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Title: Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions

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Populations	Interventions	Comparators	Outcomes
Individuals: • With focal articular cartilage lesion(s) of the weight-bearing surface of the femoral condyles or trochlea	Interventions of interest are: • Autologous chondrocyte implantation	Comparators of interest are: • Marrow stimulation • Osteochondral autografts	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Functional outcomes • Quality of life

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Populations	Interventions	Comparators	Outcomes
Individuals: • With focal articular cartilage lesions of joints other than the knee	Interventions of interest are: • Autologous chondrocyte implantation	Comparators of interest are: • Marrow stimulation • Osteochondral autografts	Relevant outcomes include: • 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.

OBJECTIVE

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

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 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

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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 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. In 2017, production of Carticel® was 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.

POLICY

A. 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:

    1. Adolescent patients should be skeletally mature with documented closure of growth plates (eg, 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 (eg, younger than 55 years); **AND**

    2. Focal, full-thickness (grade III or IV) unipolar lesions on the weight bearing surface of the femoral condyles or trochlea at least 1.5 cm^2 in size; **AND**

    3. 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; **AND**

    4. Normal knee biomechanics, or alignment and stability achieved concurrently with autologous chondrocyte implantation.

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

Policy Guidelines

1. For smaller lesions (eg, smaller than 4 cm^2), if débridement is the only prior surgical treatment, then consideration should be given to marrow-stimulating techniques before autologous chondrocyte implantation (ACI) is performed.
2. The average defect size reported in the literature is about 5 cm^2; many studies treated lesions as large as 15 cm^2.
3. Severe obesity, eg, body mass index (BMI) greater than 35 kg/m^2, may affect outcomes due to the increased stress on weight bearing surfaces of the joint.
4. 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.

5.   The entire matrix-induced autologous chondrocyte implantation (ACI) procedure consists of 4 steps:
    a.   the initial arthroscopy and biopsy of normal cartilage,
    b.   culturing of chondrocytes on an absorbable collagen matrix,
    c.   a separate arthrotomy to place the implant, and
    d.   post-surgical 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.

Outerbridge cartilage grading scale
Grade I: softening and swelling of the cartilage
Grade II: shows fragmentation and fissuring of the superficial cartilage of less than one-half in diameter
Grade III: fragmentation and deeper fissuring of more than one-half inch
Grade IV: shows erosion of the cartilage down to the bone

RATIONALE
This policy has been updated regularly with searches of the MEDLINE database. The most recent update with literature review covers the period through February 5, 2018.

This evidence review was informed by a TEC Assessment (2003) of autologous chondrocyte implantation (ACI), which updated previous TEC Assessments on the same subject.[1-4]

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events

and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

ACI for Focal Articular Cartilage Lesion(s) of the Knee
<u>Systematic Reviews</u>
Cartilage Repair Procedures
Riboh et al (2017) reported on a network meta-analysis assessing 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 matrix-induced ACI (MACI), ACI with a collagen membrane, ACI with a periosteal membrane, osteochondral autograft transfer (OAT), and microfracture. Outcomes evaluated included graft hypertrophy, hyaline cartilage, Lysholm Knee Scoring System score, reoperation in the 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, OAT, 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)[6] included a subset of the RCTs in the Riboh 2017 review.

Mundi et al (2016) reported on a systematic review of level I studies for cartilage restoration of the knee.[7] Included were 12 randomized trials (total N=765 patients) and a mean lesion size of 3.9 cm^2. Five trials compared ACI with marrow stimulation, three compared ACI with OAT, one compared OAT with microfracture, and three compared different generations of ACI. Eleven of the 12 trials were conducted in Europe. Four trials reported significant differences in function with ACI vs marrow stimulation. However, a 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 OAT 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 systematic review by Harris et al (2010) 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 OAT (n=42).[9] The mean study quality was rated as 54 (/100), with no studies considered of good or excellent quality, seven considered fair, and six 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, one showed better outcomes after microfracture, and three 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 OAT showed similar short-term clinical outcomes, with more rapid improvement but an increase in arthrofibrosis and donor-site morbidity following OAT. 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 cm^2 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. Three RCTs were identified specifically on MACI. They are described next.

MACI vs ACI
Bartlett et al (2005) reported on a randomized comparison between MACI and ACI with a collagen cover in 91 patients.[10] Overall, results were comparable for both treatments. The modified Cincinnati Knee Rating System score improved by 17.6 points in the ACI group and by 19.6 points in the MACI group (p=0.32). 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=0.3). The authors did not report whether the study was adequately powered for this comparison. Histology from 14 ACI and 11 MACI patients showed similar percentages of hyaline-like cartilage (42.9% ACI, 36.4% MACI).

MACI vs Microfracture
SUMMIT was the pivotal, industry-sponsored multicenter randomized open-label trial; it was reported by Saris et al (2014) and compared MACI with microfracture for larger cartilage defects (≥3 cm^2), which typically fare worse than smaller lesions when treated with microfracture.[11] Patients (N=144) included 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 KOOS pain value (<55). Average lesion size was 4.8 cm^2 (range, 3-20 cm^2), and 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 in sport and recreation (coprimary outcome; difference, 11.41; p=0.16) as well as the other KOOS subscales (function in 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). Results through 5 years are reported on www.ClinicalTrials.gov (NCT01251588). However, there was differential follow-up for the 2 groups in the extension study (loss of higher responding MACI patients and lower responding microfracture patients), resulting in little to no differences between groups. Statistical analysis was not reported.

Basad et al (2010) reported on a small randomized trial that compared MACI (n=40) with microfracture (n=20) in patients who had a single posttraumatic chondral defect between 4 and 10 cm^2.[12] Both groups improved at the 2-year follow-up, with a significant advantage of MACI over microfracture on the Lysholm Knee Score (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.[13] 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 OAT and microfracture, with good results.

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

Tibiofemoral vs Patellofemoral Lesions
Fewer data are available on MACI for patellofemoral lesions, but comparative observational studies have suggested outcomes that do not differ substantially from those using MACI for tibiofemoral lesions.

Systematic Reviews: Schuette et al (2017) published a systematic review of mid- to long-term clinical outcomes from use of MACI in the knee.[14] They included 10 studies (2 level I, 1 level II, 1 level III, 6 level IV studies), with a total of 442 tibiofemoral and 136 patellofemoral lesions/patients and follow-up of at least 5 years, published through September 2016. Four of the studies used the type I and III collagen matrix, five used Hyalograft C, and one used both. The 2 level I studies compared early with late weight-bearing following MACI. Individual study quality was rated as good to fair, with an average rating of fair. Clinical outcomes, weighted for age and defect size, improved from baseline to latest follow-up. At follow-up the failure rate was 12.4% (3 studies, n=145 patients; range, 3.2%-21.6%) for tibiofemoral joints and 4.7% (4

studies, n=106 patients; range, 0%-50%) for patellofemoral joints (p=0.037). The highest failure rates were reported in studies with the largest lesions and the longest follow-up.

One of the studies included in the Schuette systematic review (Meyerkort et al [2014])[15] was a prospective cohort of 23 patients who were treated with MACI for patellofemoral lesions. The mean defect size was 3.5 cm^2, and 9 (39%) of the patients underwent concurrent patellofemoral realignment procedures. At the 5-year follow-up, MRI indicated an intact appearance in most grafts, with graft height of more than 50% of the surrounding cartilage in 82% of patients. Patient-reported outcomes, measured with the KOOS and 36-Item Short-Form Health Survey (SF-36), improved significantly compared with preoperative scores. The increase in distance walked in 6 minutes was statistically significant (p<0.001) but modest (from 570 to 590 m). Graft hypertrophy was detected in 3 (13%) patients by MRI, but symptoms were considered sufficient to merit débridement in only 1 (4.3%) patient.

A report by Zak et al (2012)[16] was also included in the Schuette review. Zak et al evaluated return to sports at 5 years in 70 patients who had MACI, 15 of whom had MACI in the patellofemoral joint. Significant improvements in the KOOS function in sport and recreation, Noyes grading system, and TAS scores were reported between presurgery and follow-up. Patients with 2 lesions had worse outcomes than patients with a single tibiofemoral lesion, but there were no significant differences in outcomes between the tibiofemoral and patellofemoral groups.

Nonrandomized Comparative Studies: Three studies assessed in the systematic review were reported by Ebert and colleagues.[17-19] Ebert et al (2017) reported on a comparative study with 24-month follow-up.[20] They evaluated 194 patients with lesions on the medial or lateral femoral condyle (n=127), patella (n=35), or trochlea (n=32). There were no significant differences between groups in demographics, defect size, prior injury, or surgical history. Patient-reported outcome measures, including the KOOS, visual analog scale for pain, SF-36, and satisfaction scores, were collected by an independent assessor. Most clinical scores were similar preoperatively except for the KOOS function in daily living and quality of life subscales, which were worse in the combined patella and trochlea group. Patellofemoral malalignment was corrected when indicated. Postoperative scores on the KOOS function in daily living, knee-related quality of life, and function in sport and recreation were significantly higher in the tibiofemoral group, but both groups improved over time. Graft hypertrophy assessed using MRI was more frequent in the tibiofemoral group (32.1%) than the patellofemoral group (10.4%). All lesions with hypertrophy were asymptomatic at the 24-month follow-up.

<u>Combined Meniscal Allograft and Cartilage Repair</u>
The systematic review by Harris et al (2011) evaluated combined meniscal allograft transplantation and cartilage repair/restoration.[21] 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), OAT (n=17), or microfracture (n=3). All studies showed improvements 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 two 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, one combined meniscal allograft and ACI

failure, and one 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.[22] 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 study by Nawaz et al (2014) evaluated functional outcomes and survival rates for ACI (periosteal or collagen membrane covered) and MACI in 869 patients.[23] For the group as a whole, graft survival was estimated by Kaplan-Meier analysis to be 78.2% (95% confidence interval, 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 might 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.[24] 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, Knee Society Score for knee and function, and SF-36 (all $p<0.001$). Graft survival was significantly longer in patients with complex vs salvage-type lesions ($p=0.03$), with concomitant high tibial osteotomy vs no high tibial osteotomy ($p=0.01$), and with primary ACI vs 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 increase in ACI failure rate after previous treatment with marrow stimulation techniques was repored by Minas et al (2009) in a cohort of 321 patients with more than 2 years of follow-up.[25] 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 that had not. 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.[23] 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 degenerative changes.

Graft Hypertrophy
Ebert et al (2015) reported on graft hypertrophy (tissue overgrowth) at 24 months after MACI in a consecutive series of 180 patients.[26] 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 OAT have shown similar outcomes with smaller lesions, and improved outcomes with ACI when a defect is greater than 4 cm^2. 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 with first-generation ACI. There is some evidence of an increase in implant hypertrophy (overgrowth) at 2 years, particularly on the femoral condyles 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. MACI for patellar lesions has been evaluated in a systematic review and a nonrandomized comparative study. The included studies reported outcomes that did not differ substantially from those using MACI for tibiofemoral lesions. Observational studies have indicated that a prior cartilage procedure may negatively impact the success of ACI, realignment procedures improve the success of ACI for patellar lesions, 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 the 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.[27] 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 meta-analysis by Niemeyer et al (2012) evaluated 16 studies (total N=213 patients) assessing ACI or MACI for lesions of the talus.[28] All were case series, with a mean sample size 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 AOFAS Ankle-Hindfoot Scale 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 use of ACI for joints other than the knee includes case series and systematic reviews of these case series. The most commonly reported use of ACI is for the talus. Comparative trials are needed to determine whether ACI improves outcomes for 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, 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.

CLINICAL INPUT FROM PHYSICIAN 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.

<u>2015 Input</u>
In response to requests regarding the use of ACI for patellar lesions, input was received from 2 physician specialty societies (6 reviewers) and 4 academic medical centers while this policy was under review in 2015. The 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^2.

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. The clinical input was generally in agreement with the stated criteria for ACI with the exception of the following: input was mixed regarding the requirement for an inadequate response to a prior surgical procedure and the requirement for an absence of meniscal pathology. Input was also mixed regarding 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. The reviewers generally agreed that ACI should be considered when all other treatments have been unsuccessfully tried in individuals who have a localized chondral defect in an otherwise normal joint articular surface. Reviewers noted the lack of alternative options for larger lesions (eg, >4 cm^2). Additional literature was provided, which was subsequently reviewed.

PRACTICE GUIDELINES AND POSITION STATEMENTS
American Academy of Orthopaedic Surgeons
In a 2010 clinical practice guideline 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 osteochondritis dissecans lesion.[29] This finding of insufficient evidence was based on a systematic review that found 4 level IV studies that addressed cartilage repair techniques for an unsalvageable OCD lesion. Since each of the level IV articles utilized different techniques, different outcome measures, and differing lengths of follow-up, the work group deemed that the evidence for any specific technique was inconclusive.

National Institute for Health and Clinical Excellence
In 2017, the National Institute for Health and Care Excellence updated its 2005 guidance on the use of autologous chondrocyte implantation.[30] "Autologous chrondrocyte implantation (ACI) is recommended 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^2; and,
- the procedure is done at a tertiary referral centre."

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS
Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

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

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
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
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
Unpublished			
NCT01251588[a]	An Extension Protocol for Participants of Genzyme-Sponsored Prospective, Randomized, Open-Label, Parallel-Group, Multicenter Study of Matrix-Induced Autologous Chondrocyte Implantation (MACI® Implant) for the Treatment of Symptomatic Articular Cartilage Defects of the Femoral Condyle Including the Trochlea for the Repair of Articular Cartilage Injuries in the Knee	128	Mar 2015 (completed)

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

27412	Autologous chondrocyte implantation, knee
29870	Arthroscopy, knee, diagnostic, with or without synovial biopsy (separate procedure)
29871	Arthroscopy, knee, surgical; for infection, lavage and drainage
29873	Arthroscopy, knee, surgical; with lateral release
29874	Arthroscopy, knee, surgical; for removal of loose body or foreign body (eg, osteochondritis dissecans fragmentation chrondral fragmentation)
29875	Arthroscopy, knee, surgical; synovectomy, limited (eg, plica or shelf resection) (separate procedure)
29876	Arthroscopy, knee, surgical; synovectomy, major, 2 or more compartments (eg, medical or lateral)
29877	Arthroscopy, knee, surgical; debridement/shaving of articular cartilage (chondroplasty)

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29879	Arthroscopy, knee, surgical; abrasion arthroplasty (includes chondroplasty where necessary) or multiple drilling or microfracture
29880	Arthroscopy, knee, surgical; with meniscectomy (medial AND lateral, including any meniscal shaving) including debridement/shaving of articular cartilage (chondroplasty), same or separate compartment(s), when performed
29881	Arthroscopy, knee, surgical; with meniscectomy (medial OR lateral, including any meniscal shaving) including debridement/shaving of articular cartilage (chondroplasty), same or separate compartment(s), when performed
29882	Arthroscopy, knee, surgical; with meniscus repair (medial OR lateral)
29883	Arthroscopy, knee, surgical; with meniscus repair (medial AND lateral)
29884	Arthroscopy, knee, surgical; with lysis of adhesions, with or without manipulation (separate procedure)
J7330	Autologous cultured chondrocytes, implant
S2112	Arthroscopy, knee, surgical for harvesting of cartilage (chondrocyte cells)

ICD-10 Diagnoses

M12.561	Traumatic arthropathy, right knee
M12.562	Traumatic arthropathy, left knee
M17.0	Bilateral primary osteoarthritis of knee
M17.11	Unilateral primary osteoarthritis, right knee
M17.12	Unilateral primary osteoarthritis, left knee
M17.2	Bilateral post-traumatic osteoarthritis of knee
M17.31	Unilateral post-traumatic osteoarthritis, right knee
M17.32	Unilateral post-traumatic osteoarthritis, left knee
M17.4	Other bilateral secondary osteoarthritis of knee
M17.5	Other unilateral secondary osteoarthritis of knee
M17.9	Osteoarthritis of knee, unspecified
M23.8X1	Other internal derangements of right knee
M23.8X2	Other internal derangements of left knee
M23.91	Unspecified internal derangement of right knee
M23.92	Unspecified internal derangement of left knee
M25.861	Other specified joint disorders, right knee
M25.862	Other specified joint disorders, left knee
M89.8X6	Other specified disorders of bone, lower leg
M89.9	Disorder of bone, unspecified
M93.261	Osteochondritis dissecans, right knee
M93.262	Osteochondritis dissecans, left knee
M94.261	Chondromalacia, right knee
M94.262	Chondromalacia, left knee
M94.8X6	Other specified disorders of cartilage, lower leg
S89.81XA	Other specified injuries of right lower leg, initial encounter
S89.81XD	Other specified injuries of right lower leg, subsequent encounter
S89.81XS	Other specified injuries of right lower leg, sequela
S89.82XA	Other specified injuries of left lower leg, initial encounter
S89.82XD	Other specified injuries of left lower leg, subsequent encounter
S89.82XS	Other specified injuries of left lower leg, sequela
S89.90XA	Unspecified injury of unspecified lower leg, initial encounter
S89.90XD	Unspecified injury of unspecified lower leg, subsequent encounter

S89.90XS   Unspecified injury of unspecified lower leg, sequela
S89.91XA   Unspecified injury of right lower leg, initial encounter
S89.91XD   Unspecified injury of right lower leg, subsequent encounter
S89.91XS   Unspecified injury of right lower leg, sequela
S89.92XA   Unspecified injury of left lower leg, initial encounter
S89.92XD   Unspecified injury of left lower leg, subsequent encounter
S89.92XS   Unspecified injury of left lower leg, sequela

REVISIONS

04-02-2015	A stand-alone policy entitled "Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions" was created from the "Transplantation for Chondral Defects" medical policy.
	Updated Description section.
	In Policy section: ▪ In Item A, removed "or osteochondritis dissecans", to read, "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 in patients who have had an inadequate response to a prior surgical procedure, when all of the following criteria are met:" ▪ In Item A #2, removed Outerbridge definition as this is defined in Policy Guidelines. ▪ In Item A #3, removed Outerbridge definition as this is defined in Policy Guidelines. ▪ Removed Item A #5 "Absence of meniscal pathology." ▪ Removed all language regarding Osteochondral Autograft Transplants for the treatment of cartilaginous defects and Osteochondral Allograft Transplant. ▪ In Policy Guidelines, added Items 1-5, and removed all language regarding Autologous Chondrocyte Transplant or Implants and Osteochondral Autograft Transplants and Osteochondral Allograft Transplants.
	Updated Rationale section.
	In Coding section: ▪ Added CPT codes 29879, 29880, 29881, 29882, 29883, and 29884. ▪ Removed CPT codes 27415, 27416, 28446, 29866, and 29867. ▪ Removed ICD-9 Diagnosis code 717.7.
	Updated Revision section.
	Updated References section.
10-13-2015	Updated Rationale section.
	Updated References section.
01-20-2016	Updated Description section.
	In Policy section: ▪ In Item A, removed "in patients who have had an inadequate response to a prior surgical procedure" to read, "Autologous chondrocyte implantation may be 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:"
	Updated Rationale section.
	Updated References section.
05-10-2017	Updated Description section.
	In Policy section:

	▪ In Item B, removed "patellar and" to read, "Autologous chondrocyte implantation for all other joints, including talar, and any indications other than those listed above is considered experimental / investigational." ▪ Removed Item C, "Matrix-induced autologous chondrocyte implantation is considered experimental / investigational." ▪ In Policy Guidelines Item 5 b, added "on an absorbable collagen matrix" to read, "culturing of chondrocytes on an absorbable collagen matrix" ▪ In Policy Guidelines Item 5 c, added "place the implant" and removed "create a periosteal flap and implant the chondrocytes" to read, "a separate arthrotomy to place the implant"
	Updated Rationale section.
	Updated References section.
03-28-2018	Updated Description section.
	In Policy section: ▪ Revised Policy Guidelines Item 4.
	Updated Rationale section.
	In Coding section: ▪ Removed ICD-9 codes.
	Updated References section.
05-23-2018	Updated Description section.
	In Policy section: ▪ Updated Policy Guidelines
	Updated Rationale section.
	Updated References section.

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