VHA Office of Integrated Veteran Care
Clinical Determination and Indication
Autologous Chondrocyte Implantation

CDI Number: 00022

Original Effective Date: November 1, 2024

Last Review Date: November 1, 2024

I. Disclaimer

This document is currently in draft and is intended to be used as a reference for non-VA providers and not intended to replace clinical judgement when determining care pathways. These guidelines do not guarantee benefits or constitute medical advice.

II. Clinical Determinations and Indications

a. Indications for Autologous Chondrocyte Implantation

Autologous chondrocyte implantation (ACI) is indicated for symptomatic articular cartilage lesions of the knee joint and is considered **medically necessary** when **ALL** the following criteria are met:

- Veteran is 18-55 years old
- Presence of grade III or grade IV full thickness articular cartilage loss on a load-bearing surface of the medial femoral condyle, lateral femoral condyle, femoral trochlea, or patella
- Lesion is symptomatic (defined as lesion-related pain; swelling or catching/locking that significantly limits activities of daily living)
- Minimal to absent degenerative changes of the surrounding articular cartilage (Outerbridge grade II or less) and normal appearance of hyaline cartilage at the border of the defect
- The focal chondral defect size is between 1.5-10 cm^2
- Defects under 4 cm^2 should have been previously managed with marrow-stimulating techniques prior to ACI
- Inadequate response to conservative therapy and/or prior arthroscopic or other surgical repair procedure (e.g., debridement, microfracture, subchondral drilling, abrasion chondroplasty, or osteochondral allograft/autograft)
- The knee must be stable and aligned (a corrective procedure in combination with or prior to ACI may be necessary to ensure stability, alignment, and normal weight distribution within the joint)

- Symptoms of disabling knee pain due to focal chondral and osteochondral defects
- Focal articular cartilage defect down to but not through the subchondral bone on a load-bearing surface of the medial femoral condyle, lateral femoral condyle, femoral trochlea, or patella

Note: Veteran's willingness and ability to consent for surgery and fully participate in a prescribed postoperative rehabilitation program is necessary to ensure optimal outcome.

b. Limitations/Exclusions

Autologous chondrocyte implantation is **not indicated** if any of the following are applicable:

- Uncorrected malalignment and instability of the affected knee joint, unless being performed at the time of the ACI
- Current infection at any of the operative sites
- Allergy or sensitivities to gentamicin, other aminoglycosides, or products of porcine or bovine origin
- Presence of kissing lesions (articular cartilage defect on the femur and tibia in the same compartment of the knee)
- History of previous cancer in the bones, cartilage, fat, or muscle of the treated limb
- Knee joint with more than 50% loss of cartilage thickness (mild to moderate arthritis)
- Poorly controlled diabetes
- Deficient soft-tissue coverage
- Body mass index (BMI) greater than or equal to 35 kg/m^2

Conditions/indications for which autologous chondrocyte implantation is **not medically necessary** include, but are not limited to, the following:

- Degenerative arthritis
- Talar (ankle) lesions, or lesions of other joints (e.g., hip and shoulder)
- Cartilaginous defect associated with osteoarthritis, rheumatoid arthritis, or inflammatory disease.

For all indications not listed in section II.a. of this document, autologous chondrocyte implantation is considered not medically necessary due to insufficient evidence of efficacy and safety.

c. Description of Treatment

Autologous chondrocyte implantation (ACI) is a form of tissue engineering where the patient's cartilage cells are harvested and proliferated for repair of

defects in the articular cartilage of the same patient. ACI is designed to address areas of damaged or missing cartilage, which may cause pain, stiffness, and limited joint mobility. It is considered an appropriate treatment option for select younger patients with single or multiple focal cartilage lesions who have not responded to conservative therapies.

Autologous chondrocyte implantation includes different techniques for use of expanded autologous derived chondrocytes which may include matrices to induce expansion. Matrix-induced autologous chondrocyte implantation (MACI) is an approved Food and Drug Administration (FDA) therapy. Carticel is a different FDA approved process for in vitro expansion of autologous chondrocytes. Both products should be used in alignment with FDA approvals.

Autologous chondrocyte implantation is a two-stage surgical procedure:

- In the first procedure, a region of healthy articular cartilage is identified and biopsied through an arthroscopic procedure from a non-weight-bearing area of the patient's knee joint. The harvested cartilage tissue contains chondrocytes, which are specialized cells responsible for cartilage production and maintenance. The extracted cartilage sample is sent to a specialized laboratory where the chondrocytes are minced, enzymatically digested, and separated by filtration. Culturing chondrocytes increases the number of viable chondrocytes. This process typically takes several weeks.
- The second procedure is performed when the desired level of chondrocytes is obtained. During this procedure, an arthrotomy (open joint surgery) is performed, and the damaged cartilage area is prepared. A biocompatible scaffold, often made of collagen or other suitable materials may be placed over the cartilage defect, or the chondrocytes may be covered with a periosteal flap at the site of the defect. The cultured chondrocytes are carefully seeded in the defect area. The chondrocytes are expected to adhere to a scaffold if used, and gradually fill the cartilage defect over time. The surgical site is closed, and the patient undergoes a rehabilitation program to protect the newly implanted cells and promote proper cartilage healing.

Postoperative rehabilitation compliance is important for a successful outcome. Weight-bearing and physical activity are typically restricted initially, gradually increasing as the cartilage heals. Physical therapy emphasizing range-of-motion of the knee and strengthening activities is prescribed. Continuous passive motion (CPM) machines to improve the graft’s success may be recommended. Research suggests an average time for return to full activity following ACI ranges from 12 to 24 months.

III. Background and Supporting Information

The following information is for reference purposes only in accordance with the medical benefits package outlined in 38 C.F.R. § 17.38(b). Each subsection supports VA's determinations for medical necessity and alignment with generally accepted standards of medical practice.

a. Background Information

Articular cartilage within joints may be damaged by either acute injuries or normal wear and tear. Signs and symptoms include pain, swelling, catching, or locking, loss of function, restricted mobility, and disability. These manifestations can severely impair activities of daily living and adversely affect quality of life. Long-standing severe damage to the articular cartilage can lead to debilitating osteoarthritis, which may require surgical treatment if non-surgical approaches are not sufficient.

Conventional treatment options for damaged articular cartilage of the knee joint include debridement, subchondral drilling, microfracture, and abrasion chondroplasty. Autologous chondrocyte implantation (ACI) falls within the group of therapies that aim to induce chondrogenesis (growth of chondrocytes) within transplanted tissue or cells for the treatment of cartilage defects in the knee. An advantage of ACI is the reduced risk of graft rejection by the patient's body since the cartilage cells are taken from the patient's own body. Studies have shown that patients who undergo ACI for articular cartilage damage of the knee experience improvements in pain, function, activity level, and quality of life.

b. Research, Clinical Trials, and Evidence Summaries

There is limited evidence that determines efficacy of ACI compared to other treatments. Available studies report that patients treated with ACI achieved various outcomes. Studies have not been able to determine if favorable outcomes are a direct result of ACI. Studies were also unable to determine if ACI was comparatively better than, the same as, or worse than the outcomes from other treatments. Further, ACI techniques have continued to evolve, so long-term trial data on ACI reflects forms and techniques that are now superseded, such as with MACI, the newest generation of ACI. The following synthesizes the most recent literature.

Na et al. (2019) conducted a systematic review to evaluate the clinical efficacy of ACI and microfracture at a minimum mean 5-year follow-up. The research team utilized MEDLINE, Embase, and Cochrane Library databases to search for literature through August 2018. Five comparative studies (three randomized controlled trials and two prospective cohort studies) met eligibility criteria and were utilized in the review. Authors found that clinical outcomes of

articular cartilage lesions of the knee treated with modified versions of ACI (ACI with a modified collagen membrane [ACI-C] or matrix-applied chondrocyte implantation [MACI]) can significantly improve patient outcomes at the midterm follow-up of five years compared to those treated with microfracture. Improved clinical results (with significant differences) were found with ACI versus microfracture as determined by the Knee Injury and Osteoarthritic Outcome Score (KOOS), activities of daily living assessment, Tegner Activity Scale score, and the International Knee Documentation Committee objective and subjective scores.

Minas et al. (2014) conducted a study to evaluate the survivorship of ACI grafts, long term functional outcomes, and analyze potential predictors for failure. Two hundred ten patients, with symptomatic cartilage defects in all compartments of the knee unresponsive to nonoperative measures, were followed for more than 10 years after ACI. Studies showed that ACI provided durable outcomes with a survivorship of 71% at 10 years, and improved function in 75% of patients with symptomatic cartilage defects of the knee at a minimum of 10 years after surgery. Fifty-three patients (25%) had at least one failed ACI graft. A history of prior marrow stimulation as well as the treatment of very large defects were associated with an increased risk of failure. Authors concluded that ACI demonstrated favorable results in over 75% of patients up to 10 years after surgery.

Saris et al. (2014) conducted a two-year prospective, multicenter, randomized, open-label, parallel-group study to compare the efficacy and safety of MACI versus microfracture (MFX) for treating patients with symptomatic cartilage defects of the knee. The study utilized the KOOS for pain and function to assess 144 patients from baseline through two years. The study found that MACI was clinically and statistically more efficacious than MFX for the treatment of symptomatic cartilage knee defects. In addition, the study showed that MACI had a similar safety profile compared to MFX. The findings from this study led the FDA in 2016 to approve MACI for the repair of symptomatic single or multiple full-thickness cartilage defects of the knee.

Nawaz et al. (2014) studied patients who underwent autologous chondrocyte implantation (ACI) for osteochondral defects of the knee from 1998-2008. The purpose was to evaluate the functional outcomes in 827 of 869 patients who had undergone ACI with Chondron, periosteum (ACI-C/ACI-P) or MACI to identify factors that influenced the outcome. Follow-up ranged from 2 to 12 years with a mean timeframe of 6.2 years. Four hundred twenty-one procedures were performed on the medial femoral condyle,109 on the lateral femoral condyle, 200 on the patella; and 50 on the trochlea. Significant postoperative improvements in function and pain scores were noted for all

outcome measures. The outcomes demonstrated an overall graft survival of 78% at 5 years and 51% beyond 10 years following both autologous chondrocyte implantation (ACI-C/ACI-P and MACI) techniques. Authors concluded that ACI for the treatment of osteochondral defects of the knee can achieve positive results.

c. U.S. Food & Drug Administration (FDA) Information

Autologous Chondrocyte Implantation has received Biologics License Application (BLA) approval by the FDA for the repair of single or multiple symptomatic, full-thickness cartilage defects of the knee with or without bone involvement in adults.

To search for more FDA-approved and licensed biological products, including licensed biosimilar and interchangeable products, regulated by the Center for Drug Evaluation and Research (CDER), please visit the FDA-licensed (approved) Biological Products Database.

Information	Description
Product Name	Matrix Induced Autologous Chondrocyte Implantation (MACI)® - Autologous Cultured Chondrocytes on a Porcine Collagen Membrane
BLA Applicant	Vericel Corporation
Address	64 Sidney Street Cambridge, MA 02139
Approval Date	12/13/2016
Approval Letter	BLA Approval Letter

Information	Description
Product Name	CARTICEL- Autologous Cultured Chondrocytes Implant
BLA Applicant	Vericel Corporation
Address	64 Sidney Street Cambridge, MA 02139
Approval Date	08/22/1997
Approval	BLA Approval

d. Medicare Coverage Determinations

There are no available Medicare coverage determinations. VA and Medicare are governed by separate laws and regulations; thus, VA coverage determinations may be different.

e. TRICARE Policy Manual

Available TRICARE coverage determinations are listed below as a resource. VA and TRICARE are governed by separate laws and regulations; thus, VA coverage determinations may be different.

TRICARE Policy Manual 6010.60-M, Chapter 4, Section 6.1

Term	Definition
Abrasion chondroplasty (knee)	Extensive tissue debridement surgery to restore articular knee lining
Arthroscopy	A minimally invasive surgical procedure involving visual examination of the interior of a joint with an arthroscope to diagnose or treat various conditions or injuries and to repair or remove injured or diseased tissue or bone
Articular	Of or relating to a joint
Autologous	Derived from the same individual, involving one individual as both donor and recipient
Biocompatible	The property of being biologically compatible by not producing a toxic, injurious, or immunologic response in living tissue
Chondrocyte	A cartilage cell that produces substances that make up cartilage tissue
Debridement	Removal of devitalized or infected tissue
Focal	Relating to a localized area
Hyaline	A type of cartilage that is predominantly type 2 collagen
Microfracture	An articular cartilage repair surgical technique that works by creating tiny fractures in the underlying bone to stimulate a healing response
Scaffold	A framework or structural element that holds cells or tissues together
Subchondral drilling	Surgical procedure where small holes are drilled through damaged joint cartilage into the underlying bone to stimulate a healing response

IV. References

Defense Health Agency (2015, April 01). Musculoskeletal System. TRICARE Policy Manual 6010.60-M. Chapter 4, Section 6.1. Retrieved September 25, 2023, from https://manuals.health.mil/pages/DisplayManualHtmlFile/2023-09-25/AsOf/TP15/C4S6_1.html

Edwards, P. K., Ackland, T., & Ebert, J. R. (2014). Clinical rehabilitation guidelines for matrix-induced autologous chondrocyte implantation on the tibiofemoral joint. The Journal of orthopaedic and sports physical therapy, 44(2), 102–119. https://doi.org/10.2519/jospt.2014.5055

MCG Health. (2023, June 27). Autologous Chondrocyte Implantation. Ambulatory Care. 27th Edition.

Minas, T., Ogura, T., & Bryant, T. (2016). Autologous Chondrocyte Implantation. JBJS essential surgical techniques, 6(2), e24. https://doi.org/10.2106/JBJS.ST.16.00018

Minas, T., Von Keudell, A., Bryant, T., & Gomoll, A. H. (2014). The John Insall Award: A minimum 10-year outcome study of autologous chondrocyte implantation. Clinical orthopaedics and related research, 472(1), 41–51. https://doi.org/10.1007/s11999-013-3146-9

Na, Y., Shi, Y., Liu, W., Jia, Y., Kong, L., Zhang, T., Han, C., & Ren, Y. (2019). Is implantation of autologous chondrocytes superior to microfracture for articular-cartilage defects of the knee? A systematic review of 5-year follow-up data. International Journal of Surgery, 68, 56–62. https://doi.org/10.1016/j.ijsu.2019.06.007

Nawaz, S. Z., Bentley, G., Briggs, T. W., Carrington, R. W., Skinner, J. A., Gallagher, K. R., & Dhinsa, B. S. (2014). Autologous chondrocyte implantation in the knee: mid-term to long-term results. The Journal of bone and joint surgery. American volume, 96(10), 824–830. https://doi.org/10.2106/JBJS.L.01695

Saris, D., Price, A., Widuchowski, W., Bertrand-Marchand, M., Caron, J., Drogset, J. O., Emans, P., Podskubka, A., Tsuchida, A., Kili, S., Levine, D., & Brittberg, M. (2014). Matrix-applied characterized autologous cultured chondrocytes versus microfracture. The American Journal of Sports Medicine, 42(6), 1384–1394. https://doi.org/10.1177/0363546514528093

Terzidis, I. P., Christodoulou, A. G., Ploumis, A. L., Metsovitis, S. R., Koimtzis, M., & Givissis, P. (2004). The appearance of kissing contusion in the acutely injured knee in the athletes. British journal of sports medicine, 38(5), 592–596. https://doi.org/10.1136/bjsm.2003.006718

U.S. Food & Drug Administration Purple Book Database. (n.d.). Retrieved August 3, 2023, from https://wayback.archive-it.org/7993/20190425002025/https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM533307.pdf

U.S. Food & Drug Administration. (n.d.). *Drugs @ FDA: FDA-approved drugs.* Retrieved February 6, 2023, from https://www.fda.gov/media/101914/download?attachment

V. CDI History/Revision Information

- Explanation of changes to the CDI

Revision Type	Date of Revision	Update(s) Made to CDI
	MM/DD/YYYY	
	MM/DD/YYYY	