Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions

Policy Number:
MM.06.002
Line(s) of Business:
HMO; PPO; QUEST
Section:
Surgery
Place(s) of Service:
Outpatient

Original Effective Date:
8/1/2009
Current Effective Date:
07/27/2018

I.   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 under a periosteal or fibrin patch.

For individuals who have focal articular cartilage lesion(s) of the weight-bearing surface of the femoral condyles or trochlea who receive ACI, the evidence includes systematic reviews, randomized controlled trials (RCTs), 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 (Carticel) was phased out and replaced with an ACI preparation that seeds the chondrocytes onto a bioresorbable collagen sponge or scaffold. This is called Matrix induced Autologous chondrocyte implantation or MACI.

Although the implantation procedure for this second-generation ACI (MACI) is less technically demanding, studies to date have not shown improved outcomes compared to first-generation ACI. Some evidence has suggested 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 (MACI) 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 1 RCT and 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. One systematic review found that outcomes following ACI treatment were inferior to microfracture. However, as has been found with cartilage lesions for the knee, marrow stimulation may have a higher failure rate with larger lesions. Comparative trials are needed to determine whether ACI improves outcomes for larger lesions in joints other than the knee. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical input was requested on multiple occasions, most recently in 2015 for the use of ACI in the patella. Prior clinical input supported use for localized chondral defects when other treatments have not been successful. The most recent clinical input was generally supportive of the use of ACI for large patellar lesions, although there was a range in the degree of support. Reviewers indicated that outcomes were improved when realignment procedures were performed concurrently with ACI of the patella, and that success rates were lower when using ACI after a prior microfracture. A majority of reviewers recommended that a prior surgical procedure not be required for lesions greater than 4 cm.

Autologous chondrocyte implantation with MACI will be done by orthopedic surgeons trained in autologous chondrocyte implantation who have completed additional training in Matrix induced chondrocyte implantation (MACI), and have been certified by the manufacturer.

II. Criteria
A. ACI with Matrix induced chondrocyte implantation (MACI) is covered (subject to Limitations and Administrative Guidelines) for the treatment of disabling full-thickness articular cartilage defects of the knee and patella caused by acute or repetitive trauma, when all of the following criteria are met:
   1. Adolescent patients are skeletally mature with documented closure of growth plates (e.g., 15 years or older) or adult patients are too young to be considered an appropriate candidate for total knee arthroplasty or other reconstructive knee surgery (e.g., younger than 55 years)
   2. Focal, full-thickness (grade III or IV) unipolar lesions of the patella or the weight bearing surface of the femoral condyles or trochlea at least 1.5 cm^2 in size
   3. Documentation of 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
   4. Normal knee biomechanics, or alignment and stability that can be achieved concurrently with MACI.
   5. BMI less than or equal to 35.

III. Limitations
A. For smaller lesions (e.g., smaller than 4 cm2), if debridement is the only prior surgical treatment, consideration should be given to marrow-stimulating techniques before MACI is performed.
B. Misalignment and instability of the joint are contraindications. Therefore, additional procedures such as repair of ligaments or tendons or creation of an osteotomy for the 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 MACI.

C. The MACI 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 when the implant is ready and the implantation procedure (ie, arthrotomy) is scheduled.

D. MACI for all other joints, including the talar, and any indications other than those listed above is not covered because it is not known to be effective in improving health outcomes.

E. Treatment of focal articular cartilage lesions with autologous minced cartilage is not covered because it is not known to be effective in improving health outcomes.

F. Treatment of focal articular cartilage lesions with allograft, either allogeneic minced cartilage (DeNovo Natural Tissue Graft) or allogeneic cartilage cells (e.g., DeNovo Engineered Tissue Graft) is not covered because it is not known to be effective in improving health outcomes.

IV. Administrative Guidelines

A. Precertification is required for harvesting of cartilage, culturing of the implant, and implantation of the autologous chondrocyte. To precertify, please complete HMSA's **Precertification Request** and and mail or fax the form, or use iExchange as indicated along with the following required documentation:
   1. Results of the MRI scan;or
   2. Previous arthroscopy; or
   3. Current arthroscopy

B. If precertification is obtained based on the MRI and findings from the procedure for harvesting of the cartilage, are not consistent with MACI, precertification will be reevaluated.

C. Applicable CPT/HCPCS Codes:

Codes that require precertification:	
CPT	**Description**
27412	Autologous chondrocyte implantation, knee
HCPCS Codes	**Description**
S2112	Arthroscopy, knee, surgical, for harvesting of cartilage (chondrocyte cells)
J7330	Autologous cultured chondrocytes, implant
Code that do not require precertification:	
CPT Codes	**Description**

| 29870-29887 | Code range, arthroscopy of the knee |

Applicable ICD-10 Codes:

ICD-10-CM Codes	Description
M17.0-M17.12	Osteoarthritis of knee primary code range
M17.4-M17.5	Osteoarthritis of knee secondary code range
M17.9	Osteoarthritis of knee unspecified code range
M12.561-M12.569	Traumatic arthropathy, knee code range
M23.90-M23.92	Unspecified, internal derangement of knee code range
M23.8x1-M23.8x9	Other internal derangement of knee code range
M25.861-M25.869	Other specified joint disorder, knee code range
M93.261-M93.269	Osteochondritis dissecans knee code range
M89.8x6	Other specified disorder of bone, lower leg
M94.8x6	Other specified disorder of cartilage, lower leg
S89.90-S89.92	Unspecified injury of lower leg code range
S99.811-S99.929	Other specified injures of ankle and foot code range

V. 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 debridement, subchondral drilling, microfracture, and abrasion arthroplasty. Debridement 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.

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 anesthesia, an arthrotomy is performed, and the chondral lesion is excised up to the normal surrounding cartilage and the cartilage is implanted.

The first-generation ACI procedure has been improved through the use of a scaffold composed of biocompatible carbohydrates, protein polymers, or synthetics (MACI) 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 U.S. Food and Drug Administration (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), a matrix-induced autologous chondrocyte implantation, was approved by FDA 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 which are cultured onto a bioresorbable porcine-derived collagen membrane. As of June 30, 2017, production of Carticel has been phased out and MACI® is the only ACI product that is 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

(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), a characterized 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 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.

VI. Rationale

This evidence review was originally created in July 1996 and has been updated regularly with searches of the MEDLINE database. The most recent update with literature review covers the period through February 5, 2018.

Assessment of efficacy for therapeutic intervention involves a determination of whether an intervention improves health outcomes compared to available alternatives. The optimal study design for this purpose is a randomized controlled trial (RCT) that compares the therapeutic intervention with existing alternative treatments and includes clinically relevant measures of health outcomes. Nonrandomized comparative studies and uncontrolled studies can sometimes provide useful information on health outcomes but are prone to biases such as noncomparability of treatment groups, placebo effect, and variable natural history of the condition.

This evidence review was informed by a 2003 TEC Assessment of autologous chondrocyte implantation (ACI), which updated previous TEC Assessments on the same subject. Some of these studies used the first-generation ACI Carticel, while others evaluated second-generation matrix-induced autologous chondrocyte implantation (MACI) products.

ACI for Focal Articular Cartilage Lesions of the Knee

Systematic Reviews

Network Meta-Analysis of Cartilage Repair Procedures
In 2016, Riboh et al reported a network meta-analysis on the comparative efficacy of cartilage repair procedures of the knee.[5] Nineteen RCTs from 15 separate cohorts (total N=855 patients) were included. The procedures selected for the network analysis were MACI, ACI with a collagen membrane, ACI with a periosteal membrane, osteochondral autografts (OCAG), and microfracture. Outcomes evaluated included graft hypertrophy, hyaline cartilage, Lysholm Knee Score (LKS), reoperation at short, mid, and long term, and Tegner Activity Scale (TAS) score. The rank order of treatment efficacy, taking into account all outcome measures, was ACI with a collagen membrane, OCAG, MACI, ACI with a periosteal membrane, and microfracture. Another systematic review of surgical treatments of cartilage defects of the knee by Devitt et al (2017) included a subset of the RCTs in the Riboh 2017 review.

In 2016, Mundi et al reported on a systematic review of level I studies for cartilage restoration of the knee. Included were 12 randomized trials with a total of 765 patients and a mean lesion size of 3.9 cm2. Five trials compared ACI with marrow stimulation, 3 compared ACI with OCAG, 1 trial compared OCAG with microfracture, and 3 trials compared different generations of ACI. Eleven of the 12 trials were conducted in Europe. Four trials reported significant differences in function with ACI versus marrow stimulation, however, meta-analysis showed no significant differences in pain or function between the 2 treatments at 24-month follow-up. The quality of the evidence was rated as poor to moderate, and only 4 trials reported a sample size calculation. Although meta-analysis could not be performed on the other comparisons, 5 of 6 trials found no significant difference in outcomes between ACI and OCAG or different generations of ACI. The percentage of grafts that failed and the relation between lesion size and success rate were not assessed in this review.

ACI vs Other Cartilage Repair Procedures
In 2017, the National Institute for Health Research (NIHR) reported on a systematic review assessing the clinical effectiveness ACI in the knee.8 The NIHR review focused on reports from previous systematic reviews including adults with symptomatic articular cartilage defects in the knee published between 2004 and 2014. Twelve systematic reviews including 19 studies (11 RCTs) were selected. The main comparator of interest was microfracture and 4 trials (n=712) were identified that compared second- and third-generation ACI with microfracture. One of the trials (ACTIVE, N=390) shared selected results with the NIHR reviewers but no results have been published. Another trial (TIG/ACT, N=118) included assessment of the ChondroCelect ACI, which was never approved in the United States and has been withdrawn from the market in Europe. The remaining 2 trials included in the NIHR review (Basad et al [2010] and SUMMIT) are detailed in the following section on RCTs. In summary, both MACI and ChondroCelect were more clinically effective than microfracture for the outcomes of reductions in pain and improvements in function on the Knee injury and Osteoarthritis Outcome Score (KOOS) over 2 to 5 years. Limited long-term data were available on the failure rates of both ACI and microfracture after 5 years; data were available from 6 observational studies. The conclusions regarding follow-up after 5 years were primarily based on one of the observational studies judged to be the highest quality (Nawaz et al [2014]; described in the following section on Durability, N=827), For ACI, failure rates were lower in patients who had no previous knee repair and in people with minimal evidence of osteoarthritis. Larger defect size was not associated with poorer outcomes in these patients.

A 2010 systematic review by Harris et al comparing ACI with other cartilage repair or restoration techniques included 13 RCTs and nonrandomized trials of 917 subjects who underwent ACI (n=604), microfracture (n=271), or OCAG (n=42).7 The mean study quality was rated as 54 (/100), with no studies considered of good or excellent quality, 7 considered fair, and 6 considered poor. Four studies compared different generations of ACI, finding no difference in outcomes but higher complication rates with open, periosteal cover, first-generation ACI. At 1- to 5-year follow-up, 3 of 7 studies showed better clinical outcomes after ACI than after microfracture, 1 study showed better outcomes after microfracture, and 3

studies showed no difference between these treatments. Clinical outcomes after microfracture deteriorated after 18 to 24 months in 3 of 7 studies. Studies comparing ACI with OCAG showed similar short-term clinical outcomes, with more rapid improvement but an increase in arthrofibrosis and donor site morbidity following OCAG. Younger patients with a shorter preoperative duration of symptoms and fewer prior surgical procedures had the best outcomes after surgical intervention. A defect size greater than 4 cm2 was the only factor predictive of better outcomes when ACI was compared with other surgical techniques.

Randomized Controlled Trials
In 2017, first-generation ACI with injection of chondrocytes under a collagen cover (sometimes called second-generation ACI) was phased out and replaced with MACI (matrix-induced). Three RCTs were identified specifically on MACI. These are described next.

MACI vs ACI
In 2005, Bartlett et al on reported a randomized comparison of MACI to ACI with a collagen cover in 91 patients.8 Overall, results were comparable for the 2 treatments. The modified Cincinnati Knee Rating System (CKRS) score improved by 17.6 points in the ACI group and by 19.6 points in the MACI group (p=*NS*). Visual analog scale scores improved from 6.0 to 4.3 in the ACI group and from 6.0 to 4.1 in the MACI group. Factors associated with worse clinical outcomes were a failed prior procedure, duration of symptoms, and patient age. Second-look arthroscopy at 1 year for 42 patients showed excellent-to-good International Cartilage Repair Society (ICRS) scores in 79.2% of ACI and in 66.6% of MACI patients (p=*NS*). The authors did not report whether the study was adequately powered for this comparison.
Histology from 14 ACI and 11 MACI patients showed a similar percentage of hyaline-like cartilage (42.9% ACI, 36.4% MACI).

MACI vs Microfracture
SUMMIT was the pivotal, industry-sponsored multicenter randomized open-label trial comparing MACI with microfracture for larger cartilage defects (≥3 cm2), which typically fare worse than smaller lesions when treated with microfracture.9 Patients (N=144) were included who had at least 1 symptomatic grade III or IV focal cartilage defect on the femoral condyles or trochlea, a stable knee, an intact or partial meniscus, and a moderate-to-severe Knee Injury and Osteoarthritis Outcome Score (KOOS) pain value (<55). Average lesion size was 4.8 cm2 (range, 3-20 cm2); 34.6% of patients had undergone a prior marrow stimulation procedure. At 2-year follow-up, the MACI group had significantly better subscores for KOOS pain (coprimary outcome; difference, 11.76; p<0.001) and function (coprimary outcome; difference, 11.41; p=0.16) as well as the other KOOS subscales (activities of daily living, knee-related quality of life, other symptoms). With response to treatment defined as a 10-point improvement in both the KOOS pain and function subscales, significantly more patients in the MACI group responded to treatment (87.5%) than in the microfracture group (68.1%; p=0.016). There were no significant differences between groups for cartilage repair, as measured by second look arthroscopy, biopsy, or magnetic resonance imaging (MRI).

In 2010, Basad et al reported on a small randomized trial that compared MACI (n=40) with microfracture (n=20) in patients with a single posttraumatic chondral defect between 4 and10 cm2. Both groups improved at the 2-year follow-up, with a significant advantage of MACI over microfracture on the LKS (92 vs 69, p=0.005), TAS (4 vs 3, p=0.04), and ICRS patient (p=0.03) and ICRS surgeon (p=0.02) scores. Patients treated with MACI from this trial, along with newly enrolled patients (n=65), were followed for 5 years. However, the rate of follow-up decreased from 93.8% at 24 months to 38.5% at 60 months, limiting interpretation of the 5-year results. Twelve (18.5%) patients developed symptoms between 6 and 36 months such as pain, locking, crepitus, or recurrent effusion. Arthroscopy of these 12 showed partial disintegration of regenerated tissue (n=5), subchondral edema (n=2), graft fibrillation (n=4), and progression to osteoarthritis (n=1). All 12 underwent additional procedures, including OCAG and microfracture, with good results.

Observational Studies
A variety of issues have been addressed with observational studies on ACI, including combination treatment with meniscal allograft, the durability of the procedure, realignment procedures performed in combination with ACI, comparison of femoral defects and patellar defects, and influence of prior marrow stimulation. They are discussed next.

Combined Meniscal Allograft and Cartilage Repair
The 2010 systematic review by Harris et al evaluated combined meniscal allograft transplantation and cartilage repair/restoration. Six level IV studies (case series) with a total of 110 patients were included. Patients underwent meniscal allograft transplantation with ACI (n=73), osteochondral allograft (n=20), OCAG (n=17), or microfracture (n=3). All studies showed improvement in clinical outcomes at final follow- up compared with the preoperative baseline. Outcomes were also compared with historical outcomes of each procedure performed in isolation. Four of the 6 studies found outcomes equivalent to procedures performed in isolation, while 2 studies found that outcomes with combined surgery were not as good as the historical controls. Across the 6 studies, 13 (12%) failures were reported; they included 11 isolated meniscal allograft transplantation failures, 1 combined meniscal allograft and ACI failure, and 1 isolated ACI failure. Three knees with failed meniscal allograft transplantation were converted to total knee arthroplasty. Nearly 50% of patients underwent 1 or more subsequent surgeries after combined meniscal allograft transplantation and cartilage repair/restoration procedures.

Durability and Effects of Realignment and Prior Procedures
Andriolo et al (2017) performed a systematic review of literature reported on the failure rate of ACI or MACI. Fifty-eight studies were included: 4 RCTs, 6 comparative observational studies, and 48 case series (total N=4294 participants). At a mean follow-up of 86 months, the failure rate was 14.9% (range, 0%-43%) and the mean time of failure was 26 months in the 19 studies reporting time to failure. However, there was high heterogeneity in how failure rates were defined in selected studies.

A 2014 study by Nawaz et al evaluated functional outcomes and survival rates for ACI (periosteal or collagen membrane covered) and MACI in 869 patients. For the group as a whole, graft survival was estimated by Kaplan-Meier analysis to be 78.2% (95% confidence interval [CI], 74.9% to 81.1%) at 5 years and 50.7% (95% CI, 45.2% to 55.9%) at 10 years. Graft survival did not differ between the first- and second-generation (MACI) procedures. Functional and pain scores were significantly better in the MACI group, but this finding may have been confounded by the shorter follow-up with the newer technique.

Minas et al (2014) prospectively followed 210 ACI-treated patients (362 grafts) for at least 10 years. Malalignment, patellar maltracking, and meniscal or ligamentous deficiency had also been corrected as needed. At a mean follow-up of 12 years, 53 (25%) patients had graft failure. For the 157 patients who had successful grafts, functional outcomes were significantly improved from baseline to follow-up, as measured by the Western Ontario and McMaster Universities Index (WOMAC), Knee Society Score (KSS) for knee and function, and 36-Item Short-Form Health Survey (all p<0.001). Graft survival was significantly longer in patients with complex versus salvage-type lesions (p=0.03), with concomitant high tibial osteotomy (HTO) versus no HTO (p=0.01), and with primary ACI versus ACI after a prior marrow stimulation procedure (p=0.004). For example, primary graft survival was 79% compared with 44% for defects previously treated with microfracture.

A 3-fold increased ACI failure after previous treatment with marrow stimulation techniques was found in a cohort of 321 patients with more than 2 years of follow-up. Independent analysis showed a failure rate of 8% (17/214) of joints without prior marrow stimulation of the lesion, compared with 26% (29/111) of joints with prior marrow stimulation. The 2014 Nawaz study of 869 patients treated with ACI or MACI (described above) found that overall graft survival was 78.2% at 5 years and 50.7% at 10 years using Kaplan-Meier analysis. Graft failure was 5 times more likely with a previously treated lesion (<25% survival at 12 years) compared with a previously untreated lesion (>75% survival at 12 years) (hazard ratio, 5.33; 95% CI, 4.07 to 6.99; p<0.001). Other factors affecting survival were graft location and the severity of erative changes.

Patellar Defects
ACI for patellar cartilage defects is typically less effective than ACI for lesions of the femoral condyles. Some studies have reported biomechanical alignment procedures and unloading to improve outcomes for retropatellar ACI. In 2013, Trinh et al reported on a systematic review of ACI combined with patellofemoral osteotomy (anteriorization and/or medialization) versus ACI alone. Eleven studies (10 with level III or IV evidence) with a total of 366 patients were included. Three studies directly compared isolated ACI and combined treatment for patellar or trochlear lesions, showing a statistically significant benefit for the combined treatment.

In 2014, Gomoll et al reported on a multicenter registry study of the treatment of mono- or bipolar patellar defects with ACI in 110 patients with a minimum of 4 years of follow-up (mean, 90 months; range, 48-192 months). Concurrent surgical procedures included tibial tubercle osteotomy in 69% of patients, lateral release in 41%, vastus medialis advancement in 20%, and

trochleoplasty in 5%. At the latest follow-up, statistically and clinically significant improvements in pain and function were obtained in International Knee Documentation Committee, CKRS, WOMAC, and KSS scores, although it was noted that results were inferior to ACI for cartilage lesions of the femoral condyles.

Graft Hypertrophy
In 2015, Ebert et al reported on graft hypertrophy (tissue overgrowth) at 24 months after MACI in a consecutive series of 180 patients. Patients were assessed clinically using the KOOS and underwent MRI at 3, 12, and 24 months post-MACI. Seventeen (9.4%) grafts had failed by 24 months. Three grafts were hypertrophic at 3 months but, the hypertrophy had resolved by 24 months. At 24 months, 47 (26.1%) grafts were hypertrophic. KOOS scores did not differ between patients with hypertrophic grafts and those with normal tissue infill. Longer follow-up is needed to evaluate whether tissue growth continues and to determine the effect of the hypertrophy on graft stability.

Section Summary: ACI for Treatment of Focal Articular Cartilage Lesions of the Knee
The evidence on ACI for the treatment of focal articular cartilage lesions of the knee includes a network analysis, systematic reviews, RCTs, and longer term observational studies. For large lesions, ACI results in better outcomes than microfracture, particularly in the long term. Studies comparing ACI with OCAG have shown similar outcomes with smaller lesions, and improved outcomes with ACI when a defect is greater than 4 cm2. In 2017, first-generation ACI was replaced with a preparation that seeds the chondrocytes onto a bioresorbable collagen sponge (MACI). Studies to date have not shown improved outcomes compared to first-generation ACI. There is some evidence of an increase in implant hypertrophy (overgrowth) at 2 years that may exceed that of the collagen membrane covered implant. Long-term studies with a larger number of patients are needed to determine whether hypertrophy impacts graft survival. Observational studies have indicated that location of a lesion on the patella or a prior cartilage procedure may negatively impact the success of ACI, realignment procedures improve the success of ACI, and ACI combined with meniscal allograft results in outcomes similar to either procedure performed alone.

ACI for Joints Other Than the Knee

There has been interest in applying ACI to cartilage defects in other joints. The most commonly reported is use of ACI for the talus.

Shimozono et al (2017) reported a systematic review of scaffolds-based therapy for osteochondral lesions of the talus and selected articles published through January 2017. Seven studies were found on use MACI and 5 studies were found on Hyalograft C. All studies were case series; the quality of evidence was rated as fair in 2 studies and poor in the remaining 11 studies. Sample sizes ranged from 10 to 46 patients (mean, 22 patients) and follow-up ranged from 21 to 87 months (mean, 46 months). Twelve of 13 studies reported pre- and postoperative American Orthopaedic Foot and Ankle Society (AOFAS) scores; mean AOFAS score improved

from 59 to 87. Three of the case series in Shimozono (2017) overlap with Niemeyer (2012) described below.

A 2012 systematic review by Niemeyer et al evaluated 16 studies (213 patients) on ACI or MACI for lesions of the talus. All were case series, with a mean sample of 13 patients (range, 2-46 patients) and mean follow-up of 32 months (range, 6-120 months). Most series were prospective. In 6 studies,periosteum-covered ACI was applied while 10 studies used second-generation MACI. Nine different methods were used to evaluate pre- and postoperative clinical function, with the most common being the American Orthopaedic Foot and Ankle Society (AOFAS) ankle-hindfoot score. Overall clinical success rate, defined as the percentage of good and excellent results, was 89.9% (range, 50%-100%).

.

Section Summary: ACI for Joints Other Than the Knee
The evidence on ACI for joints other than the knee includes systematic reviews primarily of observational studies. The most commonly reported use of ACI is for the talus. Comparative trials are needed to determine whether ACI improves outcomes for larger lesions of the talus.

Summary of Evidence

For individuals who have focal articular cartilage lesion(s) of the weight-bearing surface of the femoral condyles or trochlea who receive autologous chondrocyte implantation (ACI), the evidence includes systematic reviews, randomized controlled trials (RCTs), 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 to first-generation ACI. Some evidence has suggested 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.

Supplemental Information

Clinical Input from Physicians Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2015 Input
In response to requests   input was received from 2 physician specialty societies (6 reviewers) and 4 academic medical centers while this policy was under review in 2015. Input was generally supportive of the use of autologous chondrocyte implantation (ACI) for large patellar lesions, although the degree of support varied. Reviewers indicated that outcomes were improved when realignment procedures were performed concurrently with ACI of the patella, and that success rates were lower when using ACI after a prior microfracture. Most reviewers recommended that a prior surgical procedure not be required for lesions greater than 4 cm2.

2011 Input
In response to requests, input was received from 2 physician specialty societies and 3 academic medical centers while this policy was under review in 2011. Input was generally in agreement with the stated criteria for ACI, with the exception of the following: input was mixed on the requirement for an inadequate response to a prior surgical procedure and the requirement for an absence of meniscal pathology. Input was also mixed on the investigational status of ACI in patellar and talar joints.

2008 Input
In response to requests, input was received from 1 physician specialty society and 3 academic medical centers while this policy was under review in 2008. Reviewers generally agreed that ACI should be considered when all other treatments have been unsuccessful in patients with a localized chondral defect in an otherwise normal joint articular surface. Reviewers noted the lack of alternative options for larger lesions (eg, >4 cm2). Additional literature was provided, which was subsequently reviewed.

Practice Guiltiness and Position Statement

American Academy of Orthopaedic Surgeons
In 2010 guidelines on the diagnosis and treatment of osteochondritis dissecans (OCD), the American Academy of Orthopaedic Surgeons (AAOS) was unable to recommend for or against a specific cartilage repair technique in symptomatic skeletally immature or mature patients with

an unsalvageable OCD lesion.This recommendation of insufficient evidence was based on a systematic review that found 4 level IV studies addressing cartilage repair techniques for an unsalvageable OCD lesion. Because each of the level IV articles used different techniques, different outcome measures, and differing lengths of follow-up, AAOS deemed the evidence for any specific technique inconclusive.

National Institute for Health and Care Excellence
In 2017, the National Institute for Health and Care Excellence (NICE) updated its 2005 guidance on the use of autologous chondrocyte implantation (ACI). The Institute

"… as an option for treating symptomatic articular cartilage defects of the knee, 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);
•   the defect is over 2 cm; and,
•   the procedure is done at a tertiary referral centre."

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01066702[a]	A Randomized Comparison of NeoCart to Microfracture for the Repair of Articular Cartilage Injuries in the Knee	245	Jun 2020
NCT01222559[a]	Prospective, Randomised, Open Label, Multicentre Phase-III Clinical Trial to Compare the Efficacy and Safety of the Treatment With the Autologous Chondrocyte Transplantation Product co.Don Chondrosphere (ACT3D-CS) With Microfracture in Subjects With Cartilage Defects of the Knee With a Defect Size Between 1 and 4 cm2	102	Dec 2020
NCT01656902[a]	A Prospective Randomized Controlled Multicenter Phase-III Clinical Study to Evaluate the Safety and Effectiveness of NOVOCART® 3D Plus Compared to the Standard Procedure Microfracture in the Treatment of Articular Cartilage Defects of the Knee	261	Mar 2021
NCT01957722[a]	A Phase 3, Prospective, Randomized, Partially Blinded Multi-Center Study to Measure the Safety and Efficacy of NOVOCART 3D Compared to Microfracture in the Treatment of Articular Cartilage Defects	233	Aug 2021
Unpublished			
NCT01251588[a]	An Extension Protocol for Participants of Genzyme-Sponsored Prospective, Randomized, Open-Label, Parallel-Group, Multicenter Study of MACI® for the Treatment of Symptomatic Articular Cartilage Defects of the Femoral Condyle Including the Trochlea	128	Mar 2015 (completed)

VII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VIII. References

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. Sep 07 2016. 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):2325967117709250. 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 g 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. Shimozono 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. 2010; http://www.aaos.org/research/guidelines/OCD_guideline.pdf. Accessed March 21, 2017.

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.

VIII. Appendix

The Outerbridge classification is a grading system for joint cartilage breakdown:

Grade	Description
0	Normal
I	Cartilage with softening and swelling
II	A partial-thickness defect with fissures on the surface that do not reach subchondral bone or exceed 1.5 cm in diameter
III	Fissuring to the level of subchondral bone in an area with a diameter more than 1.5 cm
IV	Exposed subchondral bone