MEDICAL POLICY

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MEDICAL POLICY DETAILS	
Medical Policy Title	**Autologous Chondrocyte Implantation (ACI)**
Policy Number	**7.01.38**
Category	**Technology Assessment**
Original Effective Date	**07/02/99**
Committee Approval 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, 08/20/20, 06/17/21, 05/19/22, 05/18/23, 10/17/24**
Current Effective Date	**02/01/25**
Archived Date	**N/A**
Archived Review Date	**N/A**
Product Disclaimer	• *Services are contract dependent; if a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan or Child Health Plus product), medical policy criteria apply to the benefit.* • *If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.* • *If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) 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.* • *If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.*

POLICY STATEMENT

I. Based upon our criteria and assessment of peer-reviewed literature, autologous chondrocyte implantation (ACI)/ autologous chondrocyte transplantation (ACT) using the matrix-induced/applied ACI (MACI) implant has been medically proven to be effective and, therefore, is considered **medically appropriate** when **ALL** of the following criteria are met:
   A. Body Mass Index (BMI) 35 or less;
   B. Age 15-55 years;
   C. Absence of inflammatory arthritis or other systemic disease affecting the joints;
   D. Presence of **ALL** of the following arthroscopic or imaging findings:
      1. Kellgren-Lawrence grade II or less on radiographs;
      2. Normal articular cartilage at the lesion border (contained lesion); **and**
      3. Full thickness distal femoral articular surface (i.e., medial condyle, lateral condyle, or trochlea) and/or patellar chondral defect of 1-10cm in size that has been identified with **ANY** of the following:
         a. CT arthrogram;
         b. MRI and the Modified Outerbridge Classification is Grade III or IV;
         c. Arthroscopy and Outerbridge Classification is Grade III or IV.
   E. Absence of **BOTH** of the following imaging findings:
      1. Absence of and osteochondritis dissecans (OCD) lesion that requires bone grafting;
      2. Absence of a Modified Outerbridge Classification Grade III or IV corresponding kissing lesion defect on the distal femur (trochlea condyles), patella, or tibia **IS REQUIRED** when performed for femoral and patellar chondral lesions.
   F. Physical exam demonstrates **BOTH** of the following findings:

1. A stable knee with intact or reconstructed ligaments (ACL or PCL) and menisci; (note: a concurrent ligament stabilization or meniscal procedure at the time of ACI would be acceptable);
2. Normal tibial-femoral and/or patella-femoral alignment.

G. Symptoms include functioning-limiting knee pain or loss of knee function which interferes with the ability to carry out age-appropriate activities of daily living;
H. Failure of provider-directed, non-surgical management for at least three (3) months in duration;

II. Based upon our criteria and assessment of the peer-reviewed literature, autologous chondrocyte implantation has not been medically proven to be effective and, therefore, is considered **not medically necessary** for **ANY** other indication or condition, including but not limited to the following:
A. Any knee joint surgery within six months before screening, excluding surgery to procure a biopsy or a concomitant procedure to prepare the knee for a MACI implant;
B. Total meniscectomy, meniscal allograft, or bucket-handle tear or displaced tear requiring more than 50% removal of the meniscus in the target knee;
C. Septic arthritis within one year before screening;
D. Known history of hypersensitivity to gentamicin, other aminoglycosides, or products of porcine or bovine origin;
E. Uncorrected congenital blood coagulation disorders;
F. Cruciate ligament instability.

III. Based upon our criteria and assessment of the 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, therefore, is considered **investigational** for the treatment of osteochondral defects.

Refer to Corporate Medical Policy #7.01.59 Osteochondral Grafting

Refer to Corporate Medical Policy #11.01.03 Experimental or Investigational Services

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 is 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 four 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 and create a periosteal flap; and (4) postsurgical rehabilitation. The initial arthroscopy

may be scheduled as a diagnostic procedure. In some cases, as part of this procedure, a cartilage defect may be identified, prompting biopsy of normal cartilage in anticipation of a possible chondrocyte transplant. The biopsied material is then sent for culturing and returned to the hospital when the implantation procedure (i.e., arthrotomy) is scheduled.

The 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 as viewed by direct visualization intraoperatively, 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;
2. Grade II – fragmentation and fissuring less than one square centimeter (1 cm^2);
3. Grade III – fragmentation and fissuring greater than one square centimeter (1 cm^2);
4. Grade IV – subchondral bone exposed.

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;
2. Grade II – fragmentation and fissuring that do not exceed one square centimeter (1 cm2);
3. Grade III – fragmentation and fissuring greater than one square centimeter (1 cm2);
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 FDA approval 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, four-year study of 154 patients (mean age: 35 years; 69% male) from 29 clinical centers. Each patient served as the patient's 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 (KOOS) 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 Score: 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 FDA approved MACI (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, with similar structural repair tissue and safety. The SUMMIT study investigators concluded that "MACI offers a more efficacious alternative to 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 American Academy of Orthopaedic Surgeons (AAOS) annual meeting. In the SUMMIT extension trial, 128 patients (men and women aged 18 to 55 years) from the original SUMMIT study continue to be followed. The co-primary endpoints of the extension study are change in KOOS pain and function scores at year three, 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 three ($p = 0.046$), 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 incidence of treatment-emergent adverse events and serious adverse events was similar between treatment groups at year three, 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. A 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, seven compared different ACI cell delivery methods, and one compared different cell source for implantation. Studies included were heterogeneous in baseline design, preventing meta-analysis. Data showed a trend toward similar outcomes when comparing ACI generations with other repair techniques and when comparing different cell delivery methods and cell source selection. A 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% of the studies. The authors concluded that, at present, there are insufficient data to conclude any superiority of ACI techniques. Considering its two-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 to be made.

The evidence reported 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. The evidence is insufficient to determine the effects of the technology (ACI for joints other than knee) on health outcomes.

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.*
- *Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).*

CPT Codes

Code	Description
27412	Autologous chondrocyte implantation, knee

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

Code	Description
M93.261- M93.269	Osteochondritis dissecans knee (code range)
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 upon our review, autologous chondrocyte implantation is not addressed in National or Regional Medicare coverage determinations or policies.