POLICY STATEMENT:

I. Based upon our criteria and assessment of peer-reviewed literature, autologous chondrocyte implantation (ACI) is **medically appropriate** for treatment of symptomatic isolated cartilage defects of the femoral condyle in a stable knee when all of the following are present:

   A. Patient has achieved mature skeletal growth or is considered an unsuitable candidate for total joint replacement;
   
   B. There is symptomatic cartilaginous defect in the medial, lateral or trochlear area of the femoral condyle. If the defect extends deep into subchondral bone, repair of the subchondral base must be addressed first;
   
   C. There are clinically significant symptoms, cartilage injury (acute or chronic), that are unresponsive to physical therapy, conservative treatment, prior arthroscopic or other surgical repair procedure (e.g. debridement, drilling, microfracture);
   
   D. The defect size greater than 2 cm$^2$;
   
   E. The knee must be stable and aligned; an osteotomy may be required to achieve this; and
   
   F. There is no evidence of osteoarthritis or inflammatory disease (e.g., rheumatoid arthritis, gout, Bechterew syndrome, chondrocalcinosis).

II. Based upon our criteria and assessment of peer-reviewed literature, autologous chondrocyte implantation (ACI) has not been medically proven to be effective and is **investigational** for use in sites other than the femoral condyle (e.g. patella, talus).

Refer to Corporate Medical Policy # 7.01.59 regarding Osteochondral Grafting.

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.

Only Carticel® has 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 is 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.

**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® (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 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.

There is insufficient evidence in the literature to support the use of chondrocyte implantation other than the femoral condyle of the knee. 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.

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

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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:**

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| 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:**

27412 Autologous chondrocyte implantation, knee

**HCPCS:**

J7330 Autologous cultured chondrocytes, implant

S2112 Arthroscopy, knee, surgical for harvesting of cartilage (chondrocyte cells)

**ICD9:**

715.16 Osteoarthritis, localized, primary, lower leg

715.26 Osteoarthritis, localized, secondary, lower leg

715.36 Osteoarthritis, localized, not specified whether primary or secondary, lower leg

715.96 Osteoarthritis, unspecified whether generalized or localized, lower leg

716.16 Traumatic arthropathy, lower leg

717.9 Unspecified internal derangement, knee

718.86 Other joint derangement, lower leg

719.86 Other specified disorders of joint, lower leg

732.7 Osteochondritis dissecans

733.90 Other unspecified disorder of bone and cartilage

**ICD10:**

M12.561-M12.569 Traumatic arthropathy (code range)

M17.0- M17.9 Osteoarthritis of knee (code range)

M23.50-M23.52 Chronic instability 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

M89.9 Disorder of bone, unspecified

M93.20 Osteochondritis dissecans of unspecified site

M93.261-M93.269 Osteochondritis dissecans knee (code range)

M94 Disorder of cartilage, unspecified

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REFERENCES:


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**KEY WORDS:**

Carticel, Matrix-induced, MACI, Minced cartilage, Neocartilage, Scaffold-induced
Based on our review, autologous chondrocyte implantation is not addressed in National or Regional Medicare coverage determinations or policies.