

**Medical Policy**



**Title: Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions**

Related Policies:	<ul style="list-style-type: none"> <li>▪ <i>Continuous Passive Motion in the Home Setting</i></li> <li>▪ <i>Meniscal Allografts and Other Meniscal Implants</i></li> <li>▪ <i>Autografts and Allografts in the Treatment of Focal Articular Cartilage Lesions</i></li> <li>▪ <i>Orthopedic Applications of Stem Cell Therapy (Including Allograft and Bone Substitute Products Used with Autologous Bone Marrow).</i></li> </ul>
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Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> <li>• With focal articular cartilage lesion(s) of the weight-bearing surface of the femoral condyles or trochlea, or patella</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• Autologous chondrocyte implantation</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Marrow stimulation</li> <li>• Osteochondral autografts</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Symptoms</li> <li>• Change in disease status</li> <li>• Morbid events</li> <li>• Functional outcomes</li> <li>• Quality of life</li> </ul>
Individuals: <ul style="list-style-type: none"> <li>• With focal articular cartilage lesions of joints other than the knee</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• Autologous chondrocyte implantation</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Marrow stimulation</li> <li>• Osteochondral autografts</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Symptoms</li> <li>• Change in disease status</li> <li>• Morbid events</li> <li>• Functional outcomes</li> <li>• Quality of life</li> </ul>

## DESCRIPTION

A variety of procedures are being developed to resurface articular cartilage defects. Autologous chondrocyte implantation involves harvesting chondrocytes from healthy tissue, expanding the cells in vitro, and implanting the expanded cells into the chondral defect. Second- and third-generation techniques include combinations of autologous chondrocytes, scaffolds, and growth factors.

## OBJECTIVE

The objective of this evidence review is to determine whether autologous chondrocyte implantation improves net health outcomes in patients with focal articular cartilage lesions of the knee and other joints.

## BACKGROUND

### Articular Cartilage Lesions

Damaged articular cartilage typically fails to heal on its own and can be associated with pain, loss of function, and disability, and may lead to debilitating osteoarthritis over time. These manifestations can severely impair a patient's activities of daily living and adversely affect quality of life.

### Treatment

Conventional treatment options include debridement, subchondral drilling, microfracture, and abrasion arthroplasty. Debridement involves the removal of synovial membrane, osteophytes, loose articular debris, and diseased cartilage, and it is capable of producing symptomatic relief. Subchondral drilling, microfracture, and abrasion arthroplasty attempt to restore the articular surface by inducing the growth of fibrocartilage into the chondral defect. Compared with the original hyaline cartilage, fibrocartilage has less capability to withstand shock or shearing force and can degenerate over time, often resulting in the return of clinical symptoms. Osteochondral

grafts and autologous chondrocyte implantation attempt to regenerate hyaline-like cartilage and thereby restore durable function. Osteochondral grafts for the treatment of articular cartilage defects are discussed in BCBSKS medical policy *Orthopedic Applications of Stem Cell Therapy (Including Allograft and Bone Substitute Products Used with Autologous Bone Marrow)*.

With autologous chondrocyte implantation, a region of healthy articular cartilage is identified and biopsied through arthroscopy. The tissue is sent to a facility licensed by the U.S. Food and Drug Administration (FDA) where it is minced and enzymatically digested, and the chondrocytes are separated by filtration. The isolated chondrocytes are cultured for 11 to 21 days to expand the cell population, tested, and then shipped back for implantation. With the patient under general anesthesia, an arthrotomy is performed, and the chondral lesion is excised up to the normal surrounding cartilage. Methods to improve the first-generation autologous chondrocyte implantation procedure have been developed, including the use of a scaffold or matrix-induced autologous chondrocyte implantation composed of biocompatible carbohydrates, protein polymers, or synthetics. The only FDA approved matrix-induced autologous chondrocyte implantation product to date is supplied in a sheet, which is cut to size and fixed with fibrin glue. This procedure is considered technically easier and less time-consuming than the first-generation technique, which required suturing of a periosteal or collagen patch and injection of chondrocytes under the patch.

Desired features of articular cartilage repair procedures are the ability (1) to be implanted easily, (2) to reduce surgical morbidity, (3) not to require harvesting of other tissues, (4) to enhance cell proliferation and maturation, (5) to maintain the phenotype, and (6) to integrate with the surrounding articular tissue. In addition to the potential to improve the formation and distribution of hyaline cartilage, use of a scaffold with matrix-induced autologous chondrocyte implantation eliminates the need for harvesting and suture of a periosteal or collagen patch. A scaffold without cells may also support chondrocyte growth.

## REGULATORY STATUS

The culturing of chondrocytes is considered by the FDA to fall into the category of manipulated autologous structural cells, which are subject to a biologic licensing requirement. In 1997, Carticel® (Genzyme; now Vericel) received the FDA approval for the repair of clinically significant, "...symptomatic cartilaginous defects of the femoral condyle (medial-lateral or trochlear) caused by acute or repetitive trauma..."

In December 2016, MACI® (Vericel) received FDA approval for "the repair of symptomatic, single or multiple full-thickness cartilage defects of the knee with or without bone involvement in adults." MACI consists of autologous chondrocytes that are cultured onto a bioresorbable porcine-derived collagen membrane. In 2017, production of Carticel was phased out, and MACI is the only autologous chondrocyte implantation product available in the United States.

A number of other second-generation methods for implanting autologous chondrocytes in a biodegradable matrix are currently in development or testing or are available outside of the United States. They include Atelocollagen (Koken), a collagen gel; Bioseed® C (BioTissue Technologies), a polymer scaffold; CaReS (Ars Arthro), collagen gel; Cartilix (Biomet), a polymer hydrogel; Chondron (Sewon Cellontech), a fibrin gel; Hyalograft C (Fidia Advanced

Polymers), a hyaluronic acid-based scaffold; NeoCart (Histogenics), an autologous chondrocyte implantation with a 3-dimensional chondromatrix in a phase 3 trial; and Novocart®3D (Aesculap Biologics), a collagen-chondroitin sulfate scaffold in a phase 3 trial. ChondroCelect® (TiGenix), characterized as a chondrocyte implantation with a completed phase 3 trial, uses a gene marker profile to determine in vivo cartilage-forming potential and thereby optimizes the phenotype (eg, hyaline cartilage vs. fibrocartilage) of the tissue produced with each autologous chondrocyte 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. Both Hyalograft C and ChondroCelect have been withdrawn from the market in Europe. In 2020, the FDA granted breakthrough status to Agili-C (CartiHeal, Ltd.), a proprietary biocompatible and biodegradable tapered-shape implant for the treatment of cartilage lesions in arthritic and non-arthritic joints that, when implanted into a pre-prepared osteochondral hole, acts as a 3-dimensional scaffold that potentially supports and promotes the regeneration of the articular cartilage and its underlying subchondral bone.

**POLICY**

- A. 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, when **ALL** of the following criteria are met:
1. Adolescent patients should be skeletally mature with documented closure of growth plates (e.g., 15 years or older). Adult patients should be too young to be considered an appropriate candidate for total knee arthroplasty or other reconstructive knee surgery (e.g., younger than 55 years) **AND**
  2. Focal, full-thickness (grade III or IV) unipolar lesions of the weight bearing surface of the femoral condyles, trochlea, or patella at least 1.5 cm<sup>2</sup> in size **AND**
  3. Documented minimal to absent degenerative changes in the surrounding articular cartilage (Outerbridge grade II or less), and normal-appearing hyaline cartilage surrounding the border of the defect **AND**
  4. Normal knee biomechanics or alignment and stability achieved concurrently with autologous chondrocyte implantation
- B. Autologous chondrocyte implantation for all other joints, including talar, and any indications other than those listed above is considered **experimental / investigational**.

**POLICY GUIDELINES**

- A. For smaller lesions (e.g., smaller than 4 cm<sup>2</sup>), if débridement is the only prior surgical treatment, then consideration should be given to marrow-stimulating techniques before autologous chondrocyte implantation (ACI) is performed.
- B. The average defect size reported in the literature is about 5 cm<sup>2</sup>; many studies treated lesions as large as 15 cm<sup>2</sup>.
- C. Severe obesity (e.g., body mass index (BMI) greater than 35 kg/m<sup>2</sup>) 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. In addition, meniscal allograft transplantation may be performed in combination, either concurrently or sequentially, with ACI.
- E. The entire matrix-induced autologous chondrocyte implantation (ACI) procedure consists of 4 steps:
1. initial arthroscopy and biopsy of normal cartilage
  2. culturing of chondrocytes on an absorbable collagen matrix
  3. a separate arthrotomy to place the implant, and
  4. post-surgical rehabilitation
- F. 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., arthroscopy) is scheduled.

<b>Outerbridge cartilage grading scale</b>	
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

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## **RATIONALE**

This evidence review was created with searches of the PubMed database. The most recent literature update was performed through February 16, 2022.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

## **AUTOLOGOUS CHONDROCYTE IMPLANTATION FOR FOCAL ARTICULAR CARTILAGE LESION(S) OF THE KNEE**

### **Clinical Context and Therapy Purpose**

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

The question addressed in this evidence review is: Does the use of autologous chondrocyte implantation improve the net health outcome in patients with focal articular cartilage lesion(s) of the weight-bearing surface of the femoral condyles, trochlea, or patella?

The following PICO was used to select literature to inform this review.

### **Populations**

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

### **Interventions**

The treatment being considered is autologous chondrocyte implantation. The first stage of implantation includes arthroscopy to obtain a biopsy of healthy articular cartilage and the second stage is the arthrotomy.

### **Comparators**

The comparators of interest are marrow stimulation or osteochondral autograft.

### **Outcomes**

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

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

Negative outcomes include hypertrophy of the transplant, disturbed fusion of the regenerative and healthy surrounding cartilage, inadequate regenerative cartilage, and delamination.<sup>1</sup>

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

Table 1 describes several outcome measurement tools used in the following studies.

**Table 1. Patient-Reported Outcome Measurement Tools<sup>a</sup>**

<b>Name</b>	<b>Description</b>	<b>Scoring</b>	<b>MCID</b>
CKRS and mCKRS <sup>2</sup>	Measure symptoms, sports activity, and ADL functioning	Likert-type scale; total range 0-100, 100 being best function CKRS: 22 questions in 6 areas: 1. Symptoms (4) 2. Patient perception (1) 3. Sports activity (4) 4. ADL function (3) 5. Sports function (3)	6 mo=14.0 12 mo=26.0 <sup>3</sup>

Name	Description	Scoring	MCID
		6. Occupational (7) mCKRS: 12 questions, 8 included in summary score: 1. Pain intensity 2. Swelling 3. Giving way 4. Overall activity level 5. Walking 6. Stairs 7. Running activity 8. Jumping or twisting	
EQ-5 VAS <sup>4</sup> ,	Generic questionnaire for measuring HRQoL. Measures patients' perceptions of their current overall health and can be used to track changes over time	5 dimensions of health: 1. Mobility 2. Self-care 3. Usual activities 4. Pain/discomfort 5. Anxiety/depression Each dimension graded "severe," "moderate," or "none"; along with "death" and "unconscious," describes 245 different health statuses. Each health state is ranked and transformed into a single "utility" score	Not available
IKDC Subjective Knee Form <sup>5</sup> ,	Assesses symptoms, daily activity, and sports function caused by conditions affecting the knee.	18 items are totaled and expressed as a percentage of the maximum possible score 100% indicates the absence of symptoms and higher functioning levels	Change score <11.5% indicates patient likely does not perceive improvement. Change score >20.5% indicates patient likely perceives improvement.
KOOS <sup>6,7</sup> ,	Assesses patients' opinion about their knee and associated problems, both short- and long-term. Items selected based on WOMAC	42 items in 5 separately scored subscales: 1. Pain (9 items) 2. Other symptoms (7) 3. Function in ADL (17) 4. Function in sports and recreation (5) 5. Knee-related quality of life (4) Measured with Likert-type scale with 5 possible answers: <ul style="list-style-type: none"> <li>• 0=no problems</li> <li>• 4=extreme problems</li> </ul>	For knee injuries (MDC): 1. Pain: 6-6.1 2. Symptoms: 5-8.5 3. ADL: 7-8 4. Sports/rec: 5.8-12 5. Quality of life: 7-7.2



Name	Description	Scoring	MCID
		Scores transformed to 0-100 scale, with 0 representing extreme knee problems, and 100 no problems	
KSS <sup>8</sup> ,	Rates knee and patients' functional abilities before and after total knee replacement	Knee score section (KS-KS): 7 items Functional score section (KS-FS): 3 items Each section scored 0-50, with lower scores indicating worse knee conditions	KS-KS: 5.3-5.9 KS-FS: 6.1- 6.4
LKQ <sup>7</sup> ,	Measures outcomes of knee ligament surgery, with emphasis on evaluation of instability and corresponding to patient's own opinion	8 items with individual scoring scales: 1. Limp (0, 3, 5) 2. Support (0, 2, 5) 3. Locking (0, 2, 6, 10, 15) 4. Instability (0, 5, 10, 15, 20, 25) 5. Pain (0, 5, 10, 15, 20, 25) 6. Swelling (0, 2, 6, 10) 7. Stair climbing (0, 2, 6, 10) 8. Squatting (0, 2, 4, 5) Possible score range, 0-100: • 100=no symptoms or disability • 95-100=excellent • 84-94=good • 65-83=fair • ≤64=poor	8.9-10.1 (MDC)
OKS <sup>7</sup> ,	For patients undergoing total knee arthroscopy to assess their knee-related health status and benefits of treatment	12 items pertaining to knee pain and function • Likert-type scale: ○ Original version, 1-5: ▪ 1=best ▪ 5=worst ○ Modified version, 0-4: ▪ 4=no problem ▪ 0=significant disability Total score summed from values selected: • Original version, range=12-60: higher score, poorer outcome • Modified version, range=0-48: lower score, better outcome	Not available

Name	Description	Scoring	MCID
SF-12 and SF-36 <sup>9,10,11,12,</sup>	Both are health-related quality of life surveys covering 8 domains including physical and mental components SF-12 is a shortened version of SF-36	8 domains: <ol style="list-style-type: none"> <li>1. Physical functioning</li> <li>2. Role - physical</li> <li>3. Bodily pain</li> <li>4. General health perceptions</li> <li>5. Vitality</li> <li>6. Social functioning</li> <li>7. Role - emotional</li> <li>8. Mental health</li> </ol> Likert-type question formats Physical and mental components are scored separately Scores range 0-100: <ul style="list-style-type: none"> <li>• 0=lowest level of health</li> <li>• 100=highest level of health</li> </ul>	4.3-5.0 (physical component)
TAS <sup>7,</sup>	Developed to complement Lysholm score Grades activity based on work and sports activities	Graduated list of ADLs, recreation, and competitive sports (11 options); patient selects 1 item that best represents their current level of activity  Possible score range, 0-10:0=sick leave or disability pension due to knee problems <ul style="list-style-type: none"> <li>• 6-10=participation in recreational or competitive sports</li> <li>• 10=participation in national or international elite sports</li> </ul>	1.0 (MDC)
WOMAC <sup>7,</sup>	Assessment of ADL, functional mobility, gait, general health, and quality of life	24 items broken into 3 subscales: <ol style="list-style-type: none"> <li>1. Pain (5)</li> <li>2. Symptoms/ stiffness (2)</li> <li>3. Physical function (17)</li> </ol> Each question scored 0-4:0=none <ul style="list-style-type: none"> <li>• 1=mild</li> <li>• 2=moderate</li> <li>• 3=severe</li> <li>• 4=extreme</li> </ul>	For Knee OA (MDC): <ol style="list-style-type: none"> <li>1. Pain: 18.8-22.4</li> <li>2. Symptoms: 27.1-29.1</li> <li>3. Function: 13.1-13.3</li> </ol>

ADL: activities of daily living; CKRS: Cincinnati Knee Rating System; EQ-5 VAS: EuroQol 5 Dimensions Visual Analog Scale; HRQoL: health-related quality of life; IKDC: International Knee Documentation Committee; KOOS: Knee Injury and Osteoarthritis Outcome Score; KSS: Knee Society Score; LKQ: Lysholm Knee Questionnaire; mCKRS: modified Cincinnati Knee Rating System; MCID: minimal clinically important difference; MDC: minimum detectable change; OA: osteoarthritis; OKS: Oxford Knee Score ;SF-12: 12-Item Short-Form Health Survey; SF-36: 36-Item Short-Form Health Survey; TAS: Tegner Activity Scale; VAS: visual analog scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

<sup>a</sup> All surveys are either patient-completed or observer-administered to patient.

## Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

## REVIEW OF EVIDENCE

### SYSTEMATIC REVIEWS

#### ***Cartilage Repair Procedures***

Abraamyan et al (2021) completed a systematic review with meta-analysis that evaluated cartilage repair techniques, including microfracture, augmented microfracture, and autologous chondrocyte implantation/matrix-induced autologous chondrocyte implantation.<sup>13</sup> The authors included a total of 14 RCTs (N=775), and changes from baseline in the 5 Knee injury and Osteoarthritis Outcome Score (KOOS) subscales, including KOOS Sport, KOOS Quality of Life, KOOS Symptoms, KOOS Pain, and KOOS Activities of Daily Living, were measured. Only the KOOS Sport subscale demonstrated statistically significant benefits with autologous chondrocyte implantation/matrix-induced autologous chondrocyte implantation procedures compared with microfracture (p=.02). The mean delta KOOS Sport after autologous chondrocyte implantation/matrix-induced autologous chondrocyte implantation procedures was 9.9 points greater than after microfracture and 11.7 points greater than after augmented microfracture. Comparisons between surgical techniques for the other subscales did not reach statistical significance.

Zamborsky et al (2020) completed a systematic review and network meta-analysis that evaluated the most appropriate surgical interventions for patients with knee articular cartilage defects.<sup>14</sup> The authors included a total of 21 articles (from 12 RCTs) in their analysis with a total population of 891 patients. Follow-up varied widely among the included studies, ranging from 12 months to 15 years. Of the surgical interventions evaluated, microfracture was associated with significantly higher failure rates compared to autologous chondrocyte implantation at 10 years of follow-up (relative risk [RR], 0.12; 95% confidence interval [CI]; 0.04 to 0.39). No significant differences in failure rates were seen between microfracture and osteochondral autograft transplantation, matrix-induced autologous chondrocyte implantation, or characterized chondrocyte implantation at 2, 5, and 10 years of follow-up. Osteochondral autograft transplantation was associated with significantly more excellent or good results at >3 years of follow-up as compared to microfracture, whereas microfracture was associated with significantly poorer results as compared to autologous chondrocyte implantation and matrix-induced autologous chondrocyte implantation. No significant differences between the interventions were noted regarding reintervention, biopsy types, or adverse events. Based on efficacy and safety, autologous chondrocyte implantation was ranked as the best intervention for failure outcome at 10 years of follow-up, followed by osteochondral autograft transplantation, then microfracture. Microfracture was consistently ranked worse than cartilage repair techniques for other outcomes including quality of tissue repair and return-to-activity rates.

Riboh et al (2017) reported on a network meta-analysis assessing the comparative efficacy of cartilage repair procedures of the knee.<sup>15</sup> Nineteen RCTs from 15 separate cohorts (N=855 ) were included. The procedures selected for the network analysis were matrix-induced autologous chondrocyte implantation, autologous chondrocyte implantation with a collagen membrane, autologous chondrocyte implantation with a periosteal membrane, osteochondral autograft transfer, and microfracture. Outcomes evaluated included graft hypertrophy, hyaline cartilage, Lysholm Knee Scoring System score, reoperation in the short-, mid-, and long-term, and Tegner Activity Scale score. The rank order of treatment efficacy, taking into account all outcome measures, was autologous chondrocyte implantation with a collagen membrane, osteochondral autograft transfer, matrix-induced autologous chondrocyte implantation, autologous chondrocyte implantation with a periosteal membrane, and microfracture. Another systematic review of surgical treatments of cartilage defects of the knee by Devitt et al (2017)<sup>16</sup>, included a subset of the RCTs in the Riboh et al (2017) review.

Mundi et al (2016) reported on a systematic review of level I studies for cartilage restoration of the knee.<sup>17</sup> Included were 12 randomized trials (N=765 ) and a mean lesion size of 3.9 cm<sup>2</sup>. Five trials compared autologous chondrocyte implantation with marrow stimulation, 3 compared autologous chondrocyte implantation with osteochondral autograft transfer, 1 compared osteochondral autograft transfer with microfracture, and 3 compared different generations of autologous chondrocyte implantation. Eleven of the 12 trials were conducted in Europe. Four trials reported significant differences in function with autologous chondrocyte implantation versus marrow stimulation. However, a meta-analysis showed no significant differences in pain or function between the 2 treatments at 24-month follow-up. The quality of the evidence was rated as poor to moderate, and only 4 trials reported a sample size calculation. Although meta-analysis could not be performed on the other comparisons, 5 of 6 trials found no significant difference in outcomes between autologous chondrocyte implantation and osteochondral autograft transfer or different generations of autologous chondrocyte implantation. The percentage of grafts that failed and the relationship between lesion size and success rate were not assessed in this review.

### ***Autologous Chondrocyte Implantation Versus Other Cartilage Repair Procedures***

In 2020, Gou et al evaluated clinical outcomes among patients with fractures of knee cartilage who were treated with autologous chondrocyte implantation (n=332) or microfracture (n=327) from 12 RCTs.<sup>18</sup> Patient age ranged from 25 to 41 years, with the majority of patients male. Treatment follow-up ranged from 1.5 to 15 years. There were diverse types of autologous chondrocyte implantation performed among the studies including matrix-induced autologous chondrocyte implantation, NeoCart, autologous chondrocyte implantation with periosteum, and ChondroSelect. Outcomes included an overall clinical score, KOOS subdomains of activities of daily living and function, quality of life, pain relief score, and failure/operation rate. Results revealed no significant differences between the interventions with regard to improvement in International Knee Documentation Committee and Lysholm scores or overall KOOS measures at 1, 2, and 5 years of follow-up. There was also no difference between the groups with regard to failure rate at 2, 3, and 5 years. Autologous chondrocyte implantation was associated with significant improvements in activities of daily living at 5 years or less of follow-up as compared to microfracture as well as improvement in quality of life and pain relief at 5 and 2 year follow-up examinations, respectively. Major limitations of this systematic review and meta-analysis

included the small number of eligible RCTs in the final analysis with regard to length of follow-up and that the studies included in the meta-analysis utilized a variety of autologous chondrocyte implantation techniques, scales and scores for outcome measures, and recruited patients with different lesion sizes. Plus, blinding of the patients or surgeons was difficult to perform given the 2-step procedure of autologous chondrocyte implantation.

In 2017, the National Institute for Health Research reported on a systematic review assessing the clinical effectiveness of autologous chondrocyte implantation in the knee.<sup>19</sup> The National Institute for Health Research review focused on reports from previous systematic reviews including adults with symptomatic articular cartilage defects in the knee published between 2004 and 2014. Twelve systematic reviews including 19 studies (11 RCTs) were selected. The main comparator of interest was microfracture, and 4 trials (N=712) were identified that compared second- and third-generation autologous chondrocyte implantation with microfracture. One of the trials, Autologous Chondrocyte Transplantation/Implantation Versus Existing Treatment (ACTIVE; N=390) shared selected results with the National Institute for Health Research reviewers but no results have been published. Another trial (ChondroCelect via autologous chondrocyte implantation vs. Microfracture in the repair of symptomatic cartilage lesions of the knee, N=118) included assessment of the ChondroCelect autologous chondrocyte implantation, which was never approved in the United States and has been withdrawn from the market in Europe. The remaining 2 trials included in the National Institute for Health Research review, Basad et al (2010) and the Superiority of matrix-induced autologous chondrocyte implantation versus Microfracture Treatment in Patients with Symptomatic Articular Cartilage Defects in the Knee (SUMMIT), are detailed in the following section on RCTs. In summary, both matrix-induced autologous chondrocyte implantation and ChondroCelect were more clinically effective than microfracture for the outcomes of reductions in pain and improvements in function on the KOOS over 2 to 5 years. Limited long-term data were available on the failure rates of both autologous chondrocyte implantation and microfracture after 5 years; data were available from 6 observational studies. The conclusions regarding follow-up after 5 years were primarily based on 1 of the observational studies judged to be the highest quality (Nawaz et al [2014]; described in the following section on durability, N=827). For autologous chondrocyte implantation, failure rates were lower in patients who had no previous knee repair and in people with minimal evidence of osteoarthritis. Larger defect size was not associated with poorer outcomes in these patients.

A systematic review by Harris et al (2010) comparing autologous chondrocyte implantation with other cartilage repair or restoration techniques, included 13 RCTs and nonrandomized trials of 917 participants who underwent autologous chondrocyte implantation (n=604), microfracture (n=271), or osteochondral autograft transfer (n=42).<sup>20</sup> 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 autologous chondrocyte implantation, finding no difference in outcomes but higher complication rates with open, periosteal cover, first-generation autologous chondrocyte implantation. At 1- to 5-year follow-up, 3 of 7 studies showed better clinical outcomes after autologous chondrocyte implantation than after microfracture, 1 showed better outcomes after microfracture, and 3 showed no difference between these treatments. Clinical outcomes after microfracture deteriorated after 18 to 24 months in 3 of 7 studies. Studies comparing autologous chondrocyte implantation with osteochondral autograft transfer showed similar short-term clinical outcomes, with more rapid

improvement but an increase in arthrofibrosis and donor-site morbidity following osteochondral autograft transfer. Younger patients with a shorter preoperative duration of symptoms and fewer prior surgical procedures had the best outcomes after surgical intervention. A defect size greater than 4 cm<sup>2</sup> was the only factor predictive of better outcomes when autologous chondrocyte implantation was compared with other surgical techniques.

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

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.<sup>21</sup> Nine clinical studies were assessed (type not specified), with 179 (>200 lesions) patients aged 18 to 49 years (mean, 27.6 years). Follow-up ranged from 6.5 months to 10 years. Results of patient-reported outcomes showed that 85% of patients reported excellent or good outcomes. All patient-reported outcome measures used across the studies (International Knee Documentation Committee Form, Lysholm Knee Questionnaire, EuroQol Visual Analog Scale, Cincinnati Rating System, and the Tegner Activity Scale) reported statistically significant improvements from preoperative to final follow-up (p-values not reported). Of the studies that reported complication and failure rates for autologous chondrocyte implantation/matrix-induced autologous chondrocyte implantation, 23 (15.7%) of 146 patients reported complications, and the failure rate was 8.2%. Unplanned reoperations were necessary for 20.5% of patients. The study results showed that autologous chondrocyte implantation/matrix-induced autologous chondrocyte implantation had the best outcomes for active young males with small lesions. Older adults and less active individuals, as well as those with lesions >6 cm<sup>2</sup>, did not fare as well. A limitation of this review was its lack of randomized trials with controls to compare to autologous chondrocyte implantation/matrix-induced autologous chondrocyte implantation.

### **Randomized Controlled Trials**

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

### ***Matrix-Induced Autologous Chondrocyte Implantation Versus Autologous Chondrocyte Implantation***

Bartlett et al (2005) reported on a randomized comparison between matrix-induced autologous chondrocyte implantation and autologous chondrocyte implantation with a collagen cover in 91 patients.<sup>22</sup> Overall, results were comparable for both treatments. The modified Cincinnati Knee Rating System score improved by 17.6 points in the autologous chondrocyte implantation group and by 19.6 points in the matrix-induced autologous chondrocyte implantation group (p=.32). Visual analog scale scores improved from 6.0 to 4.3 in the autologous chondrocyte implantation group and from 6.0 to 4.1 in the matrix-induced autologous chondrocyte implantation group. Factors associated with worse clinical outcomes were a failed prior procedure, duration of symptoms, and patient age. Second-look arthroscopy at 1 year for 42 patients showed excellent-to-good International Cartilage Repair Society scores in 79.2% of autologous chondrocyte implantation and in 66.6% of matrix-induced autologous chondrocyte implantation

patients ( $p=.3$ ). The authors did not report whether the study was adequately powered for this comparison. Histology from 14 autologous chondrocyte implantation and 11 matrix-induced autologous chondrocyte implantation patients showed similar percentages of hyaline-like cartilage (42.9% autologous chondrocyte implantation, 36.4% matrix-induced autologous chondrocyte implantation).

### ***Matrix-Induced Autologous Chondrocyte Implantation Versus Microfracture***

The SUMMIT trial was the pivotal, industry-sponsored, multicenter randomized open-label trial; it was reported by Saris et al (2014) and compared matrix-induced autologous chondrocyte implantation with microfracture for larger cartilage defects ( $\geq 3 \text{ cm}^2$ ), which typically fare worse than smaller lesions when treated with microfracture.<sup>23</sup> Patients (N=144) included had at least 1 symptomatic grade III or IV focal cartilage defect on the femoral condyles or trochlea, a stable knee, an intact or partial meniscus, and a moderate-to-severe KOOS pain value ( $< 55$ ). Average lesion size was  $4.8 \text{ cm}^2$  (range, 3 to  $20 \text{ cm}^2$ ), and 34.6% of patients had undergone a prior marrow stimulation procedure. At 2-year follow-up, the matrix-induced autologous chondrocyte implantation group had significantly better subscores for KOOS pain (coprimary outcome; difference, 11.76;  $p<.001$ ) and function in sport and recreation (coprimary outcome; difference, 11.41;  $p=.16$ ) as well as the other KOOS subscales (function in daily living, knee-related quality of life, other symptoms). With response to treatment defined as a 10-point improvement in both the KOOS pain and function subscales, significantly more patients in the matrix-induced autologous chondrocyte implantation group responded to treatment (87.5%) than in the microfracture group (68.1%;  $p=.016$ ). There were no significant differences between groups for cartilage repair, as measured by second-look arthroscopy, biopsy, or magnetic resonance imaging (MRI).

Brittberg et al (2018) reported on a 5-year follow-up of the SUMMIT trial.<sup>24</sup> Five years post-procedure, the KOOS pain and function score was still significantly better, both clinically and statistically, for matrix-induced autologous chondrocyte implantation than for microfracture ( $p=.022$ ). Changes from baseline to year 5 were also higher for matrix-induced autologous chondrocyte implantation than microfracture for activities of daily living ( $p=.007$ ), quality of life ( $p=.070$ ), and other symptoms ( $p=.078$ ). Over 5 years, 4 patients (1 matrix-induced autologous chondrocyte implantation, 3 microfractures) had treatment failures. The proportion of patients who required subsequent surgical procedures was similar in the 2 groups (10.8% in matrix-induced autologous chondrocyte implantation and 9.5% in microfracture). Limitations were potential bias from allowing participants to choose whether to continue with the extended study. In addition, the SUMMIT study was not blinded. However, the use of standardized surgical and rehabilitation procedures, validated clinical outcome instruments, and consistent outcomes among the multiple investigators strengthened the study.

Basad et al (2010) reported on a small randomized trial that compared matrix-induced autologous chondrocyte implantation ( $n=40$ ) with microfracture ( $n=20$ ) in patients who had a single posttraumatic chondral defect between 4 and  $10 \text{ cm}^2$ .<sup>25</sup> Both groups improved at the 2-year follow-up, with a significant advantage of matrix-induced autologous chondrocyte implantation over microfracture on the Lysholm Knee Score (92 vs. 69,  $p=.005$ ), Tegner Activity Score (4 vs. 3,  $p=.04$ ), and International Cartilage Repair Society patient ( $p=.03$ ) and International Cartilage Repair Society surgeon ( $p=.02$ ) scores. Patients treated with matrix-induced autologous chondrocyte implantation from this trial, along with newly enrolled patients

(n=65), were followed for 5 years.<sup>26</sup> However, the rate of follow-up decreased from 93.8% at 24 months to 38.5% at 60 months, limiting interpretation of the 5-year results. Twelve (18.5%) patients developed symptoms between 6 and 36 months such as pain, locking, crepitus, or recurrent effusion. Arthroscopy of these 12 showed partial disintegration of regenerated tissue (n=5), subchondral edema (n=2), graft fibrillation (n=4), and progression to osteoarthritis (n=1). All 12 underwent additional procedures, including osteochondral autograft transfer and microfracture, with good results.

### **Observational Studies**

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

### ***Tibiofemoral Versus Patellofemoral Lesions***

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

### **Systematic Reviews**

Schuetz et al (2017) published a systematic review of mid- to long-term clinical outcomes from use of matrix-induced autologous chondrocyte implantation in the knee.<sup>27</sup> They included 10 studies (2 level I, 1 level II, 1 level III, 6 level IV studies), with a total of 442 tibiofemoral and 136 patellofemoral lesions/patients and follow-up of at least 5 years, published through September 2016. Four of the studies used the type I and III collagen matrix, 5 used Hyalograft C, and 1 used both. The 2 level I studies compared early with late weight-bearing following matrix-induced autologous chondrocyte implantation. Individual study quality was rated as good to fair, with an average rating of fair. Clinical outcomes, weighted for age and defect size, improved from baseline to latest follow-up. At follow-up the failure rate was 12.4% (3 studies, N=145 ; range, 3.2% to 21.6%) for tibiofemoral joints and 4.7% (4 studies, N=106 ; range, 0% to 50%) for patellofemoral joints (p=.037). The highest failure rates were reported in studies with the largest lesions and the longest follow-up.

One of the studies included in the Schuetz et al (2017) systematic review, Meyerkort et al (2014)<sup>28</sup>, was a prospective cohort of 23 patients who were treated with matrix-induced autologous chondrocyte implantation for patellofemoral lesions. The mean defect size was 3.5 cm<sup>2</sup>, and 9 (39%) of the patients underwent concurrent patellofemoral realignment procedures. At the 5-year follow-up, MRI indicated an intact appearance in most grafts, with graft height of more than 50% of the surrounding cartilage in 82% of patients. Patient-reported outcomes, measured with the KOOS and 36-Item Short Form Health Survey (SF-36), improved significantly compared with preoperative scores. The increase in distance walked in 6 minutes was statistically significant (p<.001) but modest (from 570 to 590 m). Graft hypertrophy was detected in 3 (13%) patients by MRI but symptoms were considered sufficient to merit debridement in only 1 (4.3%) patient.



A report by Zak et al (2012)<sup>29</sup>, was also included in the Schuette et al (2017) review. Zak et al (2012) evaluated return to sports at 5 years in 70 patients who had matrix-induced autologous chondrocyte implantation, 15 of whom had matrix-induced autologous chondrocyte implantation in the patellofemoral joint. Significant improvements in the KOOS function in sport and recreation, Noyes grading system, and Tenger Activity Score scores were reported between presurgery and follow-up. Patients with 2 lesions had worse outcomes than patients with a single tibiofemoral lesion but there were no significant differences in outcomes between the tibiofemoral and patellofemoral groups.

### **Nonrandomized Comparative Studies**

Three studies assessed in the systematic review were reported by Ebert et al (2017) and colleagues.<sup>30,31,32</sup> Ebert et al (2017) reported on a comparative study with 24-month follow-up.<sup>33</sup> They evaluated 194 patients with lesions on the medial or lateral femoral condyle (n=127), patella (n=35), or trochlea (n=32). There were no significant differences between groups in demographics, defect size, prior injury, or surgical history. Patient-reported outcome measures, including the KOOS, visual analog scale for pain, SF-36, and satisfaction scores, were collected by an independent assessor. Most clinical scores were similar preoperatively except for the KOOS function in daily living and quality of life subscales, which were worse in the combined patella and trochlea group. Patellofemoral malalignment was corrected when indicated. Postoperative scores on the KOOS function in daily living, knee-related quality of life, and function in sport and recreation were significantly higher in the tibiofemoral group but both groups improved over time. Graft hypertrophy assessed using MRI was more frequent in the tibiofemoral group (32.1%) than the patellofemoral group (10.4%). All lesions with hypertrophy were asymptomatic at the 24-month follow-up.

### ***Combined Meniscal Allograft and Cartilage Repair***

The systematic review by Harris et al (2011) evaluated combined meniscal allograft transplantation and cartilage repair/restoration.<sup>34</sup> Six level IV studies (case series) with a total of 110 patients were included. Patients underwent meniscal allograft transplantation with autologous chondrocyte implantation (n=73), osteochondral allograft (n=20), osteochondral autograft transfer (n=17), or microfracture (n=3). All studies showed improvements in clinical outcomes at final follow-up compared with the preoperative baseline. Outcomes were also compared with historical outcomes of each procedure performed in isolation. Four of the 6 studies found outcomes equivalent to procedures performed in isolation, while 2 found that outcomes with combined surgery were not as good as the historical controls. Across the 6 studies, 13 (12%) failures were reported; they included 11 isolated meniscal allograft transplantation failures, 1 combined meniscal allograft and autologous chondrocyte implantation failure, and 1 isolated autologous chondrocyte implantation failure. Three knees with failed meniscal allograft transplantation were converted to total knee arthroplasty. Nearly 50% of patients underwent 1 or more subsequent surgeries after combined meniscal allograft transplantation and cartilage repair/restoration procedures.

### ***Durability and Effects of Realignment and Prior Procedures***

Andriolo et al (2017) performed a systematic review of literature that reported on the failure rate of autologous chondrocyte implantation or matrix-induced autologous chondrocyte implantation.<sup>35</sup> Fifty-eight studies were included: 4 RCTs, 6 comparative observational studies, and 48 case series (N=4294 ). At a mean follow-up of 86 months, the failure rate was 14.9%

(range, 0% to 43%) and the mean time of failure was 26 months in the 19 studies reporting time to failure. However, there was high heterogeneity in how failure rates were defined in selected studies.

A study by Nawaz et al (2014) evaluated functional outcomes and survival rates for autologous chondrocyte implantation (periosteal or collagen membrane-covered) and matrix-induced autologous chondrocyte implantation in 869 patients.<sup>36</sup> For the group as a whole, graft survival was estimated by Kaplan-Meier analysis to be 78.2% (95% CI, 74.9% to 81.1%) at 5 years and 50.7% (95% CI, 45.2% to 55.9%) at 10 years. Graft survival did not differ between the first- and second-generation (matrix-induced autologous chondrocyte implantation) procedures. Functional and pain scores were significantly better in the matrix-induced autologous chondrocyte implantation group but this finding might have been confounded by the shorter follow-up with the newer technique.

Minas et al (2014) prospectively followed 210 autologous chondrocyte implantation-treated patients (362 grafts) for at least 10 years.<sup>37</sup> Malalignment, patellar maltracking, and meniscal or ligamentous deficiency had also been corrected as needed. At a mean follow-up of 12 years, 53 (25%) patients had graft failure. For the 157 patients who had successful grafts, functional outcomes were significantly improved from baseline to follow-up, as measured by the Western Ontario and McMaster Universities Index, Knee Society Score for knee and function, and SF-36 (all  $p < .001$ ). Graft survival was significantly longer in patients with complex versus salvage-type lesions ( $p = .03$ ), with concomitant high tibial osteotomy versus no high tibial osteotomy ( $p = .01$ ), and with primary autologous chondrocyte implantation versus autologous chondrocyte implantation after a prior marrow stimulation procedure ( $p = .004$ ). For example, primary graft survival was 79% compared with 44% for defects previously treated with microfracture.

A 3-fold increase in autologous chondrocyte implantation failure rate after previous treatment with marrow stimulation techniques was reported by Minas et al (2009) in a cohort of 321 patients with more than 2 years of follow-up.<sup>38</sup> Independent analysis showed a failure rate of 8% (17/214) of joints without prior marrow stimulation of the lesion, compared with 26% (29/111) of joints that had not. The Nawaz et al (2014) study of 869 patients treated with autologous chondrocyte implantation or matrix-induced autologous chondrocyte implantation (described above) found that overall graft survival was 78.2% at 5 years and 50.7% at 10 years using Kaplan-Meier analysis.<sup>36</sup> Graft failure was 5 times more likely with a previously treated lesion (<25% survival at 12 years) compared with a previously untreated lesion (>75% survival at 12 years) (hazard ratio, 5.33; 95% CI, 4.07 to 6.99;  $p < .001$ ). Other factors affecting survival were graft location and the severity of degenerative changes.

### ***Graft Hypertrophy***

Ebert et al (2015) reported on graft hypertrophy (tissue overgrowth) at 24 months after matrix-induced autologous chondrocyte implantation in a consecutive series of 180 patients.<sup>39</sup> Patients were assessed clinically using the KOOS and underwent MRI at 3, 12, and 24 months post-matrix-induced autologous chondrocyte implantation. Seventeen (9.4%) grafts had failed by 24 months. Three grafts were hypertrophic at 3 months but the hypertrophy had resolved by 24 months. At 24 months, 47 (26.1%) grafts were hypertrophic. KOOS did not differ between patients with hypertrophic grafts and those with normal tissue infill. Longer follow-up is needed

to evaluate whether tissue growth continues and to determine the effect of the hypertrophy on graft stability.

### **Section Summary: Autologous Chondrocyte Implantation for Treatment of Focal Articular Cartilage Lesion(s) of the Knee**

The evidence on autologous chondrocyte implantation for the treatment of focal articular cartilage lesions of the knee includes network analyses, systematic reviews, RCTs, and longer-term observational studies. For large lesions, autologous chondrocyte implantation results in better outcomes than microfracture, particularly in the long term. Studies comparing autologous chondrocyte implantation with osteochondral autograft transfer have shown similar outcomes with smaller lesions, and improved outcomes with autologous chondrocyte implantation when a defect is greater than 4 cm<sup>2</sup>. In 2017, first-generation autologous chondrocyte implantation was replaced with a preparation that seeds the chondrocytes onto a bioresorbable collagen sponge (matrix-induced autologous chondrocyte implantation). Studies to date have not shown improved outcomes compared with first-generation autologous chondrocyte implantation. There is some evidence of an increase in implant hypertrophy (overgrowth) at 2 years, particularly on the femoral condyles that may exceed that of the collagen membrane-covered implant. Long-term studies with a larger number of patients are needed to determine whether hypertrophy impacts graft survival. Matrix-induced autologous chondrocyte implantation for patellar lesions has been evaluated in a systematic review and a nonrandomized comparative study. The included studies reported outcomes that did not differ substantially from those using matrix-induced autologous chondrocyte implantation for tibiofemoral lesions. Observational studies have indicated that a prior cartilage procedure may negatively impact the success of autologous chondrocyte implantation, realignment procedures improve the success of autologous chondrocyte implantation for patellar lesions, and autologous chondrocyte implantation combined with meniscal allograft results in outcomes similar to either procedure performed alone.

## **AUTOLOGOUS CHONDROCYTE IMPLANTATION FOR JOINTS OTHER THAN THE KNEE**

### **Clinical Context and Therapy Purpose**

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

The question addressed in this evidence review is: Does the use of autologous chondrocyte implantation improve the net health outcome in patients with focal articular cartilage lesions of joints other than the knee?

The following PICO was used to select literature to inform this review.

### ***Populations***

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

### ***Interventions***

The treatment being considered is autologous chondrocyte implantation. The first stage of implantation includes arthroscopy to obtain a biopsy of healthy articular cartilage and the second stage is the arthrotomy.

### **Comparators**

The comparators of interest are marrow stimulation or osteochondral autograft.

### **Outcomes**

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

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

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

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

### **Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

## **REVIEW OF EVIDENCE**

### **Systematic Reviews**

Two systematic reviews with meta-analysis have evaluated autologous chondrocyte implantation for patients with focal articular cartilage lesions of the talus.<sup>40</sup>

Hu et al (2021) reported a systematic review with meta-analysis of studies published through November 2020.<sup>41</sup> The authors included a total of 23 case series (N=458) with a mean duration of 12 to 154.8 months. In 6 studies, periosteum-covered autologous chondrocyte implantation was applied while 17 studies used second-generation matrix-induced autologous chondrocyte implantation. Results demonstrated an 89% success rate (defined as American Orthopedic Foot and Ankle Society [AOFAS] score >80) with autologous chondrocyte implantation. Furthermore, AOFAS scores significantly improved after treatment. Twelve of the case series in Hu et al (2021) overlap with Niemeyer et al (2012), described below.

A meta-analysis by Niemeyer et al (2012) evaluated 16 studies (N=213 ).<sup>40</sup> All were case series, with a mean sample size of 13 patients (range, 2 to 46 patients) and mean follow-up of 32 months (range, 6 to 120 months). Most series were prospective. In 6 studies, periosteum-covered autologous chondrocyte implantation was applied while 10 studies used second-generation matrix-induced autologous chondrocyte implantation. Nine different methods were used to evaluate preoperative and postoperative clinical function, with the most common being the AOFAS score. Overall clinical success rate, defined as the percentage of good and excellent results, was 89.9% (range, 50% to 100%). Change in AOFAS scores was not reported.

**Table 2. Comparison of Trials/Studies Included in SR & M-A**

Study	Hu et al (2021) <sup>41</sup> ,	Niemeyer et al (2012) <sup>40</sup> ,
Giannini (2001)	●	●
Koulalis (2002)		●
Cherubino (2003)		●
Dorotka (2004)	●	●
Giannini (2005)	●	●
Whittaker (2005)	●	●
Baums (2006)	●	●
Caumo (2007)	●	●
Giannini (2008)	●	●
Thermann (2008)		●
Giannini (2009)	●	●
Nam (2009)	●	●
Quirbach (2009)		●
Schneider (2009)	●	●
Giza (2010)	●	●
Lee (2010)	●	●
Battaglia (2011)	●	
Haene (2012)	●	
Lee (2013)	●	
Kwak (2014)	●	
Buda (2015)	●	

Study	Hu et al (2021) <sup>41</sup> ,	Niemeyer et al (2012) <sup>40</sup> ,
Desando (2017)	●	
Chan (2018)	●	
Pagliazzi (2018)	●	
Kreulen (2018)	●	
López-Alcorocho (2019)	●	
Lenz (2020)	●	

MA:meta-analysis; SR:systematic review.

**Table 3. SR & M-A Characteristics**

Study	Dates	Trials	Participants	Mean N (Range)	Design	Duration
Hu et al (2021) <sup>41</sup> ,	Through November 2020	23	N=458 patients undergoing autologous chondrocyte implantation for lesions of the talus.	Mean not provided (7 to 46)	Case series	12 to 154.8 mo
Niemeyer et al (2012) <sup>40</sup> ,	1994 to February 2011	16	N=213 patients undergoing autologous chondrocyte implantation or matrix-induced autologous chondrocyte implantation for lesions of the talus.	13 (2 to 46)	Case series	Follow up, 32 mo (6 to 120)

MA:meta-analysis; SR:systematic review.

**Table 4. SR & M-A Results**

Study	Clinical Success Rate	AOFAS Score
Hu et al (2021) <sup>41</sup> ,		
Total N	458	458
Pooled effect (95% CI)	89% (85 to 92)	86.33% (83.33 to 89.33)
p-value	<.001	<.001
Niemeyer et al (2012) <sup>40</sup> ,		
Total N	213	
Pooled effect (95% CI)	89.9 (50 to 100)	NR

AOFAS: American Orthopedic Foot and Ankle Society; CI: confidence interval; MA:meta-analysis; NR: not reported; SR:systematic review.

Shimozono et al (2017) reported a systematic review without meta-analysis of scaffolds-based therapy for osteochondral lesions of the talus and selected articles published through January 2017.<sup>42</sup> Seven studies were found on the use of matrix-induced autologous chondrocyte

implantation and 5 studies were found on Hyalograft C. All studies were case series; the quality of evidence was rated as fair in 2 studies and poor in the remaining 11 studies. Sample sizes ranged from 10 to 46 patients (mean, 22 patients) and follow-up ranged from 21 to 87 months (mean, 46 months). Twelve of 13 studies reported preoperative and postoperative AOFAS scores; the mean AOFAS score improved from 59 to 87.

### **Section Summary: Autologous Chondrocyte Implantation for Joints Other Than the Knee**

The evidence on use of autologous chondrocyte implantation for joints other than the knee includes systematic reviews of case series. The most commonly reported use of autologous chondrocyte implantation is for the talus. Comparative trials are needed to determine whether autologous chondrocyte implantation improves outcomes for lesions of the talus.

### **Summary of Evidence**

For individuals who have focal articular cartilage lesion(s) of the weight-bearing surface of the femoral condyles, trochlea, or patella who receive autologous chondrocyte implantation, the evidence includes systematic reviews, RCTs, and prospective observational studies. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, and quality of life. There is a large body of evidence on autologous chondrocyte implantation for the treatment of focal articular cartilage lesions of the knee. For large lesions, autologous chondrocyte implantation results in better outcomes than microfracture, particularly in the long term. In addition, there is a limit to the size of lesions that can be treated with osteochondral autograft transfer, due to a limit on the number of osteochondral cores that can be safely harvested. As a result, autologous chondrocyte implantation has become the established treatment for large articular cartilage lesions in the knee. In 2017, first-generation autologous chondrocyte implantation with a collagen cover was phased out and replaced with an autologous chondrocyte implantation preparation that seeds the chondrocytes onto a bioresorbable collagen sponge. Although the implantation procedure for this second-generation autologous chondrocyte implantation is less technically demanding, studies to date have not shown improved outcomes compared with first-generation autologous chondrocyte implantation. Some evidence has suggested an increase in hypertrophy (overgrowth) of the new implant that may exceed that of the collagen membrane-covered implant. Long-term studies with a larger number of patients will be needed to determine whether this hypertrophy impacts graft survival. Based on mid-term outcomes that approximate those of first-generation autologous chondrocyte implantation and the lack of alternatives, second-generation autologous chondrocyte implantation may be considered an option for large disabling full-thickness cartilage lesions of the knee. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have focal articular cartilage lesions of joints other than the knee who receive autologous chondrocyte implantation, the evidence includes systematic reviews of case series. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, and quality of life. The greatest amount of literature is for autologous chondrocyte implantation of the talus. Comparative trials are needed to determine whether autologous chondrocyte implantation improves outcomes for lesions in joints other than the knee. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

**SUPPLEMENTAL INFORMATION**

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

**Clinical Input From 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.

**2015 Input**

In response to requests, input was received from 2 physician specialty societies (6 reviewers) and 4 academic medical centers while this policy was under review in 2015. Input was generally supportive of the use of autologous chondrocyte implantation for large patellar lesions, although the degree of support varied. Reviewers indicated that outcomes were improved when realignment procedures were performed concurrently with autologous chondrocyte implantation of the patella and that success rates were lower when using autologous chondrocyte implantation after a prior microfracture. Most reviewers recommended that a prior surgical procedure not be required for lesions greater than 4 cm<sup>2</sup>.

**2011 Input**

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. Input was generally in agreement with the stated criteria for autologous chondrocyte implantation, except the following: input was mixed on the requirement for an inadequate response to a prior surgical procedure and the requirement for an absence of meniscal pathology. Input was also mixed on the investigational status of autologous chondrocyte implantation in patellar and talar joints.

**Practice Guidelines and Position Statements**

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

**American Academy of Orthopaedic Surgeons**

In its 2010 guidelines on the diagnosis and treatment of osteochondritis dissecans, the American Academy of Orthopaedic Surgeons did not recommend for or against a specific cartilage repair technique in symptomatic skeletally immature or mature patients with an unsalvageable osteochondritis dissecans lesion.<sup>43</sup> This finding of insufficient evidence was based on a systematic review that found 4 level IV studies addressing cartilage repair techniques for an unsalvageable osteochondritis dissecans lesion. Because each level IV article used different techniques, different outcome measures, and differing lengths of follow-up, the Academy deemed the evidence for any specific technique inconclusive.

**National Institute for Health and Care Excellence**



In 2018, NICE updated its 2005 guidance on the use of autologous chondrocyte implantation.<sup>44</sup> The NICE recommendations are stated below:

"...as an option for treating symptomatic articular cartilage defects of the femoral condyle and patella of the knee (International Cartilage Repair Society grade III or IV) in adults, only if:

- the person has not had previous surgery to repair articular cartilage defects;
- there is minimal osteoarthritic damage to the knee (as assessed by clinicians experienced in investigating knee cartilage damage using a validated measure for knee osteoarthritis); and
- the defect is over 2 cm<sup>2</sup>."

### U.S. Preventive Services Task Force Recommendations

Not applicable.

### Ongoing and Unpublished Clinical Trials

Some currently ongoing trials that might influence this review are listed in Table 5.

**Table 5. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT04785092	All Autologous Cartilage Regeneration in the Treatment of the Knee Cartilage Defects	20	March 2024
NCT03219307	Safety and Efficacy of NOVOCART 3D in the Treatment of Articular Cartilage Defects Following Failure on Microfracture	30	Dec 2021
NCT01656902 <sup>a</sup>	A Prospective Randomized Controlled Multicenter Phase-III Clinical Study to Evaluate the Safety and Effectiveness of NOVOCART® 3D Plus Compared to the Standard Procedure Microfracture in the Treatment of Articular Cartilage Defects of the Knee	263	June 2023
NCT04744402	A Multi-Center, Active-Controlled, Open-Label, Phase 2 Trial to Compare the Efficacy and Safety of CartiLife®, and Microfracture for Patients With Articular Cartilage Defects in the Knee	50	Dec 2023
NCT01957722 <sup>a</sup>	A Phase 3, Prospective, Randomized, Partially Blinded Multi-Center Study to Measure the Safety and Efficacy of NOVOCART 3D Compared to Microfracture in the Treatment of Articular Cartilage Defects	233	Aug 2026

NCT: national clinical trial.

<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

**CODING**

**The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.**

**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.**

**The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.**

<b>CPT/HCPCS</b>	
27412	Autologous chondrocyte implantation, knee
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 (e.g., osteochondritis dissecans fragmentation, chondral fragmentation)
29875	Arthroscopy, knee, surgical; synovectomy, limited (e.g., plica or shelf resection) (separate procedure)
29876	Arthroscopy, knee, surgical; synovectomy, major, 2 or more compartments (e.g., medial or lateral)
29877	Arthroscopy, knee, surgical; debridement/shaving of articular cartilage (chondroplasty)
29879	Arthroscopy, knee, surgical; abrasion arthroplasty (includes chondroplasty where necessary) or multiple drilling or microfracture
29880	Arthroscopy, knee, surgical; with meniscectomy (medial AND lateral, including any meniscal shaving) including debridement/shaving of articular cartilage (chondroplasty), same or separate compartment(s), when performed
29881	Arthroscopy, knee, surgical; with meniscectomy (medial OR lateral, including any meniscal shaving) including debridement/shaving of articular cartilage (chondroplasty), same or separate compartment(s), when performed
29882	Arthroscopy, knee, surgical; with meniscus repair (medial OR lateral)
29883	Arthroscopy, knee, surgical; with meniscus repair (medial AND lateral)
29884	Arthroscopy, knee, surgical; with lysis of adhesions, with or without manipulation (separate procedure)
J7330	Autologous cultured chondrocytes, implant
S2112	Arthroscopy, knee, surgical for harvesting of cartilage (chondrocyte cells)

<b>ICD-10 DIAGNOSES</b>	
M12.561	Traumatic arthropathy, right knee
M12.562	Traumatic arthropathy, left knee

<b>ICD-10 DIAGNOSES</b>	
M17.0-M17.12	Osteoarthritis of knee primary code range
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
S89.90-S89.92	Unspecified injury of lower leg code range

<b>REVISIONS</b>	
04-02-2015	A stand-alone policy entitled "Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions" was created from the "Transplantation for Chondral Defects" medical policy.
	Updated Description section.
	In Policy section: <ul style="list-style-type: none"> <li>▪ In Item A, removed "or osteochondritis dissecans", to read, "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 in patients who have had an inadequate response to a prior surgical procedure, when all of the following criteria are met:"</li> <li>▪ In Item A #2, removed Outerbridge definition as this is defined in Policy Guidelines.</li> <li>▪ In Item A #3, removed Outerbridge definition as this is defined in Policy Guidelines.</li> <li>▪ Removed Item A #5 "Absence of meniscal pathology."</li> </ul>

<b>REVISIONS</b>	
	<ul style="list-style-type: none"> <li>▪ Removed all language regarding Osteochondral Autograft Transplants for the treatment of cartilaginous defects and Osteochondral Allograft Transplant.</li> <li>▪ In Policy Guidelines, added Items 1-5, and removed all language regarding Autologous Chondrocyte Transplant or Implants and Osteochondral Autograft Transplants and Osteochondral Allograft Transplants.</li> </ul>
	Updated Rationale section.
	In Coding section: <ul style="list-style-type: none"> <li>▪ Added CPT codes 29879, 29880, 29881, 29882, 29883, and 29884.</li> <li>▪ Removed CPT codes 27415, 27416, 28446, 29866, and 29867.</li> <li>▪ Removed ICD-9 Diagnosis code 717.7.</li> </ul>
	Updated Revision section.
	Updated References section.
10-13-2015	Updated Rationale section.
	Updated References section.
01-20-2016	Updated Description section.
	In Policy section: <ul style="list-style-type: none"> <li>▪ In Item A, removed "in patients who have had an inadequate response to a prior surgical procedure" to read, "Autologous chondrocyte implantation may be medically necessary for the treatment of disabling full-thickness articular cartilage defects of the knee caused by acute or repetitive trauma, when all of the following criteria are met:"</li> </ul>
	Updated Rationale section.
	Updated References section.
05-10-2017	Updated Description section.
	In Policy section: <ul style="list-style-type: none"> <li>▪ In Item B, removed "patellar and" to read, "Autologous chondrocyte implantation for all other joints, including talar, and any indications other than those listed above is considered experimental / investigational."</li> <li>▪ Removed Item C, "Matrix-induced autologous chondrocyte implantation is considered experimental / investigational."</li> <li>▪ In Policy Guidelines Item 5 b, added "on an absorbable collagen matrix" to read, "culturing of chondrocytes on an absorbable collagen matrix"</li> <li>▪ In Policy Guidelines Item 5 c, added "place the implant" and removed "create a periosteal flap and implant the chondrocytes" to read, "a separate arthrotomy to place the implant"</li> </ul>
	Updated Rationale section.
	Updated References section.
03-28-2018	Updated Description section.
	In Policy section: <ul style="list-style-type: none"> <li>▪ Revised Policy Guidelines Item 4.</li> </ul>
	Updated Rationale section.
	In Coding section: <ul style="list-style-type: none"> <li>▪ Removed ICD-9 codes.</li> </ul>
	Updated References section.
05-23-2018	Updated Description section.
	In Policy section: <ul style="list-style-type: none"> <li>▪ Updated Policy Guidelines</li> </ul>
	Updated Rationale section.
	Updated References section.
06-05-2019	Updated Rationale section.

<b>REVISIONS</b>	
	Updated References section.
03-08-2020	Description section updated In Policy section: ▪ In Item A 2 added "or patella" to read "Focal, full-thickness (grade III or IV) unipolar lesions of the weight bearing surface of the femoral condyles, trochlea, or patella at least 1.5 cm <sup>2</sup> in size"
06-03-2021	Updated Description section. Updated Rationale section. Updated References section.
05-20-2022	Updated Description Section Updated Coding Section ▪ Converted ICD-10 codes to ranges Updated Rationale Section Updated References Section

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