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Medical Policy Manual Surgery, Policy No. 87

Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Autologous chondrocyte implantation (ACI) involves harvesting chondrocytes from healthy tissue, expanding the cells in vitro, and implanting the expanded cells to resurface articular cartilage defects.

MEDICAL POLICY CRITERIA

I. Autologous chondrocyte implantation (See Policy Guidelines) may be considered **medically necessary** for the treatment of disabling full-thickness articular cartilage defects of the knee caused by acute or repetitive trauma, when all of the following criteria are met:

   A. 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)

   B. Focal, full-thickness (grade III or IV) unipolar lesions of the patella or on the weight-bearing surface of the femoral condyles or trochlea at least 1.5 centimeters squared in size

C. 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

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

E. Body mass index (BMI) < 35

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

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

- MACI® is a next-generation matrix-induced autologous chondrocyte implantation (ACI), and is the only is the only ACI therapy on the market currently approved by the FDA.
- For smaller lesions (e.g., smaller than 4 cm^2), if debridement is the only prior surgical treatment, then consideration should be given to marrow-stimulating techniques before autologous chondrocyte implantation (ACI) is performed.
- The average defect size reported in the literature is about 5 cm^2; however, many studies treated lesions as large as 15 cm^2.
- Severe obesity, e.g., body mass index greater than 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 ACI.

CROSS REFERENCES

1. Orthopedic Applications of Stem-Cell Therapy, Medicine, Policy No. 142

BACKGROUND

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 a patient's activities of daily living and adversely affect quality of life. Conventional treatment options include débridement, subchondral drilling, microfracture, and abrasion arthroplasty. Débridement involves the removal of synovial

membrane, osteophytes, loose articular debris, and diseased cartilage and is capable of producing symptomatic relief. Subchondral drilling, microfracture, and abrasion arthroplasty attempt to restore the articular surface by inducing the growth of fibrocartilage into the chondral defect. Compared with the original hyaline cartilage, fibrocartilage has less capability to withstand shock or shearing force and can degenerate over time, often resulting in the return of clinical symptoms. Osteochondral grafts and ACI attempt to regenerate hyaline-like cartilage and thereby restore durable function.

With ACI, a region of healthy articular cartilage is identified and biopsied through arthroscopy. The tissue is sent to a facility licensed by the 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. A periosteal flap is removed from the proximal medial tibia and sutured to the surrounding rim of normal cartilage. The cultured chondrocytes are then injected beneath the periosteal flap. ACI may be considered more effective for larger lesions than microfracture or osteochondral grafts, but it is technically difficult, requiring two procedures and harvesting of periosteum. In addition, use of the FDA-indicated periosteal cover may result in hypertrophy, as well as donor-site morbidity.

The ACI procedure consists of four steps:

1. Initial arthroscopy and biopsy of normal cartilage,
2. Culturing of chondrocytes,
3. A separate arthrotomy to create a periosteal flap and implant the chondrocytes, and
4. Postsurgical rehabilitation.

The initial arthroscopy may be scheduled as a diagnostic procedure and as part of this procedure, a cartilage defect may be identified, prompting biopsy of normal cartilage in anticipation of a possible chondrocyte transplant. The biopsied material is then sent for culturing and returned to the hospital when the implantation procedure (i.e., arthrotomy) is scheduled.

Methods to improve the ACI procedure are being investigated, including the use of a scaffold or matrix-induced ACI (MACI) composed of biocompatible carbohydrates, protein polymers, or synthetics. Desired features of articular cartilage repair procedures are the ability to:

1. Implant easily,
2. Reduce surgical morbidity,
3. not to require harvesting of other tissues,
4. Enhance cell proliferation and maturation,
5. Maintain the phenotype, and
6. 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 patch. A scaffold without cells may also support chondrocyte growth.

REGULATORY STATUS

First-generation Autologous Chondrocyte Implantation

The culturing of chondrocytes is considered by FDA to fall into the category of manipulated autologous structural (MAS) cells, which are subject to a biologic licensing requirement. At the present time, only Carticel™ (Vericel Corporation) has received FDA approval for the culturing of chondrocytes through a biologics license. 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.…" The labeled indication was revised in October 1999 to read as follows:

> "Carticel is indicated for the repair of symptomatic cartilaginous defects of the femoral condyle (medial, lateral, or trochlear), caused by acute or repetitive trauma, in patients who have had an inadequate response to a prior arthroscopic or other surgical repair procedure." Thus, the revised labeling suggests a more restricted use of autologous chondrocytes (i.e., as a second-line therapy after failure of initial arthroscopic or surgical repair).
>
> "Carticel is not indicated for the treatment of cartilage damage associated with osteoarthritis. Carticel should only be used in conjunction with débridement, placement of a periosteal flap and rehabilitation. The independent contributions of the autologous cultured chondrocytes and other components of the therapy to outcome are unknown. Data regarding functional outcomes beyond 3 years of autologous cultured chondrocyte treatment are limited."
>
> Carticel was retired from the market in 2017 and replaced by MACI, a next generation matrix-induced method of ACI.

Second- and Third-generation Autologous Chondrocyte Implantation

Second-generation ACI procedures have focused on developing three-dimensional constructs using native and synthetic biomaterials. Third-generation ACI products are now being engineered to deliver biofactors in sufficient quantities and in a temporally specific manner to induce a favorable chondrogenic response in the seeded cells and in cells of the host tissue, and to inhibit local or systemic tissue degenerative activities.

A number of second- and third-generation methods for implanting autologous chondrocytes in a biodegradable matrix are currently in development/testing or are available only outside of the United States. These include:

- Atelocollagen (collagen gel; Koken)
- BioCart II (ProChon Biotech)
- Bioseed C (polymer scaffold; BioTissue Technologies)
- CaReS (collagen gel; Ars Arthro)
- Cartilix (polymer hydrogel; Biomet)
- Cartipatch® (agarose-alginate matrix, TBF Tissue Engineering)
- ChondroCelect® (characterized chondrocyte implantation; TiGenix)
- Chondron (fibrin gel; Sewon Cellontech)
- Hyalograft C (hyaluronic acid-based scaffold; Fidia Advanced Polymers)
- NeoCart (ACI with a 3-dimensional chondromatrix; Histogenics)
- NOVOCART®3D (collagen-chondroitin sulfate scaffold; Aesculap Biologics)

Although clinical use of these second- and third-generation ACI products has been reported in Europe and Asia, MACI® is the only one approved for use in the United States at this time.

EVIDENCE SUMMARY

AUTOLOGOUS CHONDROCYTE IMPLANTATION OF THE KNEE

Systematic Reviews

There have been a number of systematic reviews on ACI of the knee. Some of these studies used Carticel™, while others have evaluated next-generation ACI products. The long-term efficacy of marrow stimulation techniques is also reviewed.

In 2017, the National Institute for Health Research (NIHR) reported on a systematic review assessing the clinical effectiveness ACI in the knee[1]. 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. 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], 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.

In 2016, DiBartola reported a systematic review of clinical outcomes after ACI in the knees of adolescents ranging from 11 to 21 years (mean age 16.2), including five case series (N=115).[2] No RCT's or comparative studies were included in this review. Overall, 99 patients (83%) underwent ACI with periosteal cover, six (5%) with type I/type III collagen cover, and 14 (12%) with matrix-induced ACI. Follow-up ranged from 12 to 74 months (mean, 52.3 months). Mean defect size was 5.3 cm^2 (range, 0.96 to 14 cm2). All studies reported significant improvement in clinical outcomes scores. Graft hypertrophy was the most common complication (7.0%). The overall percentage increase in clinical outcome scores was 35.7% (SD, 14.2%). Limitations of this review include the fact that no RCT's or comparative studies were included in this review, and all of the studies were considered to be of fair, not good quality in terms of their methodology.

In 2016, Adrade reported a systematic review of surgical outcomes from articular cartilage and/or osteochondral lesions in the knees of soccer players.[3] Five studies were included in the review that met inclusion criteria, one of which was a small case series that used ACI as treatment[4] and one small nonrandomized study that compared matrix-induced ACI (MACI) to microfracture.[5] The other included studies were small case series using mosaicplasty, microfracture and chondral debridement as surgical treatments. The reviewers reported that ACI treatment provided the slowest return to competition and slower clinical and functional results compared to all other treatments reviewed. However, ACI and MACI procedures appeared to enhance longstanding clinical and functional results. Overall, chondral debridement was concluded to be the surgical technique that yielded the most positive results for all outcomes measured.

In 2016, DiBartola published the largest systematic review to date on the use of different surgical treatments for cartilage lesions of the knee, focusing on histological outcomes including the degree of defect repair, integration to boarder zone, and macroscopic appearance (to calculate the IRCS score), as well as histological appearance such as hyaline-like cartilage, fibrocartilage, fibrous tissue, or mixed fibrocartilage and hyaline-like cartilage.[6] Grades included normal/excellent (ICRS score = 12), nearly normal/good (IRCS score = 8 to 11), abnormal/fair (ICRS score = 7–4), or severely abnormal/poor (ICRS score = 1 to 3). Thirty-three small case series and RCTs (N=1511 patients) were included. Thirty evaluated ACI or one of its subtypes, six evaluated microfracture (MF), and seven evaluated osteochondral autografting (OATS). No significant difference was found cartilage quality using ICRS grading criteria among OATS, ACI-C, MACI, and ACI-P (ranging from 8.8 to 9.59 – nearly normal/good), however, ICRS scores for microfracture were significantly poorer compared to other treatments. Interestingly, the reviewers were unable to correlate histological outcomes with clinical outcomes, regardless of the method used.

Systematic reviews on ACI for chondral defects of the knee concurred that existing randomized clinical trials showed some promising results or found no difference between different techniques for ACI in the treatment of focal cartilage lesions.[7-11] For example, in 2015, Mundi reported a systematic review of level 1 studies of cartilage restoration of the knee.[12] 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 osteoarthritis (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 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 the 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 were not assessed in this review.

A 2011 systematic review by Harris included 13 randomized and nonrandomized controlled trials of 917 subjects who underwent ACI (n=604), microfracture (n=271), or osteochondral autograft (OA) (n=42).[13] The mean study quality was rated as 54 of 100, with no studies considered of good or excellent quality, seven were considered fair, and six were considered poor. Four studies compared different generations of ACI, finding no difference in outcomes but higher complication rates with open, periosteal cover, first-generation ACI. At 1- to 5-year follow-up, three of the 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 the 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 4 cm^2 was the only factor predictive of better outcomes when ACI was compared with other surgical techniques.

A 2010 publication by Vasiliadis reviewed combined meniscal allograft transplantation and cartilage repair/restoration.[14] 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.

A 2008 systematic review by Magnussen assessed whether “advanced” cartilage repair techniques (osteochondral transplantation or autologous chondrocyte transplantation) showed superior outcomes in comparison with traditional abrasive techniques for the treatment of isolated articular cartilage defects. Finding a total of five randomized controlled trials and one prospective comparative trial that met their selection criteria, Magnussen and colleagues concluded that no one technique had been shown to produce superior clinical results for treatment of articular cartilage defects with the available follow-up. They stated that, “any differences in outcome based on the formation of articular rather than fibrocartilage in the defect may be quite subtle and only reveal themselves after many years of follow-up.“

Randomized Controlled Trials

Autologous Chondrocyte Implantation versus Marrow Stimulating Techniques

In 2004 results from a randomized controlled trial (RCT) were published of 80 patients randomized to either ACI or microfracture of the knee (an arthroscopic marrow-stimulation procedure), Knutsen reported no significant differences in the treatment groups at 2-year follow-up in macroscopic and histologic findings.[15] The Lysholm and pain scores were also not significantly different at 1 and 2 years. The Physical Component Summary score of the 36-Item Short-Form Health Survey (SF-36) was worse in the ACI group, which the authors suggest may be related to the greater surgical involvement. Five-year follow-up on all 80 patients in 2007 revealed 9 failures (23%) for both groups.[16] There was a trend (p=0.10) for earlier failure in the ACI group (26 vs 38 months, respectively) with no difference in subjective measures of pain or function between the ACI and microfracture groups. Thus, the more invasive ACI open surgical procedure was not associated with any added clinical benefit.

In 2004, Visna published an RCT of 50 patients with full-thickness, moderate-to-large chondral defects of 2.0 to 10.0 cm^2 of the femoral condyle, trochlea, or patella (43 cases due to injury) who were randomized to either Johnson abrasion techniques or ACI of the knee using a preparation of autologous chondrocytes using a fibrin tissue glue rather than a periosteal patch to seal the implanted chondrocytes.[17] The study reported improvements after 12 months in the Lysholm, International Knee Documentation Committee (IKDC), and Tegner activity scores, which were significantly better among the 25 ACI patients compared with the 25 patients in the abrasion group. Additional procedures (28 in the ACI group, 20 in the abrasion group) included anterior cruciate ligament (ACL) replacement, meniscectomy, and lateral release.

Autologous Chondrocyte Implantation versus Osteochondral Autografts

In 2005, Dozin reported results from a multicenter RCT in which ACI was compared with OA.[18] Forty-four subjects (61% male, 39% female) aged 16 to 40 years (mean, 28.7±7.8), who had a focal, symptomatic chondral injury of Outerbridge grade III or IV with no previous surgical treatment, were randomly assigned to ACI or mosaicplasty six months after undergoing arthroscopic débridement. The average lesion size was 1.9 cm. Only 12 of 22 (54%) in the ACI group and 11 of 22 (50%) of the mosaicplasty group actually underwent the assigned procedure. Dropouts comprised 14 patients (32%) who reported spontaneous improvement following arthroscopy and did not undergo subsequent surgery, five who did not show up at the presurgery examination and could not be further traced, and two who refused surgery for personal reasons. Because of the substantial dropout rate, the original primary outcome measure, the mean Lysholm Knee Scoring Scale (LKSS) assessed 12 months postsurgery was converted into a scale in which improvement was categorized by proportions of responders (LKSS <60, LKSS 60-90, LKSS 90-100). With this scale, and including 10 patients who were cured by débridement (intention-to-treat analysis) the percentages of patients who achieved complete success were 89% (16/18 evaluable cases) in the mosaicplasty arm versus 68% (13/19 evaluable cases) in the ACI arm (test for trend, p=0.093). The high rate of spontaneous improvement after simple débridement raises questions about the appropriateness of additional surgical intervention in patients similar to those included in this trial. These results are not sufficient to permit conclusions regarding the effect of ACI on health outcomes in comparison with mosaicplasty or to demonstrate an independent effect of the use of ACI versus débridement and exercise rehabilitation.

In 2003, Horas reported 2-year follow-up on a study of 40 patients (18-42 years old) with an articular lesion of the femoral condyle (range, 3.2-5.6 cm^2) who were randomly assigned to undergo either autologous chondrocyte transplant or osteochondral autografting.[19] Eleven (28%) had prior surgical treatment. The authors reported that both treatments resulted in an improvement in symptoms (85% of each group), although those in the OA group responded more quickly. Histomorphologic evaluation of five biopsy specimens at 2- years or less after transplantation indicated that the osteochondral cylinders had retained their hyaline character, although the investigators noted a persistent interface between the transplant and the surrounding original cartilage. Evaluation of autologous chondrocyte implants indicated a rigid, elastic tissue, with partial roughening and the presence of fibrocartilage.

In 2003, Bentley randomized 100 consecutive patients with symptomatic lesions of the knee (average, 4.7 cm^2; range, 1-12 cm^2) to ACI or mosaicplasty.[20] Seventy-four percent of lesions were on the femoral condyle, and 25% of lesions were on the patella. Ninety-four patients had undergone previous surgical interventions, and the average duration of symptoms before surgery was seven years. Clinical assessment at 1-year showed excellent or good results in 98% of the ACI patients and in 69% of the mosaicplasty patients. The mosaicplasty plugs showed incomplete healing of the spaces between the grafts, fibrillation of the repair tissue, and disintegration of the grafts in some patients. This finding may be related to the unusual prominent placement of the plugs in this study, which was intended to allow contact with the opposite articular surface. Arthroscopy at 1-year showed filling of the defects following ACI, but soft tissue was observed in 50% of patients. Biopsy specimens taken from 19 ACI patients revealed a mixture of hyaline and fibrocartilage. In 2012, Bentley et al. published long term follow-up findings. With six patients lost to follow-up at a minimum 10-years after the index surgery, repair was found to have failed in 17% of patients treated with ACI and 55% of patients treated with mosaicplasty.[21]

Other Randomized Trials

Gooding randomized 68 patients with osteochondral defects (mean, 4.5 cm^2; range, 1-12 cm^2) of the femoral condyle (54%), trochlea (6%), or patella (40%) to ACI with either a periosteal or collagen cover.[22] At 2-years, 74% of the patients with the collagen cover had good-to-excellent results compared with 67% of the patients with the periosteal cover. Hypertrophy required shaving in 36% of patients treated with the periosteal cover. None of the collagen covers required shaving.

Nonrandomized Studies

A variety of issues have been addressed with observational studies, including durability of the procedure, influence of age, comparison of femoral versus patellar defects, combination treatment with meniscal allograft, influence of prior marrow stimulation, and treatment of early OA. These are discussed below.

Study of the Treatment of Articular Repair

In 2009, results from the Study of the Treatment of Articular Repair (STAR) trial were published, which were previously available in the Carticel package insert, and from a meeting presentation in July 2007.[23-25] STAR was a prospective, nonblinded, 4-year study in 154 patients (mean age, 35 years; 69% male) from 29 clinical centers. Each patient served as his or her own control, undergoing ACI after having failed or experienced an inadequate response to a prior cartilage repair procedure (e.g., 78% underwent débridement, 29% microfracture, 12% subchondral drilling) on a distal femur index lesion (109 medial femoral condyle, 32 lateral femoral condyle, 46 trochlea). The median lesion size was 4.6 cm^2 (range, 1-30 cm^2), with 26% involving osteochondritis dissecans. Fifty patients (32%) had multiple lesions in the reference knee, and 29 (19%) received multiple cellular implants. Prior treatment inadequacy was defined as both patient and surgeon agreement that the patient's symptoms or function required surgical retreatment of the defect and a patient's rating of overall condition of the knee was a score of 5 or less, using the Modified Cincinnati Knee Rating System (MCKRS). In this group, the median time to meet the failure criteria was 3.4 months for the prior index procedure, with more than 90% of patients having failed within 10.3 months. Patients who met these criteria were treated with ACI and assessed every six months for up to 4-years.

The primary outcome, treatment failure for ACI, was defined as any of the following: (1) patient underwent surgical retreatment that violated the subchondral bone or repeated ACI for the same index defect; (2) complete delamination or removal of the graft; or (3) a patient's rating of the overall condition of the knee using the MCKRS failed to improve from the baseline knee score over three consecutive 6-month time intervals. Withdrawals from the study were considered as failures at the last follow-up. The mean overall MCKRS for the entire patient population at baseline was 3.3 (n=154), and 126 (82%) completed 4-year follow-up. Thirty-seven patients (24%) were considered failures; 11 failed based on the surgical failure criterion, and 26 failed based on the MCKRS criterion. Most of the 37 failures (92%) occurred within 30 months. At 48 months, three-fourths of all patients in the study (76%) showed good to excellent results with a mean MCKRS score of 6.3 (n=115). Secondary outcome measures also showed improvement, including pain, symptoms, sports and recreation, knee-related quality of life, and activities of daily living. There was no relationship between the size of the lesion at baseline and treatment outcomes with ACI.

Over half of the population (54%) experienced at least one serious adverse event secondary to ACI, and 40% of patients underwent subsequent surgical procedures on the index knee related to ACI. Adverse events included arthrofibrosis (16%), graft overgrowth (15%), chondromalacia

or chondrosis (12%), graft complications (ie, fraying or fibrillation, 10%), graft delamination (6%), and joint adhesion (5%). Subsequent surgical procedures (regardless of relationship to ACI) included débridement of cartilage lesion (31%), lysis of adhesions (14%), other débridement (10%), meniscectomy (6%), loose body removal (5%), microfracture of the index lesion (5%), and scar tissue removal (5%). The most common cause for a subsequent surgical procedure was periosteal patch hypertrophy. Most (61%) patients who had a subsequent surgical procedure went on to have successful results, while 39% were eventually considered treatment failures. The results of the STAR trial suggest that ACI may improve knee symptoms and function in some patients with severe, debilitating, previously treated cartilage lesions of the distal femur for at least 4-years after the procedure. Additional surgical procedures may be expected.

Marrow Stimulation Procedures

Montgomery reported a study of articular cartilage procedures of the knee from a national database of insurance billing records.[26] There were 216 million orthopedic procedures identified over a 6-year period. For the 163,448 articular cartilage procedure codes reported over this period, 98% were microfracture (n=36,095) or chondroplasty (n=125,245). Efficacy of the microfracture technique was examined in a 2009 systematic review.[27] Twenty-eight studies describing 3122 patients were included in the review; six of the studies were RCTs. Microfracture was found to improve knee function in all studies during the first 24 months after the procedure, but the reports on durability were conflicting. A prospective longitudinal study of 110 patients by Solheim et al found that at a mean of 12 years (range, 10-14) after microfracture, 45.5% of patients had poor outcomes, including 43 patients who required additional surgery.[28]

Other Nonrandomized Studies

In 2016, Niethammer published results from a small prospective study assessing third-generation ACI (NOVOCART 3D) to treat cartilage defects in the knee joint.[29] The investigators analyzed graft integration into the surrounding cartilage and graft thickness. The average graft thickness significantly increased between three and six months after ACI, and continued to increase over two years post-operatively. However, 44 cases (55.7%) had mild to moderate incomplete filling of the defect, which occurred significantly more often in women ($p = 0.021$).

ACI for patellar cartilage defects is typically reported as less effective than ACI for lesions of the femoral condyles, and some studies have reported biomechanical alignment procedures and unloading to improve outcomes for retropatellar ACI.[30,31] In 2014, Gomoll reported a multicenter registry study of the treatment of mono or bipolar patellar defects with ACI in 110 patients with a minimum of 4-year follow-up (mean, 90 months; range, 48-192 months).[32] Concurrent surgical procedures included tibial tubercle osteotomy in 69% of patients, lateral release in 41%, vastus medialis advancement in 20%, and trochleoplasty in 5%. At the latest follow-up, statistically and clinically significant improvements in pain and function were obtained on the IKDC, Cincinnati Rating Scale, WOMAC and KSS, although it was noted that results were inferior to ACI for cartilage lesions of the femoral condyles. Excluding repeat arthroscopy for graft hypertrophy or lysis of adhesions, nine patients were considered treatment failures. Results were not divided according to the type of implant (ACI or matrix-induced ACI), although it was reported that two patients with hypertrophy of the implant were from the group treated with periosteal patch covered ACI. In addition, these results are limited

by the retrospective design and loss to follow-up, and would be applicable only to those patients without varus or valgus deformity.

In 2014. Biant published results from a prospective study of long-term follow-up study of patients who were treated between 1998 and 2001 after ACI for large cartilage defects of the knee, including lesions on the patella.[33] Out of 104 total procedures, 36 were performed for the patella. Seventy percent of patients had undergone a prior surgical procedure. Clinicians who were independent of the original surgery conducted the assessment at 10 to 12 years follow-up and were able to contact all but four patients. Twenty six percent of patients overall experienced graft failure at a mean of 5.7 years after ACI. The percentage of failures in the subgroup with ACI of the patella was similar; 25% experienced graft failure at a mean of 5.8 years after ACI. Out of the 32 patients who had not undergone a prior surgery, six (19%) had failed, compared with 21 of 72 (29%) who had a prior cartilage repair procedure, supporting other recent studies showing poorer outcomes for lesions that had failed after a prior surgical procedure.

In 2014, Minas published results from a prospective study that followed 210 ACI-treated patients (362 grafts) for at least 10 years.[34] Malalignment, patellar maltracking and meniscal or ligamentous deficiency had also been corrected as needed. At a mean of 12 years of 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.

In 2012, Pestka reported a matched-pair comparison of ACI after failed microfracture versus ACI as a first-line treatment.[35] A total of 56 patients were retrospectively matched for sex, age, defect size, and defect location. The average defect size was 4.65 cm^2. Follow-up was conducted by mail, with a mean follow-up time of 48.0 months for ACI as a second-line treatment and 41.4 months for ACI as a first-line treatment. The failure rate was significantly greater when ACI was used as a second-line treatment (25% vs 3.6%), and there was a trend ($p=0.058$) for lower IKDC scores (58.4 vs 69.0). Two Knee Injury and Osteoarthritis Outcome Score (KOOS) subscales (Pain and Activities of Daily Living) were significantly lower for second-line treatment; there was a trend for lower scores in the remaining subscales. There are several limitations to this study; one is a potential for selection bias if patients who respond poorly to microfracture also respond poorly to ACI. Time since symptom onset might also be a factor.[36] However, the results add to a growing body of literature suggesting inferior outcomes when ACI is performed following a failed microfracture.[37]

In 2010, Peterson reported on 224 patients who replied to questionnaires at 10- to 20-year follow-up.[38] This represents 38% of a total of 590 patients who underwent ACI at their institution between 1987 and 1998. The average age of the patients was 33 years (range, 14-61 years) at the time of the ACI, and the indication for treatment was any symptomatic full-thickness cartilage lesion up to 16 cm^2, including patients with meniscal (34% of patients) or ACL lesions (19%). Fifty-five patients (25%) had multiple lesions, 73 patients (33%) had

unipolar or bipolar patellar lesions, and 26 patients (12%) had osteochondritis dissecans. Three hundred forty-one surveys were mailed to the treated patients; the response rate was 65%. Information about baseline measurements was collected from the patients' charts or from prior studies and when available, compared with the questionnaire responses at follow-up. At a mean of 12.8 years of follow-up, 74% of the patients reported their status as better or the same as the previous years, and 92% were satisfied with the operation. The average Lysholm score improved from 60.3 preoperatively to 69.5 postoperatively, Tegner from 7.2 to 8.2, and the Brittberg-Peterson from 59.4 to 40.9. At the final measurement, the KOOS score averaged 74.8 for pain, 63 for symptoms, 81 for activities of daily living, 41.5 for sports, and 49.3 for quality of life. The average Noyes score was 5.4. Patients with bipolar lesions had a worse final outcome than patients with multiple unipolar lesions. The presence of meniscal injuries before ACI or history of bone marrow procedures before the implantation did not seem to affect the final outcomes.

In 2010, Minas assessed the influence of ACI on the need for joint replacement surgery in 153 patients (155 knees) with a mean age of 38 years (range, 17-60 years), evidence of early OA at the time of surgery (peripheral intra-articular osteophyte formation and/or 0%-50% joint space narrowing), and 2 years or more of follow-up.[39] (Patients with >50% loss of joint space were not eligible for treatment with ACI.) Patients were also included in the study if they had normal radiographs but evidence of bipolar lesions or generalized chondromalacia noted at the time of surgery. An average of 2.1 defects per knee were treated, with a mean defect size of 4.9 cm^2 and a total mean defect area of 10.4 cm^2. Defects were located on the femoral condyle (n=150), trochlea (n=85), patella (n=60), and tibial plateau (n=14). There were 42 (27%) bipolar lesions, most of which were patellofemoral. Concurrent procedures included correction of tibiofemoral malalignment (31% of knees) and patellar maltracking (28% of knees). At 5 years postoperatively (range, 24-132 months), 12 knees (8%) were considered treatment failures and underwent arthroplasty due to graft failure (n=3), inadequate pain relief (n=1), and progression of osteoarthritic disease beyond the originally transplanted defect area (n=8). The remaining 92% of patients showed improvements in all scores from baseline to final follow-up. For example, there was 52% improvement in WOMAC subscales, and the proportion of patients who experienced severe or extreme pain while walking on a flat surface decreased by 73%. Subsequent surgical procedures after the index implantation were performed in 95 knees (61%), including 52 cases of periosteal hypertrophy, 32 cases of arthrofibrosis, 23 graft complications, and 11 for periosteal delamination.

In 2009, Pascual-Garrido reported outcomes from 52 patients (83% follow-up) who underwent ACI of the patellofemoral joint (patella or trochlea).[40] In addition to ACI of the patella, 67% of patients had concomitant procedures performed, including anteromedialization (n=28), lateral release (n=4), lateral meniscal transplant (n=2), and OA (n=1). Questionnaires were administered preoperatively, 6-months and 1-year postoperatively, and then annually. At an average follow-up of 4-years (range, 2-7 years), there was significant improvement in the Lysholm, IKDC, KOOS Pain, KOOS Symptoms, KOOS Activities of Daily Living, KOOS Sport, Cincinnati, Tegner, and SF-12 Physical. Patients reported the overall condition of their knee as excellent, very good, or good in 71% of the cases. There were four failures (8%), defined as poor clinical outcome accompanied by evidence of graft failure or need for conversion to knee arthroplasty or OA. In 2008, a study from Europe described clinical results from 70 of 95 patients (74%) treated with ACI or matrix-induced ACI (MACI) for full-thickness defects of the patella.[41] Objective evaluation performed by an independent examiner who was blinded to data obtained at the time of surgery showed normal or nearly normal results in 47 patients (67%) at an average follow-up of 38 months.

In 2009, Minas published results from a nonrandomized study that examined cartilage defects pretreated with marrow stimulation. 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 (of 332 treated).[37] The average lesion was 8 cm², and the indications for treatment of cartilage defects with ACI included one or more full-thickness chondral defects of the knee, with consistent history, physical examination, imaging, and arthroscopy; no or correctable ligamentous instability, malalignment, or meniscal deficiency; and not more than 50% loss of joint space on weight-bearing radiographs. 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 1000 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, with no significant difference in survival rates between ACI and MACI procedures or for different defect sizes (range, .64-20.75 cm^2).[42] 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). Survival of grafts in the lateral femoral condyle was superior to grafts in the medial femoral condyles, trochlea, or patella.

In 2008, Rosenberger reported an average 4.7-year follow-up (range, 2-11 years) on a cohort of 56 patients (45-60 years old) with lesions of the femoral condyle (49%), trochlea (29%), or patella (22%).[43] Results were generally similar to those observed in younger patients, with 72% rating themselves as good or excellent, but 43% requiring additional arthroscopic procedures for periosteal-related problems and adhesion.

In 2007, Farr described outcomes from a prospective series of 36 patients who underwent ACI together with meniscal transplantation in the same compartment.[44] Lesions ranged from 1.5 to 12.1 cm². Patients identified with advanced chondrosis during staging arthroscopy were excluded from the study. Four patients received treatment for bipolar lesions, while 16 of the procedures were done concomitant with another procedure such as osteotomy, patellar realignment, or ACL reconstruction. Four patients (11%) were considered failures before 2-years, and three were lost to follow-up (8%), resulting in 29 evaluable patients at an average of 4.5-years after surgery. The Lysholm score improved from an average score of 58 to 78; maximum pain decreased an average 33% (from 7.6 to 5.1). Excluding the four failures, 68% of the patients required additional surgeries; 52% had one additional surgery, and 16% required two or more additional surgeries. The most common procedures were trimming of periosteal overgrowth or degenerative rims of the transplanted meniscus. Another report described average 3.1- years of follow-up from a prospective series of 30 patients (31 procedures) who had undergone combined meniscal allograft transplantation with ACI (52%) or OA transplantation (48%).[45] The Lysholm score improved in both the ACI (from 55 to 79) and OA (from 42 to 68) groups; 48% of patients (60% ACI, 36% OA) were considered to be normal or nearly normal at the latest follow-up. Patients treated with OA were on average older (average, 37 vs 23 years) and with larger lesions (5.5 cm^2 vs 3.9 cm^2). Two patients were considered failures (7%) and five (17%) underwent subsequent surgery. Although results seemed promising, evidence is insufficient to permit conclusions regarding the effect of combined transplantation-implantation procedures on health outcomes.

In 2005, Browne published 5-year outcomes from 87 of the first 100 patients (40 centers, 87% follow-up) treated with ACI for lesions on the distal femur from the FDA-regulated Carticel safety registry maintained by Genzyme Biosurgery.[46] The registry is a multicenter program initiated in 1995, and was designed to longitudinally track changes in function and symptoms in

patients treated with ACI or other cartilage repair procedures. Patients were an average of 37-years old, with a mean lesion size of 4.9 cm^2 (range, 0.8-23.5 cm^2). Seventy percent of the patients had failed at least one previous cartilage procedure. At 5-years following the index procedure, the average self-rated overall condition had improved from 3.2 (poor to fair) to 5.8 (fair to good), a 2.6-point improvement on the 10-point scale. Sixty-two patients (71%) reported improvement, 25 (29%) reported no change or worsening. Thirty-seven patients (42%) had 51 operations after ACI. The most common findings were adhesions (n=6), hypertrophic changes of the graft (n=5), loose bodies (n=4), loose or delaminated periosteal patch (n=4), and meniscal tears (n=4). In 2010, this group of investigators published a 6- to 10-year follow-up (mean, 9.2 years) on 72 patients in the cartilage repair registry.[47] Fifty-four patients (75%) met the eligibility criteria of the study, which included ACI treatment of lesions on the distal femur and improvement at the 1- to 5-year follow-up period. Of these 54 patients, 47 (87%) sustained a mean improvement of 3.8 points from baseline at the later follow-up period. For the cohort of 72 patients, 69% reported improvement, 17% failed, and 12.5% reported no change from baseline to follow-up.

Other studies from Europe reported patellofemoral cartilage defects treated with second generation matrix-induced ACI implants;[48-51] however, these products are not approved in the United States and are, therefore, considered investigational.

AUTOLOGOUS CHONDROCYTE IMPLANTATION FOR JOINTS OTHER THAN THE KNEE

There has been interest in applying ACI to cartilage defects in other joints, particularly in the treatment of osteochondral lesions of the talus.

Systematic Reviews

In 2016, Marquez-Lara published results from a systematic review of arthroscopic treatments of chondral defects of the hip, comparing debridement, microfracture and ACI treatments from 12 studies.[52] Included studies were case series, comparative studies, but no RCTs. There were 579 (64.7%) debridements, 279 (31.2%) microfracture, and 37 (4.1%) ACIs performed. Patients were followed for an average of 27.1 months (range: 5 to 72 months). All lesions treated with either a microfracture or ACI were high grade (Outerbridge 3 to 4). However, lesion size was significantly larger in ACI-treated patients compared with those who underwent microfracture (357.3 ± 96.0 mm(2)v 149.5 ± 20.7 mm(2); p = 0.020). The reviewers reported no difference in improvement of clinical outcomes between the three treatments in patients with high-grade chondral defects in the hip in the short- and midterm follow-up. In addition, although there were no differences in patient characteristics and demographics based on the surgical technique, lesion size varied significantly between arthroscopic techniques, patients undergoing ACI having the largest lesion size.

In 2011 Niemeyer published results from a systematic review that included 16 studies (213 patients) on ACI or MACI for lesions of the talus.[53] All were case series with a mean of 13 patients (range, 2-46 patients) and mean follow-up of 32 months (range, 6-120 months). Most of the studies were prospective. In six studies periosteum-covered ACI was applied while 10 studies used second-generation MACI. MACI uses a matrix seeded with cultured autologous chondrocytes, and unlike first-generation ACI, does not require tibial or fibular osteotomy to gain adequate surgical access. For the studies using periosteum-covered ACI, the number of subjects ranged from four to 12. 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%). Interpretation of these results is limited by the inclusion of poor quality studies, lack of a comparator, and lack of blinding.

Zengerink published a systematic review of treatment of osteochondral lesions of the talus in 2010.[54] Fifty-one nonrandomized and one randomized trial were included in the review. Success rates were 85% for bone marrow stimulation, 87% for osteochondral autografting, and 76% for ACI. Because of the high cost of ACI and the morbidity seen with osteochondral autografting in the knee, the authors concluded that bone marrow stimulation is the treatment of choice for primary osteochondral talar lesions.

Randomized Controlled Trials

One RCT from Italy randomized 32 patients with osteochondral lesions of the talus to chondroplasty, microfracture, or osteochondral autograft transfer (OAT).[48] This small study found similar improvements (approximately 40 points) for the three treatment groups as measured by the American Orthopaedic Foot and Ankle Society Ankle-Hindfoot Score (baseline score of 31 to 37) and the Subjective Assessment Numeric Evaluation (baseline score of 35 to 36). Complication rates were also similar, with persistent pain reported by one patient following chondroplasty, by two patients following microfracture, and by two patients following OAT. Postoperative pain, measured by Numeric Pain Intensity Scores, was greater following OAT (5.25) than chondroplasty (3.3) or microfracture (3.4).

PRACTICE GUIDELINE SUMMARY

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 was unable to recommend for or against a specific cartilage repair technique in symptomatic skeletally immature or mature patients with an unsalvageable OCD lesion.[55] 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. Because each of the level IV articles used different techniques, different outcome measures, and differing lengths of follow-up, the work group deemed that the evidence for any specific technique was inconclusive.

SUMMARY

AUTOLOGOUS CHONDROCYTE IMPLANTATION OF THE KNEE

Current evidence indicates that autologous chondrocyte implantation (ACI) can improve symptoms in some patients with lesions of the articular cartilage of the knee. These patients, who are too young for total knee replacement, have limited options. Therefore, ACI may be considered medical necessary when criteria are met. Conversely, ACI for treatment of lesions of the articular cartilage of the knee in patients that do not meet criteria is considered investigational due to lack of evidence showing improvement in health outcomes.

AUTOLOGOUS CHONDROCYTE IMPLANTATION FOR JOINTS OTHER THAN THE KNEE

The evidence is currently insufficient to evaluate the efficacy of autologous chondrocyte implantation (ACI) for joints other than the knee. Additionally, the current evidence is

insufficient to determine the impact of these procedures on health outcomes. Lastly, there are no clinical practice guidelines that recommend the use of ACI for the treatment of cartilage lesions of any type. Therefore, ACI for all other joints, including the patella and talar, are considered investigational.

REFERENCES

1. Mistry, H, Connock, M, Pink, J, et al. Autologous chondrocyte implantation in the knee: systematic review and economic evaluation. *Health technology assessment (Winchester, England)*. 2017 Feb;21(6):1-294. PMID: 28244303
2. DiBartola, AC, Wright, BM, Magnussen, RA, Flanigan, DC. Clinical Outcomes After Autologous Chondrocyte Implantation in Adolescents' Knees: A Systematic Review. *Arthroscopy*. 2016 May 7. PMID: 27161508
3. Andrade, R, Vasta, S, Papalia, R, et al. Prevalence of Articular Cartilage Lesions and Surgical Clinical Outcomes in Football (Soccer) Players' Knees: A Systematic Review. *Arthroscopy*. 2016 Jul;32(7):1466-77. PMID: 27090724
4. Mithofer, K, Peterson, L, Mandelbaum, BR, Minas, T. Articular cartilage repair in soccer players with autologous chondrocyte transplantation: functional outcome and return to competition. *Am J Sports Med*. 2005;33:1639-46. PMID: 16093535
5. Kon, E, Filardo, G, Berruto, M, et al. Articular cartilage treatment in high-level male soccer players: a prospective comparative study of arthroscopic second-generation autologous chondrocyte implantation versus microfracture. *Am J Sports Med*. 2011;39:2549-57. PMID: 21900624
6. DiBartola, AC, Everhart, JS, Magnussen, RA, et al. Correlation between histological outcome and surgical cartilage repair technique in the knee: A meta-analysis. *Knee*. 2016 Jun;23(3):344-9. PMID: 26898766
7. Ruano-Ravina, A, Jato Diaz, M. Autologous chondrocyte implantation: a systematic review. *Osteoarthritis Cartilage*. 2006;14:47-51. PMID: 16242355
8. Wasiak, J, Clar, C, Villanueva, E. Autologous cartilage implantation for full thickness articular cartilage defects of the knee. *The Cochrane database of systematic reviews*. 2006(3):CD003323. PMID: 16856003
9. Magnussen, RA, Dunn, WR, Carey, JL, Spindler, KP. Treatment of focal articular cartilage defects in the knee: a systematic review. *Clin Orthop Relat Res*. 2008 Apr;466(4):952-62. PMID: 18196358
10. Richter, DL, Schenck, RC, Jr., Wascher, DC, Treme, G. Knee Articular Cartilage Repair and Restoration Techniques: A Review of the Literature. *Sports health*. 2015 Oct 12. PMID: 26502188
11. Trinh, TQ, Harris, JD, Siston, RA, Flanigan, DC. Improved outcomes with combined autologous chondrocyte implantation and patellofemoral osteotomy versus isolated autologous chondrocyte implantation. *Arthroscopy*. 2013 Mar;29(3):566-74. PMID: 23312875
12. Mundi, R, Bedi, A, Chow, L, et al. Cartilage Restoration of the Knee: A Systematic Review and Meta-Analysis of Level 1 Studies. *Am J Sports Med*. 2015 Jul 2. PMID: 26138733
13. Harris, JD, Cavo, M, Brophy, R, Siston, R, Flanigan, D. Biological Knee Reconstruction: A Systematic Review of Combined Meniscal Allograft Transplantation and Cartilage Repair or Restoration. *Arthroscopy*. 2011 Oct 26;27(3):409-18. PMID: 21030203
14. Vasiliadis, HS, Wasiak, J. Autologous chondrocyte implantation for full thickness

articular cartilage defects of the knee. *The Cochrane database of systematic reviews*. 2010(10):CD003323. PMID: 20927732
15. Knutsen, G, Engebretsen, L, Ludvigsen, TC, et al. Autologous chondrocyte implantation compared with microfracture in the knee. A randomized trial. *J Bone Joint Surg Am*. 2004 Mar;86-A(3):455-64. PMID: 14996869
16. Knutsen, G, Drogset, JO, Engebretsen, L, et al. A randomized trial comparing autologous chondrocyte implantation with microfracture. Findings at five years. *J Bone Joint Surg Am*. 2007 Oct;89(10):2105-12. PMID: 17908884
17. Visna, P, Pasa, L, Cizmar, I, Hart, R, Hoch, J. Treatment of deep cartilage defects of the knee using autologous chondrograft transplantation and by abrasive techniques--a randomized controlled study. *Acta Chir Belg*. 2004 Nov-Dec;104(6):709-14. PMID: 15663280
18. Dozin, B, Malpeli, M, Cancedda, R, et al. Comparative evaluation of autologous chondrocyte implantation and mosaicplasty: a multicentered randomized clinical trial. *Clin J Sport Med*. 2005 Jul;15(4):220-6. PMID: 16003035
19. Horas, U, Pelinkovic, D, Herr, G, Aigner, T, Schnettler, R. Autologous chondrocyte implantation and osteochondral cylinder transplantation in cartilage repair of the knee joint. A prospective, comparative trial. *J Bone Joint Surg Am*. 2003 Feb;85-A(2):185-92. PMID: 12571292
20. Bentley, G, Biant, LC, Carrington, RW, et al. A prospective, randomised comparison of autologous chondrocyte implantation versus mosaicplasty for osteochondral defects in the knee. *J Bone Joint Surg Br*. 2003 Mar;85(2):223-30. PMID: 12678357
21. Bentley, G, Biant, LC, Vijayan, S, Macmull, S, Skinner, JA, Carrington, RW. Minimum ten-year results of a prospective randomised study of autologous chondrocyte implantation versus mosaicplasty for symptomatic articular cartilage lesions of the knee. *J Bone Joint Surg Br*. 2012 Apr;94(4):504-9. PMID: 22434467
22. Gooding, CR, Bartlett, W, Bentley, G, Skinner, JA, Carrington, R, Flanagan, A. A prospective, randomised study comparing two techniques of autologous chondrocyte implantation for osteochondral defects in the knee: Periosteum covered versus type I/III collagen covered. *Knee*. 2006 Jun;13(3):203-10. PMID: 16644224
23. Improvement in Symptoms and Function after Autologous Chondrocyte Implantation (ACI, Carticel®) in Patients who Failed Prior Treatment, Results of the Study of Treatment of Articular Repair (STAR). [cited 07/23/2018]; Available from: http://ajs.sagepub.com/content/37/1/42
24. Caritcel prescribing information. [cited 07/23/2018]; Available from: http://www.carticel.com/
25. Zaslav, K, Cole, B, Brewster, R, et al. A prospective study of autologous chondrocyte implantation in patients with failed prior treatment for articular cartilage defect of the knee: results of the Study of the Treatment of Articular Repair (STAR) clinical trial. *Am J Sports Med*. 2009 Jan;37(1):42-55. PMID: 18927254
26. Montgomery, SR, Foster, BD, Ngo, SS, et al. Trends in the surgical treatment of articular cartilage defects of the knee in the United States. *Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA*. 2014 Sep;22(9):2070-5. PMID: 23896943
27. Mithoefer, K, McAdams, T, Williams, RJ, Kreuz, PC, Mandelbaum, BR. Clinical efficacy of the microfracture technique for articular cartilage repair in the knee: an evidence-based systematic analysis. *Am J Sports Med*. 2009 Oct;37(10):2053-63. PMID: 19251676
28. Solheim, E, Hegna, J, Inderhaug, E, Oyen, J, Harlem, T, Strand, T. Results at 10-14

years after microfracture treatment of articular cartilage defects in the knee. *Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA*. 2014 Nov 23. PMID: 25416965
29. Niethammer, TR, Pietschmann, MF, Ficklscherer, A, Gulecyuz, MF, Hammerschmid, F, Muller, PE. Incomplete defect filling after third generation autologous chondrocyte implantation. *Arch Med Sci*. 2016;12:785-92. PMID: 27478460
30. Henderson, IJ, Lavigne, P. Periosteal autologous chondrocyte implantation for patellar chondral defect in patients with normal and abnormal patellar tracking. *Knee*. 2006 Aug;13(4):274-9. PMID: 16750370
31. Farr, J. Autologous chondrocyte implantation improves patellofemoral cartilage treatment outcomes. *Clin Orthop Relat Res*. 2007 Oct;463:187-94. PMID: 17960681
32. Gomoll, AH, Gillogly, SD, Cole, BJ, et al. Autologous chondrocyte implantation in the patella: a multicenter experience. *Am J Sports Med*. 2014 May;42(5):1074-81. PMID: 24595400
33. Biant, LC, Bentley, G, Vijayan, S, Skinner, JA, Carrington, RW. Long-term results of autologous chondrocyte implantation in the knee for chronic chondral and osteochondral defects. *Am J Sports Med*. 2014;42:2178-83. PMID: 25002462
34. Minas, T, Von Keudell, A, Bryant, T, Gomoll, AH. The John Insall Award: A minimum 10-year outcome study of autologous chondrocyte implantation. *Clin Orthop Relat Res*. 2014 Jan;472(1):41-51. PMID: 23979923
35. Pestka, JM, Bode, G, Salzmann, G, Sudkamp, NP, Niemeyer, P. Clinical outcome of autologous chondrocyte implantation for failed microfracture treatment of full-thickness cartilage defects of the knee joint. *Am J Sports Med*. 2012 Feb;40(2):325-31. PMID: 22056348
36. Vanlauwe, J, Saris, DB, Victor, J, Almqvist, KF, Bellemans, J, Luyten, FP. Five-year outcome of characterized chondrocyte implantation versus microfracture for symptomatic cartilage defects of the knee: early treatment matters. *Am J Sports Med*. 2011 Dec;39(12):2566-74. PMID: 21908720
37. Minas, T, Gomoll, AH, Rosenberger, R, Royce, RO, Bryant, T. Increased failure rate of autologous chondrocyte implantation after previous treatment with marrow stimulation techniques. *Am J Sports Med*. 2009 May;37(5):902-8. PMID: 19261905
38. Peterson, L, Vasiliadis, HS, Brittberg, M, Lindahl, A. Autologous chondrocyte implantation: a long-term follow-up. *Am J Sports Med*. 2010 Jun;38(6):1117-24. PMID: 20181804
39. Minas, T, Gomoll, AH, Solhpour, S, Rosenberger, R, Probst, C, Bryant, T. Autologous chondrocyte implantation for joint preservation in patients with early osteoarthritis. *Clin Orthop Relat Res*. 2010 Jan;468(1):147-57. PMID: 19653049
40. Pascual-Garrido, C, Slabaugh, MA, L'Heureux, DR, Friel, NA, Cole, BJ. Recommendations and treatment outcomes for patellofemoral articular cartilage defects with autologous chondrocyte implantation: prospective evaluation at average 4-year follow-up. *Am J Sports Med*. 2009 Nov;37 Suppl 1:33S-41S. PMID: 19861699
41. Niemeyer, P, Steinwachs, M, Erggelet, C, et al. Autologous chondrocyte implantation for the treatment of retropatellar cartilage defects: clinical results referred to defect localisation. *Arch Orthop Trauma Surg*. 2008 Nov;128(11):1223-31. PMID: 17710423
42. Nawaz, SZ, Bentley, G, Briggs, TWR, et al. Autologous chondrocyte implantation in the knee. *J Bone Joint Surg Am*. 2014;96(Update reference when available in pubmed):824-30. PMID:
43. Rosenberger, RE, Gomoll, AH, Bryant, T, Minas, T. Repair of large chondral defects of the knee with autologous chondrocyte implantation in patients 45 years or older. *Am J*

Sports Med. 2008 Dec;36(12):2336-44. PMID: 18725654
44. Farr, J, Rawal, A, Marberry, KM. Concomitant meniscal allograft transplantation and autologous chondrocyte implantation: minimum 2-year follow-up. *Am J Sports Med*. 2007 Sep;35(9):1459-66. PMID: 17435058
45. Rue, JP, Yanke, AB, Busam, ML, McNickle, AG, Cole, BJ. Prospective evaluation of concurrent meniscus transplantation and articular cartilage repair: minimum 2-year follow-up. *Am J Sports Med*. 2008 Sep;36(9):1770-8. PMID: 18483199
46. Browne, JE, Anderson, AF, Arciero, R, et al. Clinical outcome of autologous chondrocyte implantation at 5 years in US subjects. *Clin Orthop Relat Res*. 2005 Jul(436):237-45. PMID: 15995447
47. Moseley, JB, Jr., Anderson, AF, Browne, JE, et al. Long-term durability of autologous chondrocyte implantation: a multicenter, observational study in US patients. *Am J Sports Med*. 2010 Feb;38(2):238-46. PMID: 20448191
48. Gobbi, A, Kon, E, Berruto, M, et al. Patellofemoral full-thickness chondral defects treated with second-generation autologous chondrocyte implantation: results at 5 years' follow-up. *Am J Sports Med*. 2009 Jun;37(6):1083-92. PMID: 19465733
49. Gigante, A, Enea, D, Greco, F, et al. Distal realignment and patellar autologous chondrocyte implantation: mid-term results in a selected population. *Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA*. 2009 Jan;17(1):2-10. PMID: 18941738
50. Filardo, G, Kon, E, Andriolo, L, Di Martino, A, Zaffagnini, S, Marcacci, M. Treatment of "patellofemoral" cartilage lesions with matrix-assisted autologous chondrocyte transplantation: a comparison of patellar and trochlear lesions. *Am J Sports Med*. 2014 Mar;42(3):626-34. PMID: 24302700
51. Niemeyer, P, Pestka, JM, Kreuz, PC, et al. Characteristic complications after autologous chondrocyte implantation for cartilage defects of the knee joint. *Am J Sports Med*. 2008 Nov;36(11):2091-9. PMID: 18801942
52. Marquez-Lara, A, Mannava, S, Howse, EA, Stone, AV, Stubbs, AJ. Arthroscopic Management of Hip Chondral Defects: A Systematic Review of the Literature. *Arthroscopy*. 2016 Jul;32(7):1435-43. PMID: 27117866
53. Niemeyer, P, Salzmann, G, Schmal, H, Mayr, H, Sudkamp, NP. Autologous chondrocyte implantation for the treatment of chondral and osteochondral defects of the talus: a meta-analysis of available evidence. *Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA*. 2011 Oct 30. PMID: 22037894
54. Zengerink, M, Struijs, PA, Tol, JL, van Dijk, CN. Treatment of osteochondral lesions of the talus: a systematic review. *Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA*. 2010 Feb;18(2):238-46. PMID: 19859695
55. Clinical practice guideline on the diagnosis and treatment of osteochondritis dissecans. [cited 07/23/2018]; Available from: http://www.aaos.org/research/guidelines/OCD_guideline.pdf
56. BlueCross BlueShield Association Medical Policy Reference Manual "Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions." Policy No. 7.01.48

CODES

Codes	Number	Description
CPT	27412	Autologous chondrocyte implantation, knee
HCPCS	J7330	Autologous cultured chondrocytes, implant

Codes	Number	Description
	S2112	Arthroscopy, knee, surgical for harvesting of cartilage (chondrocyte cells)

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