

Protocol

Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions

(70148)

Medical Benefit		Effective Date: 04/01/18	Next Review Date: 01/20
Preauthorization	Yes	Review Dates: 02/07, 02/08, 03/09, 01/10, 01/11, 09/11, 09/12, 09/13, 07/14, 07/15, 01/16, 01/17, 01/18, 01/19	

Preauthorization is required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> With focal articular cartilage lesion(s) of the weight-bearing surface of the femoral condyle, trochlea, or patella 	Interventions of interest are: <ul style="list-style-type: none"> Autologous chondrocyte implantation 	Comparators of interest are: <ul style="list-style-type: none"> Marrow stimulation Osteochondral autografts 	Relevant outcomes include: <ul style="list-style-type: none"> Symptoms Change in disease status Morbid events Functional outcomes Quality of life
Individuals: <ul style="list-style-type: none"> With focal articular cartilage lesions of joints other than the knee 	Interventions of interest are: <ul style="list-style-type: none"> Autologous chondrocyte implantation 	Comparators of interest are: <ul style="list-style-type: none"> Marrow stimulation Osteochondral autografts 	Relevant outcomes include: <ul style="list-style-type: none"> Symptoms Change in disease status Morbid events Functional outcomes Quality of life

DESCRIPTION

A variety of procedures are being developed to resurface articular cartilage defects. Autologous chondrocyte implantation (ACI) 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.

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 ACI, the evidence includes systematic reviews, randomized controlled trials, and prospective 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 ACI for the treatment of focal articular cartilage lesions of the knee. For large lesions, ACI 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, ACI has become the established treatment for large articular cartilage lesions in the knee. In 2017, first-generation

ACI with a collagen cover was phased out and replaced with an ACI preparation that seeds the chondrocytes onto a bioresorbable collagen sponge. Although the implantation procedure for this second-generation ACI is less technically demanding, studies to date have not shown improved outcomes compared with first-generation ACI. 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 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.

For individuals who have focal articular cartilage lesions of joints other than the knee who receive ACI, the evidence includes systematic reviews of case series. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, and quality of life. The greatest amount of literature is for ACI of the talus. Comparative trials are needed to determine whether ACI improves outcomes for lesions in joints other than the knee. The evidence is insufficient to determine the effects of the technology on health outcomes.

POLICY

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 patients should be skeletally mature with documented closure of growth plates (e.g., 15 years or older). Adult patients should be too young to be considered an appropriate candidate for total knee arthroplasty or other reconstructive knee surgery (e.g., younger than 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 cm² 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 (e.g., smaller than four cm²) if debridement is the only prior surgical treatment, then consideration should be given to marrow-stimulating techniques before ACI is performed.

The average defect size reported in the literature is about five cm²; many studies treated lesions as large as 15 cm².

Severe obesity (e.g., body mass index greater than 35 kg/m²) 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 ACI.

The entire matrix-induced ACI procedure consists of four 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 (i.e., arthrotomy) is scheduled.

BACKGROUND

ARTICULAR CARTILAGE LESIONS

Damaged articular cartilage typically fails to heal on its own and can be associated with pain, loss of function, and disability and may lead to debilitating osteoarthritis over time. These manifestations can severely impair a patient's activities of daily living and adversely affect quality of life.

Treatment

Conventional treatment options include débridement, subchondral drilling, microfracture, and abrasion arthroplasty. Débridement involves the removal of synovial membrane, osteophytes, loose articular debris, and diseased cartilage and is capable of producing symptomatic relief. Subchondral drilling, microfracture, and abrasion arthroplasty attempt to restore the articular surface by inducing the growth of fibrocartilage into the chondral defect. Compared with the original hyaline cartilage, fibrocartilage has less capability to withstand shock or shearing force and can degenerate over time, often resulting in the return of clinical symptoms. Osteochondral grafts and autologous chondrocyte implantation (ACI) attempt to regenerate hyaline-like cartilage and thereby restore durable function. Osteochondral grafts for the treatment of articular cartilage defects are discussed in the Autografts and Allografts in the Treatment of Focal Articular Cartilage Lesions Protocol.

With ACI, a region of healthy articular cartilage is identified and biopsied through arthroscopy. The tissue is sent to a facility licensed by the U.S. Food and Drug Administration (FDA) where it is minced and enzymatically digested, and the chondrocytes are separated by filtration. The isolated chondrocytes are cultured for 11 to 21 days to expand the cell population, tested, and then shipped back for implantation. With the patient under general anesthesia, an arthrotomy is performed, and the chondral lesion is excised up to the normal surrounding cartilage. Methods to improve the first-generation ACI procedure have been developed, including the use of a scaffold or matrix-induced autologous chondrocyte implantation (MACI) composed of biocompatible carbohydrates, protein polymers, or synthetics. 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 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.

Desired features of articular cartilage repair procedures are the ability (1) to be implanted easily, (2) to reduce surgical morbidity, (3) not to require harvesting of other tissues, (4) to enhance cell proliferation and maturation, (5) to maintain the phenotype, and (6) to integrate with the surrounding articular tissue. In addition to the potential to improve the formation and distribution of hyaline cartilage, use of a scaffold with MACI eliminates the need for harvesting and suture of a periosteal or collagen patch. A scaffold without cells may also support chondrocyte growth.

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 approved for "the repair of symptomatic, single or multiple full-thickness cartilage defects of the knee with or without bone involvement in adults." 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 ACI 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 ACI with a 3-dimensional chondromatrix in a phase 3 trial; and Novocart®3D (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 (e.g., hyaline cartilage versus fibrocartilage) of the tissue produced with each ACI 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.

RELATED PROTOCOLS

Autografts and Allografts in the Treatment of Focal

Articular Cartilage Lesions

Continuous Passive Motion in the Home Setting

Meniscal Allografts and Other Meniscal Implants

Orthopedic Applications of Stem Cell Therapy (Including Allograft and Bone Substitutes Used With Autologous Bone Marrow)

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

1. Blue Cross and Blue Shield Association Technology Evaluation Center. Autologous chondrocyte transplantation. TEC Assessment. 1996;Volume 11:Tab 8.
2. Blue Cross and Blue Shield Association Technology Evaluation Center. Autologous chondrocyte transplantation. TEC Assessment. 1997;Volume 12:Tab 26.
3. Blue Cross and Blue Shield Association Technology Evaluation Center. Autologous chondrocyte transplantation. TEC Assessment. 2000;Volume 15:Tab 12.
4. Blue Cross and Blue Shield Association Technology Evaluation Center. Autologous chondrocyte transplantation of the knee. TEC Assessment. 2003;Volume 18:Tab 2.
5. Riboh JC, Cvetanovich GL, Cole BJ, et al. Comparative efficacy of cartilage repair procedures in the knee: a network meta-analysis. *Knee Surg Sports Traumatol Arthrosc.* Dec 2017;25(12):3786-3799. PMID 27605128
6. Devitt BM, Bell SW, Webster KE, et al. Surgical treatments of cartilage defects of the knee: Systematic review of randomised controlled trials. *Knee.* Jun 2017;24(3):508-517. PMID 28189406
7. Mundi R, Bedi A, Chow L, et al. Cartilage restoration of the knee: a systematic review and meta-analysis of level 1 studies. *Am J Sports Med.* Jul 2016;44(7):1888-1895. PMID 26138733
8. Mistry H, Connock M, Pink J, et al. Autologous chondrocyte implantation in the knee: systematic review and economic evaluation. *Health Technol Assess.* Feb 2017;21(6):1-294. PMID 28244303
9. Harris JD, Siston RA, Pan X, et al. Autologous chondrocyte implantation: a systematic review. *J Bone Joint Surg Am.* Sep 15 2010;92(12):2220-2233. PMID 20844166
10. Bartlett W, Skinner JA, Gooding CR, et al. Autologous chondrocyte implantation versus matrix-induced autologous chondrocyte implantation for osteochondral defects of the knee: a prospective, randomised study. *J Bone Joint Surg Br.* May 2005;87(5):640-645. PMID 15855365
11. Saris D, Price A, Widuchowski W, et al. Matrix-applied characterized autologous cultured chondrocytes versus microfracture: two-year follow-up of a prospective randomized trial. *Am J Sports Med.* Jun 2014; 42(6): 1384-1394. PMID 24714783
12. Basad E, Ishaque B, Bachmann G, et al. Matrix-induced autologous chondrocyte implantation versus microfracture in the treatment of cartilage defects of the knee: a 2-year randomised study. *Knee Surg Sports Traumatol Arthrosc.* Apr 2010;18(4):519-527. PMID 20062969
13. Basad E, Wissing FR, Fehrenbach P, et al. Matrix-induced autologous chondrocyte implantation (MACI) in the knee: clinical outcomes and challenges. *Knee Surg Sports Traumatol Arthrosc.* Dec 2015;23(12):3729-3735. PMID 25218576
14. Schuette HB, Kraeutler MJ, McCarty EC. Matrix-assisted autologous chondrocyte transplantation in the knee: a systematic review of mid- to long-term clinical outcomes. *Orthop J Sports Med.* Jun 2017;5(6):2325967117 709250. PMID 28620621
15. Meyerkort D, Ebert JR, Ackland TR, et al. Matrix-induced autologous chondrocyte implantation (MACI) for chondral defects in the patellofemoral joint. *Knee Surg Sports Traumatol Arthrosc.* Oct 2014;22(10):2522-2530. PMID 24817164
16. Zak L, Aldrian S, Wondrasch B, et al. Ability to return to sports 5 years after matrix-associated autologous chondrocyte transplantation in an average population of active patients. *Am J Sports Med.* Dec 2012; 40(12):2815-2821. PMID 23108635
17. Ebert JR, Fallon M, Wood DJ, et al. A prospective clinical and radiological evaluation at 5 years after arthroscopic matrix-induced autologous chondrocyte implantation. *Am J Sports Med.* Jan 2017;45(1):59-69. PMID 27587741

18. Ebert JR, Fallon M, Zheng MH, et al. A randomized trial comparing accelerated and traditional approaches to postoperative weightbearing rehabilitation after matrix-induced autologous chondrocyte implantation: findings at 5 years. *Am J Sports Med.* Jul 2012;40(7):1527-1537. PMID 22539536
19. Ebert JR, Smith A, Edwards PK, et al. Factors predictive of outcome 5 years after matrix-induced autologous chondrocyte implantation in the tibiofemoral joint. *Am J Sports Med.* Jun 2013;41(6):1245-1254. PMID 23618699
20. Ebert JR, Schneider A, Fallon M, et al. A comparison of 2-year outcomes in patients undergoing tibiofemoral or patellofemoral matrix-induced autologous chondrocyte implantation. *Am J Sports Med.* Sep 01 2017: 363546517724761. PMID 28910133
21. Harris JD, Cavo M, Brophy R, et al. Biological knee reconstruction: a systematic review of combined meniscal allograft transplantation and cartilage repair or restoration. *Arthroscopy.* Oct 26 2011;27(3):409-418. PMID 21030203
22. Andriolo L, Merli G, Filardo G, et al. Failure of autologous chondrocyte implantation. *Sports Med Arthrosc Rev.* Mar 2017;25(1):10-18. PMID 28045868
23. Nawaz SZ, Bentley G, Briggs TW, et al. Autologous chondrocyte implantation in the knee: mid-term to long-term results. *J Bone Joint Surg Am.* May 21 2014;96(10):824-830. PMID 24875023
24. Minas T, Von Keudell A, Bryant T, et al. The John Insall Award: A minimum 10-year outcome study of autologous chondrocyte implantation. *Clin Orthop Relat Res.* Jan 2014;472(1):41-51. PMID 23979923
25. Minas T, Gomoll AH, Rosenberger R, et al. Increased failure rate of autologous chondrocyte implantation after previous treatment with marrow stimulation techniques. *Am J Sports Med.* May 2009;37(5):902-908. PMID 19261905
26. Ebert JR, Smith A, Fallon M, et al. Incidence, degree, and development of graft hypertrophy 24 months after matrix-induced autologous chondrocyte implantation: association with clinical outcomes. *Am J Sports Med.* Sep 2015;43(9):2208-2215. PMID 26163536
27. Shimozone Y, Yasui Y, Ross AW, et al. Scaffolds based therapy for osteochondral lesions of the talus: A systematic review. *World J Orthop.* Oct 18 2017;8(10):798-808. PMID 29094011
28. Niemeyer P, Salzmann G, Schmal H, et al. Autologous chondrocyte implantation for the treatment of chondral and osteochondral defects of the talus: a meta-analysis of available evidence. *Knee Surg Sports Traumatol Arthrosc.* Sep 2012;20(9):1696-1703. PMID 22037894
29. American Academy of Orthopaedic Surgeons. *Clinical Practice Guideline on the Diagnosis and Treatment of Osteochondritis Dissecans.* Rosemont, IL: AAOS; 2010.
30. National Institute for Health and Care Excellence (NICE). *Autologous chondrocyte implantation for treating symptomatic articular cartilage defects of the knee [TA477].* 2017; <https://www.nice.org.uk/guidance/ta477>. Accessed March 21, 2018.