BlueCross BlueShield Federal Employee Program.

# FEP Medical Policy Manual

## FEP 7.01.48 Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions

### Annual Effective Policy Date: July 1, 2024

### Original Policy Date: December 2011

### Related Policies:

7.01.15 - Meniscal Allografts and Other Meniscal Implants
8.01.52 - Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used With Autologous Bone Marrow)

## Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions

### Description

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A variety of procedures are being developed to resurface articular cartilage defects. Autologous chondrocyte implantation involves harvesting chondrocytes from healthy tissue, expanding the cells in vitro, and implanting the expanded cells into the chondral defect. Second- and third-generation techniques include combinations of autologous chondrocytes, scaffolds, and growth factors.

## OBJECTIVE

The objective of this evidence review is to determine whether autologous chondrocyte implantation improves net health outcomes in individuals with focal articular cartilage lesions of the knee and other joints.

# POLICY STATEMENT

Autologous chondrocyte implantation may be considered **medically necessary** for the treatment of disabling full-thickness articular cartilage defects of the knee caused by acute or repetitive trauma when all of the following criteria are met:

- Adolescent individuals should be skeletally mature with documented closure of growth plates (eg, ≥15 years). Adult individuals should be too young to be considered an appropriate candidate for total knee arthroplasty or other reconstructive knee surgery (eg, <55 years)
- Focal, full-thickness (grade III or IV) unipolar lesions of the weight-bearing surface of the femoral condyles, trochlea, or patella at least 1.5 $cm^2$ in size
- Documented minimal to absent degenerative changes in the surrounding articular cartilage (Outerbridge grade II or less), and normal-appearing hyaline cartilage surrounding the border of the defect
- Normal knee biomechanics or alignment and stability achieved concurrently with autologous chondrocyte implantation.

Autologous chondrocyte implantation for all other joints, including the talar, and any indications other than those listed above is considered **investigational**.

# POLICY GUIDELINES

For smaller lesions (eg, <4 $cm^2$), if debridement is the only prior surgical treatment, then consideration should be given to marrow-stimulating techniques before autologous chondrocyte implantation is performed.

The average defect size reported in the literature is about 5 $cm^2$; many studies treated lesions as large as 15 $cm^2$.

Severe obesity (eg, body mass index >35 $kg/m^2$) may affect outcomes due to the increased stress on weight-bearing surfaces of the joint.

Misalignment and instability of the joint are contraindications. Therefore, additional procedures, such as repair of ligaments or tendons or creation of an osteotomy for realignment of the joint, may be performed at the same time. In addition, meniscal allograft transplantation may be performed in combination, either concurrently or sequentially, with autologous chondrocyte implantation. The charges for the culturing component of the procedure are submitted as part of the hospital bill.

The entire matrix-induced autologous chondrocyte implantation 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, 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.

# BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

# FDA REGULATORY STATUS

The culturing of chondrocytes is considered by the FDA to fall into the category of manipulated autologous structural cells, which are subject to a biologic licensing requirement. In 1997, Carticel (Genzyme; now Vericel) received FDA approval for the repair of clinically significant, "...symptomatic cartilaginous defects of the femoral condyle (medial-lateral or trochlear) caused by acute or repetitive trauma..."

In December 2016, MACI (Vericel) received FDA approval for "the repair of symptomatic, single or multiple full-thickness cartilage defects of the knee with or without bone involvement in adults."[3,] MACI consists of autologous chondrocytes that are cultured onto a bioresorbable porcine-derived collagen membrane. In 2017, production of Carticel was phased out, and MACI is the only autologous chondrocyte implantation product available in the United States.

A number of other second-generation methods for implanting autologous chondrocytes in a biodegradable matrix are currently in development or testing or are available outside of the United States. They include Atelocollagen (Koken), a collagen gel; Bioseed C (BioTissue Technologies), a polymer scaffold; CaReS (Ars Arthro), collagen gel; Cartilix (Biomet), a polymer hydrogel; Chondron (Sewon Cellontech), a fibrin gel; Hyalograft C (Fidia Advanced Polymers), a hyaluronic acid-based scaffold; NeoCart (Histogenics), an autologous chondrocyte implantation with a 3-dimensional chondromatrix in a phase 3 trial; and Novocart3D (Aesculap Biologics), a collagen-chondroitin sulfate scaffold in a phase 3 trial. ChondroCelect (TiGenix), characterized as a chondrocyte implantation with a completed phase 3 trial, uses a gene marker profile to determine in vivo cartilage-forming potential and thereby optimizes the phenotype (eg, hyaline cartilage vs. fibrocartilage) of the tissue produced with each autologous chondrocyte implantation cell batch. Each batch of chondrocytes is graded based on the quantitative gene expression of a selection of positive and negative markers for hyaline cartilage formation. Both Hyalograft C and ChondroCelect have been withdrawn from the market in Europe. In 2020, the FDA granted breakthrough status to Agili-C™ (CartiHeal, Ltd.), a proprietary cell-free biocompatible and biodegradable tapered-shape implant for the treatment of cartilage lesions in arthritic and non-arthritic joints that, when implanted into a pre-prepared osteochondral hole, acts as a 3-dimensional scaffold that potentially supports and promotes the regeneration of the articular cartilage and its underlying subchondral bone. Agili-C was FDA-approved in 2021 for the treatment of knee-joint surface lesions with a treatable area of 1 to 7 $cm^2$ without severe osteoarthritis.[4,]

# RATIONALE

## Summary of Evidence

For individuals who have focal articular cartilage lesion(s) of the weight-bearing surface of the femoral condyles, trochlea, or patella who receive autologous chondrocyte implantation, the evidence includes systematic reviews, randomized controlled trials (RCTs), and observational studies. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, and quality of life. There is a large body of evidence on autologous chondrocyte implantation for the treatment of focal articular cartilage lesions of the knee. For large lesions, autologous chondrocyte implantation results in better outcomes than microfracture, particularly in the long term. In addition, there is a limit to the size of lesions that can be treated with osteochondral autograft transfer, due to a limit on the number of osteochondral cores that can be safely harvested. As a result, autologous chondrocyte implantation has become the established treatment for large articular cartilage lesions in the knee. In 2017, first-generation autologous chondrocyte implantation with a collagen cover was phased out and replaced with an autologous chondrocyte implantation preparation that seeds the chondrocytes onto a bioresorbable collagen sponge. Although the implantation procedure for this second-generation autologous chondrocyte implantation is less technically demanding, studies to date have not shown improved outcomes compared with first-generation autologous chondrocyte implantation. Some evidence has suggested an increase in hypertrophy (overgrowth) of the new implant that may exceed that of the collagen membrane-covered implant. Long-term studies with a larger number of patients will be needed to determine whether this hypertrophy impacts graft survival. Based on mid-term outcomes that approximate those of first-generation autologous chondrocyte implantation and the lack of alternatives, second-generation autologous chondrocyte implantation 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 an improvement in the net health outcome.

For individuals who have focal articular cartilage lesions of joints other than the knee who receive autologous chondrocyte implantation, the evidence includes case series, systematic reviews of case series, and a network meta-analysis of prospective (none of which evaluated autologous chondrocyte implantation) and retrospective studies. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, and quality of life. The greatest amount of literature is on autologous chondrocyte implantation of the talus. Comparative trials are needed to determine whether autologous chondrocyte implantation improves outcomes for lesions in joints other than the knee. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

# SUPPLEMENTAL INFORMATION

## Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information" if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

## American Academy of Orthopaedic Surgeons

In its 2023 guidelines on the diagnosis and treatment of osteochondritis dissecans, the American Academy of Orthopaedic Surgeons did not recommend for or against a specific cartilage repair technique in symptomatic skeletally mature patients with an unsalvageable osteochondritis dissecans lesion, or symptomatic skelletally immautre patients with unsalvagable fragment.[55,]The finding of insufficient evidence forsymptomatic skeletally mature patients with an unsalvageable osteochondritis dissecanslesion was based on a systematic review that found 4 level IV studies addressing cartilage repair techniques for an unsalvageable osteochondritis dissecans lesion. Because each level IV article used different techniques, different outcome measures, and differing lengths of follow-up, the Academy deemed the evidence for any specific technique inconclusive. The finding of insufficient evidence for symptomatic skeletally immature patients with unsalvageable fragments was based on a Level II study; this study did not address many outcomes and techniques and had inconclusive results.

## National Institute for Health and Care Excellence

In 2018, NICE updated its 2005 guidance on the use of autologous chondrocyte implantation.[56,] The NICE recommendations are stated below:

"...as an option for treating symptomatic articular cartilage defects of the femoral condyle and patella of the knee (International Cartilage Repair Society grade III or IV) in adults, only if:

- the person has not had previous surgery to repair articular cartilage defects;
- there is minimal osteoarthritic damage to the knee (as assessed by clinicians experienced in investigating knee cartilage damage using a validated measure for knee osteoarthritis); and
- the defect is over 2 $cm^2$."

# U.S. Preventive Services Task Force Recommendations

Not applicable.

# Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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## POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

| Date | Action | Description |
|---|---|---|
| December 2011 | New policy | |
| September 2013 | Replace policy | Policy updated with literature review, references 12 and 39-42 added; sections and statements on minced cartilage moved to policy No.7.01.78. Policy title change (Osteochondral Autografts and Allografts and Other Cell-based Treatments removed from title. |
| September 2015 | Replace policy | Policy updated with literature review; references 5 and 7 added; policy statements unchanged. |
| June 2017 | | Clinical input reviewed; references 8 and 32-33 added. Autologous chondrocyte implantation of the patella considered medically necessary; need for a prior surgical procedure removed from policy statement. Policy updated with literature review through March 2, 2017; references5, 7, 10, 12, and 19 added. Rationale extensively revised to focus on available products. Investigational statement on matrix-induced autologous chondrocyte implantation removed. |
| March 2018 | Replace policy | Policy updated with literature review through November 13, 2017, focusing on matrix-induced autologous chondrocyte implantation of the patella; references 12-18 added. Matrix-induced autologous chondrocyte implantation of the patella is considered medically necessary. In the investigational statement the wording: "and any indications other than those listed above€š changed to "and any non-FDA approved indications€š for clarification. |
| June 2018 | Replace policy | Policy updated with literature review through February 5, 2018; references 6, 8, 22, 27, and 30 added. Policy statements unchanged. |
| April 2019 | Replace policy | Policy updated with literature review through February 5, 2019, no references added; reference 30 updated. Policy statements unchanged. |
| June 2020 | Replace policy | Policy updated with literature review through February 11, 2020; references added. Policy statements unchanged. |
| June 2021 | Replace policy | Policy updated with literature review through February 23, 2021; references added. Policy statements unchanged. |
| June 2022 | Replace policy | Policy updated with literature review through February 16, 2022; references added. Policy statements unchanged. |
| June 2023 | Replace policy | Policy updated with literature review through February 16, 2023; references added. Policy statements unchanged. |
| June 2024 | Replace policy | Policy updated with literature review through February 20, 2024; references added. Policy statements unchanged. |