BlueCross BlueShield of Louisiana

An independent licensee of the Blue Cross and Blue Shield Association.

Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions

Policy # 00006
Original Effective Date: 08/26/2002
Current Effective Date: 08/20/2014

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider autologous chondrocyte implantation (ACI) 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 to be **eligible for coverage** when all of the following criteria are met:

Patient Selection Criteria
Coverage eligibility will be considered 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 (ACI).

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers autologous chondrocyte implantation (ACI) for all other joints, including patellar and talar, and any indications other than those listed above to be **investigational**.*

Based on review of available data, the Company considers matrix-induced autologous chondrocyte implantation (ACI) to be **investigational**.*

The use of autologous chondrocyte implantation (ACI) 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

Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions

Policy # 00006
Original Effective Date: 08/26/2002
Current Effective Date: 08/20/2014

response to a prior surgical procedure when patient selection criteria are not met is considered to be **investigational.***

Background/Overview

A variety of procedures are being developed to resurface articular cartilage defects. ACI involves harvesting chondrocytes from healthy tissue, expanding the cells in vitro, and implanting the expanded cells into the chondral defect under a periosteal or fibrin patch. Second- and third-generation techniques include combinations of autologous chondrocytes, scaffolds, and growth factors.

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 2 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.

Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions

Policy # 00006
Original Effective Date: 08/26/2002
Current Effective Date: 08/20/2014

FDA or Other Governmental Regulatory Approval

U.S. FDA
The culturing of chondrocytes is considered by the FDA to fall into the category of manipulated autologous structural (MAS) cells, 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 autologous chondrocytes in a biodegradable matrix are currently in development/testing. These include Atelocollagen (collagen gel, Koken), BioCart II (ProChon Biotech, Phase II trial), Bioseed C (polymer scaffold, BioTissue Technologies) CaReS (collagen gel, Ars Arthro), Cartilix (polymer hydrogel, Cartilix), Cartipatch (solid scaffold with an agarose-alginate matrix, TBF Tissue Engineering, Phase III trial), Chondron (fibrin gel, Sewon Cellontech), Hyalograft C (hyaluronic acid-based scaffold, Fidia Advanced Polymers), MACI®‡ (matrix-induced ACI, Verigen and Genzyme, available outside of the U.S.), NeoCart (ACI with a 3-dimensional chondromatrix, Histogenics. Phase III trial), and Novocart (collagen-chondroitin sulfate scaffold, B. Braun-Tetec). ChondroCelect (characterized chondrocyte implantation, TiGenex, Phase III trial completed) uses a gene marker profile to determine in vivo cartilage-forming potential and thereby optimizes 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.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination.

Rationale/Source

This policy was based on a 2003 TEC Assessment of ACI, which updates earlier 1996, 1997, and 2000 TEC Assessments on the same subject. 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.

Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions

Policy # 00006
Original Effective Date: 08/26/2002
Current Effective Date: 08/20/2014

At the time of this TEC Assessment, only 1 ACI product (Carticel) had been evaluated in the published literature.

Updated literature searches, conducted periodically between 2003 and May 14, 2014, identified the following published studies. Some of these 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, 7 considered fair, and 6 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 1- to 5-year follow-up, 3 of 7 studies showed better clinical outcomes after ACI in comparison with microfracture, 1 study showed better outcomes after microfracture, and 3 studies showed no difference in these treatments. Clinical outcomes after microfracture were found to deteriorate after 18 to 24 months in 3 of 7 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 4 cm^2 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 6 studies found outcomes equivalent to procedures performed in isolation, while 2 studies found that outcomes with combined surgery were not as good as the historical controls. Across the 6 studies, 13 failures (12%) were reported; these included 11 isolated meniscal allograft transplantation failures, 1 combined meniscal allograft and ACI failure, and 1 isolated ACI failure. Three knees with failed meniscal allograft transplantation were converted to total knee arthroplasty. Nearly 50% of the patients underwent 1 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; 6 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.

Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions

Policy # 00006
Original Effective Date: 08/26/2002
Current Effective Date: 08/20/2014

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 2-year follow-up in macroscopic and histologic findings. The Lysholm and pain scores were also not significantly different at 1 and 2 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 9 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 10.0 cm^2 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 2-year follow-up on a study of 40 patients (between 18 and 42 years old) with an articular lesion of the femoral condyle (range, 3.2-5.6 cm^2) 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 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 et al randomized 100 consecutive patients with symptomatic lesions of the knee (average, 4.7 cm^2; range, 1-12 cm^2) 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 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. With 6 patients lost to follow-up at a minimum 10 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 6 months after undergoing arthroscopic débridement. 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 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 10 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 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 (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 4.6 cm^2 (range, 1-30 cm^2), 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) 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 3 consecutive 6-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 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 1 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 4 years after the procedure. Additional surgical procedures may be expected.

Gooding et al randomized 68 patients with osteochondral defects (mean, 4.5 cm^2; range, 1–12 cm^2) of the femoral condyle (54%), trochlea (6%), or patella (40%) to ACI with either a periosteal or collagen cover. 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.

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 4.65 cm^2. 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. (19) 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 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. 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 4.9 cm^2 (range, 0.8-23.5 cm^2). Seventy percent of the patients had failed at least 1 previous cartilage procedure. At 5 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 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). In 2010, this group of investigators published 6- to 10-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 1- to 5-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 10 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 7 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 10- 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 16 cm^2, 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 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. 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 4 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 trocleoplasty 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, 9 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, 6 months and 1 year postoperatively, and then annually. At an average follow-up of 4 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 4 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 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.

Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions

Policy # 00006
Original Effective Date: 08/26/2002
Current Effective Date: 08/20/2014

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 cm^2. 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 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 1 additional surgery, and 16% required 2 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 (5.5 cm^2 vs 3.9 cm^2). Two patients were considered failures (7%) and 5 (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 3-fold 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). The average lesion was 8 cm^2, and the indications for treatment of cartilage defects with ACI included 1 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 5 years and 50.7% at 10 years by Kaplan-Meier analysis, with no significant difference in survival rates between ACI and MACI procedures or for different defect sizes (range, .64-20.75 cm^2). Graft failure was 5 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 2 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 were treated, with a mean defect size of 4.9 cm^2 and a total mean defect area of 10.4 cm^2. 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 5 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 1 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 1.5 cm^2 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 1.5 cm^2. Three of 58 ankles (5.2%) with a defect area of less than 1 cm^2 showed clinical failure, while 7 of 37 ankles (18.9%) with a defect area between 1.0 and 1.5 cm^2 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 6 studies periosteum-covered ACI was applied while 10 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 4 to 12. 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 3 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 1 patient following chondroplasty, by 2 patients following

microfracture, and by 2 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 3 RCTs, 10 comparative studies, 33 case series, and 5 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 5 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 (≥3 cm^2), which typically fare worse than smaller lesions when treated with microfracture. Patients (n=144) were included who had at least 1 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 4.8 cm^2 (range, 3-20 cm^2); 34.6% of patients had undergone a prior marrow stimulation procedure. At 2-year follow-up, the MACI group had significantly better subscores for KOOS pain (coprimary outcome, difference of 11.76, $p<0.001$) and function (coprimary 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 10-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 and10 cm^2.(45) Both groups improved at the 2-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 8 cm^2 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 4.3 cm^2, and patients had undergone an average of 2 prior surgeries on the affected knee. Postoperatively, there was no significant difference between the 2 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 2.8 cm^2. 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 (eg, 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 10 percentage points in at least 3 of the 4 KOOS subdomains or a decrease of at least 20 percentage points in VAS scores for pain. At 36 months after surgery, 2 ACI (3.9%) and 7 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 5 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 3 years, with a change in KOOS of 26 compared with 15 for the microfracture group. For patients with symptom onset of 3 years or more, the change in KOOS was similar for the 2 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; 1 center performed ACI and 2 centers performed microfracture. The 2 patient groups were comparable for age, defect size, location, previous and combined surgery, and follow-up. Patients were evaluated prospectively at 2 years and at a final mean 7.5-year follow-up (minimum, 4 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 8 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 2 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 2 years to 79.0 at final follow-up), whereas the ACI group had stable results between 2 years and final follow-up (90.5 and 91.0, respectively). The IKDC objective score was similar in the 2 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 trochleoplasty. Patients were followed for 5 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.

Ongoing Clinical Trials
A search of the online clinical trials database www.ClinicalTrials.gov in May 2014 identified a number of trials with second- and third-generation ACI/MACI. In addition, Zimmer Orthobiologics is conducting 2 large postmarketing studies with DeNovo NT, Natural Tissue Graft, for the knee (NCT01329445) and ankle (NCT01347892). Both studies will have 5-year follow-up with estimated completion in 2018.

Clinical Input Received Through Physician Specialty Societies and Academic Medical Centers
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.

2008
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. The reviewers generally agreed that ACI should be considered when all other treatments have been unsuccessfully tried in patients who have a localized

chondral defect in an otherwise normal joint articular surface. Reviewers noted the lack of alternative options for larger lesions (eg, >4 cm^2). Additional literature was provided, which was subsequently reviewed.

2011
In response to requests, input was received from 2 physician specialty societies and 3 academic medical centers while this policy was under review in 2011. The clinical input was generally in agreement with the stated criteria for ACI with the exception of the following: input was mixed regarding the requirement for an inadequate response to a prior surgical procedure and the requirement for an absence of meniscal pathology. Input was also mixed regarding the investigational status of ACI in patellar and talar joints.

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 randomized controlled trials with short- term follow-up comparing MACI with ACI, and no MACI products are approved in the U.S.; therefore, these are considered investigational.

References

1. Blue Cross and Blue Shield Association Medical Policy Reference Manual, "Autologous Chondrocyte Transplantation and Other Cell-based Treatments of Focal Articular Cartilage Lesions", 7.01.48, 6:2014.
2. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Autologous chondrocyte transplantation. TEC Assessments 1996; Volume 11, Tab 8.
3. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Autologous chondrocyte transplantation. TEC Assessments 1997; Volume 12, Tab 26.
4. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Autologous chondrocyte transplantation. TEC Assessments 2000; Volume 15, Tab 12.
5. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Autologous chondrocyte transplantation of the knee. TEC Assessments 2003; Volume 18, Tab 2.
6. Harris JD, Cavo M, Brophy R et al. Biological Knee Reconstruction: A Systematic Review of Combined Meniscal Allograft Transplantation and Cartilage Repair or Restoration. Arthroscopy 2011; 27(3):409-18.

7. Mithoefer K, McAdams T, Williams RJ et al. Clinical efficacy of the microfracture technique for articular cartilage repair in the knee: an evidence-based systematic analysis. Am J Sports Med 2009; 37(10):2053-63.
8. Knutsen G, Engebretsen L, Ludvigsen TC et al. Autologous chondrocyte implantation compared with microfracture in the knee. A randomized trial. J Bone Joint Surg Am 2004; 86-A(3):455-64.
9. Knutsen G, Drogset JO, Engebretsen L et al. A randomized trial comparing autologous chondrocyte implantation with microfracture. Findings at five years. J Bone Joint Surg Am 2007; 89(10):2105-12.
10. Visna P, Pasa L, Cizmar I et al. Treatment of deep cartilage defects of the knee using autologous chondrograft transplantation and by abrasive techniques--a randomized controlled study. Acta Chir Belg 2004; 104(6):709-14.
11. Horas U, Pelinkovic D, Herr G et al. Autologous chondrocyte implantation and osteochondral cylinder transplantation in cartilage repair of the knee joint. A prospective, comparative trial. J Bone Joint Surg Am 2003; 85-A(2):185-92.
12. Bentley G, Biant LC, Carrington RW et al. A prospective, randomised comparison of autologous chondrocyte implantation versus mosaicplasty for osteochondral defects in the knee. J Bone Joint Surg Br 2003; 85(2):223-30.
13. Bentley G, Biant LC, Vijayan S et al. Minimum ten-year results of a prospective randomised study of autologous chondrocyte implantation versus mosaicplasty for symptomatic articular cartilage lesions of the knee. J Bone Joint Surg Br 2012; 94(4):504-9.
14. Dozin B, Malpeli M, Cancedda R et al. Comparative evaluation of autologous chondrocyte implantation and mosaicplasty: a multicentered randomized clinical trial. Clin J Sport Med 2005; 15(4):220-6.
15. Cole B, Brewster R, DeBerardino T et al. Improvement in Symptoms and Function after Autologous Chondrocyte Implantation (ACI, Carticel®) in Patients who Failed Prior Treatment, Results of the Study of Treatment of Articular Repair (STAR). *AOSSM* 2007. Available online at: http://www.sportsmed.org/tabs/education/downloads/AM2007%20Final%20Abstracts.pdf. Last accessed February, 2011.
16. Genzyme Biosurgery. Caritcel prescribing information. 2007. Available online at: http://www.genzymebiosurgery.com/pdfs/carticel_package_insert.pdf. Last accessed February, 2011.
17. Zaslav K, Cole B, Brewster R et al. A prospective study of autologous chondrocyte implantation in patients with failed prior treatment for articular cartilage defect of the knee: results of the Study of the Treatment of Articular Repair (STAR) clinical trial. Am J Sports Med 2009; 37(1):42-55.
18. Gooding CR, Bartlett W, Bentley G et al. A prospective, randomised study comparing two techniques of autologous chondrocyte implantation for osteochondral defects in the knee: Periosteum covered versus type I/III collagen covered. Knee 2006; 13(3):203-10.
19. Pestka JM, Bode G, Salzmann G et al. Clinical outcome of autologous chondrocyte implantation for failed microfracture treatment of full-thickness cartilage defects of the knee joint. Am J Sports Med 2012; 40(2):325-31.
20. Vanlauwe J, Saris DB, Victor J et al. Five-year outcome of characterized chondrocyte implantation versus microfracture for symptomatic cartilage defects of the knee: early treatment matters. Am J Sports Med 2011; 39(12):2566-74.
21. Minas T, Gomoll AH, Rosenberger R et al. Increased failure rate of autologous chondrocyte implantation after previous treatment with marrow stimulation techniques. Am J Sports Med 2009; 37(5):902-8.
22. Browne JE, Anderson AF, Arciero R et al. Clinical outcome of autologous chondrocyte implantation at 5 years in US subjects. Clin Orthop Relat Res 2005; (436):237-45.
23. Moseley JB, Jr., Anderson AF, Browne JE et al. Long-term durability of autologous chondrocyte implantation: a multicenter, observational study in US patients. Am J Sports Med 2010; 38(2):238-46.
24. Minas T, Von Keudell A, Bryant T et al. The John Insall Award: A minimum 10-year outcome study of autologous chondrocyte implantation. Clin Orthop Relat Res 2014; 472(1):41-51.
25. Peterson L, Vasiliadis HS, Brittberg M et al. Autologous chondrocyte implantation: a long-term follow-up. Am J Sports Med 2010; 38(6):1117-24.
26. Rosenberger RE, Gomoll AH, Bryant T et al. Repair of large chondral defects of the knee with autologous chondrocyte implantation in patients 45 years or older. Am J Sports Med 2008; 36(12):2336-44.
27. Niemeyer P, Pestka JM, Kreuz PC et al. Characteristic complications after autologous chondrocyte implantation for cartilage defects of the knee joint. Am J Sports Med 2008; 36(11):2091-9.
28. Henderson IJ, Lavigne P. Periosteal autologous chondrocyte implantation for patellar chondral defect in patients with normal and abnormal patellar tracking. Knee 2006; 13(4):274-9.
29. Farr J. Autologous chondrocyte implantation improves patellofemoral cartilage treatment outcomes. Clin Orthop Relat Res 2007; 463:187-94.
30. Gomoll AH, Gillogly SD, Cole BJ et al. Autologous chondrocyte implantation in the patella: a multicenter experience. Am J Sports Med 2014; 42(5):1074-81.

31. Pascual-Garrido C, Slabaugh MA, L'Heureux DR et al. Recommendations and treatment outcomes for patellofemoral articular cartilage defects with autologous chondrocyte implantation: prospective evaluation at average 4-year follow-up. Am J Sports Med 2009; 37 Suppl 1:33S-41S.
32. Niemeyer P, Steinwachs M, Erggelet C et al. Autologous chondrocyte implantation for the treatment of retropatellar cartilage defects: clinical results referred to defect localisation. Arch Orthop Trauma Surg 2008; 128(11):1223-31.
33. Gobbi A, Kon E, Berruto M et al. Patellofemoral full-thickness chondral defects treated with second-generation autologous chondrocyte implantation: results at 5 years' follow-up. Am J Sports Med 2009; 37(6):1083-92.
34. Gigante A, Enea D, Greco F et al. Distal realignment and patellar autologous chondrocyte implantation: mid-term results in a selected population. Knee Surg Sports Traumatol Arthrosc 2009; 17(1):2-10.
35. Filardo G, Kon E, Andriolo L et al. Treatment of "patellofemoral" cartilage lesions with matrix-assisted autologous chondrocyte transplantation: a comparison of patellar and trochlear lesions. Am J Sports Med 2014; 42(3):626-34.
36. Farr J, Rawal A, Marberry KM. Concomitant meniscal allograft transplantation and autologous chondrocyte implantation: minimum 2-year follow-up. Am J Sports Med 2007; 35(9):1459-66.
37. Rue JP, Yanke AB, Busam ML et al. Prospective evaluation of concurrent meniscus transplantation and articular cartilage repair: minimum 2-year follow-up. Am J Sports Med 2008; 36(9):1770-8.
38. Nawaz SZ, Bentley G, Briggs TWR et al. Autologous chondrocyte implantation in the knee. J Bone Joint Surg Am 2014; 96(10):824-30.
39. Minas T, Gomoll AH, Solhpour S et al. Autologous chondrocyte implantation for joint preservation in patients with early osteoarthritis. Clin Orthop Relat Res 2010; 468(1):147-57.
40. Zengerink M, Struijs PA, Tol JL et al. Treatment of osteochondral lesions of the talus: a systematic review. Knee Surg Sports Traumatol Arthrosc 2010; 18(2):238-46.
41. Choi WJ, Park KK, Kim BS et al. Osteochondral lesion of the talus: is there a critical defect size for poor outcome? Am J Sports Med 2009; 37(10):1974-80.
42. Niemeyer P, Salzmann G, Schmal H et al. Autologous chondrocyte implantation for the treatment of chondral and osteochondral defects of the talus: a meta-analysis of available evidence. Knee Surg Sports Traumatol Arthrosc 2012; 20(9):1696-703.
43. Gobbi A, Francisco RA, Lubowitz JH et al. Osteochondral lesions of the talus: randomized controlled trial comparing chondroplasty, microfracture, and osteochondral autograft transplantation. Arthroscopy 2006; 22(10):1085-92.
44. Kon E, Filardo G, Di Matteo B et al. Matrix assisted autologous chondrocyte transplantation for cartilage treatment: A systematic review. Bone Joint Res 2013; 2(2):18-25.
45. Saris D, Price A, Widuchowski W et al. Matrix-Applied Characterized Autologous Cultured Chondrocytes Versus Microfracture: Two-Year Follow-up of a Prospective Randomized Trial. Am J Sports Med 2014.
46. Basad E, Ishaque B, Bachmann G et al. Matrix-induced autologous chondrocyte implantation versus microfracture in the treatment of cartilage defects of the knee: a 2-year randomised study. Knee Surg Sports Traumatol Arthrosc 2010; 18(4):519-27.
47. Crawford DC, DeBerardino TM, Williams RJ, 3rd. NeoCart, an autologous cartilage tissue implant, compared with microfracture for treatment of distal femoral cartilage lesions: an FDA phase-II prospective, randomized clinical trial after two years. J Bone Joint Surg Am 2012; 94(11):979-89.
48. Zeifang F, Oberle D, Nierhoff C et al. Autologous chondrocyte implantation using the original periosteum-cover technique versus matrix-associated autologous chondrocyte implantation: a randomized clinical trial. Am J Sports Med 2010; 38(5):924-33.
49. Saris DB, Vanlauwe J, Victor J et al. Characterized chondrocyte implantation results in better structural repair when treating symptomatic cartilage defects of the knee in a randomized controlled trial versus microfracture. Am J Sports Med 2008; 36(2):235-46.
50. Saris DB, Vanlauwe J, Victor J et al. Treatment of symptomatic cartilage defects of the knee: characterized chondrocyte implantation results in better clinical outcome at 36 months in a randomized trial compared to microfracture. Am J Sports Med 2009; 37 Suppl 1:10S-19S.
51. Kon E, Filardo G, Berruto M et al. Articular cartilage treatment in high-level male soccer players: a prospective comparative study of arthroscopic second-generation autologous chondrocyte implantation versus microfracture. Am J Sports Med 2011; 39(12):2549-57.
52. American Academy of Orthopaedic Surgeons. Clinical practice guideline on the diagnosis and treatment of osteochondritis dissecans. 2010. Available online at: http://www.aaos.org/research/guidelines/OCD_guideline.pdf. Last accessed March, 2011.
53. National Institute for Health and Clinical Excellence. The use of autologous chondrocyte implantation for the treatment of cartilage defects in knee joints. *Technology Appraisal Guidance No. 89* 2005. Available online at: http://www.nice.org.uk/page.aspx?o=TA089guidance. Last accessed March, 2011.

Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions

Policy # 00006
Original Effective Date: 08/26/2002
Current Effective Date: 08/20/2014

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2013 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	27412, 29866
HCPCS	J7330, S2112
ICD-9 Diagnosis	715.16, 715.26, 715.36, 715.96, 716.16, 717.0 thru 717.9, 718.06, 718.86, 719.86, 732.7, 733.90, 959.7
ICD-9 Procedure	80.16, 80.26

Policy History

Original Effective Date: 08/26/2002
Current Effective Date: 08/20/2014

07/01/2001	Medical Director review
07/18/2002	Medical Policy Committee review
08/2620/02	Managed Care Advisory Council approval
06/2420/02	Format revision. No substance change to policy
08/10/2004	Medical Director review
08/31/2004	Medical Director review
09/21/2004	Medical Policy Committee review. Format revision. No Substance change to policy
09/27/2004	Managed Care Advisory Council approval
09/07/2005	Medical Director review
09/20/2005	Medical Policy Committee review. Format revision. Coverage eligibility unchanged.
09/22/2005	Quality Care Advisory Council approval
07/12/2006	Medical Director review
07/19/2006	Medical Policy Committee approval. Format changes. FDA information added. Coverage eligibility unchanged.
05/02/2007	Medical Director review

Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions

Policy # 00006
Original Effective Date: 08/26/2002
Current Effective Date: 08/20/2014

05/23/2007	Medical Policy Committee approval. Added when patient selection criteria are not met is considered to be investigational.
05/07/2008	Medical Director review
05/21/2008	Medical Policy Committee approval. Rationale updated.
05/07/2009	Medical Director review
05/20/2009	Medical Policy Committee approval. No change to coverage eligibility.
06/03/2010	Medical Director review
06/16/2010	Medical Policy Implementation Committee approval. No change to coverage eligibility.
05/05/2011	Medical Director review
05/18/2011	Medical Policy Implementation Committee approval. No change to coverage eligibility
05/03/2012	Medical Director review
05/16/2012	Medical Policy Implementation Committee approval. No change to coverage eligibility
08/01/2013	Medical Director review
08/21/2013	Medical Policy Implementation Committee approval. Sections and statements on minced cartilage moved to policy (Osteochondral Autografts and Allografts) and “Other Cell-based Treatments” removed from title.
08/07/2014	Medical Director review
08/20/2014	Medical Policy Implementation Committee approval. No change to coverage.

Next Scheduled Review Date: 08/2015

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and 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.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions

Policy # 00006
Original Effective Date: 08/26/2002
Current Effective Date: 08/20/2014

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.