BlueCross BlueShield of Alabama

Name of Policy:

Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions

Policy #: 156
Category: Surgery

Latest Review Date: May 2018
Policy Grade: A

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *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.*

Description of Procedure or Service:

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. Second- and third- generation techniques include combinations of autologous chondrocytes, scaffolds, and growth factors.

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 an individual's activities of daily living and adversely affect the 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. Osteochondral grafts for the treatment of articular cartilage defects are discussed in Medical Policy #248, *Autografts and Allografts in the Treatment of Focal Articular Cartilage Lesions.*

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.

Policy:

Effective for dates of service on or after May 1, 2017:

Autologous chondrocyte implantation meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the treatment of disabling full-thickness articular cartilage defects of the knee caused by acute or repetitive trauma, when **all** of the following criteria are met:

- Adolescent patients should be skeletally mature with documented closure of growth plates (e.g., 15 years or older). Adult patients should be too young to be considered an appropriate candidate for total knee arthroplasty or other reconstructive knee surgery (e.g., younger than 55 years); **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 cm^2 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.

Autologous chondrocyte implantation does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage for all other joints, including talar, and any indications other than those listed above is therefore considered investigational.

Effective for dates of service on or after November 1, 2015 through April 30, 2017:

Autologous chondrocyte implantation meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the treatment of disabling full-thickness articular cartilage defects of the knee caused by acute or repetitive trauma, when **all** of the following criteria are met:

- Adolescent patients should be skeletally mature with documented closure of growth plates (e.g., 15 years or older). Adult patients should be too young to be considered an appropriate candidate for total knee arthroplasty or other reconstructive knee surgery (e.g., younger than 55 years); **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 cm^2 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.

Autologous chondrocyte implantation does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage for all other joints, including talar, and any indications other than those listed above is therefore considered investigational.

Matrix-induced autologous chondrocyte implantation does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is therefore considered investigational.

This procedure may be performed at the same time as other surgical procedures such as repair of tendons or ligaments, osteotomies for realignment of a joint, or meniscal allograft transplantation.

Prophylactic harvesting of cells during other reconstructive or reparative procedures for possible future implantation **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage.

Effective for dates of service on or after June 13, 2013 and prior to November 1, 2015:

Autologous chondrocyte implantation meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage 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:

- 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 cm^2 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.

Autologous chondrocyte implantation does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage for all other joints, including patellar and talar, and any indications other than those listed above is therefore considered investigational.

Matrix-induced autologous chondrocyte implantation does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is therefore considered investigational.

This procedure may be performed at the same time as other surgical procedures such as repair of tendons or ligaments, osteotomies for realignment of a joint, or meniscal allograft transplantation.

Prophylactic harvesting of cells during other reconstructive or reparative procedures for possible future implantation **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administer benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical

judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

This policy was initially based on a 2003 TEC Assessment of autologous chondrocyte implantation (ACI), which updates earlier TEC Assessments on the same subject. Updated literature searches, conducted most recently through February 5, 2018, identified the following published studies.

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 Treatment of Focal Articular Cartilage Lesions of the Knee

Systematic Reviews

Cartilage Repair Procedures

In 2017, Riboh et al reported on 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 matrix-induced autologous chondrocyte implantation (MACI), autologous chondrocyte implantation (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 Score, reoperation in the short, mid, and long term, and Tegner Activity Scale 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) included a subset of the RCTs in the Riboh 2017 review.

In 2016, Mundi et al reported a systematic review of level 1 studies of cartilage restoration of the knee. Included were 12 randomized trials with a total of 765 patients and a mean lesion size of 3.9 cm^2. Five trials compared ACI with marrow stimulation (three were second generation ACI), three compared ACI with osteochondral autographs (OA) one trial compared OA with microfracture, and three trials compared different generations of ACI. Eleven of the 12 trials were conducted in Europe. Four trials reported significant differences in function with ACI compared versus marrow stimulation, however, meta-analysis showed no significant differences in pain or function between the two treatments at 24 month follow-up. The quality of the evidence was rated as poor to moderate, and only four trials reported a sample size calculation. Although meta-analysis could not be performed on the other comparisons, five of six trials found no significant difference in outcomes between ACI and OA or different generations of ACI. The percentage of grafts that failed and the relation between lesion size and success rate was 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. 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). The mean study quality was rated as 54 of 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 one- to five-year follow-up, three of seven studies showed better clinical outcomes after ACI in comparison with microfracture, one study showed better outcomes after microfracture, and three studies showed no difference in these treatments. Clinical outcomes after microfracture were found to deteriorate after 18 to 24 months in three of seven studies. Studies comparing ACI

and OA showed similar short-term clinical outcomes, with more rapid improvement but an increase in arthrofibrosis and donor site morbidity following OA. 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 4cm^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 (matrix-induced). Three RCTs were identified specifically on MACI. These are described next.

MACI Compared to 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 score improved 17.6 in the ACI group and 19.6 in the ACI group (p=ns). VAS 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 age of the patient. Second look arthroscopy at 1-year for 42 patients showed excellent to good ICRS [International Cartilage Repair Society] scores in 79.2% of ACI and 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 and 36.4% MACI).

MACI Compared to Microfracture

SUMMIT was the pivotal industry-sponsored multicenter randomized open-label trial (NCT00719576) comparing MACI® with microfracture for larger cartilage defects (≥3cm^2), which typically fare worse than smaller lesions when treated with microfracture. Patients (n=144) were included who had at least one 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). The average lesion size was 4.8cm^2 (range, 3-20cm^2); 34.6% of patients had undergone a prior marrow stimulation procedure. At two-year follow-up, the MACI® group had significantly better subscores for KOOS pain (co-primary outcome, difference of 11.76, p<0.001) and function (co-primary outcome, difference of 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 ten-point improvement in both the KOOS pain and function subscales, significantly more patients in the MACI group responded to treatment compared with the microfracture group (87.5% vs 68.1%, p=0.016). There were no significant differences between the groups for cartilage repair, as measured by second look arthroscopy, biopsy, or MRI. Results through 5 years are reported on www.clinicaltrials.gov (NCT 01251588). However, there was a 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.

In 2010, Basad et al reported a small randomized trial that compared MACI® (n=40) with microfracture (n=20) in patients with a single posttraumatic chondral defect between 4 and10cm^2. Both groups improved at the two-year follow-up, with a significant advantage of

MACI over microfracture on the Lysholm (92 vs 69, p=0.005), Tegner (4 vs 3, p=0.04), and ICRS patient (p=0.03) and ICRS surgeon scores (p=0.02). Patients treated with MACI from this trial, along with newly enrolled patients (total 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). These 12 patients underwent additional procedures, including OCAG 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

In 2017, Schuette et al published a systematic review of mid- to long-term clinical outcomes from use of MACI in the knee. They included 10 studies (2 level 1, 1 level 2, 1 level 3, 6 level 4 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 1 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) 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 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 Tegner Activity Scale 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 in the systematic review were by Ebert and colleagues. In 2017, Ebert et al reported a comparative study with 24-month follow-up. The study included 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.

Combined Meniscal Allograft and Cartilage Repair

A publication by Harris et al in 2010 was a systematic review of combined meniscal allograft transplantation and cartilage repair/restoration. Six level IV studies (case series) with a total of 110 patients were included in the review. Patients underwent meniscal allograft transplantation with either ACI (n=73), osteochondral allograft (n=20), OA (n=17), or microfracture (n=3). All studies showed improvement in clinical outcomes at final follow-up compared with the preoperative condition. Outcomes were also compared with historical outcomes of each individual procedure performed in isolation. Four of the six studies found outcomes equivalent to procedures performed in isolation, while two studies found that outcomes with combined surgery were not as good as the historical controls. Across the six studies, 13 failures (12%) were reported; these 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 the patients underwent one 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 of 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% 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 more recent technique.

Minas et al prospectively followed 210 ACI-treated patients (362 grafts) for at least ten years. Malalignment, patellar maltracking and meniscal or ligamentous deficiency had also been corrected as needed. At a mean of 12 years' follow-up, 53 patients (25%) had graft failure. Nineteen of these patients (9%) went on to arthroplasty, 27 patients (13%) were salvaged with revision cartilage repair, and seven patients declined further treatment. For the 157 patients who had successful grafts, functional outcomes were significantly improved from baseline to follow-up, as measured by the Western Ontario & McMaster Universities Index (WOMAC), Knee Society Score (KSS) for knee and function, and SF-36 (all $p<0.001$). Survival of the graft was significantly higher 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, ACI graft survival was 79% compared with 44% for knees with defects that had been previously treated with microfracture.

A 3-fold increased failure of ACI 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% of joints (17/214) that did not have prior marrow stimulation of the lesion, compared with 26% (29/111 joints) that had previously been treated with marrow stimulation. A study of 869 patients treated with ACI or MACI found that overall graft survival was 78.2% at 5 years and 50.7% at 10 years by 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) (HR=5.33, 95% CI = 4.07 to 6.99, $p<0.001$). Other factors affecting survival were the location of the grafts and the severity of degenerative changes.

Graft Hypertrophy

In 2015, Ebert et al reported on graft hypertrophy (tissue overgrowth) at 24 months after MACI implantation in a consecutive series of 180 patients. Patients were assessed clinically using the KOOS and underwent MRI at 3, 12, and 24 months after MACI. Seventeen grafts (9.4%) had failed by 24 months. Three grafts were hypertrophic at 3 months but 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 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 meta-analysis by Niemeyer et al included 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 studies 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 Score. Overall clinical success rate, defined as the percentage of good and excellent results, was 89.9% (range, 50%-100%).

Section Summary: ACI for Treatment of Focal Articular Cartilage Lesions of 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.

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. This recommendation of insufficient evidence was based on a systematic review that found four 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. The Institute recommended autologous chondrocyte implantation:

"… 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.

Key Words:

Autologous chondrocyte transplantation (ACT), autologous chondrocyte implant (ACI), articular cartilage, chondrocytes, Carticel®, osteochrondritis dissecans (OCD), ChondroCelect, BioCart II, Cartilix, MACI®, Cartipatch, NeoCart, Hyalograft C

Approved by Governing Bodies:

The culturing of chondrocytes is considered by the U.S. Food and Drug Administration (FDA) to fall into the category of manipulated autologous structural (MAS) cells, which are subject to a biologic licensing requirement. In 1997, Carticel 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 2016, MACI® (matrix-induced autologous chondrocyte implantation [ACI]; Vericel), received FDA approval for the repair of symptomatic, full-thickness cartilage defects of the knee in adult patients. MACI® consists of autologous chondrocytes which are cultured onto a bio-resorbable porcine-derived collagen membrane. MACI is indicated "for the repair of symptomatic, single or multiple full-thickness cartilage defects of the knee with or without bone involvement in adults." In 2017, production of Carticel was phased out and MACI® is the only ACI product that is available in the U.S.

A number of other second-generation methods for implanting autologous chondrocytes in a biodegradable matrix are currently in development/testing or are available only outside of the United States. They include Atelocollagen (collagen gel; Koken), Bioseed® C (polymer scaffold; BioTissue Technologies) CaReS (collagen gel; Ars Arthro), Cartilix (polymer hydrogel; Biomet), Chondron (fibrin gel; Sewon Cellontech), Hyalograft C (hyaluronic acid-based scaffold; Fidia Advanced Polymers), NeoCart (ACI with a 3-dimensional chondromatrix; Histogenics, phase 3 trial), and Novocart®3D (collagen-chondroitin sulfate scaffold; Aesculap Biologics, phase 3 trial). ChondroCelect® (characterized chondrocyte implantation; TiGenix; phase 3 trial completed) uses a gene marker profile to determine in vivo cartilage-forming potential and thereby optimizes the phenotype (e.g., 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. Although clinical use of these second-generation ACI products has been reported in

Europe and Asia, only MACI® is approved for use in the United States at this time. Both Hyalograft C and ChondroCelect® have been withdrawn from the market in Europe.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply
FEP contracts: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Coding:

CPT codes:	**27412**	Autologous chondrocyte implantation, knee
	27899	Unlisted procedure, leg or ankle
	29870-29887	Code range, arthroscopy of the knee
HCPCS:	**J7330**	Autologous cultured chondrocytes, implant
	S2112	Arthroscopy, knee, surgical for harvesting of cartilage (chondrocyte cells)

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Policy History:

Medical Policy Group, April 2004 (1)
Medical Policy Administration Committee, April 2004
Available for comment June 30-July 15, 2004
Medical Policy Group, May 2005 **(2)**
Medical Policy Administration Committee, June 2005
Available for comment June 16-July 30, 2005
Medical Policy Group, April 2007 **(1)**
Medical Policy Administration Committee, May 2007
Available for comment May 8-June 21, 2007
Medical Review Group, November 2009 **(2)**
Medical Policy Administration Committee, December 2009
Available for comment December 4, 2009-January 19, 2010

Medical Policy Group, March 2010 **(3)**
Medical Policy Administration Committee April 2010
Available for comment April 15-May 29, 2010
Medical Policy Group, June 2011; Updated Policy, Key Points & References
Medical Policy Administration Committee July 2011
Available for comment July 6 through August 22, 2011
Medical Policy Group, June 2012 **(3)**: 2012 Update includes Key Points and References
Medical Policy Panel, June 2013
Medical Policy Group, June 2013 **(3)**: 2013 Updates to Title, Description, Policy Statement, Key Points, References, and Key words; removed "Transplantation" and replaced with "Implantation" and removed "and Other Cell-based Treatments of" from title; and treatments with autologous minced cartilage and allogeneic minced cartilage or cartilage cells from policy statements
Available for comment June 27 through August 10, 2013
Medical Policy Group, September 2013 **(3)**: ad hoc clarification statement added to policy sections noting prophylactic harvesting of cells for possible future implantation does not meet criteria for coverage
Medical Policy Panel, June 2014
Medical Policy Group, June 2014 **(3)**: 2014 Updates to Description, Key Points & References; no change in policy statement
Medical Policy Panel, June 2015
Medical Policy Group, July 2015 (**2**): 2015 Updates to Description, Key Points, and References, no change to policy statement.
Medical Policy Panel, October 2015
Medical Policy Group, October 2015 (**2**): 2015 Updates to Policy, Key Points, Approved by Governing Bodies, and References; updated policy statement to include coverage criteria for focal, full-thickness unipolar lesions of the patella.
Medical Policy Administration Committee November 2015
Medical Policy Panel, April 2017
Medical Policy Group, April 2017 **(7)**: 2017 Updates to Description, Key Points, Approved by Governing Bodies, and References. Policy statement- updated policy statement to include coverage for matrix induced autologous chondrocyte implantation; deleted policy statement prior to June 13, 2013.
Medical Policy Administration Committee, May 2017
Available for comment April 26 through June 10, 2017
Medical Policy Panel, December 2017
Medical Policy Group, December 2017 **(7)**: 2017 Updates to Description, Key Points and References. No change in Policy Statement.
Medical Policy Panel, April 2018
Medical Policy Group, May 2018 (7): Updates to Key Points, Approved by Governing Bodies and References. No change in Policy Statement.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.