

Articular Cartilage Defect Repairs

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[Instructions for Use](#)

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Related Community Plan Policies
<ul style="list-style-type: none"> Surgery of the Knee Outpatient Surgical Procedures – Site of Service
Commercial Policy
<ul style="list-style-type: none"> Articular Cartilage Defect Repairs

Application

This Medical Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

State	Policy/Guideline
Indiana	Articular Cartilage Defect Repairs (for Indiana Only)
Kentucky	Articular Cartilage Defect Repairs (for Kentucky Only)
Louisiana	Articular Cartilage Defect Repairs (for Louisiana Only)
Nebraska	Articular Cartilage Defect Repairs (for Nebraska Only)
New Jersey	Articular Cartilage Defect Repairs (for New Jersey Only)
Pennsylvania	Articular Cartilage Defect Repairs (for Pennsylvania Only)
Tennessee	Articular Cartilage Defect Repairs (for Tennessee Only)

Coverage Rationale

ACT and Microfracture

Autologous chondrocyte transplantation (ACT) is proven and medically necessary for treating individuals with symptomatic full-thickness articular cartilage defects when all of the following criteria are met:

- The lesion is:
 - Greater than or equal to 2 squared centimeters
 - A result of acute or repetitive trauma
 - Single or multiple full thickness (Outerbridge Classification of grade III or IV) articular cartilage defect of the femoral condyle (medial, lateral or trochlea) and/or patella
- Knee is stable with intact menisci and ligaments
- Normal joint space and alignment confirmed by X-ray
- No active inflammatory or other arthritis, clinically and by X-ray
- Failed non-surgical conservative management (e.g., physical therapy, braces, and/or nonsteroidal anti-inflammatory drugs)

- Inadequate response to a prior arthroscopic or other surgical repair procedure (e.g., debridement, microfracture, drilling/abrasion arthroplasty, or osteochondral allograft/autograft)
- Individual is less than 55 years of age.

ACT is unproven and not medically necessary for treating individuals with the following indications due to insufficient evidence of efficacy:

- Treatment of joints other than the knee
- Growth plates have not closed
- History of partial-thickness defects
- Osteochondritis dissecans (OCD)
- Malignancy in the bone, cartilage, fat, or muscle of the treated limb
- Active infection in the affected knee
- Instability of the knee
- History of total meniscectomy
- Repeat ACT
- Active inflammatory degenerative, rheumatoid or osteoarthritis
- As initial or first line of surgical therapy

Microfracture repair to treat full and partial thickness chondral defects of the knee is proven and medically necessary when all of the following criteria are met.

- Symptomatic focal cartilage defects of the weight-bearing femoral condyles, tibial plateau, trochlea, and patella
- Defect has been identified by Magnetic resonance imaging (MRI), arthrogram or arthroscopy
- Outerbridge Grade 3-4 cartilage lesions
- Measure less than or equal to 4 square centimeters

Osteochondral Autograft and Allograft Transplantation

Osteochondral Autograft and Allograft transplantation is proven and medically necessary for treating individuals with cartilage defects of the knee. For medical necessity clinical coverage criteria for Osteochondral Autograft and Allograft Transplantation, refer to the InterQual® CP: Procedures:

- Arthroscopy or Arthroscopically Assisted Surgery, Knee
- Arthroscopy or Arthroscopically Assisted Surgery, Knee (Pediatric)
- Arthrotomy, Knee

Click [here](#) to view the InterQual® criteria.

Focal Articular Cartilage Repair

Focal articular cartilage repair is unproven and not medically necessary for treating individuals with any of the following due to insufficient evidence of efficacy:

- Osteochondral Autograft and Allograft transplantation for all other indications than those listed above
- Use of minced articular cartilage repair (whether synthetic, allograft or autograft) for treating osteochondral defects of the knee
- Use of cryopreserved viable Osteochondral Allograft products (e.g., Cartiform)
- Microfracture repair of the knee with any of the following indications:
 - Misalignment of the knee
 - Osteoarthritis
 - Systemic immune-mediated disease, disease-induced arthritis, or cartilage disease
 - Unwilling or unable to participate in post-operative physical rehabilitation program

Definitions

Allograft: The transplant of an organ, tissue, or cells from one individual to another individual of the same species who is not an identical twin (National Cancer Institute, 2017).

Allografts: Grafts of bone and cartilage harvested from a cadaver joint (may be fresh or cryopreserved), which is then implanted in the defect (AAOS, 2011).

Allograft Discs (e.g., Cartiform, ProChondrix CR): Wafer-thin allografts where the bony portion of the allograft is reduced. The discs contain hyaline cartilage with chondrocytes, growth factors, and extracellular matrix proteins. The graft is often used in conjunction with marrow stimulation purportedly allowing the host mesenchymal stem cells to infiltrate the graft from the underlying bone marrow after stimulation to provide dense extracellular matrix intended to enhance biomechanical stability and promote chondrogenesis (Hayes, 2018).

Autografts: Grafts of bone and cartilage harvested from either the patient's non-weight bearing surfaces (or surfaces that bear less weight), which is then implanted in the defect. Autografting is typically used to repair smaller defects. Tissue transplanted from one part of the body to another in the same individual (AAOS, 2011).

Autologous Chondrocyte Transplantation (ACT): Also referred to as autologous chondrocyte implantation (ACI), is a form of tissue engineering that creates a graft from a patient's own cartilage cells to repair defects in the articular cartilage. For first-generation ACI, the process involves removal, expansion (culture), and reimplantation of the patient's own chondrocytes under a piece of periosteal membrane that is excised from the tibia of the patient and sutured over the site of knee injury. With ACT, 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 the chondrocytes are separated (Camp et al., 2014).

Femoral Condyles: Large flared prominences on the distal end of the femur, identified as lateral and medial femoral condyles. They are covered with a thick layer of hyaline cartilage and articulate with the patella and the tibia at the knee joint.

Focal Defect: A defect of the articular cartilage due to any inflammation, injury, or trauma causing partial or full thickness cartilage defect in a well-defined focal area.

Juvenile Cartilage Allograft Tissue Implantation (e.g., DeNovo® NT Natural Tissue Graft): A tissue based articular cartilage graft that is processed from healthy donors less than 13 years of age and greater than 6 lbs. in weight. Donors are sourced through appropriate Organ and Tissue Procurement Organizations (OTPOs) (Hayes, 2018).

Matrix-Induced Autologous Chondrocyte Implantation (MACI) Procedure: MACI is a multistage procedure using autologous cultured chondrocytes on porcine collagen membrane. The procedure involves two surgeries. During an initial arthroscopic surgery, a biopsy of healthy cartilage is obtained. The cartilage sample is then sent to a laboratory where chondrocytes are isolated from the biopsy and expanded in vitro for a period of weeks. After an appropriate concentration of chondrocytes has been achieved, the chondrocytes are seeded onto a 3-dimensional matrix. Then, during a second surgical procedure (with arthroscopic or mini-arthrotomy approach), surgeons conduct a debridement of the damaged cartilage site and glue the seeded matrix to fill the entirety of the defect (Hayes, 2020).

Microfracture: Microfracture utilizes the body's healing potential and stem cells found in bone marrow to initiate cartilage growth. Cartilage is first debrided, and the calcified layer of bone is removed. Then the surgeon makes microfractures (small holes) in the subchondral bone exposing the bone marrow creating a blood clot in the chondral defect, ultimately recruiting mesenchymal stem cells that heal the defect with a fibrocartilaginous scar (Weber, 2018).

Minced Cartilage Repair: This procedure uses minced pieces of cartilage seeded over a scaffold which allows for even distribution of the chondrocytes to expand within the defect providing structural and mechanical protection (McCormick et al., 2008).

Mosaicplasty: A technique of creating an osteochondral autograft by harvesting and transplanting multiple small cylindrical osteochondral plugs from the less weight-bearing periphery of the patellofemoral area and inserting them into drilled tunnels in the defective section of cartilage (International Cartilage Regeneration and Joint Preservation Society, 2018).

Osteochondral Allograft (OCA): Involves transplantation of a piece of articular cartilage and attached subchondral bone from a cadaver donor to a damaged region of the articular surface of a joint. The goal of this procedure is to provide viable chondrocytes and supporting bone that will be sufficient to maintain the cartilage matrix and thereby relieve pain and reduce further damage to the articular surface of the joint (International Cartilage Regeneration and Joint Preservation Society, 2018).

Osteochondral Autograft Transfer System (OATS): This procedure is similar to mosaicplasty; however, it involves the use of a larger, single plug that usually fills an entire defect (e.g., those associated with anterior cruciate ligament (ACL) tears) (AAOS, 2011).

Osteochondral Autologous Transplant (OAT): Involves the placement of viable hyaline cartilage grafts obtained from the individual into a cartilage defect. The grafts are harvested from a non-weight bearing region of the joint during an open or arthroscopic procedure and then transplanted into a cartilage defect to restore the articular surface of the bone (AAOS, 2011).

Outerbridge Classification of Articular Lesions by Severity: Cartilage injuries are described and classified based on the location of injury, size of the injury, and the depth of the injury. Grade I–II are often termed mild to moderate and grades III–IV severe.

Grade	Modified Outerbridge Classification System
0	Normal cartilage
I	Softening and swelling
II	Partial-thickness defect with fissures on the surface that do not reach subchondral bone or exceed 1.5 cm in diameter
III	Fissuring to the level of subchondral bone in an area with a diameter more than 1.5 cm
IV	Exposed subchondral bone head

Source: *Campbell's Operative Orthopaedics*, 2007

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
27412	Autologous chondrocyte implantation, knee
27415	Osteochondral allograft, knee, open
27416	Osteochondral autograft(s), knee, open (e.g., 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[s])
29867	Arthroscopy, knee, surgical; osteochondral allograft (e.g., mosaicplasty)
29879	Arthroscopy, knee, surgical; abrasion arthroplasty (includes chondroplasty where necessary) or multiple drilling or microfracture

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HCPCS Code	Description
J7330	Autologous cultured chondrocytes, implant
S2112	Arthroscopy, knee, surgical for harvesting of cartilage (chondrocyte cells)

Description of Services

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. Cartilage healing and repair are affected by factors such as age, the degree and depth of

damage, associated joint instability, the underlying cause, previous meniscectomy, misalignment, and genetic factors. Only in limited situations can the damaged articular cartilage remodel and rebuild itself. Nonsurgical treatment options for damage to articular cartilage include weight loss, physical therapy, braces, orthotics, and pain management.

The knee joint is responsible for much of an individual's weight bearing capability because of its location at the end of two long bones, the femur, and the tibia. Weight is distributed throughout the knee joint, and pressure is placed on the femoral condyles, trochlea and patella during flexion and extension. Cartilage defects can be classified as chondral (cartilage loss) or osteochondral (OC) (cartilage plus bone loss) fractures. Chondral defects are categorized further into partial-thickness or full-thickness, the latter of which extends to the subchondral bone.

A focal articular cartilage lesion is an area of damage to cartilage and possibly the bone beneath it. When cartilage is damaged, over time it can deteriorate to the point where all of the cartilage is worn away and the bone beneath is affected. This is known as a full thickness defect. Grafting a small amount of bone and cartilage is one way to treat severe or large areas of damage. The graft material can be taken from a person's own tissue (this is known as an autograft) or from donor tissue (allograft).

Though the different articular cartilage procedures differ in the used technologies and surgical techniques, they all share the aim to repair articular cartilage. Various methods of cartilage repair have been investigated to achieve symptomatic relief and repair and restoration of articular defects. Some of these include Autologous Chondrocyte Transplantation (ACT), Osteochondral Grafting, and microfracture.

The autologous chondrocyte implantation (ACI) procedure, first introduced by Brittberg et al. (2018), has been the most widely used surgical procedure. This procedure aims to provide complete hyaline repair tissues for articular cartilage repair. Autologous chondrocyte implantation is a cell-based therapy that involves transplantation of autogenous cells into articular cartilage defects.

Osteochondral autografting (OCG) is a surgical procedure used to repair full-thickness chondral defects involving a joint. Mosaicplasty and osteochondral autograft transfer system (OATS) are systems used to perform this procedure.

Microfracture (MFX) is considered a first-line treatment for articular cartilage injury by many orthopedists. The procedure is performed by removing all damaged articular cartilage then making a series of small holes in the subchondral plate with awls or picks. This leads to bleeding, clot formation, as well as the introduction of marrow derived stem cells to the site. These stem cells are thought to mediate a fibrocartilaginous repair of the defect.

Clinical Evidence

Autologous Chondrocyte Transplantation

For individuals who have focal articular cartilage lesion(s) of the weight-bearing surface of the femoral condyles, trochlea, or patella who receive ACT, the evidence includes systematic reviews, randomized controlled trials (RCTs), and prospective observational studies. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, and quality of life. There is a large body of evidence on ACT for the treatment of focal articular cartilage lesions of the knee.

Migliorini (2020) published a systematic review evaluating the clinical outcomes of Autologous Chondrocyte Implantation (ACI) and Mesenchymal Stem Cell (MSC) injections for the treatment of focal chondral defects of the knee. Forty-three publications were included in the analysis of which eleven were RCTs and thirty-two were cohort studies, and pooled analyses were conducted in data from 3,340 procedures. ACI procedures were analyzed as either first-generation (p-ACI) in which a periosteal patch is harvested from the proximal tibia is utilized, second-generation (c-ACI) in which a graft containing type I/III collagen membrane is utilized, or third generation (m-ACI), in which autologous chondrocytes are seeded and cultured on type I and III collagen membranes is utilized. Twelve studies reported on p-ACI procedure, eight studies reported on c-ACI procedures, and 13 studies reported on m-ACI procedures. The authors conclude that ACI techniques are considered a concrete solution to treat focal chondral defects of the knee, and significant improvements from first- to third-generation techniques has been observed. This systematic review has some limitations. The majority of the included studies are retrospective or prospective studies, relegating the review to the inherent limitations of this level of evidence.

ECRI reviewed literature for Autologous Chondrocyte Implantation (ACI). They concluded that ACI is an established procedure to treat localized cartilage defects of the knee. The efficacy has been proven with multiple long term studies showing superiority for ACI against other surgical procedures (ECRI, 2020).

Hayes reviewed literature for Matrix-Induced Autologous Chondrocyte Implantation (MACI®) for repair of articular cartilage of the knee and concluded that there was sufficient published evidence to evaluate this technology. A large, moderate-quality body of evidence suggests that MACI is associated with improved symptoms, function, QOL, and ability to perform normal ADL for young and middle-aged and typically nonobese adults with symptomatic articular cartilage defects of the knee. Evidence also suggests that benefits may be durable beyond follow-up periods of 5 years. (Hayes, 2020).

According to a Hayes review a large body of overall low-quality evidence suggests that second- and third generation ACI are promising and reasonably safe treatments for articular cartilage defects of the knee over short- and intermediate-term follow up. Despite its large size, this body of evidence does not provide definitive conclusions concerning the efficacy and safety of second- and third-generation ACI relative to other procedures, including microfracture, mosaicplasty, and first-generation ACI, and additional high-quality studies are needed to confirm results of the available studies and to evaluate the long-term efficacy and safety of second-generation ACI and of all the different scaffold materials that have been used for third-generation ACI (Hayes 2018).

A systematic review by Sacolick et al (2019) examined the patient-reported outcomes, complication rates, and failure rates of autologous chondrocyte implantation and matrix-induced autologous chondrocyte implantation for osteochondritis dissecans in adults. Nine clinical studies were assessed (type not specified), with 179 (> 200 lesions) patients aged 18 to 49. Follow-up ranged from 6.5 months to 10 years. Results of patient reported outcomes showed that 85% of patients reported excellent or good outcomes. All patient-reported outcome measures used across the studies (International Knee Documentation Committee Form, Lysholm Knee Questionnaire, EuroQol Visual Analog Scale, Cincinnati Rating System, and the Tegner Activity Scale) reported statistically significant improvements from preoperative to final follow-up (p-values not reported). Of the studies that reported complication and failure rates for autologous chondrocyte implantation/matrix-induced autologous chondrocyte implantation, 23 (15.7%) of 146 patients reported complications, and the failure rate was 8.2%. Unplanned reoperations were necessary for 20.5% of patients. The study results showed that autologous chondrocyte implantation/matrix-induced autologous chondrocyte implantation had the best outcomes for active young males with small lesions. Older adults and less active individuals, as well as those with lesions > 6 cm², did not fare as well. A limitation of this review was its lack of randomized trials with controls to compare to autologous chondrocyte implantation/matrix-induced autologous chondrocyte implantation.

Brittenberg et al., (2018) conducted a 5-year follow-up of the SUMMIT (Superiority of MACI Implant Versus Microfracture Treatment) clinical trial conducted at 14 study sites in Europe. Of the 144 patients randomized in the SUMMIT trial, 128 signed informed consent and continued observation in the Extension study: 65 MACI (90.3%) and 63 microfracture (87.5%). The improvements in Knee Injury and Osteoarthritis Outcome Score (KOOS) Pain and Function domains previously described were maintained over the 5-year follow-up. Five years after treatment, the improvement in MACI over microfracture in the co-primary endpoint of KOOS pain and function was maintained and was clinically and statistically significant. Improvements in activities of daily living remained statistically significantly better (in MACI patients, with quality of life and other symptoms remaining numerically higher in MACI patients but losing statistical significance relative to the results of the SUMMIT 2-year analysis. Magnetic resonance imaging (MRI) evaluation of structural repair was performed in 120 patients at year 5. As in the 2-year SUMMIT (MACI00206) results, the MRI evaluation showed improvement in defect filling for both treatments; however, no statistically significant differences were noted between treatment groups. The authors concluded that symptomatic cartilage knee defects 3 cm² or larger treated with MACI were clinically and statistically significantly improved at 5 years compared with microfracture treatment. No remarkable adverse events or safety issues were noted in this heterogeneous patient population.

In 2017, the National Institute for Health Research (NIHR) reported on a systematic review assessing the clinical effectiveness ACI in the knee. The NIHR review focused on reports from previous systematic reviews including adults with symptomatic articular cartilage defects in the knee published between 2004 and 2014. Twelve systematic reviews including 19 studies (11 RCTs) were selected. The main comparator of interest was microfracture and four trials were identified that compared second- and third generation ACI with microfracture. One of the trials shared selected results with the NIHR reviewers but no results have been published. In summary, both Matrix Autologous Chondrocyte Transplantation (MACI®) and ChondroCelect were more clinically effective than microfracture for the outcomes of reductions in pain and improvements in function on the Knee Injury and Osteoarthritis Outcome Score (KOOS) over 2 to 5 years. Limited long-term data were available on the failure rates of

both ACI and microfracture after 5 years; data were available from six observational studies. The conclusions regarding follow-up after 5 years were primarily based on one of the observational studies judged to be the highest quality (Nawaz et al [2014], For ACI, failure rates were lower in patients who had no previous knee repair and in people with minimal evidence of osteoarthritis. Larger defect size was not associated with poorer outcomes in these patients. (Mistry, 2017).

Devitt et al. (2017) conducted a systematic review of randomized controlled trials to provide updates on the most appropriate surgical procedures for knee cartilage defects. Two reviewers independently searched three databases for RCTs comparing at least two different treatment techniques for knee cartilage defects. Strict inclusion and exclusion criteria were used to identify studies with patients aged between 18 and 55 years with articular cartilage defects sized between one and 15cm. Risk of bias was performed using a Coleman Methodology Score. Data extracted included patient demographics, defect characteristics, clinical outcomes, and failure rates. Ten articles were included (861 patients). Eight studies compared microfracture to other treatment; four to autologous chondrocyte implantation (ACI) or matrix induced ACI (MACI®); three to osteochondral autologous transplantation (OAT); and one to BST. Two studies reported better results with OAT than with microfracture and one reported similar results. Two studies reported superior results with cartilage regenerative techniques than with microfracture, and two reported similar results. At 10 years significantly more failures occurred with microfracture compared to OAT and with OAT compared to ACI. Larger lesions (> 4.5cm²) treated with cartilage regenerative techniques (ACI / MACI®) had better outcomes than with microfracture. Based on the evidence from this systematic review, the authors concluded that no single treatment can be recommended for the treatment of knee cartilage defects, and this highlights the need for further RCTs, preferably patient-blinded, using an appropriate reference treatment or a placebo procedure.

Ebert et al (2017) conducted a randomized controlled trial to investigate a 6 week return to full weight bearing after matrix-induced autologous chondrocyte implantation. A total of 37 knees (n = 35 patients) were randomly allocated to either an 8 week return to full WB that the authors considered current best practice based on the existing literature (CR group; n = 19 knees) or an accelerated 6-week WB approach (AR group; n = 18 knees). Patients were evaluated preoperatively and at 1, 2, 3, 6, 12, and 24 months after surgery, using the Knee Injury and Osteoarthritis Outcome Score, 36-Item Short Form Health Survey, visual analog pain scale, 6-minute walk test, and active knee range of motion. Isokinetic dynamometry was used to assess peak knee extension and flexion strength and limb symmetry indices (LSIs) between the operated and non-operated limbs. Magnetic resonance imaging (MRI) was undertaken to evaluate the quality and quantity of repair tissue as well as to calculate an MRI composite score. The results showed significant improvements observed in all subjective scores, active knee flexion and extension, 6-minute capacity, peak knee extensor torque in the operated limb, and knee extensor LSI, although no group differences existed. Although knee flexor LSIs were above 100% for both groups at 12 and 24 months after surgery, LSIs for knee extensor torque at 24 months were 93.7% and 87.5% for the AR and CR groups, respectively. The MRI composite score and pertinent graft parameters significantly improved over time, with some superior in the AR group at 24 months. All patients in the AR group (100%) demonstrated good to excellent infill at 24 months, compared with 83% of patients in the CR group. Two cases of graft failure were observed, both in the CR group. At 24 months, 83% of patients in the CR group and 88% in the AR group were satisfied with the results of their MACI® surgery. The authors concluded that patients in the AR group who reduced the length of time spent ambulating on crutches produced comparable outcomes up to 24 months, without compromising graft integrity.

Schuette et al. (2017) completed a systematic review to investigate mid- to long-term clinical outcomes of Matrix-assisted autologous chondrocyte transplantation (MACT) in the patellofemoral (PF) and tibiofemoral (TF) joints. A systematic review was performed by searching PubMed, Embase, and the Cochrane Library to find studies evaluating minimum 5-year clinical outcomes of patients undergoing MACT in the knee joint. Patients were evaluated based on treatment failure rates, magnetic resonance imaging, and subjective outcome scores. Study methodology was assessed using the Modified Coleman Methodology Score (MCMS). The results included 10 studies and 587 patients (two level 1, one level 2, one level 3, and six level 4 evidence) that met inclusion and exclusion criteria, for a total of 442 TF patients and 136 PF patients. Treatment failure occurred in 9.7% of all patients, including 4.7% of PF patients and 12.4% of TF patients. Weighted averages of subjective outcome scores, including Knee injury and Osteoarthritis Outcome Score, Short Form-36 Health Survey, and Tegner scores, improved from baseline to latest follow-up in both TF and PF patients. The mean MCMS was found to be 57.4, with a standard deviation of 18.5. The authors concluded that patients undergoing MACT in the knee show favorable mid- to long-term clinical outcomes, with a significantly higher treatment failure rate found in patients undergoing MACT in the TF joint compared with the PF joint. The authors identified some limitations to this study; level 1 to 4 evidence studies were included; although 587 patients were included in this review, not all patients were evaluated using the same outcome measures, and therefore sample sizes were limited for particular outcomes; Of the defects compared, there was a significant disparity in defect numbers

between those in the TF group (442) and those in the PF group; variation in different scaffold types, and overlapping of patients in studies with no mention of this in the individual studies.

DiBartola et al. (2016) performed a systematic review of the use of autologous chondrocyte implantation in the adolescent knee. PubMed, MEDLINE, SCOPUS, CINAHL, and Cochrane Collaboration Library databases were searched systematically. Outcome scores recorded included the International Knee Documentation Committee score, the International Cartilage Repair Society score, the Knee Injury and Osteoarthritis Outcome Score, the visual analog scale, the Bentley Functional Rating Score, the Modified Cincinnati Rating System, Tegner activity Lysholm scores, and return athletics. Outcome scores were compared among studies based on proportion of adolescents achieving specific outcome quartiles at a minimum 1-year follow-up. All five included studies were case series. The authors concluded that cartilage repair in adolescent knees using ACI provides success across different clinical outcomes measures. The only patient- or lesion-specific factor that influenced clinical outcome was the shorter duration of preoperative symptoms. The findings are limited by lack of comparison group.

Oussedik et al (2015) performed a systematic review of the treatment of articular cartilage lesions of the knee by microfracture or ACI to determine the differences in patient outcomes after these procedures. These investigators searched PubMed/Medline, Embase, and The Cochrane Library databases in the period from January 10 through January 20, 2013 and included 34 articles in this qualitative analysis. All studies showed improvement in outcome scores in comparison with baseline values, regardless of the treatment modality. The authors concluded that microfracture appeared to be effective in smaller lesions and are usually associated with a greater proportion of fibrocartilage production, which may have an effect on durability and eventual failure. Autologous chondrocyte implantation is an effective treatment that may result in a greater proportion of hyaline-like tissue at the repair site.

Ebert et al. (2015) conducted a prospective clinical and radiologic evaluation of patellofemoral matrix-induced autologous chondrocyte implantation. They prospectively evaluated the clinical and radiologic outcome of MACI® in the patellofemoral joint. In 47 consecutive patients undergoing patellofemoral MACI®, clinical (Knee injury and Osteoarthritis Outcome Score, 36 Item Short Form Health Survey, visual analog scale for pain, 6-minute walk test, knee range of motion, and strength assessment) and magnetic resonance imaging (MRI) assessments were undertaken before and 3, 12, and, 24 months after surgery. The MRI was performed to assess graft infill and determine an overall MRI composite score. Results were analyzed according to (1) the patient sample overall and (2) after stratification into four subgroups per implant location (patella or trochlea) as well as whether or not adjunct tibial tubercle transfer for patellofemoral malalignment was required. The overall patient sample, as well as each of the four procedural subgroups, demonstrated clinically and statistically significant improvements over time for all clinical scores. Graft infill and the MRI composite score also demonstrated statistically significant improvements over time, with no evidence of a main effect for procedure group or interaction between procedure group and time. At 24 months after surgery, 40.4% of patients exhibited complete graft infill comparable with the adjacent native cartilage, with a further 6.4% demonstrating a hypertrophic graft. A further 31.9% of patients exhibited 50% to 100% tissue infill, and 17% demonstrated < 50% tissue infill. Two patients (4.3%) demonstrated graft failure. At 24 months after surgery, 85% of patients were satisfied with the results of their MACI® surgery. The authors concluded that these results demonstrate that MACI® provides improved clinical and radiologic outcomes to 24 months in patients undergoing treatment specifically for articular cartilage defects on the patella or trochlea, with and without concurrent realignment of the extensor mechanism if required. The authors identify a number of limitations to this study; there is currently no agreement on a gold standard PRO measure for the evaluation of cartilage repair surgery; employed the 6-minute walk test as a basic measure of function, and while this test has been used in ACI patients it has not been validated; the MOCART scoring tool has not been validated against arthroscopic or histologic repair tissue findings. The findings are further limited by lack of comparison group.

Saris et al.(2014), conducted SUMMIT trial (Superiority of MACI implant versus Microfracture Treatment in patients with symptomatic articular cartilage defects in the knee), a Phase 3 two year, prospective, multicenter, randomized, open-label, parallel-group study that enrolled a total of 144 patients, ages 18 to 54 years, with at least one symptomatic Outerbridge Grade III or IV focal cartilage defect on the medial femoral condyle, lateral femoral condyle, and/or the trochlea co-primary efficacy endpoint was change from baseline to Week 104 for the subject's Knee injury and Osteoarthritis Outcome Score (KOOS) in 2 subscales: Pain and Function (Sports and Recreational Activities [SRA]). Patients from the two-year SUMMIT study also had the option to enroll in a three-year follow-up study (extension study). The majority of the patients who completed the SUMMIT study also participated in a three-year extension study. The FDA concluded that the overall efficacy data support a long-term clinical benefit from the use of the MACI implant in patients with cartilage defects of the knee.

Zhang et al. (2014) conducted a study aimed to evaluate whether MACI® is a safe and efficacious cartilage repair treatment for patients with knee (patella or trochlear) cartilage lesions. The primary outcomes were the Knee Injury and Osteoarthritis Outcome Score (KOOS) domains and magnetic resonance imaging (MRI) results, compared between baseline and postoperative months 3, 6, 12, and 24. A total of 15 patients (20 knees), with an average age of 33.9 years, had a mean defect size of 4.01 cm². By 6-month follow-up, KOOS results demonstrated significant improvements in symptoms and knee-related quality of life. MRI showed significant improvements in four individual graft scoring parameters at 24 months postoperatively. At 24 months, 90% of MACI® grafts had filled completely and 10% had good-to-excellent filling of the chondral defect. Most (95%) of the MACI® grafts were isointense and 5% were slightly hyperintense. Histologic evaluation at 15 and 24 months showed predominantly hyaline cartilage in newly generated tissue. There were no postoperative complications in any patients and no adverse events related to the MACI® operation. The authors concluded that this 2-year study has confirmed that MACI® is safe and effective with the advantages of a simple technique and significant clinical improvements. Further functional and mechanistic studies with longer follow-up are needed to validate the efficacy and safety of MACI® in patients with articular cartilage injuries. This study is limited by low number of participants and lack of randomization or control.

Gomoll et al. (2014) conducted a multicenter case series to show the repair of patellar cartilage defects with autologous chondrocyte implantation (ACI) can provide lasting improvements in pain and function. Patients were treated at 1 of 4 participating cartilage repair centers with ACI for cartilage defects in the patella; bipolar (patella + trochlea) defects were included as well. All patients were followed prospectively for at least 4 years with multiple patient-reported outcome instruments, including the International Knee Documentation Committee, Short Form - 12, modified Cincinnati Rating Scale, Western Ontario and McMaster Universities Osteoarthritis Index, and Knee Society scores. Treatment failure was defined as structural failure of the graft combined with pain requiring revision surgery. A total of 110 patients were available for analysis. As a group, they experienced both statistically significant and clinically important improvements in pain and function in all physical outcome scales. The International Knee Documentation Committee improved from 40 ±14 preoperatively to 69 ±20 at the last follow-up; the Cincinnati Rating Scale, from 3.2 ±1.2 to 6.2 ±1.8; and the Western Ontario and McMaster Universities Osteoarthritis Index, from 50 ±22 to 29 ±22. Ninety-two percent of patients stated that they would choose to undergo ACI again, and 86% rated their knees as good or excellent at the time of final follow-up. Nine patients (8%) were considered treatment failures, and 16% reported that their knees were not improved. The authors concluded that while cartilage repair in the patellofemoral joint is arguably not without its challenges, and autologous chondrocyte implantation remains off-label in the patella, when performed with attention to patellofemoral biomechanics, self-rated subjective good and excellent outcomes can be achieved in more than 80% of patients treated with ACI, even in a patient population with large and frequently bipolar defects such as the one presented in this study. However, final functional scores, although significantly improved, still reflected residual disability in this challenging group of patients. The findings are limited by lack of comparison group.

Harris et al. (2011) conducted a systematic review to compare autologous chondrocyte implantation with other cartilage repair or restoration techniques. Thirteen studies (randomized controlled trials or cohort studies only, n = 917) were included. Patients underwent autologous chondrocyte implantation (n = 604), microfracture (n = 271), or osteochondral autograft (n = 42). Three of seven studies showed better clinical outcomes after autologous chondrocyte implantation in comparison with microfracture after 1 to 3 years of follow-up, whereas one study showed better outcomes 2 years after microfracture and three other studies showed no difference in these treatments after 1 to 5 years. Clinical outcomes after microfracture deteriorated after 18 to 24 months (in 3 of 7 studies). Autologous chondrocyte implantation and osteochondral autograft demonstrated equivalent short-term clinical outcomes, although there was more rapid improvement after osteochondral autograft (2 studies). A defect size of > 4 cm (2) was the only factor predictive of better outcomes when autologous chondrocyte implantation was compared with a non-autologous chondrocyte implantation surgical technique. The authors concluded that all of the cartilage repair/restoration techniques provide short-term success.

Basad et al. (2010) compared the clinical outcomes of patients with symptomatic cartilage defects treated with matrix-induced autologous chondrocyte implantation (MACI®) or microfracture (MF). The 60 patients included were 18 to 50 years of age with symptomatic, post-traumatic, single, isolated chondral defects (4 - 10 cm²) and were randomized to receive MACI® (40) or MF (20). Patients were followed up 8 to 12, 22 to 26 and 50 to 54 weeks post-operatively for efficacy and safety evaluation. The difference between baseline and 24 months post-operatively for both treatment groups was significant for the Lysholm, Tegner, patient ICRS and surgeon ICRS scores. However, MACI® was significantly more effective over time (24 months versus baseline) than MF according to the Lysholm, Tegner, ICRS patient and ICRS surgeon scores. According to the authors, MACI® is superior to MF in the treatment of articular defects over 2 years.

A systematic review of nine different trials by Vasiliadis et al. (2010) found that ACI is an effective treatment for full thickness chondral defects of the knee, providing an improvement of clinical outcomes. The authors note, however, that there is insufficient data to say whether ACI is superior to other treatment strategies in full thickness articular cartilage defects of the knee. Additional studies are needed before specific clinical recommendations can be made.

Vavken and Samartzis (2010) conducted a systematic review of nine studies to compare ACI to other methods of cartilage repair or placebo. The authors found that there was no clear recommendation concerning the efficacy of ACI compared to other treatment options such as microfracture or osteochondral grafts. There is, however, some evidence for better clinical outcomes for ACI compared with osteochondral grafts and equivalent outcomes compared with microfracture. Additional studies are needed to further assess the benefits of ACI compared to other treatments.

Clinical Practice Guidelines

American Academy of Orthopaedic Surgeons (AAOS)

In an updated 2015 Appropriate Use Criteria for Management of Osteochondritis Dissecans of the Femoral Condyle, the AAOS stated that ACI "may be appropriate" for some patients with osteochondritis dissecans but considers it "rarely appropriate" for most patients.

National Institute for Health and Clinical Excellence (NICE)

In 2018, NICE updated its 2005 guidance on the use of autologous chondrocyte implantation (ACI) of the knee:

(ACI) is recommended as an option for treating symptomatic articular cartilage defects of the femoral condyle and patella of the knee, only if:

- The person has not had previous surgery to repair articular cartilage defects;
- There is minimal osteoarthritic damage to the knee (as assessed by clinicians experienced in investigating knee cartilage damage using a validated measure for knee osteoarthritis); and
- The defect is over 2 cm².

German Cartilage Registry (KnorpelRegister DGOU)

In October 2013 the German Cartilage Registry (KnorpelRegister DGOU) was initiated in order to study indications, epidemiology and (clinical) outcome of different cartilage repair techniques. An evaluation of the registry baseline data was initiated to report common practices of cartilage repair surgery in Germany. A total of 1,065 consecutive patients who underwent surgical cartilage treatment of the knee have been included between October 1, 2013 and June 30, 2015. The authors concluded that the analysis of data from the German Cartilage Registry showed that the vast majority of cartilage repair procedures were applied in degenerative, non-traumatic cartilage defects. Experts in Germany appeared to follow the national and international guidelines in terms that bone marrow stimulation is applied in smaller cartilage defects while cell-based therapies are used for the treatment of larger cartilage defects. In patellar cartilage defects a trend towards the use of cell-based therapies has been observed (Niemeyer et al (2016).

Osteochondral Autograft Transplantation of the Knee

Evidence from the peer-reviewed published scientific literature, textbook and some professional societies support short to intermediate-term efficacy of osteochondral autograft transplant of the knee in specific patient subgroups.

A Hayes Medical Technology Directory report on the comparative effectiveness of mosaicplasty for the treatment of articular cartilage injuries does not recommend this procedure for children due to insufficient clinical evidence of safety and efficacy for this patient population. Results from a large body of moderate-quality evidence suggest that mosaicplasty may provide some benefits for patients with articular cartilage defects of the knee. However, the comparative long-term efficacy and safety of mosaicplasty is unclear, as the majority of controlled or comparative studies (13 of 14 studies) enrolled fewer than 100 patients, half of the studies involved less than 5 years of follow up, and only six studies reported complications separately for the treatment groups. (Hayes, 2020)

In a large-scale, systematic review and network meta-analysis, Zamborsky and Danisovic (2020) examined the most appropriate surgical interventions for patients with knee articular cartilage defects from the level I randomized clinical trials. Treatments were compared using network meta-analysis to boost the number of included studies per comparison. They studied 21 articles that included 891 patients. There were significantly higher failure rates in the microfracture (MF) group compared to autologous

chondrocyte implantation (ACI) group at 10-year follow-up. Individuals who underwent OAT had higher return-to-activity rates than those with MF. It should be noted that the KOOS was higher in patients who underwent characterized chondrocyte implantation or MACI compared to MF. Finally, there were no significant differences among the various interventions regarding re-intervention, biopsy types or adverse events (AEs). The authors concluded that cartilage repair techniques, other than MF, provided higher quality repair of tissue and had lower failure and higher return-to-activity rates. The authors stated that future studies continue to require longer follow-up periods and more representative populations to examine the safety and efficacy of these interventions.

According to the National Institute for Health and Care Excellence (NICE) guidance document on mosaicplasty for symptomatic articular cartilage defects of the knee, current evidence on the safety and efficacy of mosaicplasty for knee cartilage defects is adequate to support the use of this procedure, providing the procedure is done by surgeons experienced in cartilage surgery and with specific training in mosaicplasty for knee cartilage defects. Additionally, standard arrangements should be in place for clinical governance, consent, and audit. However, their Interventional Procedures Advisory Committee (IPAC) concedes that “the terms mosaicplasty and osteochondral autograft transfer refer to slight variations of the same procedure and may have been used interchangeably in the literature” that was reviewed to reach their conclusion (NICE 2018).

Hangody et al. (2010) evaluated if mosaicplasty is effective in returning elite athletes to participation in sports. The results of mosaicplasty were prospectively evaluated at 6 weeks, 3 months, 6 months, and yearly in 354 patients. Good to excellent results were found in 91% of femoral mosaicplasties, 86% of tibial, and 74% of patellofemoral; 92% of talar mosaicplasties had similar results. The investigators concluded that despite a higher rate of preoperative osteoarthritic changes in the athletic patients, clinical outcomes of mosaicplasty in this group demonstrated a success rate similar to that of less athletic patients. Higher motivation resulted in better subjective evaluation. Slight deterioration in results occurred during the 9.6-year follow-up. The authors stated that autologous osteochondral mosaicplasty may be a useful alternative for the treatment of 1.0 to 4.0 cm² focal chondral and osteochondral lesions in competitive athletes.

Osteochondral Allograft Transplantation

Knee

The current medical literature regarding osteochondral allografting of the knee shows that this procedure has demonstrated acceptable long-term results measured by reduction in pain, improved physical function, and sustained osteochondral graft viability. There is also sufficient evidence to support the use of osteochondral allograft of the knee in patients who are physically active, have failed standard medical and surgical treatments, and are considered too young for total knee arthroplasty.

Gortz et al. (2010) evaluated osteochondral allografts for treatment of steroid-associated osteonecrosis in 22 patients (28 knees). Patient average age was 24.3 years (range, 16 to 44 years). The mean graft surface area was 10.8 cm (2). The minimum follow-up was 25 months (mean, 67 months). Five knees failed. The graft survival rate was 89% (25 of 28). According to the authors, osteochondral allografting is a reasonable salvage option for osteonecrosis of the femoral condyles. Total knee arthroplasty (TKA) was avoided in 27 of the 28 of knees at last follow-up.

Gross et al. (2008) examined histologic features of 35 fresh osteochondral allograft specimens retrieved at the time of subsequent graft revision, osteotomy, or total knee arthroplasty (TKA). Histologic features of early graft failures were lack of chondrocyte viability and loss of matrix cationic staining. Histologic features of late graft failures were fracture through the graft, active and incomplete remodeling of the graft bone by the host bone, and resorption of the graft tissue by synovial inflammatory activity at graft edges. Histologic features associated with long-term allograft survival included viable chondrocytes, functional preservation of matrix, and complete replacement of the graft bone with the host bone. Given chondrocyte viability, long-term allograft survival depends on graft stability by rigid fixation of host bone to graft bone. According to the investigators, with the stable osseous graft base, the hyaline cartilage portion of the allograft can survive and function for 25 years or more.

Emmerson et al. (2007) evaluated 66 knees in 64 patients who underwent fresh osteochondral allografting for the treatment of osteochondritis dissecans. Mean follow-up was 7.7 years (range, 2 to 22 years). There were 45 men and 19 women with a mean age of 28.6 years (range, 15 to 54 years). All patients had undergone previous surgery. Forty-one lesions involved the medial femoral condyle, and 25 involved the lateral femoral condyle. All were osteochondritis dissecans type 3 or 4. The mean allograft size was 7.5 cm (2). One knee was lost to follow-up. Of the remaining 65 knees, 47 (72%) were rated good/excellent, 7 (11%) were rated fair, and 1 (2%) was rated poor. Ten patients (15%) underwent reoperation. The authors concluded that with greater

than 70% good or excellent results, fresh osteochondral allograft transplantation is a successful surgical treatment for osteochondritis dissecans of the femoral condyle.

Clinical Practice Guidelines

American Academy of Orthopaedic Surgeons (AAOS)

In an updated consensus statement, the AAOS states that skeletally immature patients, who have continued or progressing symptoms and signs of loosening, are unlikely to heal without treatment and may be at higher risk of severe osteoarthritis (osteoarthrosis) at an early age. Therefore, even in the absence of reliable evidence, symptomatic skeletally immature patients with salvageable unstable or displaced OCD lesions should be offered the option of surgery. However, no specific surgical procedures were recommended (AAOS 2015).

An AAOS information statement for use of musculoskeletal tissue allografts indicates that the AAOS believes that for appropriate patient's musculoskeletal allografts represent a therapeutic alternative. These tissues should be acquired from facilities that demonstrate compliance, use well-accepted banking methodology and follow Food and Drug Administration (FDA) Good Tissue Practices. The AAOS urges all tissue banks to follow rigorous national guidelines and standards and recommends the use of tissue from banks that are accredited by the American Association of Tissue Banks (AAOS 2011).

Osteochondral Autograft Transplantation

Elbow

There is insufficient evidence in the peer-reviewed, published scientific literature evaluating the use of osteochondral autograft transplantation to treat lesions of the elbow. Many of the trials consist of small patient populations, lack control or comparative groups and evaluate short-term outcomes (Shimada, et al., 2005; Tsuda, et al., 2005; Yamamoto, et al., 2006; Iwasaki, et al., 2006; Ansah, et al., 2007; Oveson, et al., 2011; Shimada, et al, 2012). Mid to long-term outcomes have been reported (Vogt, et al, 2011), however the sample population of this trial were small, and the study was not designed to be comparative. The results of some studies demonstrate improved pain scores in addition to radiograph confirmation of graft incorporation. The outcomes reported regarding pain, return to sports and elbow function were satisfactory however the authors noted further long-term clinical trials supporting efficacy are needed. Larger clinical trials evaluating long-term outcomes compared to conventional methods of treatment are needed to support widespread use of this procedure.

Talus

Evidence evaluating the use of autograft for osteochondral defects of the talus is still elusive. The use of osteochondral autograft in ankles is limited to retrospective and prospective case series and few randomized controlled trials, nonrandomized controlled trials involving small patient populations and published reviews. The evidence base is not as robust when compared to that evaluating the knee, although reported clinical outcomes extend short-to intermediate-term; on average two to eight years post-operatively. In general, the clinical outcomes have been mixed regarding improvement in postoperative pain and function, with some authors reporting high failure rates and the need for further surgery. Authors have acknowledged further well-designed studies with larger sample size are needed to assess improved long-term outcomes.

In a systematic review, Lambers et al. (2018) identified the most effective surgical treatment for talar osteochondral defects after failed primary surgery. These investigators carried out a literature search to find studies published from January 1996 till July 2016 using PubMed (Medline), Embase, CDSR, DARE and CENTRAL. A total of 21 studies (299 patients with 301 talar OCDs that failed primary surgery) were examined; eight studies were retrospective case series, 12 were prospective case series and there was one RCT. Because of the low level of evidence and the scarce number of patients, no methodologically proper meta-analysis could be performed. The authors concluded that multiple surgical treatments were used for talar osteochondral defects (OCDs) after primary surgical failure. More invasive methods were administered in comparison with primary treatment. No methodologically proper meta-analysis could be performed because of the low level of evidence and the limited number of patients. Thus, it was inappropriate to draw firm conclusions from the collected results. Besides an expected difference in outcome between the autograft transfer procedure and the more extensive procedures of mosaicplasty and the use of an allograft, neither a clear nor a significant difference between therapeutic options could be demonstrated. The authors stated that the need for sufficiently powered prospective studies in a randomized comparative clinical setting remains high. The findings of this systematic review could be used in order to inform patients regarding expected outcome of the various therapeutic options used after failed primary surgery.

Zengerink M, et al. (2010) – The aim of this study was to summarize all eligible studies to compare the effectiveness of treatment strategies for osteochondral defects (OCD) of the talus. For each treatment strategy, study size weighted success rates were calculated. Fifty-two studies described the results of 65 treatment groups of treatment strategies for OCD of the talus. Nine of the studies were for osteochondral transplantation (OATS). OATS scored success rates of 87%, respectively. However, due to great diversity in the articles and variability in treatment results, no definitive conclusions can be drawn. Further sufficiently powered, randomized clinical trials with uniform methodology and validated outcome measures should be initiated to compare the outcome of surgical strategies for OCD of the talus.

In 2004 Kolker et al. reported their concern as to the overall efficacy of the procedure when used in the treatment of full-thickness, advanced, osteochondral defects of the talar dome. Open bone grafting did not predictably improve symptoms and yielded poor results in the patient population studied. The authors have acknowledged further well-designed studies with larger sample size are needed to assess improved long-term outcomes (Balzer and Arnold, 2005; Scranton, et al., 2006 Imhoff et al., 2011, Liu et.al, 2011).

Clinical Practice Guidelines

American Orthopaedic Foot and Ankle Society (AOFAS)

In 2013 the AOFAS published a position statement regarding osteochondral transplantation for the treatment of osteochondral lesions of the talus. According to this position statement the AOFAS supports the use of osteochondral transplantation for the treatment of osteochondral lesions of the talus that have failed other management, especially for large diameter lesions and cystic lesions. To this end, the AOFAS considers osteochondral transplantation to be a treatment option with demonstrated improved outcomes. This position is based on multiple reports from the peer-reviewed scientific literature.

Minced Cartilage Repair

Minced cartilage techniques are either not approved in the United States and/or in the early stages of development and testing (e.g., particulated juvenile articular cartilage). Early results from case series appear to show similar outcomes compared with other treatments for cartilage defects, but these case series do not permit conclusions regarding the effect of this treatment on health outcomes. Further studies with a larger number of patients and longer follow-up are needed, especially randomized controlled trials that directly compare particulated juvenile articular cartilage with other established treatments.

Hayes reviewed literature for DeNovo NT Natural Tissue Graft for Articular Cartilage Repair of the Knee or Ankle. The authors concluded that there was very-low-quality body of evidence. This comprised small, poor- to very-poor-quality studies and is insufficient to draw conclusions regarding the balance of benefits and harms associated with DeNovo NT for articular cartilage repair. (Hayes, 2019).

Farr et al. (2014) performed a case study of twenty-five patients that were followed pre- and post-operatively through 2 years. Physical knee examinations, as well as multiple clinical surveys and MRI were performed at baseline and 3-, 6-, 12-, and 24-month intervals. In some cases, patients voluntarily underwent diagnostic arthroscopic surgery with cartilage biopsy at 2 years post-op to assess the histological appearance of the cartilage repair. Clinical outcomes demonstrated statistically significant increases at 2 years compared with baseline, with improvement seen as early as 3 months. MRI results suggested the development of normal cartilage by 2 years. Histologically, biopsied repair tissue was noted to be composed of a mixture of hyaline and fibrocartilage and there appeared to be excellent integration of the transplanted tissue with the surrounding native articular cartilage.

Farr et al (2012) noted that the DeNovo Natural Tissue is a novel treatment option for focal articular cartilage defects in the knee. In the laboratory and in animal models, DeNovo NT has demonstrated the ability of the transplanted cartilage cells to "escape" from the extracellular matrix, migrate, multiply, and form a new hyaline-like cartilage tissue matrix that integrates with the surrounding host tissue. In clinical practice, the technique for DeNovo NT is straightforward, requiring only a single surgery to affect cartilage repair. Clinical experience is limited, with short-term studies demonstrating the procedure to be safe, feasible, and effective, with improvements in subjective patient scores, and with magnetic resonance imaging evidence of good defect fill. The authors concluded that while this treatment option appears promising, prospective randomized controlled studies are needed to refine the indications and contraindications for DeNovo NT.

In 2011, Cole et al. reported on a multicenter trial with 29 patients (of 582 screened). Individuals were randomized in a 1:2 ratio to microfracture or Cartilage Autograft Implantation System (CAIS). In the single-stage CAIS procedure, autologous hyaline

cartilage was harvested, minced, affixed on a synthetic absorbable scaffold, and fixed on the lesion site with absorbable staples. At baseline, there were no significant differences between groups in the duration of symptoms, ICRS grade, and area and depth of the chondral defect. There was a difference in the sex and work status of the two groups. At 3-week and 6-month follow-ups, there were no significant differences in outcomes between the two groups, but, at later time points, there were differences reported. The IKDC score was significantly higher in the CAIS group compared with the microfracture group at both 12 (73.9 vs. 57.8) and 24 (83.0 vs. 59.5) months. All subdomains of the KOOS 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 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 two groups.

Microfracture Repair

In a comparative study, Solheim and colleagues (2020) examined survival of cartilage repair in the knee by microfracture or mosaicplasty osteochondral autograft transfer. The long-term failure rate (62% overall) was significantly higher in the microfracture (MFX) group compared with the OAT group. The mean time to failure was significantly shorter in the MFX group, 4.0 years compared with the OAT group, 8.4 years. In the OAT group, the survival rate stayed higher than 80% for the first 7 years, and higher than 60% for 15 years, while the survival rate dropped to less than 80% within 12 months, and to less than 60% within 3 years in the MFX group. The same pattern was found in a subgroup of patients of same age (less than 51 years) and size of treated lesion (less than 500 mm²). The non-failures (48%) were followed for a median of 15 years (1 to 18). The authors concluded that MFX articular cartilage repairs failed more often and earlier than the OAT repairs, both in the whole cohort and in a subgroup of patients matched for age and size of treated lesion, indicating that the OAT repair is the more durable.

Ossendorff et al (2019) conducted a study to compare the clinical and radiographical long-term outcome of microfracture (MFX) and first-generation periosteum-covered autologous chondrocyte implantation (ACI-P). All subjects (n = 86) who had been treated with knee joint ACI-P or microfracture (n = 76) with a post-operative follow-up of at least ten years were selected. Clinical pre- and post-operative outcomes were analyzed by numeric analog scale (NAS) for pain, Lysholm, Tegner, IKDC, and KOOS score. Radiographical evaluation was visualized by magnetic resonance imaging (MRI). Assessment of the regenerate quality was performed by the magnetic resonance observation of cartilage repair tissue (MOCART) and modified knee osteoarthritis scoring system (mKOSS). Relaxation time (RT) of T2 maps enabled a microstructural cartilage analysis. The results showed that MFX and ACI of 44 patients resulted in a good long-term outcome with low pain scores and significant improved clinical scores. The final Lysholm and functional NAS scores were significantly higher in the MFX group. The MOCART score did not show any qualitative differences. KOSS analysis demonstrated that cartilage repair of small defects resulted in a significant better outcome. T2-relaxation times were without difference between groups at the region of the regenerate tissue. The authors concluded that this study did not demonstrate coherent statistical differences between both cartilage repair procedures, and MFX might be superior in the treatment of small cartilage defects.

Shanmugaraj et al. (2019) systematically assessed the trends in surgical techniques, outcomes, and complications of cartilage restoration of the patellofemoral (PF) joint. Electronic databases were searched from January 1, 2007 to April 30, 2018. The Methodological Index for Non-randomized Studies (MINORS) was used to assess study quality. A two-proportion z test was used to determine whether the differences between the proportions of cartilage restoration techniques used from 2007 to 2012 and 2013 to 2018 were statistically significant. Overall, 28 studies were identified, including 708 patients (824 knees) with a mean age of 39.5 years and a mean follow-up of 39.1 months. The majority of patients were treated with ACI (45.5%) and MFX (29.6%). A significant increase in the use of the third generation ACI occurred with a simultaneous decreased usage of the conventional MFX over the last 5 years. The authors concluded that all techniques had significant improvements in clinical outcomes. The overall complication rate was 9.2%, of which graft hypertrophy was the most prevalent. Overall, the various cartilage restoration techniques reported improvements in patient reported outcomes with low complication rates. Definitive conclusions on the optimal treatment remain elusive due to a lack of high-quality comparative studies.

Orth et al. (2019) systematically reviewed and evaluated clinical data following microfracture treatment of knee articular cartilage defects. A systematic review was performed clinical trials on microfracture treatment, published between 2013 and 2018. Titles, abstracts, and articles were reviewed, and data concerning patient demographics, study design, pre-, intra-, and postoperative findings were extracted. Eighteen studies including 1,830 defects (1,759 patients) were included. Of them, 8 (59% of patients) were cohort studies without a comparison group. Overall study quality was moderate, mainly due to low patient numbers, short follow-up periods, and lack of control groups. Microfracture treatment of full-thickness articular cartilage defects was performed at 43.4 ±68.0 months of symptom duration. Postoperative assessment at 79.5 ±27.2 months revealed

failure rates of 11 to 27% within 5 years and 6 to 32% at 10 years. Imaging analysis was conducted in 10 studies; second-look arthroscopies were reported twice and revealed well integrated fibrocartilaginous repair tissue. The authors concluded that microfracture provides good function and pain relief at the mid-term and clinically largely satisfying results thereafter. Standardized, high-quality future study designs will better refine optimal indications for microfracture in the context of cartilage repair strategies.

In a case-control study, Weber et al. (2018) sought to retrospectively evaluate prospectively collected patient-reported outcomes (PROs) after microfracture, as well as determine patient-related and defect-related factors associated with clinical outcomes, and which factors predict the need for additional surgery. 101 patients with a mean defect size, $2.635 \pm 1.805 \text{ cm}^2$, between the ages of 10 and 70 years who underwent microfracture by the senior author for a focal chondral defect of the knee between January 1, 2005, and March 1, 2010, were eligible for study enrollment. (Patients were excluded if they underwent concomitant procedures that violated the subchondral bone). Functional outcomes were determined using preoperative and final follow-up PROs, including the Lysholm, International Knee Documentation Committee (IKDC), Knee injury and Osteoarthritis Outcome Score (KOOS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Short Form-12 (SF-12), and overall satisfaction scores. Patient-related factors (sex, age, body mass index [BMI]) and defect-related factors (lesion size, location, concomitant procedures, and prior procedures) were analyzed for correlations with outcome scores. All patient-related and defect-related factors were also analyzed as predictors for subsequent surgery. Microfracture was performed alone in 72 of 102 knees. At a mean follow-up of 5.66 years clinically meaningful and statistically significant improvements were seen in all PROs except the SF-12 mental component score. Patients who had an isolated tibial plateau defect or multiple defects demonstrated reduced improvements in the symptom rate. Patients with a BMI $> 30 \text{ kg/m}^2$ had lower postoperative scores on the KOOS activities of daily living subscale and poorer WOMAC function and WOMAC pain scores ($p = .029$ and $.0307$, respectively). Patient BMI, age, sex, defect location, concomitant procedures, and operative side were not significant predictors for additional surgery. Larger defect size ($> 3.6 \text{ cm}^2$) and prior knee surgery were independent risk factors for additional knee surgery after microfracture. The authors concluded that after microfracture, all PROs demonstrated clinically and statistically significant improvements at 5.7 years.

Riboh et al. (2017) conducted a network meta-analysis to synthesize the data regarding surgical treatments for cartilage defects of the knee, allowing comparisons of all treatment options and treatment rankings based on multiple measures of efficacy into a comprehensive model. Databases were searched systematically up to January 2015. The primary outcome was re-operation measured at 2, 5, and 10 years. Secondary outcomes included Tegner and Lysholm scores, the presence of hyaline cartilage on post-operative biopsy and graft hypertrophy. A random-effects network meta-analysis was performed, and the results presented as odds ratios and mean differences with 95% CIs. The authors ranked the comparative effects of all treatments with surface under the cumulative ranking probabilities. Nineteen RCT from 15 separate cohorts including 855 patients were eligible for inclusion. The results showed no differences were seen in re-operation rates at 2 years. At 5 years osteochondral autografts (OC Auto) had a lower re-operation rate than microfracture, and at 10 years OC Auto had a lower re-operation rate than microfracture, but a higher re-operation rate than second-generation ACI. No significant differences in Tegner or Lysholm scores were seen at 2 years. Functional outcome data at 5 and 10 years were not available. Hyaline repair tissue was more common with OC Auto and second generation ACI than microfracture, though the clinical significance of this is unknown. Second-generation ACI and MACI[®] had significantly lower rates of graft hypertrophy than first-generation ACI. Second-generation ACI, OC Auto and MACI[®] were the highest ranked treatments (in order) when all outcome measures were included. The authors concluded that microfracture and advanced cartilage repair techniques have similar re-operation rates and functional outcomes at 2 years. However, advanced repair techniques provide higher-quality repair tissue and might afford lower re-operation rates at 5 and 10 years.

Pareek et al. (2016) conducted a comprehensive review and meta-analysis of the literature to compare microfracture (MFX) and osteochondral autograft transfer (OAT) surgical techniques to determine (1) postoperative activity level, (2) subjective patient outcomes, (3) failure rates, and (4) assess if any lesion characteristics favored one technique over the other. Studies included were all prospective studies that reported on activity-based outcome measures such as Tegner activity scores and subjective outcomes such as the International Knee Documentation Committee score. Failure rates, as determined by the authors, were recorded for each study. Meta-analyses were conducted using a random-effects model. Paired standardized mean differences were used for continuous outcome measures, and risk ratios for dichotomous outcome measures. Six prospective studies satisfied the eligibility criteria and included 249 patients with an average age of 26.4 years and follow-up of 67.2 months. Tegner scores were superior in patients treated with OAT compared with MFX. Failure rates of MFX were higher than OAT. OAT was superior to MFX at 3 years in relation to subjective outcome scores. When assessing OAT lesions larger than 3 cm^2 , OAT was superior to MFX with respect to activity level. The authors concluded that OAT may achieve higher activity levels and lower risk

of failure when compared with MFX for cartilage lesions greater than 3 cm² in the knee, although there was no significant difference for lesions less than 3 cm² at midterm. However, because of variability in patient-specific factors such as age, preinjury activity level, lesion location and size, the superiority of OAT over MFX cannot be generalized to all patient populations and therefore requires individualized patient care.

Steadman et al. (2015) conducted a study to document outcomes following microfracture for full-thickness cartilage defects of the knee in adolescents. Patients < 19 years old with full-thickness knee articular cartilage defects treated with microfracture between January 1992 and June 2008 were identified. Surgical, demographic data, Lysholm score, Tegner activity scale, and patient satisfaction were collected prospectively. A total of 26 patients met inclusion criteria. Ninety-six percent of lesions were patellar or femoral condyle defects. Minimum 2-year follow-up was obtained in 22/26 patients (85%) with average follow-up of 5.8 years. Average postoperative Lysholm score was 90 (range: 50 to 100). Median Tegner scale was 6 (range: 2 to 10). Median patient satisfaction with outcome was 10 (range: 1 to 10). Lysholm correlated with Tegner scale ($\rho = 0.586$; $p = 0.011$) and patient satisfaction ($\rho = 0.70$; $p = 0.001$). Average postoperative Lysholm score in males was 93 and 86 in females. One patient underwent revision microfracture. This study showed that adolescent patients who underwent microfracture for treatment of full-thickness knee chondral defects demonstrated increased activity levels and excellent function following surgery.

Goyal et al. (2013) conducted a comprehensive review of the literature to assess and report on the current status of Level I and II evidence studies related to microfracture techniques. A literature search was carried out for Level I and II evidence studies on cartilage repair using the PubMed database. Fifteen studies (6 long-term and 9 short-term) that dealt with microfracture techniques were selected. These studies compared the clinical outcomes of microfracture with those of other treatments such as autologous chondrocyte implantation and osteochondral cylinder transfers. The majority of the studies reported poor clinical outcomes, whereas two studies reported the absence of any significant difference in the results. Small-sized lesions and younger patients showed good results in the short-term. However, osteoarthritis and treatment failures were observed at later postoperative periods of 5 to 10 years. The authors concluded that the use of microfracture for the treatment of small lesions in patients with low postoperative demands was observed to result in good clinical outcomes at short-term follow-up. Beyond 5 years postoperatively, treatment failure after microfracture could be expected regardless of lesion size. Younger patients showed better clinical outcomes.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Refer to the following website for more information regarding products used for Autologous Chondrocyte Transplantation and search by product name in device name section: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm> (Accessed October 19, 2021)

Transplantation of osteochondral autografts is a surgical procedure and, as such, is not subject to regulation by the FDA. However, the FDA does regulate manufacturing practice requirements applicable to drugs and devices. The FDA does regulate certain aspects of tissue banking, and tissues are subject to FDA requirements for good tissue practices, and infectious disease screening and testing, as well as to the good manufacturing practice requirements applicable to drugs and devices.

Donor tissue products derived from human cartilage, such as the DeNovo NT tissue graft, are regulated under the guidelines for Human Cell, Tissues and Cellular and Tissue-Based Products (HCT/P) issued by the Center for Biologics Evaluation and Research (CBER) of the FDA. The CBER does not regulate the transplantation of these products per se, but it does require tissue establishments to register with the FDA in the Establishment Registration & Device Listing database. As part of the FDA regulations, tissue establishments are required to screen and test donors, to prepare and follow written procedures for the prevention of the spread of communicable disease, and to maintain records.

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Policy History/Revision Information

Date	Summary of Changes
07/01/2022	<p>Application <i>Mississippi and North Carolina</i></p> <ul style="list-style-type: none">Updated language to indicate this Medical Policy applies to the states of Mississippi and North Carolina (retired state-specific policy versions) <p>Supporting Information</p> <ul style="list-style-type: none">Archived previous policy version CS006.O

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state, or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state, or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state, or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state, or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

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