

# MEDICAL POLICY



MEDICAL POLICY DETAILS	
Medical Policy Title	AUTOLOGOUS CHONDROCYTE IMPLANTATION
Policy Number	7.01.38
Category	Technology Assessment
Effective Date	07/02/99
Revised Date	02/01/01, 01/17/02, 03/20/03, 01/15/04, 01/20/05, 11/17/05, 07/20/06, 06/21/07, 05/14/08, 04/16/09, 05/27/10, 05/19/11, 05/24/12, 04/18/13, 03/20/14, 03/19/15, 02/18/16, 04/20/17, 04/18/18, 06/21/18, 06/20/19
Product Disclaimer	<ul style="list-style-type: none"> <li>• If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.</li> <li>• If a commercial product (including an Essential Plan product) or a Medicaid product covers a specific service, medical policy criteria apply to the benefit.</li> <li>• If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.</li> </ul>

## POLICY STATEMENT

- I. Based upon our criteria and assessment of peer-reviewed literature, autologous chondrocyte implantation (ACI) using the MACI™ implant is **medically appropriate** for treatment of symptomatic single or multiple full-thickness cartilage defects of the distal femoral articular surface (e.g., medial condyle, lateral condyle or trochlea) and/or patella caused by acute or repetitive trauma when ALL of the following are present:
- Severe, disabling pain and a loss of knee function which interferes with the ability to carry out age appropriate activities of daily living and/or demands of employment;
  - A distal femoral articular surface (i.e., medial condyle, lateral condyle or trochlea) defect of 1-10 cm<sup>2</sup> in size has been identified during arthroscopy or during an MRI or CT arthrogram which is classified by the Modified Outerbridge Scale as Grade III or Grade IV or symptomatic, full-thickness articular cartilage lesions of the trochlea;
  - Failure of provider-directed non-surgical management for at least 3 months in duration;
  - Presence of both of the following on physical examination:
    - A stable knee with intact or reconstructed ligaments (ACL or PCL); and
    - Normal joint alignment.
  - Absence of an osteochondritis dissecans (OCD) lesion that requires bone grafting;
  - Absence of inflammatory arthritis or other systemic disease affecting the joints;
  - Minimal to absent osteoarthritic changes in the surrounding articular cartilage (e.g. Kellgren-Lawrence Grade 2 or less);
  - Previous arthroscopic or other traditional surgical procedure (i.e., microfracture, drilling, abrasion, osteochondral graft) which has resulted in an unsatisfactory outcome;
  - Normal articular cartilage at the lesion border (contained lesion);
  - For femoral and patellar chondral lesions, absence of corresponding tibial or patellar lesion (“kissing lesion”) with a Modified Outerbridge Scale of Grade III or Grade IV of the distal femur (trochlea, condyles), patella or tibia;
  - Body Mass Index (BMI) 35 or less; and
  - Age 15-55 years.
- II. Based upon our criteria and assessment of the peer-reviewed literature, autologous chondrocyte implantation is considered **not medically necessary** for any other indication or condition, including when ANY of the following criteria is present:
- Any knee joint surgery within six (6) months before screening excluding surgery to procure a biopsy or a concomitant procedure to prepare the knee for a MACI implant;
  - Modified Outerbridge grade III or IV defect(s) on the tibia;

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- C. Presence of Kellgren-Lawrence Grade 3 or 4 osteoarthritic changes in the surrounding articular cartilage;
  - D. Total meniscectomy, meniscal allograft, or bucket-handle tear or displaced tear requiring more than 50% removal of the meniscus in the target knee;
  - E. Septic arthritis within one (1) year before screening;
  - F. Known history of hypersensitivity to gentamicin, other aminoglycosides, or products of porcine or bovine origin;
  - G. Uncorrected congenital blood coagulation disorders;
  - H. Cruciate ligament instability.
- III. Based upon our criteria and assessment of peer-reviewed literature, hybrid autologous chondrocyte implantation (ACI) performed with osteochondral autograft transfer system (Hybrid ACI/OATS) technique has not been medically proven to be effective and is **investigational** for the treatment of osteochondral defects.

*Refer to Corporate Medical Policy # 7.01.59 regarding Osteochondral Grafting.*

*Refer to Corporate Medical Policy #11.01.03 regarding Experimental and Investigational Services.*

### **POLICY GUIDELINES**

The Federal Employee Health Benefit Program (FEHBP/FEP) requires that procedures, devices or laboratory tests approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational and thus these procedures, devices or laboratory tests may be assessed only on the basis of their medical necessity.

### **DESCRIPTION**

Destruction of the articulating surface of the synovial joint of the knee results in increased pain and loss of function to the joint. Damaged articular cartilage fails to heal on its own making repair of articular surfaces difficult. Autologous chondrocyte implantation (ACI) is a surgical treatment for patients with deep cartilage defects in the knee. The procedure involves the collection and culture of an individual's own 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.

Carticel® received FDA approval through a biologics license for the culturing of chondrocytes. The approval restricted Carticel® to use 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.

Methods to improve the ACI procedure have been investigated, including the use of a scaffold or matrix-induced/applied ACI (MACI) composed of biocompatible carbohydrates, protein polymers or synthetics (e.g., matrix based ACI, Hyalograft C, Cartipatch). The use of minced cartilage techniques are also under development. The tissue fragments are mixed intra-operatively with fibrin glue before implantation. It is thought that mincing the tissue helps with cell migration.

In 2017, Carticel®, the first generation ACI with a collagen cover was being phased out and replaced with a preparation of ACI that seeds the chondrocytes onto a bio-resorbable collagen sponge. The only FDA-approved MACI product to date is supplied in a sheet, which is cut to size and fixed with fibrin glue. This procedure is considered to be technically easier and less time consuming than the first generation technique, which required suturing of a periosteal or collagen patch and injection of chondrocytes under the patch. The entire matrix-induced ACI procedure consists of 4 steps: (1) initial arthroscopy and biopsy of normal cartilage, (2) culturing of chondrocytes on an absorbable collagen matrix, (3) a separate arthrotomy to place the implant create a periosteal flap and, and (4) postsurgical rehabilitation. The initial arthroscopy may be scheduled as a diagnostic procedure; as part of this procedure, a cartilage defect may be identified, prompting biopsy of normal cartilage in anticipation of a possible chondrocyte transplant. The biopsied material is then sent for culturing and returned to the hospital when the implantation procedure (ie, arthrotomy) is scheduled.

Modified Outerbridge Classification is a system that has been developed for judging articular cartilage 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:

1. Grade I – softening with swelling;

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2. Grade II – fragmentation and fissuring less than one square centimeter (1 cm<sup>2</sup>);
3. Grade III – fragmentation and fissuring greater than one square centimeter (1 cm<sup>2</sup>);
4. Grade IV – subchondral bone exposed.

The Kellgren-Lawrence Grading System is a radiographic grading system that has been developed for describing osteoarthritic changes to the knee. When used, the radiographic findings are typically reported within one of the following categories:

1. Grade 0 – No radiographic features of osteoarthritis are present;
2. Grade I – Doubtful narrowing of joint space and possible osteophytic lipping;
3. Grade II – Definite osteophytes and possible narrowing of joint space;
4. Grade III – Moderate multiple osteophytes, definite narrowing of joint space, some sclerosis, and possible deformity of bone contour;
5. Grade IV – Large osteophytes, marked narrowing of joint space, severe sclerosis, and definite deformity of bone contour.

### **RATIONALE**

Genzyme Tissue Repair's Carticel autologous chondrocytes received approval by the FDA of its biologics license for 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. There is sufficient data published in the peer-reviewed literature to conclude that autologous chondrocyte transplantation results in relief of symptoms and improved function in patients who had failed conservative management and arthroscopic or other surgical treatments. Several studies include reports of histological examinations of the graft site showing stable hyaline cartilage after surgery. Studies in the United States enrolled patients between the ages of 15 and 45 years.

K Zaslav and colleagues (2009) conducted a prospective, cohort study (STAR) to assess the effectiveness of autologous chondrocyte implantation in patients who failed prior treatments for articular cartilage defects of the knee. 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. Outcomes included change from baseline in knee function, knee pain, quality of life, and overall health. Duration of benefit after autologous chondrocyte implantation was compared with the failed prior non-autologous chondrocyte implantation procedure. One hundred twenty-six patients (82%) completed the protocol. Seventy-six percent of patients were treatment successes at study end, while 24% were deemed treatment failures. Preoperative mean knee pain score was 3.0 (SD, 1.8; 0 = severe, 10 = normal). Mean improvements were observed from baseline to all time points ( $P < .001$ ) for all outcome measures. Preoperative to 48-month values, respectively, were as follows: On the Knee Injury and Osteoarthritis Outcome Score subscales of pain: 48.7 to 72.2; other symptoms: 51.8 to 70.8; sports/recreation: 25.8 to 55.8; knee quality of life: 20.9 to 52.2; and activities of daily living: 58.6 to 81.0; on the Modified Cincinnati Overall Knee score: 3.3 to 6.3; on the visual analog scale: 28.8 to 69.9; and on the SF-36 Overall Physical Health: 33.0 to 44.4. Seventy-six patients (49%) had subsequent surgical procedure(s), predominantly arthroscopic. The authors concluded that patients with moderate to large chondral lesions with failed prior cartilage treatments can expect sustained and clinically meaningful improvement in pain and function after autologous chondrocyte implantation.

In December 2016, the U.S. Food and Drug Administration (FDA) approved MACI<sup>®</sup> (autologous cultured chondrocytes on porcine collagen membrane) for the repair of symptomatic single or multiple full-thickness cartilage defects of the knee with or without bone involvement in adults. MACI is the first FDA-approved cellularized scaffold product that applies tissue engineering processes to grow cells on scaffolds using healthy cartilage tissue from the patient's own knee. The approval of MACI is based on the SUMMIT study (Superiority of MACI implant versus Microfracture Treatment in patients with symptomatic articular cartilage defects in the knee). In the open-label, multi-center Phase 3 SUMMIT study, 144 patients with symptomatic articular cartilage defects in the knee were randomized to receive treatment with MACI implant or microfracture bone marrow stimulation (MFX) and followed for two years (D Saris, et al. 2014). The study found that treatment with MACI was clinically and statistically significantly better, as measured by greater improvement in KOOS pain and function (SRA) scores in the MACI group compared to the microfracture groups ( $p=0.001$ ) than MFX,

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with similar structural repair tissue and safety. The SUMMIT study investigators concluded that "MACI offers a more efficacious alternative than MFX with a similar safety profile for the treatment of symptomatic articular cartilage defects of the knee." Patients from the two-year SUMMIT study had the option to enroll in a three-year follow-up study (extension study). A majority of the patients who completed the SUMMIT study also participated in the extension study. Overall efficacy data support a long-term clinical benefit from the use of MACI in patients with cartilage defects of the knee.

Three-year follow-up results of the SUMMIT extension study were presented at the 2015 AAOS annual meeting. In the SUMMIT Extension trial, 128 patients (men and women aged 18 to 55) from the original SUMMIT study continue to be followed. The co-primary endpoints of the extension study are change in knee injury and osteoarthritis outcome (KOOS) pain and function scores at year 3, the same primary endpoint from the two-year SUMMIT trial. Patients treated with MACI versus MFX continue to show a statistically significant improvement from baseline in the co-primary endpoint of KOOS pain and function at year 3 ( $p = 0.046$ ) with higher responder rates in the MACI group (81.5%) than in the MFX group (66.7%). Patients treated with MACI versus MFX also showed significant improvement in knee-related quality of life and other measures. The authors concluded that "the co-primary endpoints of pain and function showed significant improvement with MACI, which was statistically significantly better than with MFX." The incidences of treatment emergent adverse events and serious adverse events were similar between treatment groups at year 3 and no unexpected safety findings were reported.

Based on mid-term outcomes that approximate those of first generation ACI and the lack of alternatives, second generation ACI may be considered an option for large disabling full-thickness cartilage lesions of the knee. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

In a systematic review, Samsudin and Kamarul (2016) evaluated the current evidence for ACI generations relative to other treatment modalities, different cell delivery methods and different cell source application. Literature search was performed to identify all level I and II studies reporting the clinical and structural outcome of any ACI generation in human knees using the following medical electronic databases: PubMed, EMBASE, Cochrane Library, CINAHL, SPORTDiscus and NICE healthcare database. The level of evidence, sample size calculation and risk of bias were determined for all included studies to enable quality assessment. A total of 20 studies were included in the analysis, reporting on a total of 1,094 patients. Of the 20 studies, 13 compared ACI with other treatment modalities, 7 compared different ACI cell delivery methods, and 1 compared different cell source for implantation. Studies included were heterogeneous in baseline design, preventing meta-analysis. Data showed a trend towards similar outcomes when comparing ACI generations with other repair techniques and when comparing different cell delivery methods and cell source selection. Majority of the studies (80 %) were level II evidence, and overall the quality of studies can be rated as average to low, with the absence of power analysis in 65 % studies. The authors concluded that at present, there are insufficient data to conclude any superiority of ACI techniques. Considering its 2-stage operation and cost, it may be appropriate to reserve ACI for patients with larger defects or those who have had inadequate response to other repair procedures until hard evidence enables specific clinical recommendations be made.

The evidence on ACI for individuals who have focal articular cartilage lesions in joints other than the knee is limited. Relevant outcomes are symptoms, functional outcomes, implant survival, quality of life, and resource utilization. The greatest amount of literature is for ACI of the talus. A systematic review (Zengerink, et al.) found that outcomes following treatment with ACI were inferior to microfracture. The evidence is insufficient to determine the effects of the technology (ACI for joints other than knee) on health outcomes.

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The use of minced cartilage techniques are also under development. DeNovo NT (natural tissue) Graft and DeNovo® ET Live Chondral Engineered Tissue Graft (Neocartilage) are produced by ISTO Technologies (exclusively distributed by Zimmer, Inc.). DeNovo NT consists of manually minced cartilage tissue pieces obtained from juvenile allograft donor joints. As there are no chemicals used and minimal manipulation, it is regulated as an allograft tissue rather than a biological implant. Therefore, the allograft tissue does not require FDA approval for marketing. DeNovo NT is currently available in the USA. Neocartilage uses juvenile allogeneic cartilage cells that are isolated and expanded in vitro, similar to other ACI techniques. Neocartilage is currently being studied in human clinical trials in the USA under an FDA approved investigational new drug (IND) application.

### CODES

- Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.
- **CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.**
- Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.

#### CPT Codes

Code	Description
27412	Autologous chondrocyte implantation, knee

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#### HCPCS Codes

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

#### ICD10 Codes

Code	Description
M12.561- M12.569	Traumatic arthropathy, knee (code range)
M17.0- M17.9	Osteoarthritis of knee (code range)
M23.50-M23.52	Chronic instability of knee (code range)
M23.8X1 – M23.8X9	Other internal derangements of knee (code range)
M23.90- M23.92	Unspecified, internal derangement of knee (code range)
M25.261- M25.269	Flail joint, knee (code range)
M25.361- M25.369	Other instability, knee (code range)
M25.861- M25.869	Other specified joint disorder, knee (code range)
M85.9	Disorder of bone density and structure, unspecified
M89.8X6	Other specified disorders of bone, lower leg
M89.9	Disorder of bone, unspecified
M93.20	Osteochondritis dissecans of unspecified site
M93.261- M93.269	Osteochondritis dissecans knee (code range)

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Code	Description
M94.8X6	Other specified disorders of cartilage, lower leg
M94.9	Disorder of cartilage, unspecified

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\*Key Article

### **KEY WORDS**

Carticel, Matrix-induced, MACI, Minced cartilage, Neocartilage, Scaffold-induced

### **CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS**

Based on our review, autologous chondrocyte implantation is not addressed in National or Regional Medicare coverage determinations or policies.