Medical Policy

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Title: Transplantation for Chondral Defects

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DESCRIPTION

Autologous Chondrocyte Transplant (ACT) or Implants (ACI) (Carticel)

Damaged articular cartilage typically fails to heal on its own and can be associated with pain, loss of function, and disability and may lead to debilitating osteoarthritis over time. These manifestations can severely impair an individual's activities of daily living and adversely affect 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 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 to the original hyaline cartilage, fibrocartilage has less capability to withstand shock or shearing force and can degenerate over time, often resulting in the return of clinical

symptoms. Osteochondral grafts and autologous chondrocyte implantation (ACI) attempt to regenerate hyaline-like cartilage and thereby restore durable function.

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 11–21 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 2 procedures and harvesting of periosteum. In addition, use of the FDA-indicated periosteal cover may result in hypertrophy, as well as donor-site morbidity.

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) be implanted easily, 2) reduce surgical morbidity, 3) not 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

The culturing of chondrocytes is considered by the 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™ (Genzyme) 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 debridement, 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."

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), MACI® (matrix-induced ACI, Verigen and Genzyme, available outside of the U.S.), 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, none are approved for use in the U.S. at this time.

Osteochondral Autograft Transplants and Osteochondral Allograft Transplant

Focal chondral defects of the knee, either due to trauma or other conditions such as osteochondritis dissecans, often fail to heal on their own and may be associated with pain, loss of function, disability, and the long-term complication of osteoarthritis. The ideal resurfacing technique would eliminate symptoms, restore normal biomechanics of the knee joint, and prevent the long-term emergence of osteoarthritis and the necessity for total knee arthroplasty. Various methods of cartilage resurfacing have been investigated including marrow-stimulation techniques such as subchondral drilling, microfracture, and abrasion arthroplasty, all of which are considered standard therapies and all of which attempt to restore the articular surface by inducing the growth of fibrocartilage into the chondral defect. However, fibrocartilage does not share the same biomechanical properties as hyaline cartilage, and thus various strategies for chondral resurfacing with hyaline cartilage have been investigated.

Both fresh and cryopreserved allogeneic osteochondral grafts have been used with some success, although cryopreservation decreases the viability of cartilage cells, and fresh allografts may be difficult to obtain and create concerns regarding infectious diseases. As a result, autologous osteochondral grafts have been investigated as an option to increase the survival rate of the grafted cartilage and to eliminate the risk of disease transmission. Autologous grafts are limited by the small number of donor sites; thus allografts are typically used for larger lesions. In an effort to extend the amount of the available donor tissue, investigators have used multiple, small osteochondral cores harvested from non-weight-bearing sites in the knee for treatment of full-thickness chondral defects. Several systems are available for performing this procedure, the Mosaicplasty System (Smith and Nephew), the Osteochondral Autograft Transfer System (OATS, Arthrex, Inc.), and the COR and COR2 systems (DePuy-Mitek). Although mosaicplasty and OATS may use different instrumentation, the underlying principle is similar; i.e., the use of multiple osteochondral cores harvested from a non-weight-bearing region of the femoral condyle and autografted into the chondral defect. These terms have been used interchangeably to describe the procedure.

Preparation of the chondral lesion involves debridement and preparation of recipient tunnels. Multiple individual osteochondral cores are harvested from the donor site, typically from a peripheral non-weight-bearing area of the femoral condyle. Donor plugs range from 6-10 mm in diameter. The grafts are press fit into the lesion in a mosaic-like fashion into the same-sized tunnels. The resultant surface consists of transplanted hyaline articular cartilage and fibrocartilage, which is thought to provide "grouting" between the individual autografts. Mosaicplasty may be performed with either an open approach or arthroscopically. Osteochondral autografting has also been investigated as a treatment of unstable osteochondritis dissecans lesions using multiple dowel grafts to secure the fragment. While osteochondral autografting is primarily performed on the femoral condyles of the knee, osteochondral grafts have also been used to repair chondral defects of the patella, tibia, and ankle. With osteochondral autografting, the harvesting and transplantation can be performed during the same surgical procedure. Technical limitations of osteochondral autografting are difficulty in restoring concave or convex articular surfaces, incongruity of articular surfaces that can alter joint contact pressures, short-term fixation strength and load-bearing capacity, donor site morbidity, and lack of peripheral integration with peripheral chondrocyte death associated with graft harvesting and insertion

Recently, a minimally processed osteochondral allograft (Chondrofix®, Zimmer) has become available for use. Chondrofix® is composed of decellularized hyaline cartilage and cancellous bone and can be used "off the shelf" with precut cylinders (7-15 mm). Multiple cylinders may be used to fill a larger defect in a manner similar to OATS or mosaicplasty.

Filling defects with minced articular cartilage (autologous or allogeneic), is another single-stage procedure that is being investigated for cartilage repair. The Cartilage Autograft Implantation System (CAIS, Johnson and Johnson, Phase III trial) harvests cartilage and disperses chondrocytes on a scaffold in a single-stage treatment. BioCartilage® (Arthrex) consists of a micronized allogeneic cartilage matrix that is intended to provide a scaffold for microfracture. DeNovo NT Graft (Natural Tissue Graft) and DeNovo® ET Live Chondral Engineered Tissue Graft (Neocartilage) are produced by ISTO Technologies with exclusive distribution rights by Zimmer. DeNovo NT consists of manually minced cartilage tissue pieces obtained from juvenile allograft donor joints. The tissue fragments are mixed intra-operatively with fibrin glue before implantation in the prepared lesion. It is thought that mincing the tissue helps both with cell migration from the extracellular matrix and with fixation. As there is no use of chemicals and minimal manipulation, the allograft tissue does not require U.S. Food and Drug Administration (FDA) approval for marketing. DeNovo® ET graft (Neocartilage) uses juvenile allogeneic cartilage cells engineered by ISTO Technologies. The FDA approved ISTO's Investigational New Drug (IND) application for Neocartilage in 2006, which allowed them to pursue Phase III clinical trials of the product in humans.

Autologous chondrocyte implantation (ACI) is another method of cartilage repair involving the harvesting of normal chondrocytes from normal non-weight-bearing articular surfaces, which are then cultured and expanded in vitro and implanted back into the chondral defect.

POLICY

A. Autologous Chondrocyte Transplant (ACT) or Implants (ACI) (Carticel)

1. Autologous chondrocyte implantation may be considered **medically necessary** for the treatment of disabling full-thickness articular cartilage defects of the knee caused by acute or repetitive trauma or osteochondritis dissecans, in patients who have had an inadequate response to a prior surgical procedure, 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 on the weight bearing surface of the femoral condyles or trochlea at least 1.5 cm^2 in size (Outerbridge cartilage grading scale: Grade III has fragmentation and deeper fissuring of more than one-half inch and Grade IV shows erosion of the cartilage down to the bone)
    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 (Outerbridge cartilage grading scale: Grade I is softening and swelling of the cartilage and Grade II shows fragmentation and fissuring of the superficial cartilage of less than one-half in diameter)
    d. Normal knee biomechanics, or alignment and stability achieved concurrently with autologous chondrocyte implantation
    e. Absence of meniscal pathology

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

3. Matrix-induced autologous chondrocyte implantation is considered **experimental / investigational.**

B. Osteochondral Autograft Transplants (OATS/mosaicplasty) for the treatment of cartilaginous defects

1. Osteochondral autografting, using 1 or more cores of osteochondral tissue, may be considered **medically necessary** for the treatment of symptomatic full-thickness cartilage defects caused by acute or repetitive trauma, in patients who have had an inadequate response to a prior surgical procedure, when all of the following have been 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) uni-polar lesions on the weight-bearing surface of the femoral condyles or trochlea that are between 1 and 2.5 cm^2 in size
(Outerbridge cartilage grading scale: Grade III has fragmentation and deeper fissuring of more than one-half inch and Grade IV shows erosion of the cartilage down to the bone)

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 (Outerbridge cartilage grading scale: Grade I is softening and swelling of the cartilage and Grade II shows fragmentation and fissuring of the superficial cartilage of less than one-half in diameter)

d. Normal knee biomechanics, or alignment and stability achieved concurrently with osteochondral grafting

e. Absence of meniscal pathology

f. Non-repairable stage III or IV osteochondritis dissecans

g. Otherwise healthy non-elderly patient who can comply with the post-operative regimen including physical therapy

h. Body mass index (BMI) less than 30

2. Osteochondral autografting for all other joints, including patellar and talar, and any indications other than those listed above, is considered **experimental / investigational**.

C. Osteochondral Allograft Transplant

1. Osteochondral allografting may be considered **medically necessary** as a technique to repair large (e.g., 10 cm^2) full-thickness chondral defects of the knee caused by acute or repetitive trauma or osteochondritis diseases or avascular necrosis lesions of the femoral condyle in patients who have had an inadequate response to a prior surgical procedure, when all of the following have been 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) uni-polar lesions on the weight-bearing surface of the femoral condyles or trochlea (Outerbridge cartilage grading scale: Grade III has fragmentation and deeper fissuring of more

than one-half inch and Grade IV shows erosion of the cartilage down to the bone)

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 (Outerbridge cartilage grading scale: Grade I is softening and swelling of the cartilage and Grade II shows fragmentation and fissuring of the superficial cartilage of less than one-half in diameter)
d. Normal knee biomechanics, or alignment and stability achieved concurrently with osteochondral grafting
e. Absence of meniscal pathology
f. Body Mass Index (BMI) of less than 30

2. Osteochondral allografting for all other joints, including patellar and talar, and any indications other than those listed above, is considered **experimental / investigational**.

3. Treatment of focal articular cartilage lesions with autologous minced cartilage is considered **experimental / investigational. NEW**

4. Treatment of focal articular cartilage lesions with allogeneic minced cartilage is considered **experimental / investigational. NEW**

Policy Guidelines

Autologous Chondrocyte Transplant (ACT) or Implants (ACI)

A. If debridement is the only prior surgical treatment, consideration should be given to marrow-stimulating techniques before autologous chondrocyte implantation is performed.

B. The average defect size reported in the literature is about 5 cm^2; many studies treated lesions as large as 15 cm^2.

C. Severe obesity, e.g., body mass index (BMI) greater than 35 kg/m^2, may affect outcomes due to the increased stress on weight bearing surfaces of the joint.

D. 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. The charges for the culturing component of the procedure are submitted as part of the hospital bill.

E. The entire autologous chondrocyte implantation (ACI) procedure consists of 4 steps:
1. the 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. post-surgical rehabilitation. The initial arthroscopy may be scheduled as a diagnostic procedure; as part of this procedure, a cartilage defect may be identified, prompting biopsy of normal cartilage in anticipation of a possible chondrocyte transplant. The biopsied material is then sent for culturing and returned to the hospital when the implantation procedure (i.e., arthrotomy) is scheduled.

Osteochondral Autograft Transplants and Osteochondral Allograft Transplants

1. If debridement is the only prior surgical treatment, consideration should be given to marrow-stimulating techniques before osteochondral grafting is performed.

2. Severe obesity, e.g., body mass index (BMI) greater than 35 kg/m^2, may affect outcomes due to the increased stress on weigh-bearing surfaces of the joint.

3. 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.

Outerbridge cartilage grading scale

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

RATIONALE

Autologous Chondrocyte Transplant (ACT) or Implants (ACI)

First Generation ACI (Carticel™) for Treatment of the Knee

First Generation ACI (Carticel™) for Treatment of the Knee: Systematic Reviews. A 2010 systematic review by Harris and colleagues included 13 randomized and non-randomized controlled trials of 917 subjects who underwent ACI (n=604), microfracture (n=271), or osteochondral autograft (n=42). The mean study quality was rated as 54 out of 100, with no studies considered of good or excellent quality, 7 considered fair, and 6 considered poor. Four studies compared different generations of ACI, finding no difference in outcomes but higher complication rates with open, periosteal cover, first-generation ACI. At 1- to 5-year follow-up, 3 of 7 studies showed better clinical outcomes after ACI in comparison with microfracture, 1 study showed better outcomes after microfracture, and 3 studies showed no difference in these treatments. Clinical outcomes after microfracture were found to deteriorate after 18 to 24 months in 3 of 7 studies. Studies comparing ACI and osteochondral autograft showed similar short-term clinical outcomes, with more rapid improvement but an increase in arthrofibrosis and donor site morbidity following osteochondral autograft. Younger patients with a shorter preoperative duration of symptoms and fewer prior surgical procedures had the best outcomes after surgical

intervention. A defect size greater than 4 cm2 was the only factor predictive of better outcomes when ACI was compared with other surgical techniques.

Another publication by Harris et al. in 2010 was a systematic review of combined meniscal allograft transplantation and cartilage repair/restoration. (5) 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), osteochondral autograft (n=17), or microfracture (n=3). All studies showed improvement in clinical outcomes at final follow-up compared to the preoperative condition. Outcomes were also compared with historical outcomes of each individual procedure performed in isolation. Four of the 6 studies found outcomes equivalent to procedures performed in isolation, while 2 studies found that outcomes with combined surgery were not as good as the historical controls. Across the 6 studies, 13 failures (12%) were reported; these included 11 isolated meniscal allograft transplantation failures, 1 combined meniscal allograft and ACI failure, and 1 isolated ACI failure. Three knees with failed meniscal allograft transplantation were converted to total knee arthroplasty. Nearly 50% of the patients underwent one or more subsequent surgeries after combined meniscal allograft transplantation and cartilage repair/restoration procedures.

Efficacy of the microfracture technique alone was examined in a 2009 systematic review. (6) Twenty-eight studies describing 3,122 patients were included in the review; 6 of the studies were randomized controlled trials (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.

First Generation ACI (Carticel™) for Treatment of the Knee: Comparative Studies: ACI (Carticel™) versus Marrow-Stimulating Techniques. In an RCT of 80 patients randomized to either ACI or microfracture of the knee (an arthroscopic marrow-stimulation procedure), Knutsen and colleagues reported no significant differences in the treatment groups at 2-year follow-up in macroscopic and histologic findings. (7) The Lysholm and pain scores were also not significantly different at 1 and 2 years. The physical component score of the Short Form (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 revealed 9 failures (23%) for both groups. (8) 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 Visna et al., 50 patients with full-thickness, moderate to large chondral defects of 2.0–10.0 cm2 of the femoral condyle, trochlea, or patella (43 cases due to injury) 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. (9) The study reported improvements after 12 months in the Lysholm, International Knee Documentation Committee, 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 and 20 in the abrasion group) included anterior cruciate ligament (ACL) replacement, meniscectomy, and lateral release.

First Generation ACI (Carticel™) for Treatment of the Knee: Comparative Studies: ACI (Carticel™) versus Osteochondral Autografts. Horas and colleagues reported 2-year follow-up on a study of 40 patients (between 18 and 42 years of age) with an articular lesion of the femoral condyle (range: 3.2 to 5.6 cm2) who were randomly assigned to undergo either autologous chondrocyte transplant or osteochondral autografting. (10) Eleven (28%) had received prior surgical treatment. The authors reported that both treatments resulted in an improvement in symptoms (85% of each group), although those in the osteochondral autografting group responded more quickly. Histomorphologic evaluation of 5 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.

Bentley and colleagues randomized 100 consecutive patients with symptomatic lesions of the knee (average 4.7 cm2; range: 1 to 12 cm2) to ACI or mosaicplasty. (11) 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 7 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. With 6 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. (12)

Dozin et al. reported results from a multicenter randomized, clinical trial in which ACI was compared to osteochondral autografting. (13) Forty-four individuals (61% male, 39% female) aged 16-40 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 6 months after undergoing arthroscopic debridement. 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, 5 who did not show up at the presurgery examination and could not be further traced, and 2 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 post-surgery 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 debridement (intention-to-treat analysis) the percentages of patients who achieved complete success were 89% (16 of 18 evaluable cases) in the mosaicplasty arm versus 68% (13 of 19 evaluable cases) in the ACI arm (test for trend p=0.093). The high rate of spontaneous improvement after simple debridement 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 debridement and exercise rehabilitation.

First Generation ACI (Carticel™) for Treatment of the Knee: Other Controlled Trials. Gooding and colleagues randomized 68 patients with osteochondral defects (mean: 4.5 cm2; range: 1–12 cm2) of the femoral condyle (54%), trochlea (6%), or patella (40%) to ACI with either a periosteal or collagen cover. (14) 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.

In 2012, Pestka et al. reported a matched-pair comparison of ACI after failed microfracture versus ACI as a first-line treatment. (15) A total of 56 patients were retrospectively matched for gender, age, defect size, and defect location. The average defect size was 4.65 cm2. 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 ($p=0.0583$) for lower International Knee Documentation Committee (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. (16) However, the results add to a growing body of literature suggesting inferior outcomes when ACI is performed following a failed microfracture. (17)

First Generation ACI (Carticel™) for Treatment of the Knee: Observational Studies. Results from the Study of the Treatment of Articular Repair (STAR) trial have been published; these were previously available in the Carticel package insert and from a meeting presentation in July 2007. (18-20) STAR was a prospective, open-label 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 (for example, 78% underwent debridement, 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 cm2 (range of 1-30 cm2), 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 6 months for up to 4 years.

The primary outcome, treatment failure for ACI, was defined as any of the following: 1) a 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 3 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 (i.e., fraying or fibrillation, 10%), graft delamination (6%), and joint adhesion (5%). Subsequent surgical procedures (regardless of relationship to ACI) included debridement of cartilage lesion (31%), lysis of adhesions (14%), other debridement (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. A majority (61%) of 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.

Browne et al. 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. (21) The registry is a multicenter program initiated in 1995 and 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 cm2 (range: 0.8 to 23.5 cm2). Seventy percent of the patients had failed at least one previous cartilage procedure, and the average self-rated overall condition was 3.2 (poor to fair). At 5 years following the index procedure, the average follow-up score was 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). Factors associated with failure in 6 patients were nonadherence with the postoperative protocol, additional injury, and uncorrected malalignment. Defect size was not found to be significantly associated with outcome; self-reported outcomes were associated with workers' compensation claims. In 2010, this group of investigators published 6- to 10-year follow-up (mean 9.2 years) on 72 patients in the cartilage repair registry. (22) Information on adverse events, treatment failures, and operations after ACI were reported on follow-up questionnaires or came from patient and surgeon reports. 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 to the later follow-up period. During the 6- to 10-

year follow-up period, ACI failed in 3 patients at a mean of 8 years after implantation. For the cohort of 72 patients, 69% reported improvement, 17% failed, and 12.5% reported no change from baseline to follow-up. During the study period, 30 patients (42%) had 42 operations after ACI, the majority of which met the study definition of treatment failure.

In 2010, Peterson and colleagues reported on 224 patients who replied to questionnaires at 10- to 20-year follow-up. (23) 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 to 61) at the time of the ACI, and the indication for treatment was any symptomatic full-thickness cartilage lesion up to 16 cm2, 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 and 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' 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, the 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.

Rosenberger et al. reported average 4.7 years' follow-up (range: 2–11 years) on a cohort of 56 patients (45 to 60 years of age) with lesions of the femoral condyle (49%), trochlea (29%), or patella (22%). (24) 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. A European group reported complications in 309 consecutive patients, 52 of whom (17%) had undergone revision surgery for persistent clinical problems. (25) Three different ACI techniques had been used, periosteum-covered, membrane-covered (Chondrogide Geistlich Biomaterials, Switzerland), and 3-dimensional matrix (BioSeed-C, Biotissue Technologies, Germany). Follow-up at a mean of 4.5 years showed that the highest rate of revision surgery was in patients with periosteum-covered ACI (27%) in comparison with membrane-covered or matrix-induced ACI (12% and 15%, respectively). There was a trend ($p=0.09$) for a higher incidence of hypertrophy with patellar defects in comparison with the femoral condyles or trochlea.

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. (26, 27) A 2008 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. (28) The average defect was 4.4 cm2. Depending on surgeon preference, patients received ACI with a periosteal patch, Chondrogide membrane, or MACI. Fourteen patients (15%) were lost to follow-up, and 11 patients (12%) were excluded from the follow-up study due to dysplasia of the femoropatellar joint and significant (more than 5 degrees) varus or valgus deformity. In addition to patient responses for the Cincinnati Sports Activity scale, Lysholm score, and International Knee Documentation Committee (IKDC) score, a

physical examination was performed by an independent examiner who was blinded to data obtained at the time of surgery, including defect size and location. Objective evaluation at an average follow-up of 38 months showed normal or nearly normal results in 47 patients (67%). Results were classified as abnormal in 14 patients (20%), and 9 patients (13%) were considered failures. Results were not divided according to the type of implant (ACI or MACI), although it was reported that 2 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. Other studies from Europe report patellofemoral cartilage defects treated with second-generation MACI implants. (29, 30) These products are not approved in the U.S. and are, therefore, considered investigational.

In 2009, Pascual-Garrido et al. reported outcomes from 52 patients (83% follow-up) who underwent ACI of the patellofemoral joint (patella or trochlea). (31) The mean defect size was 4.2 cm2. 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 osteochondral autograft (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 to 7), there was significant improvement in the Lysholm (37 to 63), IKDC (31 to 57), KOOS Pain (48 to 71), KOOS Symptoms (51 to 70), KOOS Activities of Daily Living (60 to 80), KOOS Sport (25 to 42), Cincinnati (43 to 63), Tegner (4 to 6), and Short Form (SF)-12 Physical (38 to 41). Patients reported the overall condition of their knee as excellent, very good, or good in 71% of the cases; 81% of the patients were satisfied with the procedure. There were 4 failures (8%), defined as poor clinical outcome accompanied by evidence of graft failure or need for conversion to knee arthroplasty or osteochondral allograft.

Farr et al. described outcomes from a prospective series of 36 patients who underwent ACI together with meniscal transplantation in the same compartment. (32) 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 3 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 4 failures, 68% of their patients required additional surgeries; 52% had one additional surgery, and 16% required 2 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 osteochondral allograft transplantation (OA; 48%). (33) The Lysholm score improved in both the ACI (from 55 to 79) and OA (from 42 to 68) groups; 48% of patients (60% ACI and 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 cm2 vs. 3.9 cm2). Two patients were considered failures (7%) and 5 (17%) and underwent subsequent surgery. Although results seemed promising, evidence is insufficient to permit conclusions regarding the effect of combined transplantation-implantation procedures on health outcomes.

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). (17) The average lesion was 8 cm2, and the indications for treatment of cartilage defects with ACI included 1 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 of 214) that did not have prior marrow stimulation of the lesion, compared with 26% (29 of 111 joints) that had previously been treated with marrow stimulation.

Minas and colleagues 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 to 60), evidence of early osteoarthritis at the time of surgery (peripheral intra-articular osteophyte formation and/or 0% to 50% joint space narrowing), and equal to or greater than 2 years of follow-up. (34) (Patients with more than 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 cm2 and a total mean defect area of 10.4 cm2. 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, the majority 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 to 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 Western Ontario and McMaster Universities Arthritis Index (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.

First Generation ACI (Carticel™) for Joints Other Than the Knee

There has been interest in applying ACI to cartilage defects in other joints. The most commonly reported is use of ACI for the talus.

In 2010, Zengerink et al. published a systematic review of treatment of osteochondral lesions of the talus. (35) Fifty-one nonrandomized and 1 randomized trial were included in the review. Success rates were 85% for bone marrow stimulation, 87% for osteochondral autografting, and 76% for ACI. Because of the high cost of ACI and the knee morbidity seen with osteochondral autografting, the authors concluded that bone marrow stimulation is the treatment of choice for primary osteochondral talar lesions. A 2009 report examined the association between defect size and outcomes following marrow stimulation techniques in 120 ankles. (36) Eight ankles subsequently underwent osteochondral transplantation, and 22 ankles were considered clinical failures (American Orthopaedic Foot and Ankle Society [AOFAS] Ankle-Hindfoot score <80). Linear regression suggested a cutoff defect size of 1.5 cm2 for marrow stimulation techniques, with an 80% failure rate compared to a 10.5% failure rate for ankles with a defect size of less

than 1.5 cm2. Three of 58 ankles (5.2%) with a defect area of less than 1 cm2 showed clinical failure, while 7 of 37 ankles (18.9%) with a defect area between 1.0 and 1.5 cm2 failed.

A systematic review by Niemeyer et al. included 16 studies (213 patients) on ACI or MACI for lesions of the talus. (37) All were case series with a mean of 13 patients (range, 2-46) and mean follow-up of 32 months (range, 6-120). A majority of the studies were prospective. In 6 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 4 to 12. Nine different methods were used to evaluate pre- and postoperative clinical function, with the most common being the American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Score. Overall clinical success rate, defined as the percentage of good and excellent results, was 89.9% (range, 50% to 100%). Interpretation of these results is limited by the inclusion of poor quality studies, lack of a comparator, lack of blinding, and the use of techniques that are not approved for use by the FDA.

A 2006 study from Italy randomized 32 patients with osteochondral lesions of the talus to chondroplasty, microfracture, or osteochondral autograft transfer (OAT). (38) This small study found similar improvements (approximately 40 points) for the 3 treatment groups as measured by the AOFAS 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 1 patient following chondroplasty, by 2 patients following microfracture, and by 2 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).

Second Generation ACI Products

Second Generation ACI Products: Systematic Reviews. Kon et al. published a systematic review of matrix-assisted ACI in 2013. (39) The review identified 51 articles, including 3 randomized controlled trials, 10 comparative studies, 33 case series, and 5 case reports that reported on functional or clinical outcomes. The review found an expanding evidence base that reports good results at short to medium follow-up, although long-term follow-up and randomized controlled trials are needed to compare MACI with other available treatments.

Second Generation ACI Products: Randomized, Controlled Trials. There are 3 RCTs of ACI using matrix assistance. Two of these compared matrix-assisted ACI with marrow-stimulating techniques, and the third RCT compared matrix-assisted ACI with ACI done without matrix assistance.

Second Generation ACI Products: MACI®. Basad et al. reported a small randomized trial that compared MACI® (n=40) to microfracture (n=20) in patients with a single post-traumatic chondral defect between 4-10 cm2. (40) Both groups improved at the 2-year follow-up, with a significant advantage of MACI over microfracture on the Lysholm (92 vs. 69), Tegner (4 vs. 3), and International Cartilage Repair Society (ICRS) patient (a higher percentage of patients with an ICRS score of I) and ICRS surgeon scores.

Second Generation ACI Products: NeoCart. In 2012, Crawford et al. reported results of an industry-sponsored, FDA-regulated, multi-center randomized Phase II trial. (41) Thirty patients with lesions less than 8 cm2 were randomized to NeoCart (n=21) or to microfracture (n=9). The SF-36, KOOS, IKDC and VAS pain scores were assessed at up to 24 months by intent-to-treat analysis, and patients were classified as responders if they had at least a 12-point improvement in the pain score of the KOOS and a 20-point improvement in the IKDC subjective score. At 24 months, there was no significant difference in the mean KOOS pain scores or IKDC scores. The NeoCart group showed significantly greater improvement in the KOOS pain score, KOOS sports, KOOS QOL, IKCD, and visual analog scale (VAS) pain scores compared to microfracture. There was a trend for a greater number of responders in the NeoCart group (p=0.097); 79% of NeoCart patients were considered to be responders, compared to 44% of the microfracture group.

Second Generation ACI Products: Bioseed. Zeifang et al. conducted a small (n=21) randomized trial comparing MACI and ACI. (42) The average size of the cartilage defects was 4.3 cm2, and patients had undergone an average of 2 prior surgeries on the affected knee. Postoperatively, there was no significant difference between the 2 groups on the IKDC score at either 12 months (72.0 for MACI and 76.7 for ACI), or 24 months (70.1 for MACI and 77.1 for ACI). Exploratory analysis found a significant inverse correlation with age (r= -0.52 at 12 months and r= -0.49 at 24 months) indicating that better results were observed in younger patients. There was no significant difference between the groups in the SF-36. The Lysholm score showed a significant improvement only in the ACI group (from 61.3 at baseline to 86.3 at 12 months and 84.0 at 24 months). The Tegner activity score did not change significantly in either group.

Second Generation ACI Products: ChondroCelect. Saris et al. published a multicenter, randomized trial of characterized chondrocyte implantation (n=57) versus microfracture (n=61) in 2008; the average lesion size was 2.8 cm2. (43) Chondrocytes were isolated from a cartilage biopsy specimen and expanded ex vivo (ChondroCelect, TiGenix, Belgium). ChondroCelect is not approved for use in the U.S. Chondrocytes that were predicted to form stable hyaline cartilage in vivo were implanted by arthrotomy approximately 27 days after chondrocyte harvest. Surgical and rehabilitation procedures were standardized, and evaluation of a biopsy specimen at 12 months was conducted by an independent evaluator. Histologic analysis showed better results with ACI for some measures of structural repair such as cartilage surface area, safranin O and collagen II ratio, and cell morphology. However, measures of integration (e.g., subchondral bone abnormalities, basal integration, vascularization) and surface architecture were not improved relative to the microfracture group. Self-assessed pain and function with the Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire were similar following ACI or microfracture at 12 or 18 months' follow-up. Joint swelling and joint crepitation were greater in the ACI group, particularly following the arthrotomy. Thus, although histologic results were somewhat improved, in this study characterized chondrocyte implantation did not improve health outcomes in comparison with microfracture at short-term follow-up.

In 2009, Saris et al. published 36-month outcomes (100% follow-up) from this randomized trial. (43, 44) The mean improvement in the overall KOOS was greater in the ACI group than the microfracture group (21 vs. 16 points, respectively). More ACI than microfracture-treated patients were considered to be treatment responders (83% vs. 62%, respectively), defined as an increase from baseline of at least 10 percentage points in at least 3 of the 4 KOOS subdomains or a decrease of at least 20 percentage points in visual analog scale (VAS) scores for pain. At 36

months after surgery, 2 ACI (3.9%) and 7 microfracture patients (11.5%) had failed treatment and subsequently underwent reintervention. Magnetic resonance imaging (MRI) showed greater worsening of the subchondral bone reaction with microfracture compared with ACI. At 5 years after treatment, the number of treatment failures was comparable for the ACI (n=7) and microfracture (n=10) groups. (16) There was a trend for the overall KOOS score to be more improved following ACI than microfracture (21 vs. 14, p=0.068). Planned exploratory subgroup analysis indicated that ACI resulted in a better outcome (both statistically and clinically significant) in patients who had a time since symptom onset of less than 3 years, with a change in KOOS of 26 compared to 15 for the microfracture group. For patients with symptom onset of 3 years or more, the change in KOOS was similar for the 2 groups (13 ACI vs. 17 microfracture). Subgroup analyses for age did not show a difference for patients who were younger than 35 years of age compared to patients who were 35 years or older.

Second Generation ACI Products: Hyalograft C. In 2011, Kon et al. reported a prospective comparative study of second generation ACI (Hyalograft C) versus microfracture in 41 professional or semiprofessional male soccer players. (45) This was a pragmatic clinical trial, with treatment allocation based on the center that patients went to; 1 center performed ACI and 2 centers performed microfracture. The 2 patient groups were comparable for age, defect size, location, previous and combined surgery, and follow-up. Patients were evaluated prospectively at 2 years and at a final mean 7.5-year follow-up (minimum, 4 years). The percentage of patients who returned to competition was similar, with 80% in the microfracture group and 86% in the ACI group. Patients treated with microfracture needed a median of 8 months before playing their first official soccer game, whereas the ACI group required a median time of 12.5 months. The International Knee Documentation Committee (IKDC) subjective score showed similar results at 2 years' follow-up but significantly better results in the ACI group at the final evaluation. In the microfracture group, results decreased over time (from 86.8 at 2 years to 79.0 at final follow-up), whereas the ACI group had stable results between 2 years and final follow-up (90.5 and 91.0, respectively). The IKDC objective score was similar in the 2 groups, with 90-95% of knees considered to be normal or nearly normal. Subjective evaluation of functional level was significantly better in the ACI group at final follow-up (91 vs. 84).

Ongoing Clinical Trials

A search of the online clinical trials database www.clinicaltrials.gov in May 2013 identified a number of trials with second and third generation ACI/MACI. In addition, Zimmer Orthobiologics is conducting 2 large post-marketing studies with DeNovo NT, Natural Tissue Graft, for the knee (NCT01329445) and ankle (NCT01347892). Both studies will have 5-year follow-up with estimated completion in 2018.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2008
In response to requests, input was received from 1 physician specialty society and 3 academic medical centers while this policy was under review in 2008. The reviewers generally agreed that ACI should be considered when all other treatments have been unsuccessfully tried in individuals who have a localized chondral defect in an otherwise normal joint articular surface. Reviewers noted the lack of alternative options for larger lesions (e.g., >4 cm2). Additional literature was provided, which was subsequently reviewed.

2011
In response to requests, input was received from 2 physician specialty societies and 3 academic medical centers while this policy was under review in 2011. The clinical input was generally in agreement with the stated criteria for ACI with the exception of the following: input was mixed regarding the requirement for an inadequate response to a prior surgical procedure and the requirement for an absence of meniscal pathology. Input was also mixed regarding the investigational status of ACI in patellar and talar joints..

Summary
Although evidence from long-term studies is limited, evidence indicates that autologous chondrocyte implantation (ACI) can improve symptoms in some patients with lesions of the articular cartilage of the knee who have failed prior surgical treatment. These patients, who are too young for total knee replacement, have limited options. Therefore, based on the clinical input, highly suggestive evidence from randomized controlled trials and prospective observational studies, it is concluded that ACI may be considered an option for the FDA-approved indication of disabling full-thickness chondral lesions of the femoral condyles or trochlea caused by acute or repetitive trauma, in patients who have had an inadequate response to a prior procedure. Additional studies are needed to evaluate whether marrow stimulation at the time of biopsy affects implant success. Recent evidence indicates that ACI combined with meniscal allograft results in outcomes similar to either procedure performed alone; therefore, combined procedures may be considered medically necessary. Evidence is currently insufficient to evaluate the efficacy of ACI in comparison with other surgical repair procedures as a primary treatment of large lesions or to evaluate the efficacy of ACI for the patella or for joints other than the knee.

Results from second generation ACI procedures (MACI) from Europe appear promising. These products use a variety of biodegradable scaffolds and have the potential to improve consistent hyaline cartilage formation and reduce complications associated with injection under a periosteal patch. To date, there are a smaller number of RCTs with short- term follow-up comparing MACI to ACI, and no MACI products are approved in the U.S.; therefore, these are considered investigational.

Practice Guidelines and Position Statements
In a 2010 clinical practice guideline on the diagnosis and treatment of osteochondritis dissecans (OCD), the American Academy of Orthopaedic Surgeons (AAOS) was unable to recommend for or against a specific cartilage repair technique in symptomatic skeletally immature or mature patients with an unsalvageable osteochondritis dissecans lesion. (46) This recommendation of insufficient evidence was based on a systematic review that found 4 level IV studies that addressed cartilage repair techniques for an unsalvageable OCD lesion. Since each of the level IV articles utilized different techniques, different outcome measures, and differing lengths of follow-up, the work group deemed that the evidence for any specific technique was inconclusive.

In 2005, the National Institute for Health and Clinical Excellence (NICE) issued an updated Technology Appraisal Guidance on the use of autologous chondrocyte implantation. (47) The NICE guidance cited insufficient evidence to determine the benefits of autologous chondrocyte implantation and indicated this technology "should not be used for the treatment of articular cartilage defects except where the treatment is part of a clinical study." The guidance noted many limitations in available trial data including length of follow-up, comparison to conservative treatment, assessment of the quality of cartilage produced, and the impact of cartilage produced on functional outcomes and health-related quality of life.

Osteochondral Autograft Transplants and Osteochondral Allograft Transplant

A 2008 systematic review by Magnussen et al. 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. (1) Finding a total of 5 randomized controlled trials (RCTs) and 1 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. 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. Similarly, complications such as donor site morbidity in OAT [osteochondral autograft transfer] may be late in their presentation and thus not be detected at short follow-up."

Harris and colleagues published a systematic review of combined meniscal allograft transplantation and cartilage repair/restoration in 2010. (2) Six level IV studies (case series) with a total of 110 patients were included in the review. Patients underwent meniscal allograft transplantation with either autologous chondrocyte implantation (ACI, n=73), osteochondral allograft (n=20), osteochondral autograft (n=17), or microfracture (n=3). All studies showed improvement in clinical outcomes at final follow-up compared to the preoperative condition. Outcomes were also compared with historical outcomes of each individual procedure performed in isolation. Four of the 6 studies found outcomes equivalent to procedures performed in isolation, while 2 studies found that outcomes with combined surgery were not as good as the historical controls. Across the 6 studies, 13 failures (12%) were reported; these included 11 isolated meniscal allograft transplantation failures, 1 combined meniscal allograft and ACI failure, and 1 isolated ACI failure. Three knees with failed meniscal allograft transplantation were converted to total knee arthroplasty. Nearly 50% of the patients underwent one or more subsequent surgeries after combined meniscal allograft transplantation and cartilage repair/restoration procedures.

Hangody, who first reported use of the mosaicplasty technique in humans in 1992, has authored a number of summaries and case series. (3-5) It is likely that these reports contain overlapping populations of patients, and few details are reported. In a 1997 article, Hangody and colleagues refer to a 1992–1994 comparison study of mosaicplasty and abrasion arthroplasty. No details of this study are provided, except to note that the mosaicplasty patients had significantly improved Hospital for Special Surgery (HSS) knee scores, compared to those undergoing abrasion arthroplasty. (1) A 2008 summary paper includes descriptions of a prospective multicenter comparison of 413 resurfacing procedures and follow-up from 1,097 mosaicplasties at the

authors' institution. (5) Although the authors report that the comparative study found hyaline-like resurfacing to result in a better clinical outcome than other techniques, the cited study is not available as a publicly available peer-reviewed publication. For the retrospective analysis, Hangody and colleagues reported 789 implantations on the femoral condyles, 147 in the patellofemoral joint, 31 on the tibia condyles, 98 on talar domes, 8 on the capitulum humeric, 3 on humeral heads, and 11 on femoral heads. About two thirds of the patients were reported to have had a localized cartilage lesion, and the remainder underwent surgery because of osteochondral defects. In 81% of patients, concomitant surgical interventions were performed; these included reconstruction of the anterior cruciate ligament (ACL) realignment osteotomies, meniscus surgery, and patellofemoral realignment procedures. Clinical scores found good to excellent results in 92% of patients with femoral condylar implantations, 87% of tibial resurfacings, 74% of patellar and/or trochlear mosaicplasties, and in 93% of talar procedures. Moderate and severe donor-site disturbances were reported in 3% of patients. Ninety-eight second-look arthroscopies were done for persistent or recurrent pain, swelling, or postoperative intra-articular bleeding (31 patients at 2 months to 11 years); second trauma (26 patients at 1–9 years); or to evaluate recovery in professional athletes (41 patients at 4–7 months). Although at least 57 (58%) second-look arthroscopies were associated with clinical symptoms, the report indicates that 81 (83%) of the evaluations indicated good gliding surfaces, histologically proven survival of the transplanted hyaline cartilage, and acceptable fibrocartilage covering of the donor sites. Slight or severe degenerative changes were seen at the recipient and/or donor sites in 17 cases (17%). The association between clinical symptoms and histological results was not discussed. Painful hemarthroses were observed in 56 (5%) patients. The authors note that although these results are encouraging for use of autologous osteochondral mosaicplasty as an alternative treatment for small- and medium-sized focal defects, postoperative bleeding from the empty donor tunnels represents a possible postoperative complication, and donor-site morbidity remains an open question. Based on their extensive experience with this procedure, Hangody and colleagues consider the optimal indications to be a lesion size of 1–4 cm2, patient age of 50 years or younger (due to decreased repair capacity with aging), and correction of instability, malalignment, and meniscal or ligamental tears. (5)

Osteochondral Autografts and Allografts for Focal Articular Cartilage Lesions of the Knee

Comparative Trials

Osteochondral Autografts in Comparison with Microfracture: Three randomized controlled trials from the same group of investigators and 1 retrospective comparative trial have been identified that compared outcomes following osteochondral autografting or microfracture.

Gudas et al. reported a well-controlled and blinded comparison of arthroscopic OAT versus microfracture for lesions of the femoral condyle (1–4 cm2) in 60 athletes between 15 and 40 years of age (mean, 24.3 years). (6) Follow-up on 95% of the athletes for up to 3 years following surgery showed that more athletes returned to sports activities (mean, 6.5 months) following OAT (93% vs. 52%), and fewer required revision (1of 28 vs. 9 of 29 – both respectively). Overall, 96% of patients treated by OAT had an excellent or good result compared with 52% treated by microfracture. At 1-year follow-up, scores on the International Cartilage Repair Society (ICRS) cartilage grading system improved from a baseline of 51 to 86 in the OAT group and 76 in the microfracture group. At 3-year follow-up, scores from HSS questionnaires improved from a baseline of 77 to 91 in the OAT group and 81 in the microfracture group. No donor-site morbidity

was observed. Blinded arthroscopic and histological assessment in a subset of patients showed hyaline cartilage of normal appearance following transplantation, whereas microfracture was frequently observed to result in surface fibrillation and soft fibroelastic tissue. At 10-year follow-up, there were 4 failures (14%) in the OAT group and 11 failures (38%) in the microfracture group. (7) The Tegner scores decreased in both groups over time, but remained significantly better following OAT than microfracture. In the subgroup of patients who were younger than 25 years of age at the time of surgery, 15 of 20 patients (75%) in the OAT group and 8 of 22 patients (37%) in the microfracture group maintained the same level of activity (competitive athletes or frequently sporting) as before the injury. The level of sporting activity was reported to decrease in older patients because of age or other reasons not related to their knee.

Another report by Gudas and colleagues was a comparison of mosaicplasty versus microfracture or debridement. One hundred and two patients with lesions associated with anterior cruciate ligament (ACL) injury were randomized to one of the 3 procedures in association with ACL repair. (8) A matched control group of 34 patients with ACL injury but no articular cartilage lesion was included for comparison. The postoperative rehabilitation protocol was the same for the 3 treatment groups. At a mean 36.1-month follow-up, patients were evaluated with the International Knee Documentation Committee (IKDC) score, Tegner activity score, and clinical assessment. All groups showed a significant improvement in the IKDC score compared to before surgery. Patients without cartilage lesions had IKDC subjective scores that were significantly better than patients with cartilage lesions. For the 3 groups of patients with cartilage lesions, the mosaicplasty group's IKDC subjective knee evaluation was significantly better than the microfracture or debridement groups, although the differences between the groups were modest. Tegner activity scores were similar for the mosaicplasty and microfracture groups (7.1 and 6.9, respectively), and slightly lower for the debridement group (6.2).

Gudas and colleagues also published a randomized trial of osteochondral transplantation (n=25) versus microfracture (n=25) in children 12 to 18 years of age (mean of 14.3 years). (9) Only children with grade 3 or 4 osteochondritis dissecans (OCD) defects of the femoral condyles were included in the study. The OCD defects were between 2 and 4 cm2 in area, and the mean duration of symptoms was 24 months. Follow-up was obtained in 94% of patients. After 1 year, the proportion of excellent to good outcomes was similar for the 2 groups (92% for osteochondral transplantation vs. 86% for microfracture). However, after a mean 4.2 years of follow-up (range 3 to 6 years), the microfracture group showed 9 failures (41% of 22). In comparison, there were no failures in the osteochondral transplantation group, and good to excellent outcomes were obtained in 83% of the children. Magnetic resonance imaging (MRI) at a mean 18 months after the operation showed no evidence of graft loosening or migration with excellent or good repair in 19 of 21 children (91%). In comparison, blinded evaluation showed excellent or good repair in 10 of 18 children (56%) after microfracture.

Krych et al. reported a retrospective comparison of 96 patients treated with either mosaicplasty or microfracture for articular cartilage defects of the knee. (10) Outcomes were measured annually at 1, 2, 3, and 5 years. At the latest follow-up, there was no significant difference between the 2 groups in the Short Form (SF)-36 physical component, the Knee Outcome Survey activities of daily living, or IKDC scores. The mosaicplasty group showed a greater improvement in the Marx Activity Rating Scale at the 2-, 3-, and 5-year follow-up.

Osteochondral Autografts in Comparison with Autologous Chondrocyte Implantation: There are several randomized controlled trials that compare outcomes following treatment with osteochondral autografts or ACI.

Bentley and colleagues randomized 100 consecutive patients with symptomatic lesions of the knee (average 4.7 cm2, range, 1 to 12 cm2) to ACI or mosaicplasty. (11) 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 7 years. Clinical assessment at 1 year showed excellent or good results in 98% of the ACI patients and 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 both the relatively large lesion size and the unusual prominent placement of the plugs in this study, which was intended to allow contact with the opposite articular surface. With 6 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. (12)

Dozin et al. reported results from a multicenter randomized clinical trial in which ACI was compared to mosaicplasty. (13) Forty-four individuals (61% male, 39% female) age 16–40 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 6 months after undergoing arthroscopic debridement. 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, 5 who did not show up at the presurgery examination and could not be further traced, and 2 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 post-surgery 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 debridement (intention-to-treat analysis), the percentages of patients who achieved complete success were 89% (16 of 18 evaluable cases) in the mosaicplasty arm versus 68% (13 of 19 evaluable cases) in the ACI arm (test for trend p=0.093). The high rate of spontaneous improvement after simple debridement raises questions about the appropriateness of additional surgical intervention in patients with small lesions similar to those included in this trial.

Horas and colleagues reported 2-year follow-up on a study of 40 patients (between 18 and 42 years of age) with an articular lesion of the femoral condyle (range of 3.2 to 5.6 cm2) who were randomly assigned to undergo either autologous chondrocyte implantation or osteochondral autografting. (14) Eleven (28%) had received prior surgical treatment. The authors reported that both treatments resulted in an improvement in symptoms (85% of each group), although those in the osteochondral autografting group responded more quickly. Histomorphologic evaluation of 5 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.

Autologous Minced Cartilage: In 2011, Cole et al. reported a multicenter trial with 29 patients (out of 582 screened) randomized in a 1:2 ratio to microfracture or Cartilage Autograft Implantation System (CAIS). (15) In the single-stage CAIS procedure, autologous hyaline cartilage was harvested, minced, affixed on a synthetic absorbable scaffold, and then fixed on the lesion site with absorbable staples. At baseline, there were no significant differences between groups in the duration of symptoms, International Cartilage Repair Society (ICRS) grade, and area and depth of the chondral defect. There was a difference in the gender and work status of the 2 groups. At 3 weeks and 6 months' follow-up, there were no significant differences in outcomes between the 2 groups, but at later time points, there were differences reported. The IKDC score was significantly higher in the CAIS group compared to the microfracture group at both 12 (73.9 vs. 57.8) and 24 (83.0 vs. 59.5) months. All subdomains of the KOOS (Knee Injury and Osteoarthritis Outcome Score - Symptoms and Stiffness, Pain, Activities of Daily Living, Sports and Recreation, Knee-related Quality of Life) were significantly increased at 24 months in the CAIS group compared with microfracture patients. Qualitative analysis of magnetic resonance imaging (MRI) at 3 weeks and 6, 12, and 24 months showed no differences in fill of the graft bed, tissue integration, or presence of subchondral cysts. Adverse events were similar for the 2 groups.

Observational Studies

There are a number of observational studies that provide additional information on outcomes, including longer follow-up, following treatment with osteochondral autografts and allografts.

Osteochondral Autografts: Ollat et al. reported a retrospective multicenter study from the French Society of Arthroscopy that included 142 patients and a mean follow-up of 8 years. (16) (The authors comment that this technique has been used extensively in France due to restrictive legislation on restoration techniques, including chondrocyte transfer.) The mean size of the lesion was 2.29 cm2, and the most common etiologies were osteochondral fractures (n=79) and OCD (n=61). The mean number of plugs was 4 (range, 1-14). Postoperative complications occurred in 19 patients (13%). Most patients (81.8%) were satisfied or very satisfied with the functional outcomes. There was a significant improvement in the ICRS, International Knee Documentation Committee (IKDC) function, and Hughston scores at follow-up. The factors for a good prognosis were found to be: male gender, location of the defect in the medial femoral condyle, OCD, deep, small defects, and a short interval before surgery. Obesity, smoking, work-related accidents, the level of sports practiced, the percentage of coverage of the defect, the number of plugs, and associated lesions did not have a statistically significant effect on the functional results in the final follow-up.

Laprell and Petersen reported 6- to 12-year follow-up from 29 of 35 patients (83%) with severe osteochondral defects (77% with OCD) who were treated by autologous osteochondral transplantation. (17) The average age of the patients at the time of surgery was 26 years. Clinical evaluation at an average 8 years after the procedure found 12 patients (41%) to be normal, 14 (48%) as nearly normal, and 3 (10%, all of whom refused correction of malalignment) as abnormal. No patient was assessed as severely abnormal. In contrast, no patients considered their functional status to be normal, 3 (10%) considered function to be nearly normal, 20 (69%) thought their function abnormal, and 6 (21%) considered their functional status to be severely abnormal.

Another report described 7-year follow-up on 30 patients who had been treated with autologous osteochondral transplantation for symptomatic grade III to IV chondral lesions (average 1.9 cm, range of 1.0 to 2.5 cm). (18) Nineteen patients received other procedures (ACL reconstruction, meniscectomy, medial collateral ligament repair) at the same time, and it is therefore not possible to assess the contribution of the osteochondral transplantation to the functional results reported. Magnetic resonance imaging at 7 years showed complete bone integration in 96% of patients, complete integration of the grafted cartilage in 75% of cases, complete filling of the cartilage defect in 63% of the patients, and congruency of the articular surface in "some" patients. Subchondral bone changes (edema or sclerosis) were noted in 71% of patients. The donor sites were filled with a tissue of different density than the surrounding bone, presumed to be fibrous tissue. No patients reported anterior knee pain. Non-painful patellar crepitus was observed in 3 (10%) patients.

Solheim and colleagues reported 5- to 9-year follow-up from 69 patients treated for articular cartilage defects of the femoral condyle (n=47), patella (n=18), or trochlea (n=4). (19) Exclusion criteria were joint space narrowing, axial malpositioning, ligament instabilities, or inability to follow the rehabilitation protocol. Four of the 73 patients (5%) who met the study criteria were not available for/or refused to participate in the long-term follow-up. In 23 patients (33%), second-look arthroscopy was performed due to insufficient improvement of symptoms between 1 and 5 years after the index procedure. Of these, 6 patients were found to have lost one or more of the transplanted grafts, while a new lesion surrounding the grafts was observed in another 6 patients; these were treated with microfracture and/or debridement. The study found significant improvement in Lysholm score and visual analogue scale (VAS) score for pain at 5- to 9-year follow-up, with 53 patients (77%) improved over the preoperative condition. Results were not reported by location of the index lesion.

Nho et al. reported average 29-month follow-up following patellar resurfacing with osteochondral autografts in 22 patients. (20) Indications for surgery were patellofemoral malalignment, isolated cartilage lesion, OCD, or patellar dislocation. Concomitant procedures, including patellar realignment, were performed according to surgeon preference. The mean lesion size was 1.6 cm2, filled with an average 1.8 plugs per defect. The International Knee Documentation Committee (IKDC) score improved from 47 preoperatively to 74 at follow-up. The activity of daily living score increased from 60 preoperatively to 85 at follow-up. There was a trend toward greater improvements in the 11 patients who did not undergo concomitant distal realignment of the patella than for the 9 patients who had distal realignment along with osteochondral autografting.

Osteochondral Allografts: Long-term outcomes with osteochondral allografting have been reported in case series. Emmerson et al. reported mean 7.7 year follow-up (range 2-22 years) from 66 knees of 64 patients who underwent fresh osteochondral allografting for the treatment of OCD of the femoral condyle. (21) All patients had undergone previous surgery, with an average of 1.7 prior surgeries on each knee. The mean allograft size was 7.5 cm2. One knee was lost to follow-up. Of the remaining 65 knees, 10 patients (15%) underwent reoperation, 47 (72%) were rated good to excellent and 8 (13%) were rated fair to poor. Kaplan-Meier survival analysis demonstrated 91% graft survival at 5 years and 76% graft survival at 10 and 15 years. The mean D'Aubigne and Postel score improved from 13.0 (fair) preoperatively to 16.4 (good) at the most recent follow-up. Subjective knee function improved from a mean of 3.4 to 8.4 on a 10-point scale.

Gross and colleagues reported minimum 5-year follow-up on a series of 60 patients who received femoral condylar grafts and 65 patients who received tibial plateau grafts for knee defects. (22) Eligible recipients of allografts were younger than 60 years and had traumatic unipolar osteochondral defects of at least 3 cm in diameter and 1 cm deep. If the meniscus was also significantly damaged, it was resected and replaced with allograft meniscus. Realignment of the involved leg was also performed to unload the graft. Patients were assessed preoperatively and postoperatively using the modified Harris Hip Score (HSS) score. If there was no outcome data in the database within the last 12 months, the patients were contacted and a follow-up visit was arranged or a questionnaire was administered by telephone. Referring physicians were also contacted to obtain recent radiographs of the knee. Follow-up was obtained on 86% of patients who received a femoral graft (average of 10 years) and 97% of patients with a tibial graft (average of 11.8 years). For the femoral grafts, 12 failed and required graft removal or conversion to total knee replacement. At the end of the study period, 48 of the 60 femoral grafts (80%) were in situ with an average HSS score of 83 out of 100. Kaplan-Meier survival analysis showed 95% graft survival at 5 years, 85% at 10 years, and 74% at 15 years. For the tibial grafts, 21 failed at a mean interval of 9.7 years. At the end of the study, 44 of 65 tibial grafts (68%) were in situ and functioning with an HSS score greater than 70 points. Survival analysis revealed 95% graft survival at 5 years, 80% at 10 years, and 65% at 15 years.

Ankle

One small randomized controlled trial and several case series have been identified on osteochondral autografting for lesions of the talus. The literature on osteochondral allografts for lesions of the talus consists mainly of small case series.

Osteochondral Autografts: Zengerink et al. published a systematic review of treatment of osteochondral lesions of the talus in 2010. (23) Fifty-one nonrandomized and 1 randomized trial were included in the review. Success rates averaged 85% for bone marrow stimulation, 87% for osteochondral autografting, and 76% for ACI. Because of the high cost of ACI and the knee morbidity seen with osteochondral autografting, the authors concluded that bone marrow stimulation is the treatment of choice for primary osteochondral talar lesions. A 2009 report examined the association between defect size and outcomes following marrow stimulation techniques in 120 ankles. (24) Eight ankles subsequently underwent osteochondral transplantation and 22 ankles were considered clinical failures (American Orthopaedic Foot and Ankle Society [AOFAS] Ankle-Hindfoot score <80). Linear regression suggested a cutoff defect size of 1.5 cm2 for marrow stimulation techniques, with an 80% failure rate compared to a 10.5% failure rate for ankles with a defect size less than 1.5 cm2. Three of 58 ankles (5.2%) with a defect area less than 1 cm2 showed clinical failure, while 7 of 37 ankles (18.9%) with a defect area between 1.0 and 1.5 cm2 had failed.

The sole controlled trial that has been identified randomized 32 patients with osteochondral lesions of the talus to chondroplasty, microfracture, or OAT. (25) This study found similar improvements (approximately 40 points) for the 3 treatment groups as measured by the AOFAS 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 2 patients following microfracture, and by 2 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).

A prospective, uncontrolled study of 32 patients who underwent open osteochondral autografting of the talus for osteochondritis dissecans was reported in 2012. (26) The osteochondral grafts were harvested from the ipsilateral knee and placed in the talus after medial maleolar osteotomy. At baseline, the average AOFAS score was 59.1. At a mean 16.8 months' follow-up (range, 12 to 24 months), the AOFAS score had improved to 87.9. All patients showed an improvement of at least 20 points. The Lysholm score, used to assess donor site morbidity, was 88 points at 6 weeks postoperatively and 98 points at 6 months. Two patients had persistent knee pain at the last follow-up.

In 2006, Scranton et al. reported a study of 50 consecutive patients with a type-V cystic talar defect who were treated with a single osteochondral graft (15 mm) taken from the ipsilateral knee. (27) Patients with larger lesions in which multiple allograft plugs were used were excluded from analysis. Thirty-two patients (64%) had undergone a previous surgical procedure on the ankle; further surgery was required in 17 patients (34%). When contacted at a mean of 36 months (range, 24 to 83) after the index procedure, 45 patients (90%) had a good to excellent score on the Karlsson-Peterson Ankle Score questionnaire. Two patients had severe degenerative changes and underwent arthrodesis.

In 2006, Kreuz et al. reported outcomes from a series of 35 patients who underwent osteochondral grafting from the ipsilateral talar articular facet (with or without osteotomy) following failed bone marrow stimulation. (28) Six of the patients had previously undergone osteochondral or cancellous bone grafting of the defect area. The mean lesion size was 6.3 mm. At a mean follow-up of 49 months (range 33 to 77 months), the AOFAS Ankle-Hindfoot score had improved from 54.5 (range 47–60) to 89.9 points (range 80-100).

In 2011, Imhoff and colleagues reported a retrospective review with long-term outcomes following osteochondral autografts of the talus in 28 consecutive patients. (29) The osteochondral grafts were harvested from the femoral condyles and malleolar osteotomies were performed whenever the osteochondral defect could not be reached from the anterior incision. One patient was lost to follow-up, and 2 patients had a revision operation on the ankle. For 16 of the remaining 25 patients (64%), the autograft was the first line of treatment, and in 9 patients (36%), it was a second surgical intervention. Between baseline and average 7 years' follow-up (range, 53-124 months), the AOFAS score increased from 50 to 78 points, the Tegner score increased from 3.1 to 3.7, and the VAS for pain decreased from 7.8 to 1.5. Patients who had transplant as a second procedure had significantly worse AOFAS (62 vs. 87) and Tegner scores (2.0 vs. 4.6) and higher VAS scores (3 vs. 0.6 – all respectively).

Hangody et al. reported 2- to 7-year follow-up in 36 consecutive patients treated with osteochondral autografting for OCD of the talus. (30) Most of the patients had previous surgical interventions and presented with Stage III or IV lesions (completely detached or displaced fragment). The average size of the defect was 1 cm, and the average number of grafts per patients was 3 (range, 1-6). At mean follow-up of 4.2 years, ankle function measured by the Hannover scoring system showed good to excellent results in 34 cases (94%). Examination by radiograph, computed tomography (CT), and magnetic resonance imaging (MRI) showed incorporation into the recipient bed and congruency of the articular surface.

In 2011, Liu et al. reported osteochondral autografting in 16 patients for acute osteochondral fractures of the talar dome associated with an ankle fracture. (31) Ankle radiographs were taken at 2, 6, and 12 weeks postoperatively and every 3 months after fracture healing. MRI was performed after 12 months and at the latest follow-up. At an average 36-month follow-up (range, 21–48 months), the AOFAS score was 95.4 (range, 86-100). At the latest follow-up, there was no radiographic evidence of post-traumatic arthritis, and MRI showed bony integration and articular congruity of the talar dome in 93.7% of the osteochondral grafts.

Donor Site Morbidity: One study evaluated donor-site morbidity in 11 of 15 patients who had undergone graft harvest from the knee (mean of 2.9 plugs) for treatment of osteochondral lesions of the talus. (32) At an average 47-month follow-up (7–77 month range), 5 patients were rated as having an excellent Lysholm score (95–100 points), 2 as good (84–94), and 4 as poor (64 or less). Reported knee problems were instability in daily activities, pain after walking 1 mile or more, having a slight limp, and difficulty squatting. Hangody et al. reported that some patients had slight or moderate complaints with physical activity during the first postoperative year, but there was no long-term donor site pain in a series of 36 patients evaluated 2-7 years after osteochondral autografting. (30) A 2009 report from Europe described osteochondral autografting for lesions of the talus in 200 patients, 112 of whom had been followed up for a minimum of 2 years. (33) The focus of this study was to determine factors contributing to donor-site morbidity in the knee, rather than outcomes for the talus. The number of grafts, size of the transplanted plugs, and patient age were not related to donor-site morbidity. Body mass index (BMI) was found to be significantly associated with knee scores, with a decrease in Lysholm score by 1 point (1%) for each point increase in BMI. Interpretation of these results is limited by the lack of preoperative assessment of knee pain and function.

Osteochondral Allografts: Use of allografts for large defects of the talus has been reported in case series. Due to the relatively rare occurrence of this condition, most series have fewer than 20 patients.

The largest series is from Bugbee et al., who reviewed outcomes of 86 ankles (82 patients) treated with bipolar fresh osteochondral allografts for arthritis of the tibiotalar joint. (34) All patients had declined arthrodesis. Patients who did not present for follow-up were contacted via telephone and/or mail to obtain subjective outcomes. At a mean follow-up of 5.3 years (range, 2 to 11), 36 ankles (42%) had undergone additional surgery. Twenty-five ankles (29%) were considered clinical failures (i.e., revision allograft, conversion to total ankle arthroplasty, arthrodesis, or amputation) and 11 ankles (13%) had undergone operations that did not involve graft removal. Radiographic evaluation categorized 29 of 63 ankles (46%) as failures, with graft collapse observed in 11 of the 29 (38%). Survivorship of the osteochondral allograft estimated by Kaplan-Meier analysis was 76% at 5 years and 44% at 10 years. For patients who did not undergo additional surgery, 62% were classified as having excellent to good results, 26% as fair, and 12% as poor.

In 2012, Haene et al. reported a prospective study of fresh talar osteochondral allografts in 16 patients (17 ankles) with large osteochondral lesions of the talus. (35) All but one of the ankles had previously undergone single or multiple procedures. Computed tomography (CT) at an average follow-up of 4.1 years (range, 2 to 6 years) identified failure of graft incorporation in 2 ankles, osteolysis in 5, subchondral cysts in 8, and degenerative changes in 7 ankles. Clinically, 5 ankles (29%) were considered failures, and 2 (12%) had poor outcomes requiring additional

surgery. Ten ankles (59%) had good to excellent results based on validated outcome scores and clinical history.

Berlet et al. reported a 2011 prospective study with minimum follow-up of 2 years in 12 patients who had received an osteochondral allograft for talar defects. (36) In another patient, the graft had failed and was not included in the analysis. All patients had failed at least one prior surgical treatment and had a mean lesion size of 1.5 cm2. At follow-up (mean 3.3 years), AOFAS Ankle-Hindfoot scores improved from 61 at baseline to 79. There was a trend toward improvement in the physical or mental health components of the Short-form (SF)-12 Health Survey, although the study was underpowered to detect a significant difference. Radiographs and MRI performed yearly showed radiolucencies in 3 grafts (25%), edema in 4 (33%), and failure to incorporate for 1 graft.

El-Rashidy et al. reported a retrospective review of 38 of 42 total patients who were treated with osteochondral allografts. (37) All patients had failed conservative management and had a mean lesion size of 1.5 cm2. Grafts were harvested from a similar anatomic location on the donor talus to match the contour and surface anatomy of the recipient bed. The average duration of follow-up was 38 months. Including scores from 4 patients (10.5%) in whom graft failure occurred, the AOFAS Ankle-Hindfoot score improved from 52 to 79 points and VAS improved from 8.2 to 3.3 points. Patient satisfaction with the outcome was rated as excellent, very good, or good by 28 of the 38 patients (74%) and as fair or poor by 10 patients (26%). Of the 15 patients who had postoperative MRI, 5 (33%) had signs of graft instability.

Raikin published results from a series of 15 patients who underwent fresh matched osteochondral allograft transplantation for talar lesions with a volume greater than 30 cm3. (38) At an average 54 months after surgery (minimum of 2 years), mean VAS for pain had improved from 8.5 to 3.3 and the mean AOFAS Ankle-Hindfoot score had improved from 38 to 83 points. Two ankles had undergone conversion to fusion. Radiographic analysis revealed some evidence of collapse or resorption in 10 of the 15 ankles (67%).

Gortz et al. reported on a series of 11 patients (12 ankles) who underwent fresh osteochondral allografting for unipolar lesions of the talus. (39) Patients had undergone an average of 1.8 prior surgeries (range, 1 to 5). The average graft size was 3.6 cm2, which was an average of 40.5% of the talar surface. At a mean 38-month follow-up (range, 24 to 107 months) 2 of the ankles had failed and undergone revision or fusion. For the remaining 10 patients, the mean Olerud-Molander Ankle Score (OMAS) improved from a score of 28 to 71. Outcomes were categorized at good to excellent in 5 ankles (42%), fair in 3 (25%), and poor in 2 (17%). All patients demonstrated radiographic union by 6 months, with an overall graft survival rate of 83%.

Allogeneic Minced Cartilage: Bleazey and Brigado conducted a retrospective review of 7 patients who were treated with juvenile minced cartilage (DeNovo NT) together with sponge allograft. (40) All patients had failed conservative therapy (walking boot and physical therapy) and 4 patients had failed microfracture. Patients were evaluated with VAS for pain and activity at 6-month follow-up. All patients showed clinically significant improvement. Pain during walking decreased from an average of 7.7 at baseline to 1.9 at 6 months. Ability to walk 4 blocks improved from a score of 4.8 to 9.2.

Osteochondritis Dissecans of the Elbow

Osteochondral Autografts: OCD of the elbow is an uncommon condition that in its early stages can be treated nonoperatively or with simple fragment removal. (41) The literature on osteochondral autografts for advanced OCD of the elbow consists of small case series, primarily from Europe and Asia.

Iwasaki et al. reported minimum 2-year follow-up after osteochondral mosaicplasty for OCD of the elbow in 19 teenage athletes (mean age of 14 years) in Japan. (42) Preoperative symptoms consisted of pain with sports activities (n=19) patients, limited range of motion (n=5), and elbow catching (n=3). Indications for surgery included failure of more than 6 months of conservative treatment or evidence on plain radiographs and MRI of unstable lesions, such as displaced (n=7) or detached (n=12) fragments. The mean defect size was 1.5 cm2 (range, 0.5 to 3.0 cm2). Two independent observers assessed clinical findings at a mean of 45 months (range, 24–87 months); the radiologist was blinded to the clinical outcomes. Graft incorporation was observed in all patients, with nearly normal surface integrity of the articular cartilage and underlying bone in 18 patients. Eighteen of the 19 patients were classified with good to excellent results and were free from elbow pain. One patient was classified as fair with mild pain. Seventeen of the 19 patients, including all pitchers, returned to a competitive level of baseball. Mild donor site pain in the knee was reported in one patient.

Yamamoto et al. reported minimum 2-year follow-up (range, 24-63 months) from 18 juvenile baseball players with OCD of the elbow who were treated with osteochondral autografts. (43) Most of the patients had failed conservative management at another hospital in Japan. For grade 3 lesions (separated but in situ), 1 or 2 osteochondral plugs from the femoral condyle or patellofemoral joint were used to restore the articular surface or fix unstable OCD lesions. For grade 4 lesions (displaced fragment), 1 to 3 plugs were used to restore the articular surface. For the 9 patients with a grade 3 lesion, the subjective score was increased (from 75.0 to 95.6), but the objective score (from 88.3 to 88.3) did not change. For the 9 patients with a grade 4 lesion, both subjective (from 65.6 to 88.9) and objective scores (from 72.8 to 88.3) were increased significantly. At 6 months after surgery, all patients but one could throw a ball without pain.

In 2011, Ovesen et al. reported mean 30-month follow-up from 10 patients (age, 13-27 years) treated with osteochondral autografts from the lateral patellofemoral joint for advanced OCD of the elbow. (44) Eight of the patients (80%) were pain-free postoperatively. The Mayo Elbow Performance Score improved from a preoperative mean of 71 points to 93.5 points postoperatively. This compared to a score of 100 points for the nonoperated elbows. The Constant functional elbow score averaged 92.5 points for the operated elbow and 100 for nonoperated elbows. Postoperative radiographs and MRI/computed tomography showed incorporation and a normal contour of the subchondral cortex in all patients. No problems were observed regarding donor site pain.

Donor Site Morbidity: Nishimura et al. evaluated recovery of the donor knee after osteochondral autograft harvesting for capitellar OCD in 12 young athletes (age range, 12 to 17 years). (45) Pain and function were assessed at 1, 2, 3, 6, 12, and 24 months after the surgery. Knee joint effusion persisted in 7 of the 12 patients at 1 month, but none of the patients had effusion at 3 months. At 3 months, muscle power of the knee extensor was reduced in 8 patients compared to the preoperative level. At 12 months, 11 patients had reached preoperative knee extensor muscle

strength. All patients were pain-free at the donor site by 6 months (mean Lysholm score of 100) and returned to the previous competitive level of their sport.

Shoulder

Osteochondral Autografts: A European study reported 9-year follow-up after osteochondral autografting for cartilage defects of the shoulder in 7 patients. (46) One additional patient was reported to have had donor-site morbidity at the knee and chose not to return for follow-up. All of the plugs showed full integration with the surrounding bone, and 6 of 7 patients showed a congruent joint surface. The Constant score improved from 76 preoperatively to 90 points at 33 months and remained at 91 points at the 9-year follow-up. Subscores for pain and activities of daily living showed significant improvement at 33-month follow-up, with a very slight non-significant decline at 9-year follow-up. None of the patients required additional shoulder surgery.

Ongoing Clinical Trials

A search of the online site www.clinicaltrials.gov in May 2013 identified an industry-sponsored Phase IV (post-marketing) trial with Chondrofix® (NCT01410136). The study has an estimated enrollment of 50 patients who may have up to 2 cartilage lesions, each measuring less than 8 cm2, of the femoral condyle or trochlea. The study will follow patients through 60 months and has an estimated completion date of September 2017.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2008

In response to requests, input was received from 1 physician specialty society and 3 academic medical centers while this policy was under review in 2008. All reviewers agreed that osteochondral autografts and allografts are considered reasonable for patients with full-thickness chondral defects who meet specific criteria.

2011

In response to requests, input was received from 3 academic medical centers while this policy was under review in 2011. The clinical input was generally in agreement with the stated criteria for osteochondral grafting with the exception of the following: input was mixed regarding the requirement for an inadequate response to a prior surgical procedure, the size of the lesion, and the requirement for an absence of meniscal pathology. Input was also mixed regarding the investigational status of osteochondral grafts in other joints, including the patellar and talar joints, and for the use of autologous minced cartilage.

Summary

Evidence is sufficient to consider osteochondral allografting medically necessary as a technique to repair large (e.g., 10 cm2) full-thickness chondral defects of the knee caused by acute or repetitive trauma. Use of allografts for large defects of the talus has been reported in small case series. Evidence is insufficient to evaluate the effect of osteochondral allografting of the talus, or

other joints, on health outcomes. Therefore, osteochondral allografts for joints other than the knee are considered investigational.

For osteochondral autografting, only 3 relatively small randomized controlled trials from the same investigators in Europe have demonstrated improved clinical outcomes with osteochondral autografting of the knee when compared with microfracture. Data regarding the long-term viability of the transplanted osteochondral hyaline cartilage is also limited. However, controlled studies demonstrate similar benefit to other cartilage resurfacing procedures in appropriately selected patients, and a number of uncontrolled studies indicate that osteochondral autografts can improve symptoms in some patients with lesions of the femoral condyle who have failed prior surgical treatment. These patients have limited options. Therefore, based on the clinical input received and additional literature reviewed, it is concluded that osteochondral autografts may be considered an option for symptomatic full-thickness chondral lesions of the femoral condyle or trochlea caused by acute or repetitive trauma, in patients who have had an inadequate response to a prior arthroscopic or other surgical repair procedure. Recent evidence indicates that osteochondral grafting combined with meniscal allograft results in outcomes similar to either procedure performed alone; therefore combined procedures may be considered medically necessary.

Evidence is currently insufficient to evaluate the efficacy of osteochondral autografts for joints other than the knee, or to evaluate the efficacy of osteochondral autografts in comparison with other surgical repair procedures as a primary treatment of small lesions. Questions also remain about the natural history of asymptomatic lesions found incidentally during other surgical procedures. Controlled trials with longer follow-up are needed to demonstrate that use of osteochondral autografts as a primary treatment results in improved clinical outcomes in comparison with traditional marrow-stimulating procedures.

Minced cartilage techniques are in the early stages of development and testing and/or not approved in the U.S.; these are considered investigational.

Practice Guidelines and Position Statements

In 2010 and 2012 clinical practice guidelines on the diagnosis and treatment of osteochondritis dissecans (OCD), the American Academy of Orthopaedic Surgeons (AAOS) was unable to recommend for or against a specific cartilage repair technique in symptomatic skeletally immature or mature patients with an unsalvageable osteochondritis dissecans lesion. (47, 48)

The Interventional Procedures Advisory Committee of the United Kingdom's National Institute for Health and Clinical Excellence (NICE) conducted a 2005 review of mosaicplasty for knee cartilage defects. (49) The corresponding NICE Guidance on mosaicplasty, released in 2006, (50) stated that "There is some evidence of short-term efficacy, but data on long-term efficacy are inadequate."

CODING

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

CPT/HCPCS

27412	Autologous chondrocyte implantation, knee
27415	Osteochondral allograft, knee, open
27416	Osteochondral autograft(s), knee, open (eg, mosaicplasty) (includes harvesting of autograft[s])
28446	Open osteochondral autograft, talus (includes obtaining graft[s])
29866	Arthroscopy, knee, surgical; osteochondral autograft(s) (e.g., mosaicplasty) (includes harvesting of the autograft)
29867	Arthroscopy, knee, surgical; osteochondral allograft (e.g., mosaicplasty)
J7330	Autologous cultured chondrocytes, implant
S2112	Arthroscopy, knee, surgical for harvesting of cartilage (chondrocyte cells)
29870	Arthroscopy, knee, diagnostic, with or without synovial biopsy (separate procedure)
29871	Arthroscopy, knee, surgical; for infection, lavage and drainage
29873	Arthroscopy, knee, surgical; with lateral release
29874	Arthroscopy, knee, surgical; for removal of loose body or foreign body (eg., osteochondritis dissecans fragmentation chrondral fragmentation)
29875	Arthroscopy, knee, surgical; synovectomy, limited (eg., plica or shelf resection) (separate procedure)
29876	Arthroscopy, knee, surgical; synovectomy, major, 2 or ore compartments (eg., medical or lateral)
29877	Arthroscopy, knee, surgical; debridement/shaving of articular cartilage (chondroplasty)

DIAGNOSES

717.7	Chondromalacia of patella
732.7	Osteochondritis dissecans (knee)
733.90	Disorder bone and cartilage; unspecified
715.16	Primary localized osteoarthrosis, lower leg
715.26	Secondary localized osteoarthrosis, lower leg
715.36	Localized osteoarthrosis not specified whether primary or secondary, lower leg
715.96	Osteoarthrosis, unspecified whether generalized or localized, lower leg
716.16	Traumatic arthropathy, lower leg
718.86	Other joint derangement, not elsewhere classified, lower leg
719.86	Other specified disorders of lower leg joint
732.7	Osteochondropathies; Osteochondritis dissecans
959.7	Injury, other and unspecified; knee, leg, ankle, and foot

ICD-10 Diagnosis *(Effective October 1, 2014)*

M12.561	Traumatic arthropathy, right knee
M12.562	Traumatic arthropathy, left knee
M17.0	Bilateral primary osteoarthritis of knee

M17.11	Unilateral primary osteoarthritis, right knee
M17.12	Unilateral primary osteoarthritis, left knee
M17.2	Bilateral post-traumatic osteoarthritis of knee
M17.31	Unilateral post-traumatic osteoarthritis, right knee
M17.32	Unilateral post-traumatic osteoarthritis, left knee
M17.4	Other bilateral secondary osteoarthritis of knee
M17.5	Other unilateral secondary osteoarthritis of knee
M17.9	Osteoarthritis of knee, unspecified
M23.8x1	Other internal derangements of right knee
M23.8x2	Other internal derangements of left knee
M23.91	Unspecified internal derangement of right knee
M23.92	Unspecified internal derangement of left knee
M25.861	Other specified joint disorders, right knee
M25.862	Other specified joint disorders, left knee
M89.8x6	Other specified disorders of bone, lower leg
M89.9	Disorder of bone, unspecified
M93.261	Osteochondritis dissecans, right knee
M93.262	Osteochondritis dissecans, left knee
M94.261	Chondromalacia, right knee
M94.262	Chondromalacia, left knee
M94.8x6	Other specified disorders of cartilage, lower leg
S89.81xA	Other specified injuries of right lower leg, initial encounter
S89.81xD	Other specified injuries of right lower leg, subsequent encounter
S89.81xS	Other specified injuries of right lower leg, sequela
S89.82xA	Other specified injuries of left lower leg, initial encounter
S89.82xD	Other specified injuries of left lower leg, subsequent encounter
S89.82xS	Other specified injuries of left lower leg, sequela
S89.90xA	Unspecified injury of unspecified lower leg, initial encounter
S89.90xD	Unspecified injury of unspecified lower leg, subsequent encounter
S89.90xS	Unspecified injury of unspecified lower leg, sequela
S89.91xA	Unspecified injury of right lower leg, initial encounter
S89.91xD	Unspecified injury of right lower leg, subsequent encounter
S89.91xS	Unspecified injury of right lower leg, sequela
S89.92xA	Unspecified injury of left lower leg, initial encounter
S89.92xD	Unspecified injury of left lower leg, subsequent encounter
S89.92xS	Unspecified injury of left lower leg, sequela

REVISIONS

07-18-2006 effective 10-01-2006	Combined two policies - Osteochrondral Knee Allograft and Autograft – effective date February 1, 1996 from the BCBSKS web site with Autologous chondrocyte implantation, knee – effective date prior to January 1, 2002 from the MR guides.
01-14-2010	Updated Description Section.
	In Policy Section: ▪ Policy language changed to current version From: "Osteochondral autograft transplantation (OATS or mosaicplasty) and osteochondral allograft may be deemed medically necessary if the patient meets all of the following criteria:

	1. Failure to respond to non-operative treatment 2. Single sided of joint only; no “kissing” lesions 3. Lesion not more than 20 mm in greatest dimension 4. No radiologic evidence of degenerative arthritis and stable correctly aligned knee (or a patient less than 40 years of age with a realignment procedure) 5. Otherwise healthy non-elderly patient who can comply with the post-operative regimen including physical therapy And one of the following conditions is met: 1. Isolated full thickness lesion surrounded by healthy tissue or, 2. Stage 4 osteochondritis or, 3. Autograft (non allograft) recommended for avascular necrosis (AVN)/osteonecrosis of the femoral condyle. A. Autologous chondrocyte implantation, (ACI, ACT, Carticel) is indicated when all the following are met: 1. Age 15 to 55 years 2. A Grade III or Grade IV fill-thickness cartilage lesion on a weight-bearing surface if the femoral condyle (lateral, medial, or trochlear). The Outerbridge cartilage grading scale is employed, where Grade I is softening and swelling of the cartilage; Grade II shows fragmentation and fissuring of the superficial cartilage of less than one-half in diameter; Grade III has fragmentation and deeper fissuring of more than one-half inch; and Grade IV shows erosion of the cartilage down to the bone. Patients with osteochondritis dissecans are also candidates for ACI. 3. Lesion-related symptoms that limit activities of daily living, such as pain, swelling, and locking or catching of the joint. 4. A defect size of 1 square cm to 10 square cm. 5. A stable and aligned knee (which can be accomplished by surgery in conjunction with ACI). ACI/ACT is contraindicated with any one of the following: 1. A total meniscectomy 2. A history of anaphylactic reaction to gentamicin or sensitivities to materials of bovine origin (gentamicin and fetal calf serum are used in culturing the cells) 3. An infection, osteoarthritis, or inflammatory disease at the operative site. 4. Instability, abnormal loading, or tracking of the knee (unless it has been corrected). 5. Body Mass index (BMI) or 30 or greater. B. Experimental/Investigational: Use of autologous chondrocyte transplantation, osteochondral allograft transplantation, osteochondral autograft transplantation (OATS/mosaicplasty) for joints other than the knee is considered experimental/investigational, including, but not limited to, the ankle (talus)."
	Added Rational Section.
	In Coding Section: ▪ Added CPT codes: 27416, 28446 ▪ Deleted CPT codes: 0012T, 0013T
	Updated Revision and References Sections.

03-27-2014	Added Medical Policy and Coding Disclaimers.
	Updated Description section.
	In Policy section: ▪ In Item A, added #3, "Matrix-induced autologous chondrocyte implantation is considered experimental / investigational." ▪ In Item C, added #3, "Treatment of focal articular cartilage lesions with autologous minced cartilage is considered experimental / investigational." ▪ In Item C, added #4, "Treatment of focal articular cartilage lesions with allogeneic minced cartilage is considered experimental / investigational."
	Updated Rationale section.
	In Coding section: ▪ Added CPT codes: 29870, 29871, 29873, 29874, 29875, 29876, 29877. ▪ Added ICD-9 codes: 715.16, 715.26, 715.36, 716.16, 718.86, 719.86, 732.7, 959.7. ▪ Added ICD-10 Diagnosis codes *(Effective October 1, 2014)*
	Updated Reference section.

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