Autologous Chondrocyte Implant for Focal Articular Cartilage Lesions

Medical Policy #: 07.01.64
Original Effective Date: May 2014
Reviewed: February 2022
Revised: February 2022

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DESCRIPTION

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

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.

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 it 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 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 *Osteochondral Allografts and Autografts 07.01.65.*

With autologous chondrocyte implantation, 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 autologous chondrocyte implantation procedure have been developed, including the use of a scaffold or matrix-induced autologous chondrocyte implantation composed of biocompatible carbohydrates, protein polymers, or synthetics. The only FDA approved matrix-induced autologous chondrocyte implantation 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.

MACI® Implant (Vericel Corporation, Cambridge, MA [formerly Genzyme Biosurgery]): Until recently, Carticel® (Vericel Corporation, Cambridge, MA [formerly Genzyme Biosurgery]) was the only technology that received FDA approval for the culturing of chondrocytes. MACI® Implant received approval from the U.S. Food and Drug Administration December 2016 as an autologous cellularized scaffold indicated for repair of single or multiple symptomatic, full-thickness cartilage defects of the knee with or without bone involvement in adults. MACI® Implant is utilized as part of an ACI procedure in which cartilage cells are removed during arthroscopy, and shipped to a laboratory, where the cells are cultured over a period of several weeks. The cells are seeded on a porcine collagen membrane, and once the culturing process is complete, the cells seeded on the membrane are returned to the surgeon for implantation during the procedure. The membrane is placed into the defect, and over several months the cells create a matrix that is intended to cover the articular surface of the knee.

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 matrix-induced autologous chondrocyte implantation eliminates the need for harvesting and suture of a periosteal or collagen patch. A scaffold without cells may also support chondrocyte growth.

Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesion(s) of the Knee

Clinical Context and Therapy Purpose

The purpose of autologous chondrocyte implantation in patients with focal articular cartilage lesion(s) of the weight-bearing surface of the femoral condyles, trochlea, or patella is to provide a treatment option that is an alternative to or an improvement on existing therapies.

Populations

The relevant population of interest is patients with focal articular cartilage lesion(s) of the weight-bearing surface of the femoral condyles, trochlea, or patella.

Interventions

The treatment being considered is autologous chondrocyte implantation, which is performed by an orthopedic surgeon. The first stage, the arthroscopy to obtain a biopsy of healthy articular cartilage, is performed in an outpatient clinical or surgical setting. The second procedure, the arthrotomy, is performed under general anesthesia, most commonly in an outpatient surgical setting.

Comparators

The comparators of interest are marrow stimulation or osteochondral autograft.

Marrow stimulation and osteochondral autograft are performed by an orthopedic surgeon in an outpatient clinical or surgical setting.

Outcomes

The general outcomes of interest are symptoms, change in disease status, morbid events, functional outcomes, and quality of life.

Positive outcomes include easy implantation, reduction in surgical morbidity, no need to harvest other tissues, enhancement of cell proliferation and maturation, maintenance of phenotype, and integration with surrounding tissues.

Negative outcomes include hypertrophy of the transplant, disturbed fusion of the regenerative and healthy surrounding cartilage, inadequate regenerative cartilage, and delamination.[1,]

The existing literature evaluating autologous chondrocyte implantation has varying lengths of follow-up, ranging from 1 to 10 years. Therefore, a minimum of 1 year of follow-up is considered necessary to demonstrate efficacy.

Outcome Measurement Tools

Name	Description	Scoring
CKRS and mCKRS	Measure symptoms, sports activity, and ADL functioning	Likert-type scale; total range 0-100, 100 being best function CKRS: 22 questions in 6 areas: 1. Symptoms (4) 2. Patient perception (1) 3. Sports activity (4) 4. ADL function (3) 5. Sports function (3) 6. Occupational (7) mCKRS: 12 questions, 8 included in summary score: 1. Pain intensity 2. Swelling 3. Giving way 4. Overall activity level 5. Walking 6. Stairs 7. Running activity 8. Jumping or twisting
EQ-5 VAS	Generic questionnaire for measuring HRQoL Measures patients' perceptions of their current overall health and can be used to track changes over time	5 dimensions of health: 1. Mobility 2. Self-care 3. Usual activities 4. Pain/discomfort 5. Anxiety/depression

		Each dimension graded “severe,” “moderate,” or “none”; along with “death” and “unconscious,” describes 245 different health statuses. Each health state is ranked and transformed into a single “utility” score
IKDC Subjective Knee Form	Assesses symptoms, daily activity, and sports function caused by conditions affecting the knee.	18 items are totaled and expressed as a percentage of the maximum possible score 100% indicates the absence of symptoms and higher functioning levels
KOOS	Assesses patients’ opinion about their knee and associated problems, both short- and long-term Items selected based on WOMAC	42 items in 5 separately scored subscales: 1. Pain (9 items) 2. Other symptoms (7) 3. Function in ADL (17) 4. Function in sports and recreation (5) 5. Knee-related quality of life (4) Measured with Likert-type scale with 5 possible answers: • 0=no problems • 4=extreme problems Scores transformed to 0-100 scale, with 0 representing extreme knee problems, and 100 no problems
KSS	Rates knee and patients’ functional abilities before and after total knee replacement	Knee score section (KS-KS): 7 items Functional score section (KS-FS): 3 items Each section scored 0-50, with lower scores indicating worse knee conditions
LKQ	Measures outcomes of knee ligament surgery, with emphasis on evaluation of instability and corresponding to patient’s own opinion	8 items with individual scoring scales: 1. Limp (0, 3, 5) 2. Support (0, 2, 5) 3. Locking (0, 2, 6, 10, 15) 4. Instability (0, 5, 10, 15, 20, 25) 5. Pain (0, 5, 10, 15, 20, 25) 6. Swelling (0, 2, 6, 10) 7. Stair climbing (0, 2, 6, 10)

		8. Squatting (0, 2, 4, 5) Possible score range, 0-100: • 100=no symptoms or disability • 95-100=excellent • 84-94=good • 65-83=fair • ≤64=poor
OKS	For patients undergoing total knee arthroscopy to assess their knee-related health status and benefits of treatment	12 items pertaining to knee pain and function • Likert-type scale: ○ Original version, 1-5: ▪ 1=best ▪ 5=worst ○ Modified version, 0-4: ▪ 4=no problem ▪ 0=significant disability Total score summed from values selected: • Original version, range=12-60: higher score, poorer outcome • Modified version, range=0-48: lower score, better outcome
SF-12 and SF-36	Both are health-related quality of life surveys covering 8 domains including physical and mental components SF-12 is a shortened version of SF-36	8 domains: 1. Physical functioning 2. Role - physical 3. Bodily pain

		4. General health perceptions 5. Vitality 6. Social functioning 7. Role - emotional 8. Mental health Likert-type question formats Physical and mental components are scored separately Scores range 0-100: • 0=lowest level of health • 100=highest level of health
TAS	Developed to complement Lysholm score Grades activity based on work and sports activities	Graduated list of ADLs, recreation, and competitive sports (11 options); patient selects 1 item that best represents their current level of activity Possible score range, 0-10:0=sick leave or disability pension due to knee problems • 6-10=participation in recreational or competitive sports • 10=participation in national or international elite sports
WOMAC	Assessment of ADL, functional mobility, gait, general health, and quality of life	24 items broken into 3 subscales: 1. Pain (5) 2. Symptoms/ stiffness (2) 3. Physical function (17) Each question scored 0-4:0=none • 1=mild • 2=moderate • 3=severe • 4=extreme

ADL: activities of daily living; CKRS: Cincinnati Knee Rating System; EQ-5 VAS: EuroQol 5 Dimensions Visual Analog Scale; HRQoL: health-related quality of life;

IKDC: International Knee Documentation Committee;
KOOS: Knee Injury and Osteoarthritis Outcome Score; KSS: Knee Society Score; LKQ: Lysholm Knee Questionnaire; mCKRS: modified Cincinnati Knee Rating System;
MCID: minimal clinically important difference;
MDC: minimum detectable change; OA: osteoarthritis; OKS: Oxford Knee Score ;SF-12: 12-Item Short-Form Health Survey; SF-36: 36-Item Short-Form Health Survey; TAS: Tegner Activity Scale; VAS: visual analog scale;
WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.
[a] All surveys are either patient-completed or observer-administered to patient.

Review of Evidence

Systematic Reviews

Cartilage Repair Procedures
Zamborsky et. al. (2020) completed a systematic review and network meta-analysis that evaluated the most appropriate surgical interventions for patients with knee articular cartilage defects.[,] The authors included a total of 21 articles (from 12 RCTs) in their analysis with a total population of 891 patients. Follow-up varied widely among the included studies, ranging from 12 months to 15 years. Of the surgical interventions evaluated, microfracture was associated with significantly higher failure rates compared to autologous chondrocyte implantation at 10 years of follow-up (relative risk [RR], 0.12; 95% confidence interval [CI]; 0.04 to 0.39). No significant differences in failure rates were seen between microfracture and osteochondral autograft transplantation, matrix-induced autologous chondrocyte implantation, or characterized chondrocyte implantation at 2, 5, and 10 years of follow-up. Osteochondral autograft transplantation was associated with significantly more excellent or good results at >3 years of follow-up as compared to microfracture, whereas microfracture was associated with significantly poorer results as compared to autologous chondrocyte implantation and matrix-induced autologous chondrocyte implantation. No significant differences between the interventions were noted regarding reintervention, biopsy types, or adverse events. Based on efficacy and safety, autologous chondrocyte implantation was ranked as the best intervention for failure outcome at 10 years of follow-up, followed by osteochondral autograft transplantation, then microfracture. Microfracture was consistently ranked worse than cartilage repair techniques for other outcomes including quality of tissue repair and return-to-activity rates.

In 2017, Riboh et. al. reported on a network meta-analysis assessing the comparative efficacy of cartilage repair procedures of the knee.[14,] Nineteen RCTs from 15 separate cohorts (N =855 patients) were included. The procedures selected for the network analysis were matrix-induced autologous chondrocyte implantation, autologous chondrocyte implantation with a collagen membrane, autologous chondrocyte implantation with a periosteal membrane, osteochondral autograft transfer, 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 score. The rank order of treatment efficacy, taking into account all outcome measures, was autologous chondrocyte implantation with a collagen membrane, osteochondral autograft transfer, matrix-induced autologous chondrocyte implantation, autologous chondrocyte implantation 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 et al (2017) review. Mundi et. al. (2016) reported on a systematic review of level I studies for cartilage restoration of the knee. Included were 12 randomized trials (N =765 patients) and a mean lesion size of 3.9 cm^2. Five trials compared autologous chondrocyte implantation with marrow stimulation, 3 compared autologous chondrocyte implantation with osteochondral autograft transfer, 1 compared osteochondral autograft transfer with microfracture, and 3 compared different generations of autologous chondrocyte implantation. Eleven of the 12 trials were conducted in Europe. Four trials reported significant differences in function with autologous chondrocyte implantation versus 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 autologous chondrocyte implantation and osteochondral autograft transfer or different generations of autologous chondrocyte implantation. The percentage of grafts that failed and the relation between lesion size and success rate were not assessed in this review.

Autologous Chondrocyte Implantation Versus Other Cartilage Repair Procedures
In 2020, Gou et. al. evaluated clinical outcomes among patients with fractures of knee cartilage who were treated with autologous chondrocyte implantation (n=332) or microfracture (n=327) from 12 RCTs. Patient age ranged from 25 to 41 years, with the majority of patients male. Treatment follow-up ranged from 1.5 to 15 years. There were diverse types of autologous chondrocyte implantation performed among the studies including MACI, NeoCart, ACI with periosteum, and ChondroCelect. Outcomes included an overall clinical score, Knee Injury and Osteoarthritis Outcome Score subdomains of activities of daily living and function, quality of life, pain relief score, and failure/operation rate. Results revealed no significant differences between the interventions with regard to improvement in International Knee Documentation Committee and Lysholm scores or overall Knee Injury and Osteoarthritis Outcome Score measures at 1, 2, and 5 years of follow-up. There was also no difference between the groups with regard to failure rate at 2, 3, and 5 years. Autologous chondrocyte implantation was associated with significant improvements in activities of daily living at 5 years or less of follow-up as compared to microfracture as well as improvement in quality of life and pain relief at 5- and 2-year follow-up examinations, respectively. Major limitations of this systematic review and meta-analysis included the small number of eligible RCTs in the final analysis with regard to length of follow-up and that the studies included in the meta-analysis utilized a variety of autologous chondrocyte

implantation techniques, scales and scores for outcome measures, and recruited patients with different lesion sizes. Plus, blinding of the patients or surgeons was difficult to perform given the 2-step procedure of autologous chondrocyte implantation.

In 2017, the National Institute for Health Research reported on a systematic review assessing the clinical effectiveness of autologous chondrocyte implantation in the knee.[7] The National Institute for Health Research 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 autologous chondrocyte implantation with microfracture. One of the trials, Autologous Chondrocyte Transplantation/Implantation Versus Existing Treatment (ACTIVE; N=390) shared selected results with the National Institute for Health Research reviewers but no results have been published. Another trial (ChondroCelect via autologous chondrocyte implantation vs. Microfracture in the repair of symptomatic cartilage lesions of the knee, N =118) included assessment of the ChondroCelect autologous chondrocyte implantation, which was never approved in the U nited States and has been withdrawn from the market in Europe. The remaining 2 trials included in the National Institute for Health Research review, Basad et al (2010) and the Superiority of MACI versus Microfracture Treatment in Patients with Symptomatic Articular Cartilage Defects in the Knee (SUMMIT), are detailed in the following section on RCTs. In summary, both matrix-induced autologous chondrocyte implantation 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 over 2 to 5 years. Limited long-term data were available on the failure rates of both autologous chondrocyte implantation and microfracture after 5 years; data were available from 6 observational studies. The conclusions regarding follow-up after 5 years were primarily based on 1 of the observational studies judged to be the highest quality (Nawaz et al [2014]; described in the following section on durability, N=827). For autologous chondrocyte implantation, 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.

Autologous Chondrocyte Implantation and Matrix-Induced Chondrocyte Implantation for Osteochondritis Dissecans

Sacolick et. al. (2019) examined the patient-reported outcomes, complication rates, and failure rates of autologous chondrocyte implantation and matrix-induced autologous chondrocyte implantation for osteochondritis dissecans in adults.[7] Nine clinical studies were assessed (type not specified), with 179 (>200 lesions) patients aged 18 to 49 years (mean, 27.6 years). Follow-up ranged from 6.5 months to 10 years. Results of patient-reported outcomes showed that 85% of patients reported excellent or good outcomes. All patient-reported outcome measures used across the studies (International Knee Documentation Committee Form, Lysholm Knee Questionnaire, EuroQol Visual Analog Scale, Cincinnati Rating System, and the Tegner Activity Scale) reported statistically

significant improvements from preoperative to final follow-up (p-values not reported). Of the studies that reported complication and failure rates for autologous chondrocyte implantation/matrix-induced autologous chondrocyte implantation, 23 (15.7%) of 146 patients reported complications, and the failure rate was 8.2%. Unplanned reoperations were necessary for 20.5% of patients. The study results showed that autologous chondrocyte implantation/matrix-induced autologous chondrocyte implantation had the best outcomes for active young males with small lesions. Older adults and less active individuals, as well as those with lesions >6 cm^2, did not fare as well. A limitation of this review was its lack of randomized trials with controls to compare to autologous chondrocyte implantation/matrix-induced autologous chondrocyte implantation.

Randomized Controlled Trials

In 2017, first-generation autologous chondrocyte implantation with injection of chondrocytes under a collagen cover (sometimes called second-generation autologous chondrocyte implantation) was phased out and replaced with matrix-induced autologous chondrocyte implantation. Three RCTs were identified specifically on matrix-induced autologous chondrocyte implantation.

Matrix-Induced Autologous Chondrocyte Implantation Versus Autologous Chondrocyte Implantation

Bartlett et. al. reported on a randomized comparison between matrix-induced autologous chondrocyte implantation and autologous chondrocyte implantation with a collagen cover in 91 patients. Overall, results were comparable for both treatments. The modified Cincinnati Knee Rating System score improved by 17.6 points in the autologous chondrocyte implantation group and by 19.6 points in the matrix-induced autologous chondrocyte implantation group (p=0.32). Visual analog scale scores improved from 6.0 to 4.3 in the autologous chondrocyte implantation group and from 6.0 to 4.1 in the matrix-induced autologous chondrocyte implantation 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 scores in 79.2% of autologous chondrocyte implantation and in 66.6% of matrix-induced autologous chondrocyte implantation patients (p=0.3). The authors did not report whether the study was adequately powered for this comparison. Histology from 14 autologous chondrocyte implantation and 11 matrix-induced autologous chondrocyte implantation patients showed similar percentages of hyaline-like cartilage (42.9% autologous chondrocyte implantation, 36.4% matrix-induced autologous chondrocyte implantation).

Matrix-Induced Autologous Chondrocyte Implantation Versus Microfacture

The SUMMIT trial was the pivotal, industry-sponsored, multicenter randomized open-label trial; it was reported by Saris et. al. (2014) and compared matrix-induced autologous chondrocyte implantation with microfracture for larger cartilage defects (≥3 cm^2), which typically fare worse than smaller lesions when treated with microfracture.[,] 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 Knee Injury and Osteoarthritis Outcome Score pain value (<55). Average lesion size was 4.8 cm^2 (range, 3 to 20 cm^2), and 34.6% of patients had undergone a prior marrow stimulation procedure. At 2-year follow-up, the matrix-induced autologous chondrocyte implantation group had significantly better subscores for Knee Injury and Osteoarthritis Outcome Score 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 Knee Injury and Osteoarthritis Outcome Score 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 Knee Injury and Osteoarthritis Outcome Score pain and function subscales, significantly more patients in the matrix-induced autologous chondrocyte implantation 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).

Brittberg et. al. (2018) reported on a 5-year follow-up of the SUMMIT trial.[23,] Five years post-procedure, the Knee Injury and Osteoarthritis Outcome Score pain and function score were still significantly better, both clinically and statistically, for matrix-induced autologous chondrocyte implantation than for microfracture (p=0.022). Changes from baseline to year 5 were also higher for matrix-induced autologous chondrocyte implantation than microfracture for activities of daily living (p=0.007), quality of life (p=0.070), and other symptoms (p=0.078). Over 5 years, 4 patients (1 matrix-induced autologous chondrocyte implantation, 3 microfractures) had treatment failures. The proportion of patients who required subsequent surgical procedures was similar in the 2 groups (10.8% in matrix-induced autologous chondrocyte implantation and 9.5% in microfracture). Limitations were potential bias from allowing subjects to choose whether to continue with the extended study. In addition, the SUMMIT study was not blinded. However, the use of standardized surgical and rehabilitation procedures, validated clinical outcome instruments, and consistent outcomes among the multiple investigators strengthened the study.

Basad et. al. (2010) reported on a small randomized trial that compared matrix-induced autologous chondrocyte implantation (n=40) with microfracture (n=20) in patients who had a single posttraumatic chondral defect between 4 and 10 cm^2.[24,] Both groups improved at the 2-year follow-up, with a significant advantage of matrix-induced autologous chondrocyte implantation over microfracture on the Lysholm Knee Score (92 vs. 69, p=0.005), Tegner Activity Score (4 vs. 3, p=0.04), and International Cartilage Repair Society patient (p=0.03) and International Cartilage Repair Society surgeon (p=0.02) scores. Patients treated with matrix-induced autologous chondrocyte implantation from this trial, along with newly enrolled patients (n=65), were followed for 5 years.[25,] 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 osteochondral autograft transfer and microfracture, with good results.

Observational Studies
A variety of issues have been addressed with observational studies on autologous chondrocyte implantation or matrix-induced autologous chondrocyte implantation, including combination treatment with meniscal allograft, the durability of the procedure, realignment procedures performed in combination with autologous chondrocyte implantation, comparison of tibiofemoral defects and patellar defects, and influence of prior marrow stimulation.

Tibiofemoral Versus Patellofemoral Lesions
Fewer data are available on matrix-induced autologous chondrocyte implantation for patellofemoral lesions, but comparative observational studies have suggested outcomes that do not differ substantially from those using matrix-induced autologous chondrocyte implantation for tibiofemoral lesions.

Systematic Reviews
Schuette et. al. (2017) published a systematic review of mid- to long-term clinical outcomes from use of matrix-induced autologous chondrocyte implantation in the knee. 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, 5 used Hyalograft C, and 1 used both. The 2 level I studies compared early with late weight-bearing following matrix-induced autologous chondrocyte implantation. 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% to 21.6%) for tibiofemoral joints and 4.7% (4 studies, N =106 patients; range, 0% to 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 et. al. (2017) systematic review, Meyerkort et al (2014), was a prospective cohort of 23 patients who were treated with matrix-induced autologous chondrocyte implantation 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 Knee Injury and Osteoarthritis Outcome Score 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 debridement in only 1 (4.3%) patient.

Nonrandomized Comparative Studies

Three studies assessed in the systematic review were reported by Ebert et al (2017) and colleagues. Ebert et. al. (2017) reported on a comparative study with 24-month follow-up. 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 Knee Injury and Osteoarthritis Outcome Score, 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 Knee Injury and Osteoarthritis Outcome Score 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 Knee Injury and Osteoarthritis Outcome Score 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

The systematic review by Harris et. al. (2011) 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 autologous chondrocyte implantation (n=73), osteochondral allograft (n=20), osteochondral autograft transfer (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 2 found that outcomes with combined surgery were not as good as the historical controls. Across the 6 studies, 13 (12%) failures were reported; they included 11 isolated meniscal allograft transplantation failures, 1 combined meniscal allograft and autologous chondrocyte implantation failure, and 1 isolated autologous chondrocyte implantation 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 that reported on the failure rate of autologous chondrocyte implantation or matrix-induced autologous chondrocyte implantation.[34,] Fifty-eight studies were included: 4 RCTs, 6 comparative observational studies, and 48 case series (N =4294 participants). At a mean follow-up of 86 months, the failure rate was 14.9% (range, 0% to 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 autologous chondrocyte implantation (periosteal or collagen membrane-covered) and matrix-induced autologous chondrocyte implantation in 869 patients.[35,] 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 (matrix-induced autologous chondrocyte implantation) procedures. Functional and pain scores were significantly better in the matrix-induced autologous chondrocyte implantation group but this finding might have been confounded by the shorter follow-up with the newer technique.

Minas et. al. (2014) prospectively followed 210 autologous chondrocyte implantation-treated patients (362 grafts) for at least 10 years.[36,] 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 versus salvage-type lesions ($p=0.03$), with concomitant high tibial osteotomy versus no high tibial osteotomy ($p=0.01$), and with primary autologous chondrocyte implantation versus autologous chondrocyte implantation 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.

Graft Hypertrophy

Ebert et. al. (2015) reported on graft hypertrophy (tissue overgrowth) at 24 months after matrix-induced autologous chondrocyte implantation in a consecutive series of 180 patients.[38,] Patients were assessed clinically using the Knee Injury and Osteoarthritis Outcome Score and underwent MRI at 3-, 12-, and 24-months post-matrix-induced autologous chondrocyte implantation. 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. Knee Injury and Osteoarthritis Outcome Score 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

The evidence on autologous chondrocyte implantation for the treatment of focal articular cartilage lesions of the knee includes network analysis, systematic reviews, RCTs, and longer-term observational studies. For large lesions, autologous chondrocyte implantation results in better outcomes than microfracture, particularly in the long term. Studies comparing autologous chondrocyte implantation with osteochondral autograft transfer have shown similar outcomes with smaller lesions, and improved outcomes with autologous chondrocyte implantation when a defect is greater than 4 cm^2. In 2017, first-generation autologous chondrocyte implantation was replaced with a preparation that

seeds the chondrocytes onto a bioresorbable collagen sponge (matrix-induced autologous chondrocyte implantation). Studies to date have not shown improved outcomes compared with first-generation autologous chondrocyte implantation. 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. Matrix-induced autologous chondrocyte implantation 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 matrix-induced autologous chondrocyte implantation for tibiofemoral lesions. Observational studies have indicated that a prior cartilage procedure may negatively impact the success of autologous chondrocyte implantation, realignment procedures improve the success of autologous chondrocyte implantation for patellar lesions, and autologous chondrocyte implantation combined with meniscal allograft results in outcomes similar to either procedure performed alone.

Autologous Chondrocyte Implantation for Joints Other than the Knee

Clinical Context and Therapy Purpose
The purpose of autologous chondrocyte implantation in patients with focal articular cartilage lesions of joints other than the knee is to provide a treatment option that is an alternative to or an improvement on existing therapies.

Populations
The relevant population of interest is patients with focal articular cartilage lesions of joints other than the knee.

Interventions
The treatment being considered is autologous chondrocyte implantation, which is performed by an orthopedic surgeon. The first stage, the arthroscopy to obtain a biopsy of healthy articular cartilage, is performed in an outpatient clinical or surgical setting. The second procedure, the arthrotomy, is performed under general anesthesia, most commonly in an outpatient surgical setting.

Comparators
The comparators of interest are marrow stimulation or osteochondral autograft.

Marrow stimulation and osteochondral autograft are performed by an orthopedic surgeon in an outpatient clinical or surgical setting.

Outcomes
The outcomes of interest are symptoms, change in disease status, morbid events, functional outcomes, and quality of life.

Positive outcomes include easy implantation, reduction in surgical morbidity, no need to harvest other tissues, enhancement of cell proliferation and maturation, maintenance of phenotype, and integration with surrounding tissues.

Negative outcomes include hypertrophy of the transplant, disturbed fusion of the regenerative and healthy surrounding cartilage, inadequate regenerative cartilage, and delamination.

The existing literature evaluating autologous chondrocyte implantation has varying lengths of follow-up, ranging from 6 to 120 months. A minimum of 1 year of follow-up would be considered necessary to demonstrate efficacy.

Review of Evidence

Systematic Reviews

In 2017, Shimozone et. al. 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 of matrix-induced autologous chondrocyte implantation 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 preoperative and postoperative American Orthopaedic Foot and Ankle Society scores; mean American Orthopaedic Foot and Ankle Society score improved from 59 to 87. Three of the case series in Shimozono et. al. (2017) overlaps with Niemeyer et al (2012), described below.

A meta-analysis by Niemeyer et al (2012) evaluated 16 studies (N =213 patients) assessing autologous chondrocyte implantation or matrix-induced autologous chondrocyte implantation for lesions of the talus. All were case series, with a mean sample size of 13 patients (range, 2 to 46 patients) and mean follow-up of 32 months (range, 6 to 120 months). Most series were prospective. In 6 studies, periosteum-covered autologous chondrocyte implantation was applied while 10 studies used second-generation matrix-induced autologous chondrocyte implantation. Nine different methods were used to evaluate preoperative and postoperative clinical function, with the most common being the American Orthopaedic Foot and Ankle Society score. Overall clinical success rate, defined as the percentage of good and excellent results, was 89.9% (range, 50% to 100%).

Section Summary

The evidence on use of autologous chondrocyte implantation for joints other than the knee includes systematic reviews of case series. The most commonly reported use of autologous chondrocyte implantation is for the talus. Comparative trials are needed to determine whether autologous chondrocyte implantation 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 autologous chondrocyte implantation, 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 autologous chondrocyte implantation for the treatment of focal articular cartilage lesions of the knee. For large lesions, autologous chondrocyte implantation 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, autologous chondrocyte implantation has become the established treatment for large articular cartilage lesions in the knee. In 2017, first-generation autologous chondrocyte implantation with a collagen cover was phased out and replaced with an autologous chondrocyte implantation preparation that seeds the chondrocytes onto a bioresorbable collagen sponge. Although the implantation procedure for this second-generation autologous chondrocyte implantation is less technically demanding, studies to date have not shown improved outcomes compared with first-generation autologous chondrocyte implantation. 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 autologous chondrocyte implantation and the lack of alternatives, second-generation autologous chondrocyte implantation 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 an improvement in the net health outcome.

For individuals who have focal articular cartilage lesions of joints other than the knee who receive autologous chondrocyte implantation, 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 autologous chondrocyte implantation of the talus. Comparative trials are needed to determine whether autologous chondrocyte implantation improves outcomes for lesions in joints other than the knee. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

American Academy of Orthopaedic Surgeons (AAOS)

In a 2010, the American Academy of Orthopaedic Surgeons (AAOS) clinical practice guideline on the diagnosis and treatment of osteochondritis dissecans (OCD), 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. Because each level IV article used different techniques, different outcome measures, and differing lengths of follow-up, the Academy deemed the evidence for any specific technique inconclusive.

National Institute for Health and Clinical Excellence (NICE)
In 2018, the National Institute for Health and Clinical Excellence (NICE), the NICE recommendations are stated below:

"As an option for treating symptomatic articular cartilage defects of the femoral condyle and patella of the knee (International Cartilage Repair Society grade III or IV) in adults, 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); and
- the defect is over 2 cm^2."

Regulatory Status

The MACI package insert is noted below:
INDICATIONS AND USAGE

- MACI® is an autologous cellularized scaffold product indicated for the repair of symptomatic, single, or multiple full-thickness cartilage defects of the knee with or without bone involvement in adults.

DOSAGE AND ADMINISTRATION

- For autologous implantation only.
- The amount of MACI implanted depends on the size (surface area in cm2) of the cartilage defect.
- MACI should be trimmed to the size and shape of the defect and implanted with the cell-side down.

DOSAGE FORMS AND STRENGTHS

- Each 3 x 5 cm cellular sheet (MACI implant) consists of autologous cultured chondrocytes on a resorbable porcine Type I/III collagen membrane, at a density of at least 500,000 cells per cm2

CONTRAINDICATIONS

- Known history of hypersensitivity to gentamicin, other aminoglycosides, or products of porcine or bovine origin.
- Severe osteoarthritis of the knee.
- Inflammatory arthritis, inflammatory joint disease, or uncorrected congenital blood coagulation disorders.
- Prior knee surgery (within 6 months), excluding surgery to procure a biopsy or a concomitant procedure to prepare the knee for a MACI implant.
- Inability to cooperate with a physician-prescribed post-surgical rehabilitation program.

WARNINGS AND PRECAUTIONS

- Safety of MACI in patients with malignancy in the area of cartilage biopsy or implant is unknown. Expansion of malignant or dysplastic cells present in biopsy tissue during manufacture and subsequent implantation may be possible.
- Because patients undergoing procedures associated with MACI are not routinely tested for transmissible infectious diseases, cartilage biopsy and MACI implant may carry risk of transmitting infectious diseases.
- Local inflammation or active infection in the bone, joint, and surrounding soft tissue, meniscal pathology, cruciate ligament instability, and misalignment should be assessed and treated prior to or concurrent with MACI implantation.
- Final sterility test results are not available at the time of shipping.

A number of second-generation methods for implanting autologous chondrocytes in a biodegradable matrix are currently in development/testing. These include Atelocollagen (collagen gel, Koken), BioCart II (ProChon Biotech, Phase II trial), Bioseed C (polymer scaffold, BioTissue Technologies) CaReS (collagen gel, Ars Arthro), Cartilix (polymer hydrogel, Cartilix), Cartipatch (solid scaffold with an agarose-alginate matrix, TBF Tissue Engineering, Phase III trial), Chondron (fibrin gel, Sewon Cellontech), Hyalograft C (hyaluronic acid-based scaffold, Fidia Advanced Polymers), , NeoCart (ACI with a 3-dimensional chondromatrix, Histogenics. Phase III trial), and Novocart (collagen-chondroitin sulfate scaffold, B. Braun-Tetec). ChondroCelect (characterized chondrocyte implantation, TiGenex, Phase III 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 implantation 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 (Chondrosphere [Spherox]), only MACI is approved for use in the U.S. at this time.

PRIOR APPROVAL

Not applicable.

POLICY

See Related Medical Policies:

- 07.01.65 Osteochondral Allografts and Autografts

Autologous chondrocyte implantation (ACI) or a autologous chondrocyte transplantation (ACT) (using the MACI implant) may be considered **medically necessary** for the treatment of symptomatic single or multiple full-thickness cartilage defects of the distal femoral articular surface (i.e. medial condyle, lateral condyle or trochlea) and/or patella caused by acute or repetitive trauma when **ALL** of the following criteria are met:

- The individual is age 15 to 55 years (adolescent individuals should be skeletally mature with documented closure of growth plates; **and**
- Body mass index (BMI) 35 or less; **and**
- Function limiting pain (e.g., loss of knee function which interferes with the ability to carry out age-appropriate activities of daily living and/or demands of employment; **and**
- Presence of **BOTH** of the following findings:
    - A stable knee with intact or reconstructed ligaments (ACL or PCL) and menisci. **(*Note**: a concurrent ligament stabilization or meniscal procedures at the time of ACI would be acceptable*).
    - Normal tibial-femoral and/or patella-femoral alignment; **and**
- Failure to respond to conservative treatments for at least two months (i.e., physical therapy, braces, ice/heat, injections); **and**
- A full-thickness distal femoral articular surface (i.e., medial condyle, lateral condyle or trochlea) and/or patellar chondral defect of 1-10cm^2 in size that has been identified during MRI or CT arthrogram, or during an arthroscopy and the Modified Outerbridge Classification or Outerbridge Classification is Grade III or Grade IV; **and**
- Absence of an osteochondritis dissecans (OCD) lesion that requires bone grafting; **and**
- Absence of inflammatory arthritis or other systemic disease affecting the joints; **and**
- Minimal to absent osteoarthritic changes in the surrounding articular cartilage (e.g., Kellgren-Lawrence Grade 2 or less); **and**
- Normal articular cartilage at the lesion border (contained lesion); **and**
- For femoral and patellar lesions, absence of corresponding "kissing lesion" with a Modifier Outerbridge Classification of Grade III or IV of the distal femur (trochlea, condyles), patella or tibia.

Autologous chondrocyte implantation (ACI) or an autologous chondrocyte transplantation (ACT) (using the MACI implant) not meeting the above criteria is considered **investigational**, because the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Autologous chondrocyte implantation (ACI) or an autologous chondrocyte transplantation (ACT) (using the MACI implant) for all other joints is considered **investigational,** because the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Combined Autologous Chondrocyte Implantation/Osteochondral Autograft transfer system (ACT/OATS) technique

Combined (hybrid repair) autologous chondrocyte implantation (ACI) or an autologous chondrocyte transplantation (ACT) (using the MACI implant) and osteochondral Autograft transfer system (ACT/OATS) technique for the treatment of the treatment of

symptomatic single or multiple full-thickness cartilage defects of the distal femoral articular surface (i.e. medial condyle, lateral condyle or trochlea) and/or patella caused by acute or repetitive trauma is considered **investigational,** because the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Policy Guidelines

Required Documentation

- Progress report, history, and/or operative notes confirming injury and prior treatments/therapies (conservative treatments); AND
- Report(s) documenting normal alignment and stability of the knee and the absence of osteoarthritis (OA) or rheumatoid arthritis (RA); AND
- If applicable report from the knee arthroscopy documenting/showing the presence of the cartilage defect (with measurements obtained during imaging or debridement) and normal cartilage surrounding the defect.
- If applicable the MRI or CT arthrogram results documenting/showing the presence of the cartilage defect (with measurements obtained during imaging or debridement) and normal cartilage surrounding the defect.

Severe obesity (e.g., body mass index >35 kg/m^2) 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 autologous chondrocyte implantation.

Classifications of Articular Cartilage Lesions by Severity

Grade	Outerbridge Classification
0	Normal cartilage
I	Softening and swelling
II	Fragmentation and fissures in area less than 0.5 inch in diameter
III	Fragmentation and fissures in area larger than 0.5 inch in diameter
IV	Exposed subchondral bone

Modified Classifications of Articular Cartilage Lesions by Severity

	MRI Results	Arthroscopy Results
GRADE 0	Normal Cartilage	Normal Cartilage
GRADE I	focal areas of hyperintensity with normal contour	cartilage with softening and swelling
GRADE	blister-like swelling/fraying of articular cartilage extending to surface	fragmentation and fissuring within soft areas of articular cartilage
II	partial thickness cartilage loss with focal ulceration	partial thickness cartilage loss with fibrillation
GRADE	full thickness cartilage loss with underlying bone reactive changes	cartilage destruction with exposed subchondral bone*

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 27412 Autologous chondrocyte implantation, knee
- J7330 Autologous cultured chondrocytes, implant
- S2112 Arthroscopy, knee, surgical, for harvesting of cartilage (chondrocyte cells)
- 27599 Unlisted procedure, femur or knee

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POLICY HISTORY

Date	Reason	Action
February 2022	Annual Review	Policy Revised
November 2021	Interim Review	Policy Revised
February 2021	Annual Review	Policy Revised
June 2020	Interim Review	Policy Revised
February 2020	Annual Review	Policy Renewed
February 2019	Annual Review	Policy Revised
February 2018	Annual Review	Policy Revised
March 2017	Annual Review	Policy Revised
March 2016	Annual Review	Policy Revised
April 2015	Annual Review	Policy Revised
May 2014		New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
Des Moines, IA 50306-9232

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