Knee: Autologous Chondrocyte Implantation (ACI) for Cartilaginous Defects

Effective Date: 3/1/2020

Technology Assessment Committee Approved Date: 4/10; 5/12; 7/14; 6/15
Medical Policy Committee Approved Date: 2/11; 2/12; 7/13; 3/16; 4/17; 6/18; 1/19; 2/2020

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

APPLIES TO:
All lines of business

BENEFIT APPLICATION
Medicaid 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.

POLICY CRITERIA

I. Autologous chondrocyte implantation (ACI) may be considered medically necessary and covered 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. – H.) are met:

A. Age 18-55 years (adolescents must have closed growth plates); and  
B. Body mass index (BMI) of <35; and  
C. Disabling knee pain from acute or chronic trauma unresponsive to conservative treatment including physiotherapy; and  
D. Defect size of 2-10 cm² in total area that affects either one of the following:  
   1. The patella; or  
   2. A weight-bearing surface of the femoral condyle or trochlear region; and
E. 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

F. The lesion is surrounded by normal or nearly normal cartilage; and

G. 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 ≥ six months prior to ACI.

H. None of the following contraindications are present:
   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 ACI; 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 investigational and not covered when the above criterion is not met, including but not limited to patients with the following:
   A. Children and adolescents under the age of 18 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 Policy Summary

POLICY GUIDELINES

Scales Used to Determine Severity of Cartilage Defects of the Knee

*International Cartilage Repair Society (ICRS)*

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.
Grades:

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. Later, the scale was slightly modified to allow for grading of all cartilage lesions.

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.

BILLING GUIDELINES

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 Cross References section below for applicable medical policies.

CPT/HCPCS CODES

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<td>Autologous cultured chondrocytes, implant</td>
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<td>S2112</td>
<td>Arthroscopy, knee, surgical for harvesting of cartilage (chondrocyte cells)</td>
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**Knee: Autologous Chondrocyte Implantation (ACI) for Cartilaginous Defects**

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**Unlisted Codes**

All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy then **prior-authorization is required.**

- 27599 | Unlisted procedure, femur or knee |
- 29999 | Unlisted procedure, arthroscopy |

**DESCRIPTION**

*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. 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®. 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.

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.

**REVIEW OF EVIDENCE**

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 October of 2018.

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

**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 2017, 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.\(^4,5\) 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 \(2 \text{ to } 10 \text{ cm}^2\).
- 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 MACI\(^6\), five-year outcomes from the MACI SUMMIT trial by Saris et al. (2014)\(^7\), and five-year outcomes from the TIG/ACT trial for the first-generation ChondroCelect.\(^8-10\)

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\(^11,12\) and newer generation
ACI products. 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.

Also 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.). 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.

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. 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%). Two-year outcomes and study design were published by Saris et al. in 2014. 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 (≥50%) was also required; meniscal repair or resection was allowed before or concurrently with the cartilage repair procedure if ≥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. 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. 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)

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. 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. review included two small case series that included patients with OCD (N=105).
- The Cochrane review published in 2010 (Vasiliadis and Wasiak) 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.6,24,25

- 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.26

- The 2013 systematic review by Negrin and Vécsei27 included one small RCT (Knutsen et al. (2007)24, 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.17 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,10 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)28 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 3.222, 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 reviews18,29 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.30,31
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:\(^2\)

“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 cm\(^2\).”

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).

CENTERS FOR MEDICARE & MEDICAID

As of 11/06/2018, the following Centers for Medicare & Medicaid (CMS) coverage guidance was identified which addresses one of the HCPCS codes applicable to this policy:

- Local Coverage Determination (LCD): Non-Covered Services (L35008)\(^3\)

This LCD indicates that the HCPCS code J7330 (Autologous cultured chondrocytes, implant ) is not medically necessary. However, no Medicare guidance on the actual procedure (coded with 27412) was identified.

Per this policy, autologous chondrocyte implantation may be considered medically necessary (procedure and/or implant) for all lines of business, including Medicare, when the policy criteria above are met.
Knee: Autologous Chondrocyte Implantation (ACI) for Cartilaginous Defects

POLICY SUMMARY

There is sufficient evidence 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.

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 Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days notice of policy changes that are restrictive in nature.

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.

REGULATORY STATUS

U.S. Food & Drug Administration (FDA)

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). 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. Prescribing information published by the FDA indicates:

“MACI® is an autologous cellularized scaffold product indicated for the repair of symptomatic, single or multiple full-thickness cartilage defects of the knee with or without bone involvement in adults.34

Limitations of Use
- Effectiveness of MACI® in joints other than the knee has not been established.
- Safety and effectiveness of MACI in patients over the age of 55 years have not been established.

Contraindications
- Known history of hypersensitivity to gentamicin, other aminoglycosides, or products of porcine or bovine origin.
- Severe osteoarthritis of the knee.
- Inflammatory arthritis, inflammatory joint disease, or uncorrected congenital blood coagulation disorders.
- Prior knee surgery (within 6 months), excluding surgery to procure a biopsy or a concomitant procedure to prepare the knee for a MACI implant.
- Inability to cooperate with a physician-prescribed post-surgical rehabilitation program.

Warnings and Precaution
- 5.1 Malignancy
  - Safety of MACI in patients with malignancy in the area of cartilage biopsy or implant is unknown. Expansion of malignant or dysplastic cells present in biopsy tissue during manufacture and subsequent implantation may be possible.... In addition, implantation of normal autologous chondrocytes could theoretically stimulate growth of malignant cells in the area of the implant.
- 5.3 Presurgical Assessment of Comorbidities
  - Local inflammation or active infection in the bone, joint, and surrounding soft tissue: patients should be deferred until complete recovery.
  - Meniscal pathology: presence of an unstable or torn meniscus requires partial resection, repair, or replacement prior to or concurrent with MACI implantation. MACI is not recommended in patients with a total meniscectomy.
  - Cruciate ligament instability: the joint should not possess excessive laxity, which may create excessive shear and rotational forces across the joint. Both anterior and posterior cruciate ligaments should be stable or undergo reconstruction prior to or concurrent with MACI implantation.
Misalignment: the tibio-femoral joint should be properly aligned, and patella tracking should be normalized. Varus or valgus misalignment of the tibio-femoral joint and abnormal patella tracking may abnormally load joint surfaces and jeopardize the implant. Misalignment and patella tracking should be addressed with a corrective osteotomy or similar corrective procedure prior to or concurrent with MACI implantation."

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.

Mental Health Parity Statement

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.

MEDICAL POLICY CROSS REFERENCES

Knee: Cartilaginous Defects: Procedures and Implants, SUR264
Knee: Meniscal Allograft Transplantation and Other Meniscal Implants, SUR266

REFERENCES

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