A separate copy of this form must accompany each policy submitted for review. Policies submitted without this form will not be considered for review.

<table>
<thead>
<tr>
<th>Plan: AmeriHealth Caritas Pennsylvania</th>
<th>Submission Date: November 1, 2019</th>
</tr>
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<tbody>
<tr>
<td>Policy Number: CCP.1293</td>
<td>Effective Date: March 1, 2017</td>
</tr>
<tr>
<td></td>
<td>Revision Date: February 6, 2018</td>
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<tr>
<td>Policy Name: Autologous chondrocyte implantation</td>
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<tr>
<td>Type of Submission – Check all that apply:</td>
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</tr>
<tr>
<td>☐ New Policy</td>
<td>☐ Revised Policy*</td>
</tr>
<tr>
<td>☑ Annual Review – No Revisions</td>
<td>☐ Statewide PDL</td>
</tr>
</tbody>
</table>

*All revisions to the policy must be highlighted using track changes throughout the document.

Please provide any clarifying information for the policy below:

No revisions have been made since last submission.

<table>
<thead>
<tr>
<th>Name of Authorized Individual (Please type or print):</th>
<th>Signature of Authorized Individual:</th>
</tr>
</thead>
<tbody>
<tr>
<td>William D. Burnham, MD</td>
<td></td>
</tr>
</tbody>
</table>
Clinical Policy Title: Autologous chondrocyte implantation

Clinical Policy Number: 14.03.07

Effective Date: March 1, 2017
Initial Review Date: February 15, 2017
Most Recent Review Date: February 6, 2018
Next Review Date: February 2020

Policy contains:
- Articular (hyaline) cartilage repair of the knee.
- Autologous cultured chondrocytes.

Related policies:
CP# 14.03.02 Major joint replacement (hip and knee)

ABOUT THIS POLICY: AmeriHealth Caritas Pennsylvania has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Pennsylvania’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by AmeriHealth Caritas Pennsylvania when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas Pennsylvania’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas Pennsylvania’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Pennsylvania will update its clinical policies as necessary. AmeriHealth Caritas Pennsylvania’s clinical policies are not guarantees of payment.

Coverage policy

AmeriHealth Caritas Pennsylvania considers the use of autologous chondrocyte implantation with a periosteal flap (Carticel®, Genzyme Biosurgery, Cambridge, Massachusetts) or autologous cultured chondrocytes on a porcine collagen membrane (MACI®, Vericel Corporation, Cambridge, Massachusetts) to be clinically proven and, therefore, medically necessary when all of the following patient criteria are met (Hayes, 2017a and 2017b; National Institute for Health and Care Excellence [NICE], 2017; U.S. Food and Drug Administration [FDA], 2016; FDA, 2007):

- Ages 15 to 55 years for Carticel, or ages 18 years and older for MACI.
- Body mass index ≤35 kg/m².
- 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 cm² to 10 cm².
− 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 Carticel or MACI are not medically necessary including:

- As initial or first-line treatment.
- Partial-thickness defects.
- Patellar defects.
- Osteochondritis disseccans.
- Lesions in other joints, including talus and glenohumeral (Gross, 2012; Niemeyer, 2012).
- Chondral defects associated with generalized osteoarthritis or inflammatory diseases.
- In the presence of a previous total meniscectomy without reconstruction.

Contraindications to Carticel or MACI include (FDA, 2016; FDA, 2007):

- 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 mal-alignment, that are not addressed prior to, or concurrent with, the Carticel or MACI 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**

Within the knee joint, healthy cartilage provides a smooth and resilient surface at the ends of bones for nearly frictionless movement and shock absorption. C-shaped medial and lateral menisci attach to top of the tibia to cushion the bones, while articular (hyaline) cartilage line the surfaces of the bones within the knee joint. Articular cartilage consists mainly of water and a collagenous extracellular matrix containing chondrocytes. Chondrocytes are responsible for the production and maintenance of the matrix.

Articular cartilage defects of the knee are common causes of pain and functional disability. Injury and certain conditions (e.g., osteochondritis dissecans) can lead to loss of cartilage alone (chondral) or loss of bone and cartilage (osteochondral), with the latter occurring more commonly in adolescents. The severity of the pain and dysfunction depends on the size, depth, and location of the injury. Classification of chondral and osteochondral injuries of the knee 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 (Cameron, 2003):

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

Grade III or IV lesions can have significant negative impact on function. Ultimately, mechanical damage to the joint surface can lead to osteoarthritis. Restoring articular cartilage can relieve pain, allow better function, and delay or prevent the onset of arthritis. Yet, articular cartilage lacks blood and nerve supplies, which limits its ability to self-repair (American Academy of Orthopaedic Surgeons [AAOS], 2009).

Treatment of articular cartilage damage consists of nonsurgical options and biologic reconstruction of the articular surfaces (Farr, 2011). Surgical techniques to repair or restore articular cartilage include marrow stimulation (including microfracture, drilling, and debridement techniques), osteochondral autografts including mosaicplasty, fresh osteochondral allografts, and autologous chondrocyte implantation; many are performed arthroscopically and often in conjunction with other procedures to repair damage to adjacent structures (Farr, 2011; AAOS, 2009). These procedures are often performed to avoid or delay total knee replacement.

**Autologous chondrocyte implantation:**

The FDA approved Carticel 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) (FDA, 2007). It is the first biologic approved for use in the orthopedic field.
Carticel should only be used in conjunction with debridement, placement of a periosteal flap, and rehabilitation. It is not indicated either for treatment of cartilage damage associated with generalized osteoarthritis or for patients with total meniscectomy, unless surgically reconstructed prior to or concurrent with Carticel implantation. Its use in children or patients over age 65 has not been assessed (FDA, 2007).

The technology 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. Using a two-step process, 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 (MACI) (Farr, 2011).

Searches

AmeriHealth Caritas Pennsylvania searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on December 21, 2017. Search terms were: “Cartilage, Articular” (MeSH), “Chondrocytes” (MeSH), “Transplantation, Autologous” (MeSH), and the free text term “autologous chondrocyte implantation.”

We included:
- Systematic reviews, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- Guidelines based on systematic reviews.
- Economic analyses, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

Findings

We identified nine 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; Mundi,
There is sufficient evidence to support Cartilce 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 cm² to 10 cm² with a mean of 1.9 cm² to 5.1 cm². Most studies included persons with a body mass index <35 kg/m² and a stable knee joint.

Moderate-quality evidence from randomized controlled trials (RCTs) and quasi-RCTs 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, Cartilce does not require that substantial amounts of tissue be harvested, and the procedure can be applied to larger lesions. Cartilce is a safe procedure, but at least 25 percent of patients required arthroscopic evaluation of symptoms or subsequent surgery.

Limited evidence of long-term outcomes >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 based on the assumption that it can generate new hyaline cartilage and prevent osteoarthritis.

Autologous chondrocyte implantation can require extended recovery postoperatively, and 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:

- Cartilce 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 FDA-approved for commercial use in the United States as of this writing.

Policy updates:
In late 2016, the FDA 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 (FDA, 2016). The biocompatible matrix reduces the problems associated with extensive suturing and cell leakage found with ACI.

FDA approval was based on the results of a two-year prospective, multicenter, RCT (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 ≥3 cm² 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.

Two new systematic reviews confirm previous findings that suggest at least comparable safety and effectiveness of autologous chondrocyte implantation procedures to other surgical procedures, including microfracture and mosaicplasty, in the short- to-intermediate-term; long-term data are still needed to inform durability and no conclusions about superiority can be made (Hayes, 2017a and 2017b). 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 (NICE, 2017; Hayes, 2017a and 2017b). The policy was revised to reflect this new information.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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</thead>
<tbody>
<tr>
<td>Hayes (2017a)</td>
<td>Key points:</td>
</tr>
<tr>
<td></td>
<td>• Systematic review of nine randomized comparative trials, five nonrandomized cohort studies, one retrospective matched-pair analysis, and four uncontrolled studies. Sample size range was 21 to 827 patients. Follow-up range was six months to 15 years.</td>
</tr>
<tr>
<td></td>
<td>• Overall quality: low.</td>
</tr>
<tr>
<td></td>
<td>• First-generation autologous chondrocyte implantation may be an efficacious and reasonably safe treatment for symptomatic articular cartilage defects of the knee and may have similar outcomes as microfracture and mosaicplasty over short- and intermediate-term follow-up.</td>
</tr>
<tr>
<td></td>
<td>• Uncertainty remains regarding long-term safety and efficacy, particularly relative to microfracture and mosaicplasty.</td>
</tr>
<tr>
<td>Hayes (2017b)</td>
<td>Key points:</td>
</tr>
<tr>
<td></td>
<td>• Systematic review of nine randomized comparative trials, eight nonrandomized cohort studies, and three uncontrolled studies. Sample size range was 21 to 827 patients with mean cartilage defect size range of 1.9 to 6.7 cm².</td>
</tr>
<tr>
<td></td>
<td>• Overall quality: fair to poor.</td>
</tr>
<tr>
<td></td>
<td>• Second- and third-generation ACI are reasonably safe and efficacious relative to other procedures, including microfracture, mosaicplasty, and first-generation ACI, but superiority cannot be determined.</td>
</tr>
<tr>
<td></td>
<td>• Long-term safety and efficacy of these treatments, particularly relative to microfracture.</td>
</tr>
<tr>
<td>Citation</td>
<td>Content, Methods, Recommendations</td>
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<tr>
<td>--------------------------</td>
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<tr>
<td>DiBartola (2016b)</td>
<td><strong>Key points:</strong></td>
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</tbody>
</table>
| Clinical outcomes after knee autologous chondrocyte implantation in adolescents | - Systematic review of five case series (115 total subjects) who underwent Carticel (95 patients, 83%), with synthetic matrix (six patients, 5%), or MACI (14 patients, 12%).  
- Overall quality: low.  
- Mean patient age was 16.2 years (range 11 to 21 years). Follow-up 12 to 74 months (mean 52.3 months). Mean defect size was 5.3 cm² (range 0.96 to 14 cm²).  
- Improved clinical outcomes scores across all studies. Overall, 35.7% (SD 14.2%) increase using a variety of outcome score tools.  
- Only shorter duration of preoperative symptoms influenced clinical outcome. |
| Elvidge (2016)            | **Key points:**                                                                                                                                                                                                                                                                                                                                              |
| Cost-effectiveness of characterized autologous chondrocyte implantation for cartilage defects of the knee in the UK | - Compared to microfracture, autologous chondrocyte implantation reduces the lifetime probability of knee replacement by 50% and increases quality-adjusted life-years (QALYs) by 0.72 (16.57 vs. 15.85).  
- Incremental cost of autologous chondrocyte implantation over microfracture = £15,299.  
- Cost per QALY gained = £21,245, the procedure is cost effective at standard thresholds used in the United Kingdom. |
| Gross (2012)              | **Key points:**                                                                                                                                                                                                                                                                                                                                              |
| Operative treatment of chondral defects in the glenohumeral (shoulder) joint | - Systematic review of 12 case series (315 total patients) including one study of autologous chondrocyte implantation (five total patients).  
- Overall quality: very low.  
- High-quality evidence is lacking, and decision-making in this patient population is performed on a case-by-case basis. |
| Niemeyer (2012)           | **Key points:**                                                                                                                                                                                                                                                                                                                                              |
| Autologous chondrocyte implantation for chondral and osteochondral defects of the talus | - Meta-analysis of 16 case series (213 total patients with osteochondral and chondral defects). Mean lesion size 2.3 cm² ± 0.6.  
- Overall quality: low, mean Coleman Methodology Score 65 (SD 11) out of 90 points. Nine different scores were used as outcome parameters. Mean follow-up of 32 ± 27 months (range six to 120 months).  
- Overall clinical success rate was 89.9%.  
- Inconclusive results. Controlled studies comparing autologous chondrocyte implantation to other surgical alternatives are needed. |

**References**

**Professional society guidelines/other:**


Peer-reviewed references:


**CMS National Coverage Determinations (NCDs):**

No NCDs identified as of the writing of this policy.

**Local Coverage Determinations (LCDs):**

No LCDs identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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<thead>
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<th>CPT Code</th>
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<td>27412</td>
<td>Autologous chondrocyte implantation, knee</td>
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<td>Arthroscopy, knee, surgical; meniscal transplantation (includes arthrotomy for meniscal insertion), medial or lateral</td>
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<td>Infectious arthropathies</td>
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<tr>
<td>M05.00 -M19.93</td>
<td>Inflammatory polyarthropathies and osteoarthritis</td>
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<td>M24.00 -M24.9</td>
<td>Other specific joint derangements</td>
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<td>M93.20 - M93.29</td>
<td>Osteochondritis dissecans</td>
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<td>Z87.892</td>
<td>Personal history of anaphylaxis [to gentamicin]</td>
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<tr>
<td>Z88.8</td>
<td>Allergy status to other drugs, medicaments and biological substances status [materials of bovine origin]</td>
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<td>J7330</td>
<td>Autologous cultured chondrocytes, implant</td>
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<td>S2112</td>
<td>Arthroscopy, knee, surgical for harvesting of cartilage (chondrocyte cells)</td>
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