



Louisiana

Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions

Policy # 00006

Original Effective Date: 08/26/2002

Current Effective Date: 04/18/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider autologous chondrocyte implantation (ACI) for the treatment of disabling full-thickness articular cartilage defects of the knee caused by acute or repetitive trauma to be **eligible for coverage** when all of the following criteria are met:

Patient Selection Criteria

Coverage eligibility will be considered when all of the following criteria are met:

- Adolescent patients should be skeletally mature with documented closure of growth plates (e.g., 15 years or older). Adult patients should be too young to be considered an appropriate candidate for total knee arthroplasty or other reconstructive knee surgery (e.g., younger than 55 years); and
- 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 cm² in size; and
- 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
- Normal knee biomechanics or alignment and stability achieved concurrently with autologous chondrocyte implantation (ACI).

Note: Grade Description of Outerbridge scale:

Grade 0 normal articular cartilage

Grade I softening or blistering of joint cartilage

Grade II cartilage fragmentation or fissuring on the surface <1cm diameter

Grade III cartilage fragmentation or fissuring > 1cm diameter

Grade IV cartilage erosion down to subchondral bone

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

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Based on review of available data, the Company considers autologous chondrocyte implantation (ACI) for all other joints, including talar, and any indications other than those listed above to be **investigational**.*

The use of autologous chondrocyte implantation (ACI) for the treatment of disabling full-thickness articular cartilage defects of the knee caused by acute or repetitive trauma when patient selection criteria are not met is considered to be **investigational**.*

Policy Guidelines

For smaller lesions (eg, <4 cm²), if débridement is the only prior surgical treatment then consideration should be given to marrow-stimulating techniques before ACI is performed.

The average defect size reported in the literature is about 5 cm²; many studies treated lesions as large as 15 cm².

Severe obesity (eg, body mass index >35 kg/m²) may affect outcomes due to the increased stress on weight-bearing surfaces of the joint.

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

The entire matrix-induced ACI procedure consists of 4 steps: (1) initial arthroscopy and biopsy of normal cartilage, (2) culturing of chondrocytes on an absorbable collagen matrix, (3) a separate arthrotomy to place the implant, and (4) postsurgical rehabilitation. The initial arthroscopy may be scheduled as a diagnostic procedure; as part of this procedure, a cartilage defect may be identified, prompting biopsy of normal cartilage in anticipation of a possible chondrocyte transplant. The biopsied material is then sent for culturing and returned to the hospital when the implantation procedure (ie, arthrotomy) is scheduled.

Background/Overview

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,

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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 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.

FDA or Other Governmental Regulatory Approval

The culturing of chondrocytes is considered by the U.S. 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

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(Ars Arthro), collagen gel; Cartilix (Biomet), a polymer hydrogel; Chondron (Sewon Cellontech), a fibrin gel; Hyalograft C (Fidia Advanced Polymers), a hyaluronic acid-based scaffold; NeoCart (Histogenics), an ACI with a 3-dimensional chondromatrix in a phase 3 trial; and Novocart[®] 3D (Aesculap Biologics), a collagen-chondroitin sulfate scaffold in a phase 3 trial. ChondroCelect[®] (TiGenix), 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.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination.

Rationale/Source

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 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 MACI products.

ACI FOR FOCAL ARTICULAR CARTILAGE LESIONS OF THE KNEE

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. 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.

Systematic Reviews

ACI vs Other Cartilage Repair Procedures

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

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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.

A 2010 systematic review by Harris et al included 13 RCTs and nonrandomized trials of 917 subjects who underwent ACI (n=604), microfracture (n=271), or OCAG (n=42). 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 reported a randomized comparison of MACI to ACI with a collagen cover in 91 patients. 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).

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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. 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 and 10 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

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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

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 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. 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.

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

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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.

In 2010, Zengerink et al published a systematic review of treatment of osteochondral lesions of the talus. Fifty-one nonrandomized and 1 randomized trial were included in the review. Success rates were 85% for bone marrow stimulation, 87% for osteochondral autografting, and 76% for ACI. Because of the high cost of

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ACI and the knee morbidity seen with osteochondral autografting, reviewers concluded that bone marrow stimulation is the treatment of choice for primary osteochondral talar lesions.

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%).

A 2009 report examined the association between defect size and outcomes following marrow stimulation techniques in 120 ankles. Eight ankles subsequently underwent osteochondral transplantation, and 22 ankles were considered clinical failures (AOFAS ankle-hindfoot score, <80). Linear regression suggested a cutoff defect size of 1.5 cm² for marrow stimulation techniques, with an 80% failure rate compared with a 10.5% failure rate for ankles with a defect size of less than 1.5 cm². Three (5.2%) of 58 ankles with a defect area of less than 1 cm² showed clinical failure, while 7 (18.9%) of 37 ankles with a defect area between 1.0 and 1.5 cm² failed.

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. One systematic review found that outcomes following treatment with ACI were inferior to microfracture. As has been found with ACI for the knee, marrow stimulation has a higher failure rate with larger lesions. 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 ACI, the evidence includes systematic reviews, 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

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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 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.

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Policy History

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|------------|---|
| 07/01/2001 | Medical Director review |
| 07/18/2002 | Medical Policy Committee review |
| 08/26/2002 | Managed Care Advisory Council approval |
| 06/24/2002 | Format revision. No substance change to policy |
| 08/10/2004 | Medical Director review |
| 08/31/2004 | Medical Director review |
| 09/21/2004 | Medical Policy Committee review. Format revision. No Substance change to policy |
| 09/27/2004 | Managed Care Advisory Council approval |
| 09/07/2005 | Medical Director review |
| 09/20/2005 | Medical Policy Committee review. Format revision. Coverage eligibility unchanged. |
| 09/22/2005 | Quality Care Advisory Council approval |
| 07/12/2006 | Medical Director review |
| 07/19/2006 | Medical Policy Committee approval. Format changes. FDA information added. Coverage eligibility unchanged. |
| 05/02/2007 | Medical Director review |
| 05/23/2007 | Medical Policy Committee approval. Added when patient selection criteria are not met is considered to be investigational. |
| 05/07/2008 | Medical Director review |
| 05/21/2008 | Medical Policy Committee approval. Rationale updated. |
| 05/07/2009 | Medical Director review |

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05/20/2009 Medical Policy Committee approval. No change to coverage eligibility.
06/03/2010 Medical Director review
06/16/2010 Medical Policy Implementation Committee approval. No change to coverage eligibility.
05/05/2011 Medical Director review
05/18/2011 Medical Policy Implementation Committee approval. No change to coverage eligibility
05/03/2012 Medical Director review
05/16/2012 Medical Policy Implementation Committee approval. No change to coverage eligibility
08/01/2013 Medical Director review
08/21/2013 Medical Policy Implementation Committee approval. Sections and statements on minced cartilage moved to policy (Osteochondral Autografts and Allografts) and "Other Cell-based Treatments" removed from title.
08/07/2014 Medical Director review
08/20/2014 Medical Policy Implementation Committee approval. No change to coverage.
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
12/03/2015 Medical Director review
12/16/2015 Medical Policy Implementation Committee approval. Removed need for a prior surgical procedure from eligibility statement. Patella added to the eligibility statement.
12/01/2016 Medical Policy Committee review
12/21/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
08/03/2017 Medical Policy Committee review
08/23/2017 Medical Policy Implementation Committee approval. Investigational statement on matrix-induced autologous chondrocyte implantation removed.
04/05/2018 Medical Policy Committee review
04/18/2018 Medical Policy Implementation Committee approval. No change to coverage.
Next Scheduled Review Date: 04/2019

Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	27412, 29866
HCPCS	J7330, S2112
ICD-10 Diagnosis	M12.561-M12.569 M17.0-M17.10-M17.9 M22.2X1-M22.2X9 M22.3X1-M22.3X9
	M22.40-M22.42 M22.8X1-M22.8X9 M22.90-M22.92 M23.000-M23.009
	M23.011-M23.069 M23.200-M23.269 M23.300-M23.369 M23.40-M23.679
	M23.8X1-M23.8X9 M23.90-M23.92 M24.80 M25.161-M25.169
	M25.261-M25.269 M25.361-M25.369 M25.861-M25.869 M85.9
	M89.9 M93.20-M93.29 M94.9 Q68.6
	S86.001A S86.002A S86.009A S86.091A
	S86.092A S86.099A S86.101A S86.102A
	S86.109A S86.191A S86.192A S86.199A
	S86.201A S86.202A S86.209A S86.291A
	S86.292A S86.299A S86.301A S86.302A
	S86.309A S86.391A S86.392A S86.399A
	S86.801A S86.802A S86.809A S86.891A
	S86.892A S86.899A S86.901A S86.902A
	S86.909A S86.991A S86.992A S86.999A
	S89.80XA S89.81XA S89.82XA S89.90XA
	S89.90XA S89.91XA S89.92XA S96.001A
	S96.002A S96.009A S96.091A S96.092A
	S96.099A S96.101A S96.102A S96.109A
	S96.191A S96.192A S96.199A S96.201A
	S96.202A S96.209A S96.291A S96.292A
	S96.299A S96.801A S96.802A S96.809A
	S96.891A S96.892A S96.899A S96.901A
	S96.902A S96.909A S96.991A S96.992A
	S96.999A S99.811A S99.812A S99.819A
	S99.821A S99.822A S99.829A S99.911A
	S99.912A S99.919A S99.921A S99.922A
	S99.929A

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

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- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 - 1. Consultation with the Blue Cross and Blue Shield Association TEC or other nonaffiliated technology evaluation center(s);
 - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 - 3. Reference to federal regulations.

****Medically Necessary (or "Medical Necessity")** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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