Name of Policy:
Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions

Policy #: 156
Category: Surgery

Latest Review Date: June 2014
Policy Grade: A

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
Description of Procedure or Service:
Traumatic articular cartilage injuries in the knee are common 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 the quality of life. Articular cartilage has no direct blood supply and a slow regeneration rate. There are many techniques to facilitate articular cartilage healing. Some conventional treatments include debridement or simple removal of cartilage and meniscal fragments. Arthroscopic washing out of loose fragments and joint fluid may also provide short-term relief. Other treatments are intended to restore the articular surface by penetrating the subchondral bone and stimulate the local cells. These include subchondral drilling, microfracture, or abrasion arthroplasty. These produce a response that synthesizes fibrocartilage, which is not as effective in maintaining joint function as hyaline cartilage. It has weaker mechanical properties, cannot distribute forces as well, and is prone to breakdown over time. This often results in the return of clinical symptoms.

Alternatively, treatments of very extensive and severe cartilage defects may be the complete replacement of the articular surface either by osteochondral grafts or artificial knee replacement. Osteochondral grafts for the treatment of articular cartilage defects are discussed in Medical Policy #248, Autografts and Allografts in the Treatment of Focal Articular Cartilage Lesions.

Autologous chondrocyte implantation (ACI) has been proposed as a surgical treatment for patients who have significant, symptomatic focal defects of the articular cartilage of the knee caused by acute or repetitive trauma. ACI attempts to regenerate hyaline-like cartilage and thereby restore function to the joint. It is a four-step process. The patient undergoes arthroscopy where normal articular cartilage is identified and biopsied. This tissue is minced and enzymatically digested. Chondrocytes are separated by filtration, and the isolated chondrocytes are cultivated in culture medium for 11 to 21 days. The chondrocytes are then ready for implantation. An arthrotomy of the knee is performed under general anesthesia, and the chondral lesion is excised up to the normal surrounding cartilage. A periosteal flap is removed from the proximal medial tibia and is sutured to the surrounding rim of normal tissue. The cultured chondrocytes are then injected beneath the periosteal flap. At the time of arthrotomy, additional procedures may be done, such as repair of ligaments or tendons or creation of an osteotomy for realignment of the joint. Finally, patients must undergo post surgical rehabilitation.

Carticel® (autologous cultured chondrocytes), by Genzyme Biosurgery, uses a commercial process to culture a patient’s own (autologous) cartilage cells, aka chondrocytes, for use in the repair of symptomatic cartilage defects of the femoral condyle. The FDA considers the culturing of chondrocytes to fall into the category of manipulated autologous structural (MAS) cells, which are subject to the biologics licensing requirement. This product, Carticel, was granted an “accelerated approval” under biological product regulations. In 1997, Carticel received FDA approval for first line use “for repair of significant, symptomatic cartilaginous defects of the femoral condyle (medial, lateral, or trochlear) caused by acute or repetitive trauma”. In October 1999, the FDA revised the labeled indication 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.

Additionally, “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 three 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 or are available only outside of the U.S. These include ChondroCelect (characterized chondrocyte implantation, TiGenex, Phase III trial completed), BioCart II (ProChon Biotech, Phase II trial), Bioseed C (polymer scaffold, BioTissue Technologies), CaReS (collagen gel, Ars Arthro), Cartilix (polymer hydrogel, Cartilix), MACI® (matrix-induced ACI, Verigen and Genzyme, available outside of the U.S.), Cartipatch (solid scaffold with an agarose-alginate matrix, TBF Tissue Engineering, Phase III trial), Chondron (fibrin gel, Sewon Cellontech), NeoCart (ACI with a 3-dimensional chondromatrix, Histogenics, Phase III trial), Hyalograft C (ACI with a hyaluronic acid-based scaffold, Fidia Advanced Polymers) and Novocart®3D (collagen-chondroitin sulfate scaffold, Aesculap Biologics, Phase III trial). ChondroCelect (characterized chondrocyte implantation, TiGenex, Phase III trial completed) uses a gene marker profile to determine in vivo cartilage-forming potential and thereby optimize the phenotype (e.g., hyaline cartilage vs. fibrocartilage) of the tissue produced with each ACI implantation cell batch. Each batch of chondrocytes is graded based on the quantitative gene expression of a selection of positive and negative markers for hyaline cartilage formation. Although clinical use of these second generation ACI products has been reported in Europe and Asia, none are approved for use in the U.S. at this time.

Policy:
Effective for dates of service on or after June 13, 2013:
Autologous chondrocyte implantation meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for the treatment of disabling full-thickness articular cartilage defects of the knee 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); AND
- 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; AND
- Documented minimal to absent degenerative changes in the surrounding articular cartilage (Outerbridge grade II or less), and normal-appearing hyaline cartilage surrounding the border of the defect; AND
- Normal knee biomechanics or alignment and stability achieved concurrently with autologous chondrocyte implantation.
**Autologous chondrocyte implantation does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for all other joints, including patellar and talar, and any indications other than those listed above is therefore considered investigational.

**Matrix-induced autologous chondrocyte implantation does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is therefore considered investigational.

This procedure may be performed at the same time as other surgical procedures such as repair of tendons or ligaments, osteotomies for realignment of a joint, or meniscal allograft transplantation.

**Prophylactic harvesting of cells** during other reconstructive or reparative procedures for possible future implantation **does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage.

**Effective for dates of service from August 23, 2011 to June 13, 2013:**

**Autologous chondrocyte implantation meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for the treatment of disabling full-thickness articular cartilage defects of the knee 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); **AND**

- 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; **AND**

- Documented minimal to absent degenerative changes in the surrounding articular cartilage (Outerbridge grade II or less), and normal-appearing hyaline cartilage surrounding the border of the defect; **AND**

- Normal knee biomechanics or alignment and stability achieved concurrently with autologous chondrocyte implantation.

**Autologous chondrocyte implantation does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage for all other joints, including patellar and talar, and any indications other than those listed above is therefore considered **investigational**.

**Matrix-induced autologous chondrocyte implantation does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is therefore considered **investigational**.

**Treatment of focal articular cartilage lesions with autologous minced cartilage does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is therefore considered **investigational**.
Treatment of focal articular cartilage lesions with allogeneic minced cartilage or cartilage cells does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is therefore considered investigational.

This procedure may be performed at the same time as other surgical procedures such as repair of tendons or ligaments, osteotomies for realignment of a joint, or meniscal allograft transplantation.

Prophylactic harvesting of cells during other reconstructive or reparative procedures for possible future implantation does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administer benefits based on the member’s contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:
This policy is based on a 2003 TEC Assessment of autologous chondrocyte transplantation (ACT), which updates earlier 1996, 1997 and 2000 TEC Assessments on the same subject. The 2003 TEC Assessment separately evaluated data regarding ACI when performed as either a first line or second-line therapy in various subgroups of patients. At the time of this TEC Assessment, only one ACI product (Carticel™) had been evaluated in the published literature.

Subsequent literature searches, conducted between 2003 and May, 2014, identified the following published studies. Some of these subsequent studies used Carticel™, while others have evaluated newer, second-generation ACI products. The evidence for the second generation products is discussed separately from the evidence on Carticel™.

First Generation ACI (Carticel™) for Treatment of the Knee
First Generation ACI (Carticel™) for Treatment of the Knee: Systematic Reviews
A 2010 systematic review by Harris et al included 13 randomized and nonrandomized controlled trials of 917 subjects who underwent ACI (n=604), microfracture (n=271), or osteochondral autograft (OA) (n=42). The mean study quality was rated as 54 of 100, with no studies considered of good or excellent quality, seven considered fair, and six considered poor. Four studies compared different generations of ACI, finding no difference in outcomes but higher complication rates with open, periosteal cover, first-generation ACI. At one- to five-year follow-up, three of seven studies showed better clinical outcomes after ACI in comparison with microfracture, one study showed better outcomes after microfracture, and three studies showed no difference in these treatments. Clinical outcomes after microfracture were found to deteriorate after 18 to 24 months in three of seven studies. Studies comparing ACI and OA showed similar
short-term clinical outcomes, with more rapid improvement but an increase in arthrofibrosis and donor site morbidity following OA. Younger patients with a shorter preoperative duration of symptoms and fewer prior surgical procedures had the best outcomes after surgical intervention. A defect size greater than 4cm² was the only factor predictive of better outcomes when ACI was compared with other surgical techniques.

Another publication by Harris et al in 2010 was a systematic review of combined meniscal allograft transplantation and cartilage repair/restoration. Six level IV studies (case series) with a total of 110 patients were included in the review. Patients underwent meniscal allograft transplantation with either ACI (n=73), osteochondral allograft (n=20), OA (n=17), or microfracture (n=3). All studies showed improvement in clinical outcomes at final follow-up compared with the preoperative condition. Outcomes were also compared with historical outcomes of each individual procedure performed in isolation. Four of the six studies found outcomes equivalent to procedures performed in isolation, while two studies found that outcomes with combined surgery were not as good as the historical controls. Across the six studies, 13 failures (12%) were reported; these included 11 isolated meniscal allograft transplantation failures, one combined meniscal allograft and ACI failure, and one isolated ACI failure. Three knees with failed meniscal allograft transplantation were converted to total knee arthroplasty. Nearly 50% of the patients underwent one or more subsequent surgeries after combined meniscal allograft transplantation and cartilage repair/restoration procedures.

Efficacy of the microfracture technique alone was examined in a 2009 systematic review. Twenty-eight studies describing 3122 patients were included in the review; six of the studies were randomized controlled trials (RCTs). 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.

First Generation ACI (Carticel™) for Treatment of the Knee: Comparative Studies: ACI (Carticel™) versus Marrow-Stimulating Techniques

In an RCT of 80 patients randomized to either ACI or microfracture of the knee (an arthroscopic marrow-stimulation procedure), Knutsen et al reported no significant differences in the treatment groups at two-year follow-up in macroscopic and histologic findings. The Lysholm and pain scores were also not significantly different at one and two years. The physical component score of the 36-Item Short-Form Health Survey (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 nine failures (23%) for both groups. There was a trend (p=0.10) for earlier failure in the ACI group (26 vs 38 months, respectively) 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.

In Visna et al, 50 patients with full-thickness, moderate to large chondral defects of 2.0 to 10.0cm² 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. The study reported improvements after 12 months in the Lysholm, International Knee Documentation Committee (IKDC), and Tegner activity scores, which were significantly
better among the 25 ACI patients compared with the 25 patients in the abrasion group. Additional procedures (28 in the ACI group, 20 in the abrasion group) included anterior cruciate ligament (ACL) replacement, meniscectomy, and lateral release.

**First Generation ACI (Carticel™) for Treatment of the Knee: Comparative Studies: ACI (Carticel™) versus Osteochondral Autografts**

Horas et al reported two-year follow-up on a study of 40 patients (between 18 and 42 years old) with an articular lesion of the femoral condyle (range, 3.2-5.6cm²) who were randomly assigned to undergo either autologous chondrocyte transplant or osteochondral autografting. 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. Histomorphologic evaluation of five biopsy specimens at two 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 et al randomized 100 consecutive patients with symptomatic lesions of the knee (average, 4.7cm²; range, 1-12cm²) to ACI or mosaicplasty. 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 seven years. Clinical assessment at one 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 one 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. With six patients lost to follow-up at a minimum ten years after the index surgery, repair was found to have failed in 17% of patients treated with ACI and 55% of patients treated with mosaicplasty.

Dozin et al reported results from a multicenter RCT in which ACI was compared with osteochondral autografting. Forty-four subjects (61% male, 39% female) aged 16 to 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 six months after undergoing arthroscopic débridement. The average lesion size was 1.9cm. 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, five who did not show up at the presurgery examination and could not be further traced, and two 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 postsurgery 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 ten patients
who were cured by débridement (intention-to-treat analysis) the percentages of patients who achieved complete success were 89% (16/18 evaluable cases) in the mosaicplasty arm versus 68% (13/19 evaluable cases) in the ACI arm (test for trend, p=0.093). The high rate of spontaneous improvement after simple débridement 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 débridement and exercise rehabilitation.

**First Generation ACI (Carticel™) for Treatment of the Knee: Other Controlled Trials**

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. STAR was a prospective, open-label four-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 (eg, 78% underwent débridement, 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 4.6cm² (range, 1-30cm²), 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 five 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 six months for up to four years.

The primary outcome, treatment failure for ACI, was defined as any of the following: (1) 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 using the MCKRS failed to improve from the baseline knee score over three consecutive six-month time intervals. Withdrawals from the study were considered as failures at the last follow-up. The mean overall MCKRS for the entire patient population at baseline was 3.3 (n=154), and 126 (82%) completed four-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 débridement of cartilage lesion (31%), lysis of adhesions (14%), other débridement (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. Most (61%) 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 four years after the procedure. Additional surgical procedures may be expected.

Gooding et al randomized 68 patients with osteochondral defects (mean, 4.5cm²; range, 1–12 cm²) of the femoral condyle (54%), trochlea (6%), or patella (40%) to ACI with either a periosteal or collagen cover. At two 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.

In 2012, Pestka et al reported a matched-pair comparison of ACI after failed microfracture versus ACI as a first-line treatment. A total of 56 patients were retrospectively matched for gender, age, defect size, and defect location. The average defect size was 4.65cm². Follow-up was conducted by mail, with a mean follow-up time of 48.0 months for ACI as a second-line treatment and 41.4 months for ACI as a first-line treatment. The failure rate was significantly greater when ACI was used as a second-line treatment (25% vs 3.6%), and there was a trend (p=0.058) for lower IKDC scores (58.4 vs 69.0). Two Knee Injury and Osteoarthritis Outcome Score (KOOS) subscales (Pain and Activities of Daily Living) were significantly lower for second-line treatment; there was a trend for lower scores in the remaining subscales. There are several limitations to this study; one is a potential for selection bias if patients who respond poorly to microfracture also respond poorly to ACI. Time since symptom onset might also be a factor. However, the results add to a growing body of literature suggesting inferior outcomes when ACI is performed following a failed microfracture.

First Generation ACI (Carticel™) for Treatment of the Knee: Observational Studies

A variety of issues have been addressed with observational studies, including durability of the procedure, influence of age, comparison of femoral versus patellar defects, combination treatment with meniscal allograft, influence of prior marrow stimulation, and treatment of early osteoarthritis. These are discussed next.

Browne et al published five-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. The registry is a multicenter program initiated in 1995 and designed to longitudinally track changes in function and symptoms in patients treated with ACI or other cartilage repair procedures. Patients were an average of 37-years-old, with a mean lesion size of 4.9cm² (range, 0.8-23.5cm²). Seventy percent of the patients had failed at least one previous cartilage procedure. At five years following the index procedure, the average self-rated overall condition had improved from 3.2 (poor to fair) to 5.8
(fair to good), a 2.6-point improvement on the ten-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). In 2010, this group of investigators published six- to ten-year follow-up (mean, 9.2 years) on 72 patients in the cartilage repair registry. Fifty-four patients (75%) met the eligibility criteria of the study, which included ACI treatment of lesions on the distal femur and improvement at the one- to five-year follow-up period. Of these 54 patients, 47 (87%) sustained a mean improvement of 3.8 points from baseline to the later follow-up period. For the cohort of 72 patients, 69% reported improvement, 17% failed, and 12.5% reported no change from baseline to follow-up.

Minas et al prospectively followed 210 ACI-treated patients (362 grafts) for at least ten years. Malalignment, patellar maltracking and meniscal or ligamentous deficiency had also been corrected as needed. At a mean of 12 years’ follow-up, 53 patients (25%) had graft failure. Nineteen of these patients (9%) went on to arthroplasty. 27 patients (13%) were salvaged with revision cartilage repair, and seven patients declined further treatment. For the 157 patients who had successful grafts, functional outcomes were significantly improved from baseline to follow-up, as measured by the Western Ontario & McMaster Universities Index (WOMAC), Knee Society Score (KSS) for knee and function, and SF-36 (all p<0.001). Survival of the graft was significantly higher in patients with complex versus salvage-type lesions (p=0.03), with concomitant high tibial osteotomy (HTO) versus no HTO (p=0.01), and with primary ACI versus ACI after a prior marrow stimulation procedure (p=0.004). For example, ACI graft survival was 79% compared with 44% for knees with defects that had been previously treated with microfracture.

In 2010, Peterson et al reported on 224 patients who replied to questionnaires at ten- to 20-year follow-up. This represents 38% of a total of 590 patients who underwent ACI at their institution between 1987 and 1998. The average age of the patients was 33 years (range, 14-61) at the time of the ACI, and the indication for treatment was any symptomatic full-thickness cartilage lesion up to 16cm², including patients with meniscal (34% of patients) or ACL lesions (19%). Fifty-five patients (25%) had multiple lesions, 73 patients (33%) had unipolar or bipolar patellar lesions, and 26 patients (12%) had osteochondritis dissecans. Three hundred and forty-one surveys were mailed to the treated patients; the response rate was 65%. Information about baseline measurements was collected from the patients’ charts or from prior studies and when available, compared with the questionnaire responses at follow-up. At a mean of 12.8 years’ follow-up, 74% of the patients reported their status as better or the same as the previous years, and 92% were satisfied with the operation. The average Lysholm score improved from 60.3 preoperatively to 69.5 postoperatively, Tegner from 7.2 to 8.2, and the Brittberg-Peterson from 59.4 to 40.9. At the final measurement, the KOOS score averaged 74.8 for pain, 63 for symptoms, 81 for activities of daily living, 41.5 for sports, and 49.3 for quality of life. The average Noyes score was 5.4. Patients with bipolar lesions had a worse final outcome than patients with multiple unipolar lesions. The presence of meniscal injuries before ACI or history of bone marrow procedures before the implantation did not seem to affect the final outcomes.
Rosenberger et al reported average 4.7 years’ follow-up (range, 2–11 years) on a cohort of 56 patients (45 to 60 years old) with lesions of the femoral condyle (49%), trochlea (29%), or patella (22%). 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. Three different ACI techniques had been used, periosteum-covered, membrane-covered (Chondrogide Geistlich Biomaterials, Switzerland), and three-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. In 2014, Gomoll et al reported a multicenter registry study of the treatment of mono or bipolar patellar defects with ACI in 110 patients with a minimum of four years’ follow-up (mean, 90 months; range, 48-192 months). Concurrent surgical procedures included tibial tubercle osteotomy in 69% of patients, lateral release in 41%, vastus medialis advancement in 20%, and tracheoplasty in 5%. At the latest follow-up, statistically and clinically significant improvements in pain and function were obtained on the IKDC, Cincinnati Rating Scale, WOMAC and KSSs, although it was noted that results were inferior to ACI for cartilage lesions of the femoral condyles. Excluding repeat arthroscopy for graft hypertrophy or lysis of adhesions, nine patients were considered treatment failures. Pascual-Garrido et al reported outcomes from 52 patients (83% follow-up) who underwent ACI of the patellofemoral joint (patella or trochlea). In addition to ACI of the patella, 67% of patients had concomitant procedures performed, including anteromedialization (n=28), lateral release (n=4), lateral meniscal transplant (n=2), and OA (n=1). Questionnaires were administered preoperatively, six months and one year postoperatively, and then annually. At an average follow-up of four years (range, 2-7), there was significant improvement in the Lysholm, IKDC, KOOS Pain, KOOS Symptoms, KOOS Activities of Daily Living, KOOS Sport, Cincinnati, Tegner, and SF-12 Physical. Patients reported the overall condition of their knee as excellent, very good, or good in 71% of the cases. There were four failures (8%), defined as poor clinical outcome accompanied by evidence of graft failure or need for conversion to knee arthroplasty or OA. 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. Objective evaluation performed by an independent examiner who was blinded to data obtained at the time of surgery showed normal or nearly normal results in 47 patients (67%) at an average follow-up of 38 months. Other studies from Europe report patellofemoral cartilage defects treated with second-generation MACI implants. These products are not approved in the U.S. and are, therefore, considered investigational.

Farr et al described outcomes from a prospective series of 36 patients who underwent ACI together with meniscal transplantation in the same compartment. 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 ACL reconstruction. Four patients (11%) were considered failures before two years, and three 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 four 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 OA transplantation (48%). The Lysholm score improved in both the ACI (from 55 to 79) and OA (from 42 to 68) groups; 48% of patients (60% ACI, 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 (5.5cm² vs 3.9cm²). Two patients were considered failures (7%) and five (17%) and underwent subsequent surgery. Although results seemed promising, evidence is insufficient to permit conclusions regarding the effect of combined transplantation-implantation procedures on health outcomes.

A three-fold increased failure of ACI after previous treatment with marrow stimulation techniques was found in a cohort of 321 patients with more than two years of follow-up (of 332 treated). The average lesion was 8cm², 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 (17/214) that did not have prior marrow stimulation of the lesion, compared with 26% (29/111 joints) that had previously been treated with marrow stimulation. A study of 1000 patients treated with ACI or MACI found that overall graft survival was 78.2% at five years and 50.7% at ten years by Kaplan-Meier analysis, with no significant difference in survival rates between ACI and MACI procedures or for different defect sizes (range, .64-20.75cm²). Graft failure was five times more likely with a previously treated lesion (<25% survival at 12 years) compared with a previously untreated lesion (>75% survival at 12 years). Survival of grafts in the lateral femoral condyle was superior to grafts in the medial femoral condyles, trochlea, or patella.

Minas et al assessed the influence of ACI on the need for joint replacement surgery in 153 patients (155 knees) with a mean age of 38 years (range, 17-60), evidence of early osteoarthritis at the time of surgery (peripheral intra-articular osteophyte formation and/or 0% to 50% joint space narrowing), and two years or more of follow-up. (Patients with more than 50% loss of joint space were not eligible for treatment with ACI.) Patients were also included in the study if they had normal radiographs but evidence of bipolar lesions or generalized chondromalacia noted at the time of surgery. An average of 2.1 defects per knee was treated, with a mean defect size of 4.9cm² and a total mean defect area of 10.4cm². Defects were located on the femoral condyle (n=150), trochlea (n=85), patella (n=60), and tibial plateau (n=14). There were 42 (27%) bipolar lesions, most of which were patellofemoral. Concurrent procedures included correction of tibiofemoral malalignment (31% of knees) and patellar maltracking (28% of knees). At five
years’ postoperatively (range, 24-132 months), 12 knees (8%) were considered treatment failures and underwent arthroplasty due to graft failure (n=3), inadequate pain relief (n=1), and progression of osteoarthritic disease beyond the originally transplanted defect area (n=8). The remaining 92% of patients showed improvements in all scores from baseline to final follow-up. For example, there was 52% improvement in WOMAC subscales, and the proportion of patients who experienced severe or extreme pain while walking on a flat surface decreased by 73%. Subsequent surgical procedures after the index implantation were performed in 95 knees (61%), including 52 cases of periosteal hypertrophy, 32 cases of arthrofibrosis, 23 graft complications, and 11 for periosteal delamination.

**First Generation ACI (Carticel™) for Joints Other Than the Knee**

There has been interest in applying ACI to cartilage defects in other joints. The most commonly reported is use of ACI for the talus.

In 2010, Zengerink et al published a systematic review of treatment of osteochondral lesions of the talus. Fifty-one nonrandomized and one randomized trial were included in the review. Success rates were 85% for bone marrow stimulation, 87% for osteochondral autografting, and 76% for ACI. Because of the high cost of ACI and the knee morbidity seen with osteochondral autografting, the authors concluded that bone marrow stimulation is the treatment of choice for primary osteochondral talar lesions. A 2009 report examined the association between defect size and outcomes following marrow stimulation techniques in 120 ankles. Eight ankles subsequently underwent osteochondral transplantation, and 22 ankles were considered clinical failures (American Orthopaedic Foot and Ankle Society [AOFAS] Ankle-Hindfoot score <80). Linear regression suggested a cutoff defect size of 1.5cm² for marrow stimulation techniques, with an 80% failure rate compared with a 10.5% failure rate for ankles with a defect size of less than 1.5cm². Three of 58 ankles (5.2%) with a defect area of less than 1cm² showed clinical failure, while seven of 37 ankles (18.9%) with a defect area between 1.0 and 1.5cm² failed.

A systematic review by Niemeyer et al included 16 studies (213 patients) on ACI or MACI for lesions of the talus. All were case series with a mean of 13 patients (range, 2-46) and mean follow-up of 32 months (range, 6-120). Most of the studies were prospective. In six studies periosteum-covered ACI was applied while ten studies used second-generation MACI. MACI uses a matrix seeded with cultured autologous chondrocytes, and unlike first generation ACI, does not require tibial or fibular osteotomy to gain adequate surgical access. For the studies using periosteum-covered ACI, the number of subjects ranged from four to twelve. Nine different methods were used to evaluate pre- and postoperative clinical function, with the most common being the AOFAS Ankle-Hindfoot Score. Overall clinical success rate, defined as the percentage of good and excellent results, was 89.9% (range, 50% to 100%). Interpretation of these results is limited by the inclusion of poor quality studies, lack of a comparator, lack of blinding, and the use of techniques that are not approved for use by FDA.

A 2006 study from Italy randomized 32 patients with osteochondral lesions of the talus to chondroplasty, microfracture, or OA transfer (OAT). This small study found similar improvements (approximately 40 points) for the three treatment groups as measured by the AOFAS Ankle-Hindfoot Score (baseline score of 31 to 37) and the Subjective Assessment Numeric Evaluation (baseline score of 35-36). Complication rates were also similar, with
persistent pain reported by one patient following chondroplasty, by two patients following microfracture, and by two patients following OAT. Postoperative pain, measured by Numeric Pain Intensity Scores, was greater following OAT (5.25) than chondroplasty (3.3) or microfracture (3.4).

**Second Generation ACI Products**

**Second Generation ACI Products: Systematic Reviews**

Kon et al published a systematic review of matrix-assisted ACI in 2013. The review identified 51 articles, including three RCTs, ten comparative studies, 33 case series, and five case reports that reported on functional or clinical outcomes. The review found an expanding evidence base that reports good results at short to medium follow-up, although long-term follow-up and RCTs are needed to compare MACI with other available treatments.

**Second Generation ACI Products: RCTs**

There are five RCTs of ACI using matrix assistance. Four of these compared matrix-assisted ACI with marrow-stimulating techniques, and the third RCT compared matrix-assisted ACI with ACI done without matrix assistance.

**Second Generation ACI Products: MACI®**

SUMMIT was an industry-sponsored multicenter randomized open-label trial (NCT00719576) comparing MACI® with microfracture for larger cartilage defects (>3cm²), which typically fare worse than smaller lesions when treated with microfracture. Patients (n=144) were included who had at least one symptomatic Grade III or IV focal cartilage defect on the femoral condyles or trochlea, a stable knee, an intact or partial meniscus, and a moderate to severe KOOS pain value (<55). The average lesion size was 4.8cm² (range, 3-20cm²); 34.6% of patients had undergone a prior marrow stimulation procedure. At two-year follow-up, the MACI® group had significantly better subscores for KOOS pain (co-primary outcome, difference of 11.76, p<0.001) and function (co-primary outcome, difference of 11.41, p=0.16) as well as the other KOOS subscales (Activities of Daily Living, Knee-Related Quality of Life, Other Symptoms). With response to treatment defined as a ten-point improvement in both the KOOS pain and function subscales, significantly more patients in the MACI group responded to treatment compared with the microfracture group (87.5% vs 68.1%, p=0.016). There were no significant differences between the groups for cartilage repair, as measured by second look arthroscopy, biopsy, or MRI. The lack of blinding in this study reduces the validity of the patient-reported outcome measures.

Basad et al reported a small randomized trial that compared MACI® (n=40) with microfracture (n=20) in patients with a single posttraumatic chondral defect between 4 and10cm². Both groups improved at the two-year follow-up, with a significant advantage of MACI over microfracture on the Lysholm (92 vs 69), Tegner (4 vs 3), and International Cartilage Repair Society (ICRS) patient (a higher percentage of patients with an ICRS score of I) and ICRS surgeon scores.

**Second Generation ACI Products: NeoCart**

In 2012, Crawford et al reported results of an industry-sponsored, FDA-regulated, multicenter randomized Phase II trial. Thirty patients with lesions less than 8cm² were randomized to NeoCart (n=21) or to microfracture (n=9). The SF-36, KOOS, IKDC, and visual analog scale (VAS) pain scores were assessed at up to 24 months by intent-to-treat analysis, and patients were
classified as responders if they had at least a 12-point improvement in the pain score of the KOOS and a 20-point improvement in the IKDC subjective score. At 24 months, there was no significant difference in the mean KOOS pain scores or IKDC scores. The NeoCart group showed significantly greater improvement in the KOOS pain score, KOOS sports, KOOS QOL, IKCD, and VAS pain scores compared with microfracture. There was a trend for a greater number of responders in the NeoCart group (p=0.097); 79% of NeoCart patients were considered to be responders, compared with 44% of the microfracture group.

Second Generation ACI Products: Bioseed
Zeifang et al conducted a small (n=21) randomized trial comparing MACI and ACI. The average size of the cartilage defects was 4.3cm², and patients had undergone an average of two prior surgeries on the affected knee. Postoperatively, there was no significant difference between the two groups on the IKDC score at either 12 months (72.0 for MACI, 76.7 for ACI), or 24 months (70.1 for MACI, 77.1 for ACI). Exploratory analysis found a significant inverse correlation with age (r=-0.52 at 12 months, r=-0.49 at 24 months) indicating that better results were observed in younger patients. There was no significant difference between the groups in the SF-36. The Lysholm score showed a significant improvement only in the ACI group (from 61.3 at baseline to 86.3 at 12 months and 84.0 at 24 months). The Tegner activity score did not change significantly in either group.

Second Generation ACI Products: ChondroCelect
Saris et al published a multicenter, randomized trial of characterized chondrocyte implantation (n=57) versus microfracture (n=61) in 2008; the average lesion size was 2.8cm². Chondrocytes were isolated from a cartilage biopsy specimen and expanded ex vivo (ChondroCelect, TiGenix, Belgium). ChondroCelect is not approved for use in the U.S. 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. Histologic 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 crepitation were greater in the ACI group, particularly following the arthrotomy. Thus, although histologic 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 2009, Saris et al published 36-month outcomes (100% follow-up) from this randomized trial. The mean improvement in the overall KOOS was greater in the ACI group than the microfracture group (21 vs 16 points, respectively). More ACI than microfracture-treated patients were considered to be treatment responders (83% vs 62%, respectively), defined as an increase from baseline of at least ten percentage points in at least three of the 4 KOOS subdomains or a decrease of at least 20 percentage points in VAS scores for pain. At 36 months after surgery, two ACI (3.9%) and seven microfracture patients (11.5%) had failed treatment and subsequently underwent reintervention. MRI showed greater worsening of the subchondral bone
reaction with microfracture compared with ACI. At five years after treatment, the number of treatment failures was comparable for the ACI (n=7) and microfracture (n=10) groups. There was a trend for the overall KOOS score to be more improved following ACI than microfracture (21 vs 14, p=0.068). Planned exploratory subgroup analysis indicated that ACI resulted in a better outcome (both statistically and clinically significant) in patients who had a time since symptom onset of less than three years, with a change in KOOS of 26 compared with 15 for the microfracture group. For patients with symptom onset of three years or more, the change in KOOS was similar for the two groups (13 ACI vs 17 microfracture). Subgroup analyses for age did not show a difference for patients who were younger than 35 years of age compared with patients who were 35 years or older.

Second Generation ACI Products: Hyalograft C

In 2011, Kon et al reported a prospective comparative study of second-generation ACI (Hyalograft C) versus microfracture in 41 professional or semiprofessional male soccer players. This was a pragmatic clinical trial, with treatment allocation based on the center patients chose; one center performed ACI and two centers performed microfracture. The two patient groups were comparable for age, defect size, location, previous and combined surgery, and follow-up. Patients were evaluated prospectively at two years and at a final mean 7.5-year follow-up (minimum, four years). The percentage of patients who returned to competition was similar, with 80% in the microfracture group and 86% in the ACI group. Patients treated with microfracture needed a median of eight months before playing their first official soccer game, whereas the ACI group required a median time of 12.5 months. The IKDC subjective score showed similar results at two years’ follow-up but significantly better results in the ACI group at the final evaluation. In the microfracture group, results decreased over time (from 86.8 at two years to 79.0 at final follow-up), whereas the ACI group had stable results between two years and final follow-up (90.5 and 91.0, respectively). The IKDC objective score was similar in the two groups, with 90% to 95% of knees considered to be normal or nearly normal. Subjective evaluation of functional level was significantly better in the ACI group at final follow-up (91 vs 84).

In 2014, the same group of investigators compared outcomes following repair of trochlear or patellar lesions with Hyalograft C. Other procedures conducted at the same time included lateral release, realignment, meniscectomy, ACL reconstruction, or tracheoplasty. Patients were followed for five years and evaluated every year with the IKDC subjective score, EuroQol VAS, Kujula score, and Tegner score. Failure was defined as the need for further surgery because of symptoms related to the primary defect. Both cohorts showed significant improvements in outcomes and patients with trochlear lesions improved more than patients with patellar lesions, although neither group reached the preinjury level.

Summary

Although evidence from long-term studies is still accumulating, current 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 the FDA-approved indication of disabling full-thickness chondral lesions of the femoral condyles or trochlea 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. Recent evidence indicates that ACI combined with meniscal allograft results in outcomes similar to either procedure performed alone; therefore, combined procedures may be considered medically necessary. 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 the patella or 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 there are a smaller number of RCTs with short term follow-up comparing MACI to ACI, and no MACI products are approved in the U.S.; therefore, these are considered investigational.

**Practice Guidelines and Position Statements**
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. This recommendation of insufficient evidence was based on a systematic review that found four level IV studies that addressed cartilage repair techniques for an unsalvageable OCD lesion. Since each of the level IV articles utilized different techniques, different outcome measures, and differing lengths of follow-up, the work group deemed that the evidence for any specific technique was inconclusive.

In 2005, the National Institute for Health and Clinical Excellence (NICE) issued an updated Technology Appraisal Guidance on the use of ACI. The NICE guidance cited insufficient evidence to determine the benefits of ACI 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 with conservative treatment, assessment of the quality of cartilage produced, and the impact of cartilage produced on functional outcomes and health-related quality of life.

**Key Words:**
Autologous chondrocyte transplantation (ACT), autologous chondrocyte implant (ACI), articular cartilage, chondrocytes, Carticel®, osteochondritis dissecans (OCD), ChondroCelect, BioCart II, Cartilix, MACI®, Cartipatch, NeoCart, Hyalograft C

**Approved by Governing Bodies:**
Carticel was initially approved by the FDA in 1997 for biologics licensure.

No second generation products have FDA approval.
**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply
FEP contracts: Special benefit consideration may apply. Refer to member’s benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

**Coding:**

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

**CPT codes:**
- **27412** Autologous chondrocyte implantation, knee
- **27899** Unlisted procedure, leg or ankle
- **29870-29887** Code range, arthroscopy of the knee

**References:**

**Policy History:**
Medical Policy Group, April 2004 (1)
Medical Policy Administration Committee, April 2004
Available for comment June 30-July 15, 2004
Medical Policy Group, May 2005 (2)
Medical Policy Administration Committee, June 2005
Available for comment June 16-July 30, 2005
Medical Policy Group, April 2007 (1)
Medical Policy Administration Committee, May 2007
Available for comment May 8-June 21, 2007
Medical Review Group, November 2009 (2)
Medical Policy Administration Committee, December 2009
Available for comment December 4, 2009-January 19, 2010
Medical Policy Group, March 2010 (3)
Medical Policy Administration Committee April 2010
Available for comment April 15-May 29, 2010
Medical Policy Group, June 2011; Updated Policy, Key Points & References
Medical Policy Administration Committee July 2011
Available for comment July 6 through August 22, 2011
Medical Policy Group, June 2012 (3): 2012 Update includes Key Points and References
Medical Policy Panel, June 2013
Medical Policy Group, June 2013 (3): 2013 Updates to Title, Description, Policy Statement, Key Points, References, and Key words; removed “Transplantation” and replaced with “Implantation” and removed “and Other Cell-based Treatments of” from title; and treatments with autologous minced cartilage and allogeneic minced cartilage or cartilage cells from policy statements
Available for comment June 27 through August 10, 2013
Medical Policy Group, September 2013 (3): ad hoc clarification statement added to policy sections noting prophylactic harvesting of cells for possible future implantation does not meet criteria for coverage

Medical Policy Panel, June 2014
Medical Policy Group, June 2014 (3): 2014 Updates to Description, Key Points & References; no change in policy statement

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.