

Autologous Chondrocyte Implantation (ACI) for
Cartilaginous Defects of the Knee

MEDICAL POLICY NUMBER: 137

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INSTRUCTIONS FOR USE: Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Company reserves the right to determine the application of medical policies and make revisions to medical policies at any time. The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement. Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

SCOPE: Providence Health Plan, Providence Health Assurance, and Providence Plan Partners as applicable (referred to individually as “Company” and collectively as “Companies”).

PLAN PRODUCT AND BENEFIT APPLICATION

☒ Commercial

☐ Medicaid/OHP*

☐ Medicare**

*Medicaid/OHP Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

Significant Injuries To Ligaments, Tendons And Menisci – Guideline Note 98

Newer Interventions For Osteoarthritis Of The Knee – Guideline Note 104

Osteochondral Allograft/Autograft Transplantation (Oat) Of The Knee – Guideline Note 220

**Medicare Members

This Company policy may be applied to Medicare Plan members only when directed by a separate Medicare policy. Note that investigational services are considered “**not medically necessary**” for Medicare members.

COVERAGE CRITERIA

- I. Autologous chondrocyte implantation (ACI) may be considered **medically necessary** for the treatment of single or multiple symptomatic articular cartilage defects of the knee (medial, lateral or trochlear femoral condyle, or patella) when **ALL** of the following criteria (A. – I.) are met:
 - A. Age 15 years or older and skeletally mature, or adults less than 55 years
 1. For individuals 18 years and younger, there must be documentation of closed growth plates; **and**
 - B. Body mass index (BMI) of <35; **and**
 - C. Symptoms from acute or chronic trauma interfere with age-appropriate activities of daily living; **and**
 - D. Symptoms have failed to improve after 3 months of conservative treatment, including physical therapy, as part of pre-operative planning for surgery; **and**
 - E. Defect size of 1.5-10 cm² in total area that affects either one of the following (1.-2.):
 1. The patella; **or**
 2. A weight-bearing surface of the femoral condyle or trochlear region; **and**
 - F. It must be a full thickness defect: grade III or IV on either the Outerbridge or the International Cartilage Repair Society scale. Please see [Policy Guidelines](#) section below for scales; **and**
 - G. The lesion is surrounded by normal or nearly normal cartilage; **and**

- H. Stable and aligned knee with full range of motion, an intact meniscus, functional ligaments (intact or reconstructed), and a normal joint space; **and**
Note: Corrective procedures (e.g. ligament or tendon repair, osteotomy for realignment, meniscal allograft transplant or repair) may be performed concurrent or $\geq$ six months prior to ACL.

- I. None of the following contraindications are present (1.-6.):
1. Known history of hypersensitivity to gentamicin, other aminoglycosides, or products of porcine or bovine origin; **or**
 2. Osteoarthritis of the knee; **or**
 3. Inflammatory arthritis, inflammatory joint disease, or uncorrected congenital blood coagulation disorders; **or**
 4. Prior knee surgery within the last 6 months, excluding surgery to procure a biopsy or a concomitant procedure to prepare the knee for ACL; **or**
 5. A symptomatic musculoskeletal condition in the lower limbs that could impede efficacy measures in the target knee; **or**
 6. Total meniscectomy, or meniscal tear requiring $>50\%$ removal of the meniscus in the target knee.

- II. Autologous chondrocyte implantation (ACI) is considered **not medically necessary** when the above criterion is not met, including but not limited to patients with the following:

- A. Children and adolescents under the age of 15 years
- B. Growth plates that have not closed
- C. Partial-thickness defects
- D. Osteochondritis dissecans (OCD)
- E. Previous history of cancer in the bones, cartilage, fat or muscle of the affected limb
- F. An unstable knee.

Link to [Evidence Summary](#)

POLICY CROSS REFERENCES

- [Osteochondral Allografts and Autografts for Cartilaginous Defects, MP149](#)
- [Meniscal Allograft Transplantation and Other Meniscal Implants, MP150](#)
- [Knee Arthroscopy and Open Procedures, MP434](#)

The full Company portfolio of current Medical Policies is available online and can be [accessed here](#).

POLICY GUIDELINES

Scales Used to Determine Severity of Cartilage Defects of the Knee

International Cartilage Repair Society (ICRS)¹

Grade 0: Normal.

Grade 1: Nearly Normal. Superficial lesions. Soft indentation and/or superficial fissures and cracks.

Grade 2: Abnormal. Lesions extending down to <50% of cartilage depth.

Grade 3: Severely Abnormal. Cartilage defects extending down >50% of cartilage depth as well as down to calcified layer and down to but not through the subchondral bone. Blisters are included in this Grade.

Grade 4: Severely Abnormal. Defects of the full thickness of cartilage involving the subchondral bone.

Outerbridge Scale

This scale was originally created to classify the macroscopic changes of chondromalacia of the patella.² Later, the scale was slightly modified to allow for grading of all cartilage lesions.³

Grade 1: Softening and swelling of the cartilage.

Grade 2: Fragmentation and fissuring in an area half an inch or less in diameter.

Grade 3: Fragmentation and fissuring in an area more than half an inch in diameter.

Grade 4: Erosion of cartilage down to the bone.

BACKGROUND

Cartilaginous Defects

The articular cartilage that covers the articulating bones in the knee, also called hyaline cartilage, is surrounded by an extracellular matrix that contains collagen and chondrocytes (mature cartilage cells). Loss of articular cartilage does not cause pain but ultimately leads to pain in surrounding tissue, swelling, locking, and/or weakness. Defects in articular cartilage can be classified as chondral (cartilage loss) or osteochondral (cartilage plus bone loss). Chondral defects are categorized further into partial thickness or full thickness, the latter of which extends to, but not into, the subchondral bone. Although partial-thickness defects do not always produce significant symptoms, over time they can become full-thickness defects and increase the risk of osteoarthritis.^{4,5}

Treatments

Currently, there is no standard approach to the treatment of articular cartilage defects in the knee. Conventional noninvasive treatments such as weight reduction, physical therapy, braces and orthotics, and/or nonsteroidal anti-inflammatory drugs may provide effective pain relief for some patients. Conventional invasive treatment options may include arthroscopic lavage and/or debridement of loose tissue and unstable cartilage fragments. If defects progress to severe osteoarthritis, total knee replacement may be required.

There are a number of techniques currently being investigated that are designed to replace or stimulate new articular cartilage, such as bone marrow stem cell infiltration, microfracture, drilling, abrasion arthroplasty, allogenic or autologous grafting, and autologous chondrocyte implantation (ACI) (also known as autologous chondrocyte transplantation [ACT]).^{4,5}

Microfracture involves removing the damaged cartilage and drilling holes into the subchondral bone to stimulate growth of new cartilage by providing a new blood supply. Drilling is similar to microfracture. Holes are drilled through the damaged cartilage to provide a new blood supply and stimulate healing.

Abrasion arthroplasty uses a high-speed burr to remove damaged cartilage and reach the subchondral bone. Allogenic and autologous grafting involves removing one or more cylindrical plugs of healthy cartilage and bone from a non-weight-bearing area and placing the cylinders into the site of injury. The use of one plug is also termed mosaicplasty.

Autologous chondrocyte implantation (ACI)

ACI is a technique that aims to stimulate articular cartilage regeneration and fill cartilaginous defects with new hyaline tissue. The techniques used to generate first-generation ACI products such as Carticel™ (See Regulatory Status section below) involve removal, expansion (through culturing), and reimplantation of the patient's own chondrocytes. In first-generation ACI, the cultured cells are injected under a periosteal membrane that is usually taken from the tibia of the patient and sutured over the knee lesion.⁴ The only first-generation ACI product approved by the Food & Drug Administration (FDA), Carticel™, has been discontinued and replaced by the more recent (second-generation) product MACI®.⁴ Second-generation ACI culturing involves the use of porcine-derived collagen membranes. In addition, third-generation ACI products, which have not been approved by the FDA at this time, use resorbable scaffolds. The chondrocyte-containing scaffolds generated by these newer ACI techniques can be cut to fit the defect and then glued into place.⁵

The reimplanted chondrocytes or chondrocyte scaffolds have the potential to generate new hyaline or hyaline-like tissue, which is advantageous over marrow stimulation techniques. ACI techniques have lower risk infection, graft rejection, and/or donor site morbidity compared to allogenic or autologous osteochondral grafting. In addition, ACI does not require that substantial amounts of tissue be harvested, and the procedure can be applied to larger lesions compared to allogenic or autologous osteochondral grafting.^{4,5}

REGULATORY STATUS

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Approval or clearance by the Food and Drug Administration (FDA) does not in itself establish medical necessity or serve as a basis for coverage. Therefore, this section is provided for informational purposes only.

Implantation of autologous chondrocytes is a surgical procedure and, as such, is not subject to regulation by the FDA. However, the FDA does license biological products through the Biologics License Application (BLA) approval pathway.

First-Generation Autologous Chondrocyte Implantation

In 1997, Carticel™ by Vericel, received BLA approval from the FDA for their autologous cultured chondrocytes for the repair of symptomatic cartilage defects of the femoral condyle (medial, lateral, or trochlea), caused by acute or repetitive trauma, in patients who have had an inadequate response to a prior arthroscopic or other surgical repair procedure (e.g., debridement, microfracture, drilling/abrasion arthroplasty, or osteochondral allograft/autograft).⁴

*This product has been discontinued and is no longer available. Vericel has phased out Carticel and now only offers the second-generation ACI product, MACI®.

Second-Generation Autologous Chondrocyte Implantation

In 2016, MACI® by Vericel, received BLA approval from the FDA for their autologous cultured chondrocytes on porcine collagen membrane for the repair of symptomatic, single or multiple full-thickness cartilage defects of the knee with or without bone involvement in adults.^{6,7}

Third-Generation Autologous Chondrocyte Implantation

Currently, there are no third-generation ACI products that have been approved by the FDA for use in the United States.

There are additional ACI products that currently approved or are actively being investigated in Europe that are not approved by the FDA for use in the United States. These products include BioSeed-C, Chondro-Gide, ChondroCelect, and OsCell.

CLINICAL EVIDENCE AND LITERATURE REVIEW

EVIDENCE REVIEW

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of autologous chondrocyte implantation (ACI) as a treatment for cartilaginous defects of the knee. Below is a summary of the available evidence identified through September 2025.

Below is an overview of the key evidence that formed the basis of the medical necessity criteria outlined in this medical policy.

Adults

Systematic Reviews

There have been a number of recent systematic reviews on ACI of the knee. Some reviews evaluated first-generation ACI products such as Carticel™, others evaluated next-generation ACI products like MACI®, and several have reviewed a combination of older and newer ACI products. Many of these reviews have included primary studies that have evaluated ACI in heterogeneous populations including patients with patellar, condyle and/or trochlear lesions. In these reviews, patients with patellar lesions comprised between 5-61% of the total study population.

- In 2023, Hayes published a systematic review evaluating the safety and efficacy of matrix-induced autologous chondrocyte implantation (MACI) procedure for repair of articular cartilage of the knee.⁸ In total, 23 publications reporting results from 21 studies were included for review, including 6 RCTs and 3 prospective cohort studies. The overall body of evidence suggests that MACI is associated with significant improvements from baseline for clinical outcomes, with follow-up ranging from 6 months to 10 years (> 5 years follow-up for the majority of studies). With regard to comparative findings, 5 of 5 studies comparing MACI with microfracture (MFX)

significantly favored MACI for at least 1 measure of effectiveness. Four studies compared MACI with older-generation autologous chondrocyte implantation (ACI) procedures; most statistical comparisons were nonsignificant, although older-generation ACI had a significantly higher reoperation rate in 1 study. One study compared MACI with bone marrow aspirate concentrate (BMAC); all of the patient comparisons were nonsignificant between groups. One study compared MACI with mosaicplasty, and favored mosaicplasty for IKDC scores.

Investigators ultimately assigned a “B” rating (some proven benefit) for use of MACI in the repair of articular cartilage of the knee. Authors stated that a large body of moderate-quality evidence suggests that MACI is associated with improved symptoms, function, quality of life, and ability to perform normal activities of daily living 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. The evidence consistently favors MACI over MFX, and more limited evidence suggests that MACI and older-generation ACI procedures have similar clinical benefit. Limitations included ongoing uncertainty as to when MACI is optimally prescribed in the chondral defect treatment hierarchy, and a lack of definitive patient selection criteria.

- In 2020, ECRI published a systematic review evaluating the safety and efficacy of all ACI generations for the treatment of osteochondral knee defects relative to other cartilage restoration procedures.⁹ Investigators searched the literature through May 2020. In total, 1 systematic review of 10 RCTs,¹⁰ and 3 additional RCTs were included for review. The combined sample size was 1,098 patients. Outcomes of interest included failure rates, knee function scores, and adverse events.

The systematic review¹⁰ showed microfracture had greater failure rates than ACI at 10-year follow-up (RR: 0.12, 95% CI 0.04 to 0.39, based on 2 RCTs). Rates did not differ at 2- and 5-year follow-up (RR 2.0, 95% CI 0.2 to 21.2 and RR 1.00 95% CI 0.4 to 2.3, respectively). Failure rates did not differ between matrix-ACI and microfracture at 2-year follow-up (RR 0.2, 95% CI 0.02 to 1.6; 5-year RR 0.3, 95% CI 0.03 to 3.02). Failure rates were comparable between ACI and osteochondral autograft transfer. One RCT¹¹ reported comparable improvements over baseline that after 2 years in overall Knee Injury and Osteoarthritis Outcome Score (KOOS) for both ACI and microfracture (81.5 for ACI and 73 for microfracture; 6.1 difference was noninferior, $p < 0.0001$). A second RCT¹² reported similar improvement after 2 years in KOOS for ACI and autologous matrix-induced chondrogenesis (68.8 for ACI and 72.2 for autologous matrix-induced chondrogenesis). A third RCT¹³ reported worse functional outcomes after matrix-ACI than after osteochondral autograft transfer (mean International Knee Documentation Committee score and score improvement after 2 years were 73.7 and 31.8, respectively, with matrix-ACI and 81.5 and 44.4, respectively, with osteochondral autograft transfer). Adverse events were reported to be distinct only in this third RCT, with more events with matrix-ACI than osteochondral autograft transfers. Limitations included the lack of homogenous patient selection and indications across studies included for review. Investigators concluded that evidence supporting the efficacy of all ACI generations for the treatment of osteochondral knee defects is inconclusive.

In 2025, ECRI published a systematic review evaluating the safety and efficacy of MACI autologous chondrocyte implant for repairing knee cartilage defects in adults.¹⁴ Authors found that evidence from 6 systematic reviews (SRs) and 2 randomized controlled trials (RCTs)

indicated that MACI is an effective treatment for repairing knee cartilage defects through 5-year follow-up, with several studies suggesting the treatment is effective up to 10 years. MACI's safety and effectiveness appeared comparable to those of other available treatments; however, the evidence did not provide a clear picture of the best treatment for cartilage defects. One SR using network meta-analysis to indirectly compare treatments suggests that autologous matrix-induced chondrogenesis may be more effective. High-quality RCTs that directly compared MACI with other treatments are needed to address evidence gaps. Authors concluded that overall evidence supporting the safety and effectiveness of MACI for knee cartilage defects was "favorable."

- In 2020 (archived 2021), Hayes published two reviews evaluating first-, second- and third-generation ACI of the knee, comparing the different generations of ACI products to each other, microfracture, mosaicplasty, or debridement/abrasion.^{4,5} All studies assessed solely patients whose symptoms did not improve with conservative treatment. Collectively, the two reviews included 24 comparative studies (16 of which were randomized controlled trials [RCTs]) and 9 uncontrolled studies. Both reviews evaluated the use of ACI in adults and older adolescents with symptomatic, full-thickness knee cartilage injuries, focusing on studies reporting outcomes such as joint pain, function and cartilage quality post-treatment. Follow-up of the included studies varied from six months to 15 years. Between the two reviews there were 15 studies which included a sizable proportion of patients undergoing ACI for patellar lesions. Neither the primary studies nor the systematic reviews evaluated patellar defects separately from condyle or trochlear defects. Although some studies reported significant improvement of select outcomes in ACI groups, overall, similar improvements in outcome measures were reported between ACI and other comparator treatments. Taken together, this indicates that in adults and older adolescents with symptomatic, full-thickness knee cartilage injuries, that ACI yields similar benefits to other surgical techniques.

Hayes states the following:

"Although surgeons have not identified ideal candidates for ACI or established strict selection criteria, the literature reflects the following consensus regarding patients who have been considered suitable candidates for ACI:

- Adults younger than 55 years who will return to a relatively high activity level.
- Symptomatic lesion.
- Single, contained (healthy articular cartilage at lesion border), unipolar (no lesion on opposing surface), full-thickness defect 2 to 10 cm².
- No significant bone loss.
- Full range of motion, intact ligaments, and physiologically correct lower limb axis (corrective procedures may be performed in combination with or prior to ACI).
- No osteoarthritis of the knee, autoimmune connective tissue disease, active rheumatoid arthritis, or malignancy.
- Patient motivated and willing to comply with rigorous rehabilitation program.
- If following a prior marrow stimulation technique has failed, several months since prior procedure."

Of note, several key RCTs comparing first-and second-generation ACI products to microfracture provided the basis for the patient selection criteria for ACI above. These RCTs include Basad et al. (2009) evaluating MACI¹⁵, five-year outcomes from the MACI SUMMIT trial by Saris et al. (2014)¹⁶, and five-year outcomes from the TIG/ACT trial for the first-generation ChondroCelect.¹⁷⁻¹⁹

- Additional recent systematic reviews, focusing on comparison studies involving ACI have drawn similar conclusions to Hayes regarding the safety and efficacy of first-generation ACI^{20,21} and newer generation ACI products.²² In addition, systematic reviews assessing both first-and second-generation products together have also arrived at similar conclusions, regardless of the ACI product/technique used.²³⁻²⁷
- In 2017, the National Institute for Health Research (NIHR) reported the results of a systematic review evaluating the clinical effectiveness newer generations of ACI compared to microfracture, specifically MACI® (available in the U.S.) and ChondroCelect (not available in the U.S.).²⁸ The NIHR review, which served as the basis for the 2017 National Institute for Health and Care Excellence (NICE) guidelines described below, included twelve recent systematic reviews including 19 studies (11 RCTs), and four RCTs (N=712) published after the reviews. The reviews were mostly inconclusive on the choice between ACI and microfracture. In the recent trials, ACI was more effective than microfracture in reducing pain and improving function on the Knee injury and Osteoarthritis Outcome Score (KOOS) scale for up to five years of follow-up. Limited long-term data (six studies) were available on the failure rates of both ACI and microfracture after five years. The conclusions regarding follow-up longer than five years were based on high-quality observational studies and indicated that ACI failure rates were lower in patients who had no previous knee repair and in patients with minimal evidence of osteoarthritis. Defect size was not found to be associated with poorer outcomes in this review. The key points highlighted by the review included:
 - “Surgical treatment may be considered for symptomatic lesions of ICRS grade 3 and 4.
 - In small defects, less than 2 cm² ACI may be considered.
 - For lesions >2 cm², cell therapy (ACI) is the most effective treatment based on current evidence.
 - Outcomes are poorer in smokers, patients with a BMI of > 30 kg/m², and those with a long duration of symptoms.
 - When ACI is considered appropriate, it should be first-line treatment because results are poorer if it is used after failure of other procedures.
 - Physical therapy may be effective in controlling symptoms and should be provided before surgery is considered.”

Regarding the use of physical therapy, the review states that “the British Association for Surgery of the Knee (BASK) UK Consensus recommends that all patients being considered for ACI should have had physical therapy first, as that may relieve symptoms.” The NICE guidelines recognize and support the BASK statement, which is a “consensus of 104 U.K. surgeons with specialist knowledge of surgical repair techniques for articular chondrocyte defects of the knee.”

Recent systematic reviews comparing ACI and microfracture have reported similar findings to the NIHR review of reviews above, in that there appears to be similar improvements in pain and functional outcomes between ACI and microfracture.²⁹

Of note, the concern raised in the NIHR review above regarding reduced ACI efficacy reported in patients who had undergone a prior cartilage repair procedure was also echoed by a more recent review by Lamplot et al.³⁰ In this 2018 review, three of the five studies included on ACI demonstrated inferior outcomes following a previous failed cartilage procedure compared with primary ACI.

Randomized Controlled Trials (RCTs)

In 2018, Brittberg et al. published 5-year follow-up results from the SUMMIT (Superiority of MACI Implant Versus Microfracture Treatment) trial, which included 65 patients randomized to Vericel's second-generation product, MACI (90.3%) and 63 to conventional microfracture surgery (87.5%).³¹ Two-year outcomes and study design were published by Saris et al. in 2014.¹⁶ The patient inclusion/exclusion criteria for this trial were as follows:

- Patients aged 18 to 55 years with ≥ 1 symptomatic focal cartilage defect (Outerbridge grade III or IV; and ≥ 3 cm²) of the femoral condyles or trochlea.
- Baseline Knee Injury and Osteoarthritis Outcome Score (KOOS) pain value < 55 (indicating moderate to severe knee-related pain)
- Osteochondritis dissecans (OCD) lesions were allowed if no bone graft was required.
- A stable knee was required; ligament reconstruction procedures were allowed before or concurrently with the study treatment.
- An intact or partial meniscus ($\geq 50\%$) was also required; meniscal repair or resection was allowed before or concurrently with the cartilage repair procedure if $\geq 50\%$ of the functional meniscus remained.
- Major exclusion criteria included:
 - Any knee joint surgery within 6 months before screening.
 - Modified Outerbridge grade III or IV defect(s) on the patella or tibia.
 - A symptomatic musculoskeletal condition in the lower limbs that could impede efficacy measures in the target knee.
 - Total meniscectomy, meniscal allograft, or bucket-handle tear or displaced tear requiring $> 50\%$ removal of the meniscus in the target knee.
 - Malalignment requiring osteotomy to correct tibial-femoral or patella-femoral alignment;
 - Kellgren-Lawrence grade 3 or 4 osteoarthritis.
 - Inflammatory disease or other condition affecting the joints; or septic arthritis within 1 year before screening.

Similar to the results reported in the Hayes and NIHR reviews above, improvement of some outcomes such as pain and function, by some but not all scales, in MACI over microfracture were observed, but improvements in other outcomes, such as improved defect filling as evidenced by MRI, were not significantly different between treatment groups.

The evidence review below has focused on the investigational indications in this policy. Due to the large body of evidence on ACI for cartilage defects of the knee, only systematic reviews and RCTs were reviewed below.

Children and Adolescents (Under 18 Years of Age)

Systematic Reviews

In 2016, DiBartola et al. published the results of the systematic review that assessed the clinical outcomes of ACI in adolescent knees.³² The review included five small case series (N= 115 subjects, studies ranged from 6-37 patients). The majority of patients underwent first-generation ACI (N= 95, 83%). Mean patient age was 16.2 years (range, 11 to 21 years). The studies were heterogenous in terms of follow-up (mean = 52.3 months, range = 12 to 74 months), defect size (mean = 5.3 cm², range = 0.96-15.8 cm²) and defect etiology. Although the review reported improvement of some outcomes as a result of ACI in adolescent populations, the review suffered from the following limitations:

- Limited number of studies in the existing literature on this patient population. This limits the ability to perform statistical analysis and the ability to draw subjective conclusions regarding the safety and efficacy of ACI in adolescents.
- Relatively high use of concurrent procedures during ACI in the included studies, which varied within and between studies. Heterogeneity in concurrent procedures made it difficult to draw definitive conclusions about the efficacy of ACI.
- None of the studies in this systematic review were comparative in nature and, in general, there is a paucity of RCTs published evaluating ACI in adolescents.
- None if the studies included information on growth plate closure, which is thought to be an important factor in healing and new cartilage formation.

In 2018, Valtanen et al. also published results of a systematic review that evaluated clinical outcomes in patients 19 years or younger following various surgical procedures to repair articular cartilage, including ACI.³³ This review only identified and included six case series on ACI in total, with two newer small series (n=27 and n=37) published in 2017 that were not included in the DiBartola review above. The authors concluded that outcome data on cartilage repair in pediatric and adolescent populations was limited. The review had limitations similar to those of the DiBartola review above.

Randomized Controlled Trials (RCTs)

No RCTs evaluating ACI in pediatric or adolescent populations were identified after the publication of the systematic reviews described above.

Osteochondritis Dissecans (OCD)

- In 2019, Sacolick and colleagues conducted a systematic review evaluating the efficacy of ACI for the treatment of OCD.³⁴ Independent investigators searched the literature through April 2018, identified eligible studies, assessed study quality and extracted data. In total, 9 studies assessing 179 patients (range: 3 to 40) were included for review. Median follow-up was 5 years. Investigators reported significant improvement in clinical outcome measures, particularly among males, active patients, smaller lesion sizes and younger patients. Limitations included the

low-quality of evidence included for review (i.e. case series) as well as studies' small sample sizes, and heterogeneous patient characteristics and treatment parameters. Investigators nonetheless concluded that autologous cartilage therapies for the treatment of OCD are clinically effective.

- Based on the 2017 NIHR systematic review described above, there is a very small body of published studies that have evaluated the efficacy of ACI in patients with OCD.²⁸ The NIHR review included the following systematic reviews but was unable to identify any RCTs that met inclusion criteria after the publication of these reviews:
 - The 2009 Kon et al.²² review included two small case series that included patients with OCD (N=105).
 - The Cochrane review published in 2010 (Vasiliadis and Wasiak)³⁵ reported that four of the six RCTs included in the review included patients with OCD. However, outcomes for this subset of patients were not reported separately in the review. Three of the four RCTs included did not analyze outcomes of the OCD patients separately, making it difficult to determine the efficacy of ACI in this subset of patients.^{15,36,37}
 - The 2003 publication of the Bentley et al. RCT included in this review did not report outcomes separately for the small number of OCD patients included. However, the 2012 publication on this RCT is the only trial to date that has reported outcomes separately for OCD patients. In the 2012 publication, reporting 5-year outcomes, 16 (11 in the ACI group and 6 who underwent mosaicplasty) OCD patients recruited were available for 5-year follow-up. At 5-years, there were no failures in the ACI group, and one failure in the mosaicplasty group. However, statistical analyses were not performed due to small patient numbers.³⁸
 - The 2013 systematic review by Negrin and Vécsei³⁹ included one small RCT (Knutsen et al. (2007)³⁶, 11 OCD patients out of 80). Neither the review, nor the RCT analyzed the outcomes of the OCD patients separately.

Osteoarthritis (OA)

The NIHR systematic review described above specifically excluded studies that recruited patients with advanced osteoarthritis (OA) of the knee.²⁸ The review stated:

“Patients with only early OA (less than grade 2 which has definite osteophytes and possible joint space narrowing) could have been included in some trials. However, no details for such a subgroup are given in the results. In the TIG/ACT trial,¹⁹ patients with advanced OA (as defined by radiographic atlas OA grade 2–3) were excluded.”

The NIHR review included a single observational study (Nawaz et al., 2014)⁴⁰ that evaluated ACI in patients with early OA. The study authors reported that the presence of OA had a significant detrimental effect on survivorship, with survivorship worsening as the OA grade increased (Grade 1: HR = 2.077, 95 % CI: 1.299 to 3.322, p = 0.002; Grade 2: HR = 3.450, 95 % CI: 2.646 to 4.498, p < 0.001; and Grade 3: HR = 3.820, 95 % CI: 2.185 to 6.677, p < 0.001). The authors concluded that the presence of even early OA increased failure rates, with patients with grade 1-2 OA having only 25% graft survival at 10-year follow-up.

Other systematic reviews^{29,41} have included single case series that evaluated ACI in patients with OA in their study cohort. However, neither of these reviews reported on ACI outcomes in this sub-population. Of note, the Filardo et al. case series reported poor clinical outcomes and high failure rates for ACI regardless of OA severity, while the Brix et al. series reported higher failure rates in patients with OA compared to those non-OA cartilage defects.^{42,43}

CLINICAL PRACTICE GUIDELINES

National Institute for Health and Care Excellence (NICE)

The 2017 NICE guidance on autologous chondrocyte implantation (ACI) for treating symptomatic articular cartilage defects of the knee recommend the following:⁴⁴

“Autologous chondrocyte implantation (ACI) is recommended as an option for treating symptomatic articular cartilage defects 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)
- the defect is over 2 cm².”

The guidance also made the following statements:

- “The indication for use of traditional ACI in the knee is for the repair of single or multiple symptomatic, full-thickness cartilage defects of the joint with or without bone involvement in adults.
- ACI is contraindicated in people with severe osteoarthritis of the knee.
- People with articular cartilage defects will first be offered best supportive care. This includes exercise, weight loss, physiotherapy, intra-articular corticosteroid injections, analgesia, off-loading, and applying heat/cold or transcutaneous electrical nerve stimulation.”

Of note, this recommendation was based on published results from four trials evaluating first- and next-generation ACI products offered in either the United Kingdom (OsCell: first-generation ChondroCelect: next-generation) or the United States (Vericel’s MACI: second-generation).

American Academy of Orthopaedic Surgeons (AAOS)

In 2016, the AAOS evaluated optimal clinical practice for the treatment of osteochondritis dissecans (OCD) of the femoral condyles.⁴⁵ Appropriateness ratings for different therapies were developed using a modified Delphi procedure. On the basis of a non-systematic review of evidence, authors determined that ACI was “appropriate” for OCD patients presenting with pain, no mechanical catching or locking symptoms, effusion, partially or fully closed growth plates, with imaging suggestive of stable and unsalvageable OCD fragments.

EVIDENCE SUMMARY

There is enough evidence to show that autologous chondrocyte implantation (ACI) is a safe and effective treatment for symptomatic articular cartilage defects of the knee in adults who meet the medical necessity criteria above. However, the efficacy of ACI appears to be diminished in patients with contraindications such as osteoarthritis or inflammatory arthritis, or those who have undergone total meniscectomy. Lastly, there is insufficient evidence that ACI is safe or effective in patients under the age of 18 years, including patients whose growth plates have not closed, patients (adult and juvenile) with osteochondritis dissecans (OCD), and for treatment of partial-thickness defects. A clinical practice guideline from the American Academy of Orthopaedic Surgeons supports the use of ACI for the treatment of OCD, however, this guideline was not based on a systematic review of evidence.

HEALTH EQUITY CONSIDERATIONS

The Centers for Disease Control and Prevention (CDC) defines health equity as the state in which everyone has a fair and just opportunity to attain their highest level of health. Achieving health equity requires addressing health disparities and social determinants of health. A health disparity is the occurrence of diseases at greater levels among certain population groups more than among others. Health disparities are linked to social determinants of health which are non-medical factors that influence health outcomes such as the conditions in which people are born, grow, work, live, age, and the wider set of forces and systems shaping the conditions of daily life. Social determinants of health include unequal access to health care, lack of education, poverty, stigma, and racism.

The U.S. Department of Health and Human Services Office of Minority Health calls out unique areas where health disparities are noted based on race and ethnicity. Providence Health Plan (PHP) regularly reviews these areas of opportunity to see if any changes can be made to our medical or pharmacy policies to support our members obtaining their highest level of health. Upon review, PHP creates a Coverage Recommendation (CORE) form detailing which groups are impacted by the disparity, the research surrounding the disparity, and recommendations from professional organizations. PHP Health Equity COREs are updated regularly and can be found online [here](#).

BILLING GUIDELINES AND CODING

- There are a number nonspecific arthrotomy and arthroscopy codes that are not appropriate for autologous chondrocyte implantation (ACI), including but not limited to 27330, 27331, 27334, and 29879. Of note, 29879 should not be billed in conjunction with ACI unless performed in a different compartment of the knee.
- Many of the codes in this policy are not specific to autologous chondrocyte implantation (ACI) and may be used for other restorative procedures for the knee, which are addressed in other medical policies. For example: 27415, 27416, 29866 and/or 29867 may also be requested for osteochondral autografting (mosaicplasty or OATS) or allografting. Please see the [Medical Policy Cross References](#) section below for applicable medical policies.

- HCPCS code S2122 is not recognized as a valid code for claim submission as indicated in the relevant Company Coding Policy (HCPCS S-Codes and H-Codes, 22.0). Providers need to use alternate available CPT or HCPCS codes to report for this service. If no specific CPT or HCPCS code is available, then an unlisted code may be used. Note that unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. Thus, if an unlisted code is billed related to a non-covered service addressed in this policy, it will be denied as not covered.

CODES*		
CPT		
	1092T	Implantation of acellular scaffold (eg, hyaluronan), knee, single implant; into chondral defect, open
	1093T	Implantation of acellular scaffold (eg, hyaluronan), knee, single implant; into a chondral or osteochondral defect, arthroscopic
	1094T	Implantation of acellular scaffold (eg, hyaluronan), knee, single implant; each additional acellular scaffold implantation (List separately in addition to code for primary procedure)
	27332	Arthrotomy, with excision of semilunar cartilage (meniscectomy) knee; medial OR lateral
	27333	Arthrotomy, with excision of semilunar cartilage (meniscectomy) knee; medial AND lateral
	27412	Autologous chondrocyte implantation, knee
	27415	Osteochondral allograft, knee, open
	27416	Osteochondral autograft(s), knee, open (eg, mosaicplasty) (includes harvesting of autograft[s])
	27599	Unlisted procedure, femur or knee
	29866	Arthroscopy, knee, surgical; osteochondral autograft(s) (eg, mosaicplasty) (includes harvesting of the autograft[s])
	29867	Arthroscopy, knee, surgical; osteochondral allograft (eg, mosaicplasty)
	29870	Arthroscopy, knee, diagnostic, with or without synovial biopsy (separate procedure)
	29871	Arthroscopy, knee, surgical; for infection, lavage and drainage
	29874	Arthroscopy, knee, surgical; for removal of loose body or foreign body (eg, osteochondritis dissecans fragmentation, chondral fragmentation)
	29877	Arthroscopy, knee, surgical; debridement/shaving of articular cartilage (chondroplasty)
	29999	Unlisted procedure, arthroscopy
HCPCS	J7330	Autologous cultured chondrocytes, implant
	S2112	Arthroscopy, knee, surgical for harvesting of cartilage (chondrocyte cells)

***Coding Notes:**

- The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.

- See the non-covered and prior authorization lists on the Company [Medical Policy, Reimbursement Policy, Pharmacy Policy and Provider Information website](#) for additional information.
- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as “medically unlikely edits” (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

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POLICY REVISION HISTORY

DATE	REVISION SUMMARY
2/2023	Converted to new policy template.
1/2024	Annual update. Update age criteria. Update noncoverage position from investigational to NMN when medical necessity criteria are not met. Title update.
11/2024	Annual update. Size requirement of defect updated.
11/2025	Annual update. No changes.
10/2026	Q4 code set update.