received ACI with a periosteal patch, Chondroglide membrane, or MACI. Fourteen patients (15%) were lost to follow-up and 11 patients (12%) were excluded from the follow-up study due to dysplasia of the femoropatellar joint and significant (more than 5 degrees) varus or valgus deformity. In addition to patient responses for the Cincinnati Sports Activity scale, Lysholm score, and International Knee Documentation Committee (IKDC) score, a physical examination was performed by an independent examiner who was blinded to data obtained at the time of surgery, including defect size and location. Objective evaluation at an average follow-up of 38 months showed normal or nearly normal results in 47 patients (67%). Results were classified as abnormal in 14 patients (20%), and 9 patients (13%) were considered failures. Results were not divided according to the type of implant (ACI or MACI), although it was reported that 2 patients with hypertrophy of the implant were from the group treated with periosteal patch covered ACI. In addition, these results are limited by the retrospective design and loss to follow-up, and would be applicable only to those patients without varus or valgus deformity. Other studies from Europe report patellofemoral cartilage defects treated with second generation MACI implants (26, 27) These products are not approved in the United States and are therefore considered investigational.

Combined meniscus transplantation and articular cartilage repair has been reported. Farr et al described outcomes from a prospective series of 36 patients who underwent ACI together with meniscal transplantation in the same compartment. (28) Lesions ranged from 1.5 to 12.1 cm². Patients identified with advanced chondrosis during staging arthroscopy were excluded from the study. Four patients received treatment for bipolar lesions, while 16 of the procedures were done concomitant with another procedure such as osteotomy, patellar realignment, or anterior cruciate ligament (ACL) reconstruction. Four patients (11%) were considered failures before 2 years, and 3 were lost to follow-up (8%), resulting in 29 evaluable patients at an average of 4.5 years after surgery. The Lysholm score improved from an average score of 58 to 78; maximum pain decreased an average 33% (from 7.6 to 5.1). Excluding the 4 failures, 68% of their patients required additional surgeries; 52% had one additional surgery, and 16% required two or more additional surgeries. The most common procedures were trimming of periosteal overgrowth or degenerative rims of the transplanted meniscus. Another report described average 3.1 years of follow-up from a prospective series of 30 patients (31 procedures) who had undergone combined meniscal allograft transplantation with ACI (52%) or osteochondral allograft transplantation (OA; 48%). (29) The Lysholm score improved in both the ACI (from 55 to 79) and OA (from 42 to 68) groups; 48% of patients (60% ACI and 36% OA) were considered to be normal or nearly normal at the latest follow-up. Patients treated with OA were on average older (average 37 vs. 23 years) and with larger lesions (5.5 cm² vs. 3.9 cm²). Two patients were considered failures (7%) and 5 (17%) underwent subsequent surgery. Although results seem promising, evidence is currently insufficient to permit conclusions regarding the effect of combined transplantation-implantation procedures on health outcomes.

A threefold increased failure of ACI after previous treatment with marrow stimulation techniques was found in a cohort of 321 patients with more than 2 years of follow-up (of 332 treated). (30) The average lesion was 8 cm², and the indications for treatment of cartilage defects with ACI included one or more full-thickness chondral defects of the knee with consistent history, physical examination, imaging, and arthroscopy; no or correctable ligamentous instability, malalignment, or meniscal deficiency; and not more than 50% loss of joint space on weight-bearing radiographs. Independent analysis showed a failure rate of 8% of joints (17 of 214) that did not have prior marrow stimulation of the lesion, compared with 26% (29 of 11 joints) that had previously been treated with marrow stimulation.

Joints Other Than the Knee

There has been interest in applying ACI to cartilage defects in other joints. For example, 1 case series of 8 patients studied the use of ACI for osteochondritis dissecans of the talus. (31) Outcome measures included arthroscopic and radiologic evidence of cartilage-like tissue with
coverage of the osteochondral defects 6 months after treatment. Another case series of 8 patients with osteochondritis due to trauma were treated with ACI and an ankle fixation device for 1 year. (32) Outcomes were improved American Foot and Ankle Society scores in 1 study with an average score of 32 of 100 points preoperatively, which improved to an average of 91 of 100 points at 24 months' follow-up. Clinical scores for all patients improved on a Finsen scale from “bad” preoperatively (score 3 or 4) to “excellent” (score of 0) or “good” (scores of 1–2) at postoperative follow-up. Histologic appearance of reconstructed cartilage with chondrocytes and expression of collagen II, characteristic of hyaline cartilage, was noted in those cases that underwent follow-up arthroscopy and biopsy.

In 2009, Nam and colleagues published a report that they described as the first U.S. prospective study of ACI of the talus. (33) The 11 patients described had failed non-surgical and prior surgical management, with a mean of 1.9 prior surgical procedures including debridement, drilling, pinning, or abrasion arthroplasty. Osteotomy was performed to access the mean 2.7-cm² talar lesions. Six of the patients also underwent cyst excavation and bone grafting for extensive subchondral cystic involvement, and the chondrocytes were injected between a sandwich of two periosteal grafts. Following treatment of the cartilage lesion with ACI, the osteotomy was reattached with screws. Rehabilitation consisted of physician-monitored gradual advancement in weight-bearing over 6 weeks, as indicated by radiographic healing of the osteotomy. This was followed by three phases of formal physical therapy, termed transitional, remodeling, and maturation phases. Ten of the patients underwent second-look arthroscopy and hardware removal at a mean of 14 months (range, 9–24 months) and 9 underwent magnetic resonance imaging (MRI) evaluation at a mean of 31 months (range, 16–48 months). At a mean 38-month clinical evaluation (range, 24–60 months), 3 patients were classified as excellent (no pain, swelling, or locking with strenuous activity), 6 were classified as good, 2 as fair, with none classified as poor. Ten of the 11 patients (91%) were considered to be improved by the procedure. Significant improvements were obtained with the Tegner activity scale (from 1.3 to 4.0), Finsen score, and the American Orthopaedic Foot and Ankle Society (AOFAS) ankle hindfoot score (from 47 to 84). Second-look arthroscopy showed smooth repair tissue with a line of demarcation between normal cartilage and the graft, with overgrowth of repair tissue requiring debridement in 2 patients (20%). The repair tissue was softer to probing than the adjacent cartilage, although an increase in firmness was noted from the 9- to 24-month observations. Use of MACI for osteochondral lesions of the talus has also been reported from overseas. (34)

**Clinical Input Received through Physician Specialty Societies and Academic Medical Centers**

In response to requests, input was received from 1 physician specialty society and 3 academic medical centers while this policy was under review in 2008. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. One reviewer considered ACI to be investigational. Three reviewers agreed that ACI should be considered when all other treatments have been unsuccessfully tried in individuals who have a localized chondral defect in an otherwise normal joint articular surface. Reviewers noted the lack of alternative options for larger lesions (e.g., >4 cm²). Additional literature was provided, which was subsequently reviewed.

**Summary**

Although long-term studies are lacking, evidence indicates that ACI can improve symptoms in some patients with lesions of the articular cartilage of the knee who have failed prior surgical treatment. These patients, who are too young for total knee replacement, have limited options. Therefore, based on the clinical input, highly suggestive evidence from randomized controlled trials and prospective observational studies, it is concluded that ACI may be considered an
option for disabling full-thickness chondral lesions of the knee caused by acute or repetitive trauma, in patients who have had an inadequate response to a prior procedure. Additional studies are needed to evaluate whether marrow stimulation at the time of biopsy affects implant success. Evidence is currently insufficient to evaluate the efficacy of ACI in comparison with other surgical repair procedures as a primary treatment of large lesions, or to evaluate the efficacy of ACI for joints other than the knee.

Results from second generation ACI procedures (MACI) from Europe appear promising. These products use a variety of biodegradable scaffolds and have the potential to improve consistent hyaline cartilage formation and reduce complications associated with injection under a periosteal patch. To date no MACI products are approved in the United States; therefore, these are considered investigational.

Technology Assessments, Guidelines and Position Statements

In 2005, the National Institute for Health and Clinical Excellence (NICE) issued an updated Technology Appraisal Guidance on the use of autologous chondrocyte implantation. (35) The NICE guidance cited insufficient evidence to determine the benefits of autologous chondrocyte implantation and indicated this technology “should not be used for the treatment of articular cartilage defects except where the treatment is part of a clinical study.” The guidance noted many limitations in available trial data including length of follow-up, comparison to conservative treatment, assessment of the quality of cartilage produced, and the impact of cartilage produced on functional outcomes and health-related quality of life.

Scientific Background and Reference Resources


**Eligible Providers**

Orthopedic Surgeons

**Billing/Coding Information**

See Attachment I

**Policy Implementation/Update information**


04/2010 Updated to mirror BCBSA Medical Policy with slightly less restrictive criteria. Reviewed by CAC 05/2010.

Minor updates 05/2011

**Approved by BCBSVT and TVHP Medical Directors**

Antonietta Sculimbren,eMD

Chair, Medical Policy Committee

**ATTACHMENT I**
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<th>Codes</th>
<th>Number</th>
<th>Description</th>
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<td>CPT</td>
<td>27412</td>
<td>Autologous chondrocyte implantation, knee</td>
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<td>27416</td>
<td>Osteochondral autograft(s) knee, open (eg, mosaicplasty includes harvesting of autograft)</td>
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<td>ICD-9 Procedure</td>
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<td>Arthroscopy of the knee</td>
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<td>80.16</td>
<td>Arthrotomy of the knee</td>
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<td>Osteoarthrosis, localized, secondary, lower leg</td>
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<td>S2112</td>
<td>Arthroscopy, knee, surgical, for harvesting of cartilage (chondrocyte cells)</td>
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