

# Autologous chondrocyte implantation

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Recent review date: 2/2024

Next review date: 6/2025

Policy contains: Articular (hyaline) cartilage repair of the knee; autologous chondrocyte implantation; MACI.

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## Coverage policy

Autologous chondrocyte implantation (e.g., matrix-induced autologous chondrocyte implantation ([MACI<sup>®</sup>]), Vericel Corp, Cambridge, Massachusetts) is clinically proven and, therefore, may be medically necessary when all of the following criteria are met (National Institute for Health and Care Excellence, 2017; U.S. Food and Drug Administration, 2021):

- Ages 18 years and older.
- Body mass index  $\leq 35$  kg/m<sup>2</sup>.
- Full thickness (Outerbridge grade III or IV) isolated or multiple symptomatic articular cartilage defects of the knee with all of the following criteria:
  - Involves the femoral condyle (medial, lateral, or trochlear).
  - Size of defect ranges from 1 cm<sup>2</sup> to 10 cm<sup>2</sup>.
  - Caused by acute or repetitive trauma.
  - Symptoms of pain, swelling, or catching/locking that limit activities of daily living.
  - Stable, aligned knee with intact menisci and normal patellar mechanics.
- Failure of at least two months of conservative therapy (e.g., physical therapy, braces, and/or nonsteroidal anti-inflammatory drugs).
- Inadequate response to a prior arthroscopic or other surgical repair procedure (e.g., debridement, microfracture, drilling/abrasion arthroplasty, or osteochondral allograft/autograft).
- Willing and able to comply with rigorous postoperative rehabilitation program and activity restrictions.

## Limitations

All other uses of autologous chondrocyte implantation are not medically necessary, including:

- As initial or first-line treatment (Gou, 2020; Schuette, 2021).
- Partial-thickness defects.
- Patellar defects.
- Osteochondritis dissecans.
- Lesions in other joints, including talus and glenohumeral (Hu, 2023; Robinson, 2019).
- Chondral defects associated with generalized osteoarthritis or inflammatory diseases.
- In the presence of a previous total meniscectomy without reconstruction.

Contraindications to autologous chondrocyte implantation include (U.S. Food and Drug Administration, 2021):

- Active infection in the affected knee.
- A history of hypersensitivity to gentamicin, other aminoglycosides, or materials of porcine or bovine origin.
- A history of cancer in the bones, cartilage, fat, or muscle of the treated limb.
- Pre-existing conditions, including meniscus tears, joint instability, or malalignment, that are not addressed prior to, or concurrent with, the autologous chondrocyte implantation procedure.
- Inflammatory arthritis, inflammatory joint disease, or uncorrected congenital blood coagulation disorders.
- Prior knee surgery (within six months), excluding surgery to procure a biopsy or a concomitant procedure to prepare the knee for the implant.

## Alternative covered services

- Physical therapy.
- Orthotics.
- Non-steroidal anti-inflammatory drugs.
- Marrow stimulation techniques (e.g., microfracture, drilling, and debridement).
- Osteochondral autograft transplantation.
- Osteochondral allograft transplantation.

## **Background**

Articular cartilage defects can lead to chondral and osteochondral loss, with the latter occurring more commonly in adolescents. Ultimately, mechanical damage to the joint surface can lead to osteoarthritis. Classification of chondral and osteochondral knee injuries describes the type of articular cartilage lesions (e.g., full-thickness lesion in which subchondral bone is exposed) and the severity of damage arthroscopically using grading systems such as the Outerbridge system as follows (Slattery, 2018):

- Grade I is very mild with softening.
- Grade II includes fissuring or crater depth less than half the full thickness.
- Grade III is damage through most of the thickness of the cartilage.
- Grade IV is a full thickness defect with exposed bone.

Surgical techniques to repair or restore articular cartilage may prevent further damage to the knee and avoid or delay total knee replacement (American Academy of Orthopaedic Surgeons, 2023). These procedures include microfracture, drilling, abrasion arthroplasty, osteochondral transplantation (autograft and allograft), and autologous chondrocyte implantation.

Autologous chondrocyte implantation involves harvesting autologous chondrocytes from articular cartilage, expanding them in culture medium containing fetal bovine serum, and implanting the cells at the site of injury. An autologous periosteal flap is sutured in place to form a watertight cover under which the chondrocyte suspension is injected. Modifications to the original method include: (1) synthetic collagen matrices, instead of using a periosteal flap, to accommodate and promote autologous chondrocyte growth in a supportive three-dimensional environment that more closely matches hyaline cartilage; and (2) seeding a biocompatible porcine collagen matrix with chondrocytes and allowing the cells to grow on the scaffold matrix before suture-free implantation (i.e., MACI) (Farr, 2011).

The U.S. Food and Drug Administration (2007) approved the product Carticel, representing the first biologic approved for use in the orthopedic field. However, Carticel is no longer commercially available. The U.S. Food and Drug Administration (2021) subsequently approved MACI for the repair of single or multiple symptomatic, full-thickness cartilage defects of the knee with or without bone involvement in adults ages 18 years and older.

## Findings

We identified seven systematic reviews and meta-analyses, one longitudinal study, two cost-effectiveness analyses, and one evidence-based guideline for this policy. The systematic reviews and meta-analyses assessed autologous chondrocyte implantation of the knee in adult populations (DiBartola, 2016a; Goyal, 2013; Mistry, 2017; Mundi, 2016; Sacolick, 2019); in adolescent knees (DiBartola, 2016b); and of the talus joint (Hu, 2023). One longitudinal study presented long-term outcome data (greater than 10 years follow-up) for the knee procedures at a single site (Minas, 2014).

One clinical practice guideline/technology appraisal from National Institute for Health and Care Excellence (2017) is undergoing an update. Elvidge (2016) examined the cost-effectiveness of autologous chondrocyte implantation in the United Kingdom. Another guideline from a German working group states autologous chondrocyte implantation is indicated for symptomatic cartilage defects starting from defect sizes of more than 3 – 4cm<sup>2</sup>, and in young/active athletes at 2.5cm<sup>2</sup>; advanced degenerative joint disease is contraindicated (Niemeyer, 2016). The American Academy of Orthopaedic Surgeons practice guideline on surgical management of knee osteoarthritis does not mention autologous chondrocyte implantation (American Academy of Orthopaedic Surgeons, 2022).

There is sufficient evidence to support Carticel as a second-line treatment of a single, symptomatic full-thickness (or minimum Outerbridge grade III) lesion of the femoral condyle in patients ages 15 to 55 years, who have had an inadequate response to prior arthroscopic or other surgical repair and who do not have specific contraindications to the procedure. Focal chondral defect size ranged from 1.0 cm<sup>2</sup> to 10 cm<sup>2</sup> with a mean of 1.9 cm<sup>2</sup> to 5.1 cm<sup>2</sup>. Most studies included persons with a body mass index less than 35 kg/m<sup>2</sup> and a stable knee joint.

Moderate-quality evidence from randomized controlled trials and quasi-randomized controlled trials suggests that short-and intermediate-term outcomes, using a variety of knee-specific scales for patient-reported functional outcomes, are similar to other established surgical approaches. Unlike other grafting procedures, Carticel does not require that substantial amounts of tissue be harvested, and the procedure can be applied to larger lesions. Carticel is a safe procedure, but at least 25% of patients required arthroscopic evaluation of symptoms or subsequent surgery.

Limited evidence of long-term outcomes greater than 10 years suggests the procedure is durable, but a history of prior marrow stimulation techniques and treatment of very large defects may increase risk of failure (Minas,

2014). The most common adverse effects were symptomatic complications related to the periosteal flap (e.g., hypertrophy and implant extrusion). Autologous chondrocyte implantation may be more cost effective than other procedures over the long term, assuming it can generate new hyaline cartilage and prevent osteoarthritis.

Autologous chondrocyte implantation can require extended postoperative recovery. Return to sport-specific activities can be prolonged, taking up to nine to 24 months after surgery (Farr, 2011). Treatment decisions must consider patient goals, physical demands, expectations, and perceptions, as well as defect size, depth, location, chronicity, previous treatments and response, and concomitant pathology (Farr, 2011).

There is insufficient evidence to support:

- Carticel as a first-line treatment, for multiple defects on a femoral condyle, for defects of the patella or trochlea, or for osteochondritis dissecans.
- Autologous chondrocyte implantation for other joints.
- MACI, as it is not approved for commercial use in the United States as of this writing.

In 2018, we added new information regarding approval of MACI for the repair of single or multiple symptomatic, full-thickness cartilage defects of the knee with or without bone involvement in adults ages 18 years and older (U.S. Food and Drug Administration, 2021). The biocompatible matrix reduces the problems associated with extensive suturing and cell leakage found with Carticel.

Approval was based on the results of a two-year prospective, multicenter, randomized controlled trial (Saris, 2014; clinicaltrials.gov identifier NCT00719576) and its three-year extension trial (clinicaltrials.gov identifier NCT01251588). Saris (2014) compared MACI to microfracture in 144 subjects, ages 18 to 54 years, with at least one symptomatic Outerbridge Grade III or IV focal cartilage defect at least 3 cm<sup>2</sup> of femoral condyle or the trochlea. The safety and effectiveness of MACI in joints other than the knee, pediatric patients, patients over the age of 55 years, or pregnant patients have not been established.

These procedures are typically indicated for older adolescent or adult patients with symptomatic, full-thickness cartilage defects of the knee who have not responded adequately to conservative therapy (National Institute for Health and Care Excellence, 2017). The policy was revised to reflect this new information.

In 2019, we removed Carticel from the coverage policy, as it is no longer commercially available. We added five systematic reviews (Kraeutler, 2018; Lamplot, 2018; Riboh, 2017; Salzman, 2018; Valtanen, 2020) to the policy, and their findings are consistent with the current policy. No policy changes are warranted. The policy ID was changed from CP# 14.03.07 to CCP.1293.

In 2020, a systematic review (Shanmugaraj, 2019) of 28 single-arm, observational studies (n = 708 adults, 824 total knees) found autologous chondrocyte implantation was the most common restoration technique with a commensurate decline in the use of conventional microfracture techniques over the latter half of the past decade ( $P < .001$ ). Overall, cartilage restoration techniques improved patient-reported outcomes with low complication rates, but the superiority of any one technique cannot be determined. No policy changes are warranted.

In 2021, we added five systematic reviews to the policy. The new evidence confirms the safety and effectiveness of autologous chondrocyte implantation as a secondary treatment for knee cartilage restoration in skeletally mature patients, which includes some adolescents younger than age 18 (Coughlin, 2019; Zamborsky, 2020).

The evidence supporting autologous chondrocyte implantation for other joints (Robinson, 2019) or as a primary treatment for knee cartilage lesions remains insufficient (Gou, 2020; Schuette, 2021). The new information requires no policy changes.

In 2022, we added systematic reviews concluding (knee) autologous chondrocyte implantation:

- Is associated with peak graft maturation about two years after the procedure (Iordache, 2021);
- Has similar outcomes whether mini-arthrotomy or arthroscopy is used (Migliorini, 2021a);
- Appears to be the preferred treatment for younger patients (Abraamyan, 2022);
- Successfully treats patellar chondral defects, but has up to a 40 – 60% reoperation rate (Su, 2021);
- Was the most common treatment for patellar chondral defects, with positive outcomes (Burger, 2022);
- Also showed positive outcomes for osteochondral defects of the talus (Hu, 2023);
- Has a cost of 14,395 British pounds per quality adjusted life year gained (Mistry, 2017).

In 2023, we added systematic reviews concluding (knee) autologous chondrocyte implantation:

- Is effective in skeletally immature patients, with a “controversial” safety profile (Migliorini, 2023);
- Is effective long-term (over two years post-operative) (Grossman, 2022);
- Results in improvements after 11-15 years, with a 10% failure rate (Colombini, 2023);
- Has a lower failure rate and better patient-reported outcomes than microfracture (Dhillon, 2022);
- Results in greater improvements for patients under age 40, versus over 40 (Jeuken, 2022).
- Is less effective and has more failures and revisions than autologous matrix-induced chondrogenesis (Migliorini, 2021b).

In 2024, we added systematic reviews/meta-analyses that showed, compared to MACI:

- (45 studies, n = 1,667); matrix-induced chondrogenesis had better outcomes (Migliorini, 2022).
- (Eight studies, n = 718); no difference using bone marrow aspirate concentrate (for talus) (Klein, 2023).

## References

On November 21, 2023, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “cartilage, articular” (MeSH), “chondrocytes” (MeSH), “transplantation, autologous” (MeSH), and the free text term “autologous chondrocyte implantation.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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## Policy updates

1/2017: initial review date and clinical policy effective date: 3/2017

3/2018: Policy references updated. Policy changed to reflect new regulatory approval of MACI.

3/2019: Policy references updated. Carticel removed from coverage policy. Policy ID changed.

3/2020: Policy references updated.

2/2021: Policy references updated.

2/2022: Policy references updated.

2/2023: Policy references updated.

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