



CIGNA HEALTHCARE COVERAGE POSITION

Subject Autologous Chondrocyte Transplantation

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Allograft Transplant of the Knee, Anterior Cruciate and Meniscal
Osteochondral Grafts for Articular Cartilage Repair (Autografts, Allografts, and Synthetic Grafts)

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Coverage Position

CIGNA HealthCare covers autologous chondrocyte transplantation as medically necessary for the treatment of symptomatic cartilaginous defects of the femoral condyle of the knee (medial, lateral or trochlear) caused by acute or repetitive trauma when ALL of the following criteria are met:

- age 15–55 years
- symptoms of at least one-year duration, with current disabling knee pain unresponsive to conservative treatment
- femoral condyle defect size of 1–12 cm² demonstrated by magnetic resonance imaging (MRI) or arthroscopy
- defect grade III to IV (full thickness)
- no generalized tibial chondromalacia
- no osteoarthritis of the knee
- no corresponding tibial or patellar lesion (“kissing” lesion) with grade III or greater chondromalacia or exposed bone chondromalacia
- stable and aligned knee (corrective procedures may be performed in combination with or prior to ACT)
- patient willing and able to comply with rigorous rehabilitation program
- normal articular cartilage at lesion border
- knee is stable with intact, fully functional menisci and ligaments
- inadequate response to prior arthroscopic or other surgical repair

CIGNA HealthCare does not cover autologous chondrocyte transplantation for the following indications because it is considered experimental, investigational, or unproven: (this list may not be all-inclusive)

- lesions of the tibia or patella
- lesions in other joints, including the ankle and shoulder
- treatment of cartilage damage associated with generalized osteoarthritis

General Background

Autologous chondrocyte transplantation (ACT), also referred to as autologous chondrocyte implantation (ACI) utilizes a patient's own cells in an effort to repair damage to articular cartilage with the goal of improving joint function and reducing pain. The procedure involves the collection and culture of articular cartilage cells (i.e., chondrocytes) that are then implanted into the cartilage defect with the intent that the cultured cells will contribute to the regeneration and repair of the articular surface.

Normal articular cartilage is a complex tissue composed of matrix, chondrocytes and water. The chondrocytes are responsible for synthesizing the matrix, which is composed primarily of collagen fibers, hyaluronate, and sulfated proteoglycans. Cartilage has a poor intrinsic ability to heal itself. When a full-thickness cartilage injury occurs, the articular surface does not usually regenerate on its own. The injury often becomes more severe over time since even small defects involving the full thickness of articular cartilage may progress to osteoarthritis, a debilitating joint disease marked by degeneration of the articular cartilage. Nonsurgical treatments for cartilage injury include physical therapy, braces and orthotics, nonsteroidal anti-inflammatory drugs, and intra-articular injection of hyaluronic acid derivatives. Surgical treatment options include arthroscopic lavage and debridement and articular resurfacing techniques. In some patients, total knee replacement may be necessary (Brittberg, et al., 1994; Hayes, 2005).

The Outer Bridge classification is the most widely used system for judging articular injury to the knee. This system allows delineation of varying areas of chondral pathology, based on the qualitative appearance of the cartilage surface and can assist in identifying those injuries that are suitable for repair techniques. The characterization of cartilage in this system is as follows:

- grade I, softening with swelling
- grade II, fragmentation and fissuring
- grade III, fragmentation and fissuring greater than one-half inch in diameter
- grade IV, subchondral bone exposed
- Grade III and IV lesions are thought to be the most suitable for repair techniques (Alleyne, et al., 2001).

ACT is performed by the harvest of healthy cartilage cells from the patient, preparation and growth of the cells in a culture medium, and implantation of the cultured cells into the articular defect. Healthy cartilage is harvested via biopsy from a minor load-bearing area on a rounded projection of the femur. Cartilage is then minced and washed in a buffered solution and placed in a medium containing digestive enzymes for 15 hours. The cells are then filtered, washed, re-suspended in culture medium containing autologous serum, and seeded in culture flasks. The cells are cultivated for 14 days to six weeks. Ochi et al. (2001) developed a modification of this procedure in which autologous chondrocytes are cultivated in a collagen gel for three weeks. An arthrotomy is performed to inject the cultured cells into the defect (Hayes, 2005).

U.S. Food and Drug Administration (FDA)

The FDA determined that Carticel[®] (Genzyme Corporation, Cambridge, MA), a commercial process of producing autologous chondrocytes for transplantation, fell outside existing regulations regarding medical technology. The FDA permitted marketing of the service while guidelines were developed for manipulated autologous structural cells. In May 1996, the FDA announced its guidelines for manipulated autologous structures, which include completion of a Biologics Licensing Application (BLA) and evidence of product safety and efficacy. On August 22, 1997, the FDA granted a Biologics License for Carticel, for provision of

autologous chondrocytes for the repair of clinically significant, symptomatic cartilaginous defects of the femoral condyle caused by acute or repetitive trauma. The FDA based its approval of Carticel primarily on a number of case reports consisting of 153 patients treated in Sweden, and early data from a US registry of patients treated with Carticel. As a condition of approval, the FDA requested that Genzyme conduct two randomized controlled studies—one to determine the contribution of the cartilage cells to the treatment of the defect, and the other to compare long-term outcomes in patients treated with Carticel to outcomes achieved with other procedures currently in use, including abrasion arthroplasty and microfracture. In addition, all patients enrolled in the Carticel Patient Registry must be followed for a minimum of two years with submission of periodic reports of safety and clinical outcomes to the FDA. Genzyme subsequently concluded that running randomized trials sufficiently large enough to satisfy these requirements would not be feasible and requested that the FDA narrow the indication for autologous cultured chondrocytes to second-line therapy for patients who have failed other therapies. The FDA granted a supplement to the Biologics License for Carticel on March 2, 2000. In response to the request made by Genzyme, FDA narrowed the indication for use of autologous cultured chondrocytes to second-line therapy for patients who have failed other therapies.

In June 2007, the FDA granted a request from Genzyme to supplement the biologics license application for Cultured Chondrocytes to revise the package insert to include safety and efficacy data from the Study of the Treatment of Articular Repair (STAR). The STAR study was presented at the American Orthopaedic Society for Sports Medicine (AOSSM) meeting in Calgary in July 2007 but has not been published in the medical literature. The STAR study fulfilled the post-approval commitment to conduct a prospective, longitudinal, multicenter study of 100 subjects with articular cartilage defects of the medial or lateral condyles or trochlear having inadequate response to prior non-Carticel surgical treatment (including marrow stimulation techniques, transplantation of cells or tissues, or debridement followed by an adequate rehab program, but not including lavage, biopsy, or diagnostic arthroscopy). The June 2007 package insert contains the following indications and usage information:

- Carticel is an autologous cellular product indicated for the repair of symptomatic cartilage defects of the femoral condyle (medial, lateral or trochlea), caused by acute or repetitive trauma, in patients who have had an inadequate response to a prior arthroscopic or other surgical repair procedure (e.g., debridement, microfracture, drilling/abrasion arthroplasty, or osteochondral allograft/autograft).
- Carticel should only be used in conjunction with debridement, placement of a periosteal flap and rehabilitation.
- Carticel is not indicated for:
 - Treatment of cartilage damage associated with generalized osteoarthritis
 - Patients with total meniscectomy, unless surgically reconstructed prior to or concurrent with Carticel implantation

The 2007 package insert listed the following as the most common serious adverse events (> 5% of patients) from the STAR study: arthrofibrosis/joint adhesions, graft overgrowth, chondromalacia or chondrosis, cartilage injury, graft complication, meniscal lesion and graft delamination.

Literature Review

Horas et al. (2003) conducted a randomized controlled trial to investigate two-year outcomes in 40 patients with an articular cartilage lesion of the femoral condyle who had been randomly treated with either transplantation of an autologous osteochondral cylinder or ACI. Biopsy specimens from representative patients of both groups were evaluated with histological staining, immunocytochemistry, and scanning electron microscopy. Both surgical treatments resulted in a decrease in symptoms, although the improvement provided by ACI lagged behind that provided by the osteochondral cylinder transplantation. The authors report that the defects treated with ACI were primarily filled with fibrocartilage, whereas the osteochondral cylinder transplants retained their hyaline character (e.g., a more favorable outcome), although there was a persistent interface between the transplant and the surrounding original cartilage. Limitations to this study included the small number of patients and limited follow-up of two years.

Knutsen et al. (2004) compared ACI to microfracture in a randomized controlled trial. Eighty patients without general osteoarthritis, who had a single symptomatic cartilage defect on the femoral condyle in a stable knee, were treated with ACI or microfracture (n=40). An independent observer performed a follow-up examination at 12 and 24 months after the procedure. A two-year postoperative arthroscopy with biopsy for histological evaluation was carried out. The authors report no significant differences regarding histological quality between the two treatment groups. Fifty percent of the biopsies in the ACI group showed some hyaline tissue. There was a tendency for the ACI procedure to result in more hyaline repair cartilage than the microfracture procedure, but the difference was not significant. Both methods appeared to have acceptable short-term results. The authors stated that younger and more active patients have better clinical results regardless of which type of treatment is received. According to the short-form (SF)-36 physical component score at two years postoperatively, the improvement in the microfracture group was significantly better than the ACI group.

Knutsen et al. published five-year results of this trial in 2007. The follow-up evaluation was carried out by the lead author. The procedure was considered to have failed if the patient required reoperation because of symptoms due to a lack of healing of the treated defect. At five years, there were nine failures (23%) in each group, compared to the two year results of two failures in the ACI group and one failure in the microfracture group. Seven patients were unavailable for examination and were contacted by mail and/or telephone, and all returned questionnaires. There were no failures in this group of patients. Failure occurred at a mean of 26.2 months after ACI and 37.8 months after microfracture treatment (p=0.101). One patient in each group with a failure received a total knee replacement. Seven patients with failure of ACI were treated with microfracture alone, and one patient received a high tibial osteotomy in addition to microfracture. Five patients with a failure of microfracture were treated with a repeat microfracture procedure, two were treated with mosaicplasty, and one received an ACI procedure. In the patients in both groups who did not have a failure, the mean Lysholm scores and mean pain scores on the visual analog scale (VAS) remained significantly improved (p<0.05). When adjustments were made for pretreatment measurements using linear regression analysis, there was no significant difference between the two treatment groups at five years in the Lysholm score (p=0.227) or VAS (p=0.278). At five years, there was no significant improvement from baseline in the SF-36 physical component score in the ACI group (p=0.309). There was a significant improvement in the microfracture group, however (p<0.001). Patients less than age 30 had a better outcome, regardless of the treatment group. The authors proposed that, based on these results, microfracture, a less costly, less invasive procedure, should be preferred as the first-line cartilage repair procedure for defects located on the medial or lateral femoral condyle of the knee. The authors stated that ACI may be preferred as a second-line treatment, particularly for large defects that are not contained.

Mandelbaum et al. (2007) conducted a case series to test the hypothesis that patients treated with ACI for moderate to large isolated lesions located on the trochlea will report improvement in the modified overall condition scale score of the Cincinnati Knee Rating System. This rating system assigns a score from one (poor) to ten (excellent). Patients from the Cartilage Repair Registry (n=40) rated their overall condition and symptoms at baseline, and at a mean follow-up of 59 ± 18 months. Patients were age 16–48, and had a mean total defect size of 4.5 cm². Many patients (48%) had failed a prior marrow stimulation procedure. Tibiofemoral osteotomy had been performed in 23% of patients at baseline, and lateral release or Fulkerson for patella maltracking had been performed on 13% of patients. Patients reported a mean improvement in their overall condition score from 3.1 ± 1.0 points at baseline, to 6.4 ± 1.7 points at follow-up (p<.0001). Pain and swelling scores also improved from 2.6 ± 1.7 to 6.2 ± 2.4 points, and 3.9 ± 2.7 to 6.3 ± 2.7 points, respectively (p<.0001). The degree of improvement was not significantly different between patients who had a concurrent procedure with ACI and those who did not. There were no failed implantations. Eleven patients received subsequent procedures for adhesions, periosteal flap detachment, chondromalacia, loose bodies, torn meniscus, fibrotic tissue, and decreased range of motion.

Jobanputra et al. (2001) conducted a systematic review commissioned by the UK National Health Service on behalf of the National Institute for Clinical Excellence (NICE). Seventeen studies (n=2600 patients) who were treated with ACT were reviewed. All reports included in the analysis were case series with variable follow-up times. The outcome of the surgery two years after treatment was rated as good or excellent by 70% of the patients. Approximately 16% of the patients required further arthroscopic surgical procedures during follow-up, and treatment was judged to have failed in 3–7% of the patients. The two-

year outcome for comparator treatments was rated as good or excellent in 10–95% of patients. The authors concluded that the literature on ACT and comparators is subject to bias because of the inherent weaknesses of case series, and stated that the long-term impact of conventional surgical treatments or no surgical treatment is poorly documented. Recommendations for further research included the need to provide more accurate data on the occurrence of hyaline cartilage defects, evaluate the natural history of cartilage defects, clarify the relationship of cartilage defects to clinical symptoms, and compare ACT with other treatments based on randomized trials.

Brown et al. (2005) conducted a multicenter cohort study to assess the clinical outcome of patients treated with ACI for lesions of the distal femur. Modified 10-point scales of the Cincinnati knee rating system were used to measure outcome assessments at baseline and at five years. Eighty-seven percent of patients completed five-year follow-up assessments. Patients were an average of age 37 and had a mean total defect size of 4.9 cm². At least one prior cartilage repair procedure had failed in 70% of the patients. At follow-up, 87 patients reported a mean improvement of 2.6 points in the overall condition score, including 62 with improved conditions, six with no change in condition, and 19 with worsened conditions. The authors stated that the factors that contributed to some treatment failures highlight the importance of careful clinical evaluation and patient selection. Ligament instability and joint malalignment should be corrected either before or concurrent with ACI. The authors also stated that ACI is not indicated for cartilage damage associated with osteoarthritis or inflammatory arthritis. Of the 62 patients who improved, the mean overall condition score improved 4.1 points at follow-up. The authors concluded that, for patients like those in the study, with few treatment options, ACI is a viable treatment option that may yield relatively long-term symptomatic relief and functional improvement.

Wood et al. (2006) reported on an investigation performed at the FDA Center for Biologics Evaluations and Research that describes the adverse events following Carticel implantation as reported to the FDA from 1996 to 2003. The review evaluated adverse event reports submitted to the FDA's Med-Watch system for information on demographic characteristics, adverse events, and surgical revisions. Adverse events were categorized into sixteen non-mutually exclusive groups. Five categories were used to classify reoperation. FDA regulations require manufacturers to report adverse events; however, reporting by clinicians and others is voluntary. Therefore, adverse event reporting is likely to underestimate the number of event occurrences. Adverse events may be either causally or coincidentally related to the product. A total of 497 adverse events among 294 patients receiving Carticel were reported. The median interval from Carticel implantation to the diagnosis of an adverse event was 240 days (range 1–2105 days). The median age of the patients was 38 years, and 63% of the patients were male. Of the 270 events for which the anatomic site was noted, 258 (96%) involved the femoral condyles. More than one adverse event was reported for 135 patients (46%). The most commonly reported events were graft failure (n= 73; 25%), delamination (n= 65; 22%), and tissue hypertrophy (n= 52; 18%). Eighteen surgical site infections were reported, including 11 joint and seven soft-tissue infections. Surgical revision subsequent to Carticel implantation was mentioned in the records for 273 patients (93%). The reasons for the 389 revision procedures included graft-related problems (187 procedures; 48.1%), periarticular soft-tissue problems (97 procedures; 24.9%), and intra-articular problems (63 procedures; 16.2%). Eight patients had a total knee replacement. Based on the manufacturer's reported distribution of 7500 Carticel lots between 1995 and 2002, 285 patients (3.8%) had an adverse event that was reported to the FDA. The authors report that the most common adverse events reported in association with the Carticel technique involved graft failure, delamination, and tissue hypertrophy.

A Cochrane systematic review of ACI for full thickness articular cartilage defects of the knee, reported by Wasiaik et al. in 2002 and updated in 2006, included four randomized controlled trials with 266 participants. The review included the Knutsen and Horas trials (described above) and trials by Basad et al. (2004) and Bentley et al. (2003). The authors concluded that the use of ACI and other chondral resurfacing techniques is becoming increasingly widespread. However, there is at present no evidence of significant differences between ACI and other interventions. Additional good quality randomized controlled trials with long-term functional outcomes are required.

The use of ACT became widely available in the U.S. following FDA approval of Carticel and early reports of success in Sweden. There is significant controversy regarding the efficacy of the procedure and indications for use. There is some medical consensus that the procedure may be appropriate in patients with the following characteristics (Hayes, 2005):

- age 15–55 years
- symptoms of at least one-year duration
- femoral condyle defect size of 1–12 cm²
- defect grade III to IV (full thickness)
- no generalized tibial chondromalacia
- no osteoarthritis of the knee
- stable and aligned knee (corrective procedures may be performed in combination with or prior to ACT)
- patient willing to comply with rigorous rehabilitation program
- normal articular cartilage at lesion border

A review of ACI by Gillogly and Myers (2005) states if a large lesion is present on the reciprocal surface (kissing lesions), with exposed bone greater than a grade III chondromalacia, the opposing surface is typically not suitable for this technique. This is particularly true when the secondary bony deformity exists as a result of the arthritic process.

Washington State Department of Labor and Industries (2004) recommendations for review of knee surgery include the following for consideration of ACI:

- physical therapy for a minimum of two months
- capable and willing to follow the rehabilitation protocol
- failure of traditional surgical interventions (i.e., microfracture, drilling, abrasion, osteochondral graft)
- single, clinically significant lesion that measures between 1–10 cm² in area that affects a weight-bearing surface of the medial femoral condyle or the lateral femoral condyle
- full-thickness lesion, grade III–IV that involves only cartilage
- knee is stable with intact, fully functional menisci and ligaments
- normal knee alignment
- normal joint space
- less than 60 years old
- body mass index (BMI) of less than 35

The efficacy of ACT, commercialized as Carticel by Genzyme Biosurgery (Cambridge, MA), compared to other available procedures used clinically, is still somewhat unclear. The importance of comparisons between ACT and other surgical procedures for cartilage repair was highlighted by a study of arthroscopic surgery of knee joints that demonstrated the positive placebo-like effects of control arms of surgical procedures (Moseley, et al., 2002). Controlled trials are needed to clarify and compare the efficacy and long-term outcomes of ACT compared to established medical and surgical treatment. Based on the available evidence and revised FDA indications for use, ACT should be limited to use as a second-line treatment for symptomatic patients with defects of the femoral condyle caused by acute or repetitive trauma who have had an inadequate response to prior arthroscopic or other surgical repair. Although additional patient selection criteria are not clearly defined, the procedure should be limited to patients with the characteristics described above, for which there is reasonable clinical consensus.

FDA approval of Carticel is limited to treatment of the femoral condyle. There is no evidence in the published medical literature of the safety and efficacy of ACT in the treatment of lesions of the tibial or patella, or for treatment of other joints, including the ankle and shoulder.

National Institute for Clinical Excellence (NICE): Guidance issued in 2005 states that autologous chondrocyte implantation (ACI) is not recommended for the treatment of articular cartilage defects of the knee joint except in the context of ongoing or new clinical studies that are designed to generate robust and relevant outcome data, including the measurement of health-related quality of life and long-term follow-up. Patients should be fully informed of the uncertainties about the long-term effectiveness and the potential adverse effects of this procedure.

Professional Societies/Organizations

International Cartilage Repair Society (ICRS) (2004): ICRS reports that rigorous evaluation of the efficacy of ACT requires standardized criteria for evaluating joint disease and objective outcome parameters. The society has proposed a comprehensive method of documentation and classification of cartilage lesions that includes etiology, size and depth of defect, location, concurrent joint abnormalities, previous treatments, radiological and magnetic resonance imaging (MRI) appearance, and general medical history; however, this classification scheme has not yet been universally adopted. Although objective measures of outcome have been proposed, including parameters such as range of motion, 50-foot walk time, arthroscopic evaluation with biopsy, and MRI examination, the majority of studies report only subjective assessments such as pain, swelling, knee-locking, and patient satisfaction. Rigorous evaluation of the efficacy of ACT requires standardized criteria for evaluating joint disease and objective outcome parameters.

Summary

The evidence is mixed in terms of effectiveness of autologous chondrocyte transplantation (ACT) for the treatment of cartilaginous defects of the knee. Prospective, randomized clinical studies are needed to assess the impact on functional status, disability, and pain. In addition, studies need to compare the effectiveness of ACT to established methods of treatment of cartilage defects of the knee. Therefore, ACT for the repair of symptomatic, cartilaginous defects of the femoral condyle should be considered only as second-line therapy in carefully selected patients who have had an inadequate response to prior arthroscopic or other surgical repair.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

CPT®* Codes	Description
27412	Autologous chondrocyte implantation, knee

HCPCS Codes	Description
J7330	Autologous cultured chondrocytes, implant
S2112	Arthroscopy, knee, surgical harvesting of cartilage (chondrocyte cells)

ICD-9-CM Diagnosis Codes	Description
717.7	Chondromalacia of patella
732.7	Osteochondritis dissecans of knee
733.90	Cartilage defect in trochlea

*Current Procedural Terminology (CPT®) © 2007 American Medical Association: Chicago, IL.

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