MEDICAL POLICY	Knee: Osteochondral Allografts and Autografts for Cartilaginous Defects
Effective Date: 10/1/2021  10/1/2021 Medical Officer Date	Medical Policy Number: 149 Technology Assessment Committee Approved Date: 8/03; 8/04; 7/05; 4/10; 3/13; 1/14; 1/15; 1/16; 3/16 Medical Policy Committee Approved Date: 9/07; 11/09; 2/11; 8/12; 4/17; 6/18; 1/19; 2/2020; 8/2020; 9/2021

See Policy CPT CODE section below for any prior authorization requirements

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

Osteochondral Allografting of the Knee

I. Osteochondral allografting may be considered **medically necessary and covered** for the treatment of symptomatic articular cartilage defects of the knee (medial, lateral or trochlear femoral condyle, or patella) when **ALL** of the following criteria (A. – G.) are met:

A. Age of <55 years; **and**
B. Symptoms from acute or chronic trauma interfere with age-appropriate activities of daily living; **and**
C. Symptoms have failed to improve after 3 months of conservative treatment, including physical therapy, as part of pre-operative planning for surgery; **and**
D. The following must be confirmed by MRI, CT or arthroscopy:
   1. Defect size of 2cm^2 in total area or greater; **and**

2. It must be a focal, full thickness defect (grade III or IV on the Outerbridge scale). Please see Policy Guidelines section for scale; **and**

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

F. The knee has normal alignment or will be surgically corrected (osteotomy) at the time of the allograft procedure; **and**

G. No inflammatory arthritis or osteoarthritis is present anywhere in the joint (surrounding the lesion or the opposing surface).

II. Osteochondral allografting is considered **investigational and not covered** when the above criteria (I.A. – I.F.) are not met.

Osteochondral Autografting of the Knee (Mosaicplasty or Osteochondral Autograft Transplant [OATS])

III. Osteochondral autografting may be considered **medically necessary and covered** for the treatment of symptomatic articular cartilage defects of the knee (medial, lateral or trochlear femoral condyle, or patella) when **ALL** of the following criteria (A. – J.) are met:

A. The patient is skeletally mature with documented closure of growth plates (e.g., 15 years or older); **and**

B. The patient is considered too young to be an appropriate candidate for total knee arthroplasty (e.g., patient is under 55 years of age); **and**

C. Body mass index (BMI) of <35; **and**

D. Symptoms from acute or chronic trauma interfere with age-appropriate activities of daily living; **and**

E. Symptoms have failed to improve after 3 months of conservative treatment, including physical therapy, as part of pre-operative planning for surgery; **and**

F. Defect size of 1-2.5 cm^2 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**

G. It must be a focal, unipolar, full thickness defect (grade III or IV on the Outerbridge scale). Please see Policy Guidelines section for scale; **and**

H. Stable and aligned knee (or achieved concurrently at time of autograft procedure); **and**

I. Documented minimal to absent degenerative changes in the surrounding articular cartilage (Outerbridge grade II or less); **and**

J. Normal-appearing hyaline cartilage surrounding the border of the defect.

IV. Osteochondral autografting is considered **investigational and not covered** when the above criteria (III.A. – I.I.) are not met.

Investigational Procedures and Implants

V. Treatments for articular cartilage defects of the knee that are considered **investigational and not covered**, include, but are not limited to the following (A.-F.):

A. Combination OATS/autologous chondrocyte implantation (ACI) procedures.
B. Minced autograft cartilage, including cartilage processed using systems such as the Cartilage Autograft Implantation System (CAIS) or the Reveille Cartilage Processor.
C. Minced allograft cartilage products (e.g., BioCartilage®, DeNovo NT, and DeNovo ET)
D. Decellularized Osteochondral Allograft Plugs (e.g., Chondrofix)
E. Reduced Osteochondral Allograft Discs (e.g., ProChondrix and Cartiform)
F. Procedures using synthetic products, including but not limited to the following (1.-2.):
   1. Granules (e.g., TRUGRAFT™)
   2. Plugs (e.g., TruFit® Plugs, POLYGRAFT™)

Link to Policy Summary

POLICY GUIDELINES

Appropriate Use Criteria for the Management of Osteochondritis Dissecans of the Femoral Condyle

In 2015, the American Academy of Orthopedic Surgeons (AAOS) published appropriate use criteria addressing the management of osteochondritis dissecans of the femoral condyle.[1] These appropriate use criteria were developed from a list of 288 patient scenarios for which 13 treatments were evaluated for appropriateness, including osteochondral allograft transplantation. Sixty-four clinical scenarios are outlined with treatments presented as "Rarely Appropriate," "May Be Appropriate," and "Appropriate." These scenarios may be accessed at the following link.[1] The 9-point appropriateness scale is defined as follows:

Rating	Explanation
7-9	**Appropriate** Appropriate for the indication provided, meaning treatment is generally acceptable and is a reasonable approach for the indication and is likely to improve the patient's health outcomes or survival.
4-6	**May Be Appropriate**: Uncertain for the indication provided, meaning treatment may be acceptable and may be a reasonable approach for the indication, but with uncertainty implying that more research and/or patient information is needed to further classify the indication.
1-3	**Rarely Appropriate:** Rarely an appropriate option for management of patients in this population due to the lack of a clear benefit/risk advantage; rarely an effective option for individual care plans; exceptions should have documentation of the clinical reasons for proceeding with this care option (i.e. procedure is not generally acceptable and is not generally reasonable for the indication).

Outerbridge Scale Used to Determine Severity of Cartilage Defects of the Knee

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.

BILLING GUIDELINES

Arthroscopy code 29879 is not appropriate for OATS or osteochondral allografting. This should not be billed in conjunction with OATS or osteochondral allografting unless performed in a different compartment of the knee.

Many of the codes in this policy are not specific to osteochondral autografting or allografting 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 autologous chondrocyte implantation (ACI). Please see the Cross References section below for applicable medical policies.

CPT CODES

All Lines of Business	
Prior Authorization Required	
27415	Osteochondral allograft, knee, open
27416	Osteochondral autograft(s), knee, open (eg, mosaicplasty) (includes harvesting of autograft[s])
29866	Arthroscopy, knee, surgical; osteochondral autograft(s) (eg, mosaicplasty) (includes harvesting of the autograft[s])
29867	Arthroscopy, knee, surgical; osteochondral allograft (eg, mosaicplasty)
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). The knee joint and its articular cartilage may be damaged by a variety of disease processes or from acute traumatic injury. Once injured or lost, articular cartilage is slow to repair itself and regenerate due to its reduced blood supply and hypocellular nature. 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). Defects are categorized further into partial thickness or full thickness, the latter of which extends to 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.[4-6]

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, autologous chondrocyte implantation (ACI), osteochondral allografting and osteochondral autograft transfer (OAT). 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. ACI harvests cells from the patient's cartilage, cultures them in the laboratory and implants the cultured chondrocytes into the site of injury.[4-6]

<u>Osteochondral Allografts and Autografts</u>

Allografts are tissue obtained from another individual, typically a cadaver. Autografts are tissue obtained from the patient in whom it will be used. Osteochondral tissue indicates a combination of articulating cartilage and the bone under it.[6]

During osteochondral autografting, autograft cartilage is harvested from a non-weight-bearing area in the form of one or more cylindrical plug(s) that contain healthy cartilage and underlying bone. The plug is matched to the defect and impacted into place in an attempt to provide a smooth cartilage surface. In general, the term OAT (or OATS) refers to the use of one or two larger cylindrical plugs and mosaicplasty is used to describe multiple cylindrical plugs. Autografts are typically only used for small cartilage defects because healthy graft tissue can be taken only from a limited area of the same joint.[6]

Allograft transplants may be considered for larger defects. The tissue is taken from a cadaver donor. A block of cartilage and bone is sterilized and prepared in a lab where it is also tested for infectious disease prior to implantation into the recipient's site of injury.[6]

Other Procedures and Implants

Autologous or allogeneic minced cartilage, decellularized osteochondral allograft plugs, and reduced osteochondral allograft discs are also being evaluated as a treatment of articular cartilage lesions.

Minced Cartilage

Filling defects with minced or particulated articular cartilage (autologous or allogeneic) is another technique being investigated for cartilage repair. It is purported that mincing the tissue helps both with cell migration from the extracellular matrix and with fixation. In the literature, this technique may be referred to as mincing, particulating, morcellating or crushing of the cartilage, or paste grafting.

- Minced Autograft Cartilage:
    - The Cartilage Autograft Implantation System (CAIS) harvests cartilage and disperses chondrocytes on a scaffold in a single-stage treatment.
    - The Reveille Cartilage Processor (Exactech Biologics) has a high-speed blade and sieve to cut autologous cartilage into small particles for implantation.
- Mined Allograft Cartilage:
    - BioCartilage® (Arthrex) consists of a dehydrated, micronized allograft articular cartilage matrix that is intended to provide a scaffold for microfracture. The small particles are mixed with a blood solution to create a paste-like consistency that is applied over a cartilage defect.
    - DeNovo NT (Natural Tissue) Graft is produced by ISTO Technologies and distributed by Zimmer. DeNovo NT consists of manually particulated cartilage obtained from juvenile allograft donor joints. The tissue fragments are mixed intraoperatively with fibrin glue before implantation in the prepared lesion.
    - DeNovo ET (Engineered Tissue) Graft is an in vitro grown, 3-dimensional hyaline-like cartilage tissue created by culturing disaggregated allogeneic chondrocytes derived from juvenile human donors.

Decellularized Osteochondral Allograft Plugs

Chondrofix (Zimmer) is a minimally processed osteochondral allograft composed of decellularized hyaline cartilage and cancellous bone. It can be used "off the shelf" with precut cylinders (7-15 mm). Multiple cylinders may be used to fill a larger defect in a manner similar to OAT/mosaicplasty.

Reduced Osteochondral Allograft Discs

ProChondrix (AlloSource) and Cartiform (Arthrex) are wafer-thin allografts where the bony portion of the allograft is reduced. The discs are laser etched or porated and contain hyaline cartilage with chondrocytes, growth factors, and extracellular matrix proteins. ProChondrix is available in dimensions

from 7 - 20 mm and Cartiform is cut to the desired size and shape. The osteochondral discs are typically inserted after microfracture and secured in place with fibrin glue and/or sutures.

Synthetic Products

Synthetic products are being proposed for the repair of osteochondral articular cartilage defects, including in a procedure termed non-autologous mosaicplasty. These implants include polymer scaffolds, granules (e.g., TRUGRAFT™) and plugs (e.g., TruFit® Plugs, POLYGRAFT™) used for grafting. These implants are thought to provide a scaffold for the growth of new bone and are gradually resorbed by the body and replaced with bone.

REVIEW OF EVIDENCE

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of osteochondral allografting, autografting and other techniques and implants as treatments for cartilaginous defects of the knee. Below is a summary of the available evidence identified through July 2021.

Osteochondral Allografts

Due to the large body of evidence on allografting and autografting techniques for cartilage defects of the knee, the evidence review below focused primarily on recent systematic reviews and RCTs.

Systematic Reviews

- In 2011, the Washington State Health Care Authority (WA HCA) published the results of a technology assessment of osteochondral allograft and autograft transplantation, including one technology assessment, two systematic reviews and primary literature.[7] The WA HCA recommended coverage of allograft and autograft transplantation for the following patient population:
    - Age <50, older at the discretion of the agency;
    - Excluding malignancy, degenerative and inflammatory arthritis in the joint; and
    - Single focal full-thickness articular cartilage defect

  Regarding allografts, the WA HCA was unable to define an appropriate patient population to be treated using allografts. However, based on consensus among three nonrandomized studies (2/3 studies), limited patient inclusion criteria were as follows:

    - "Mention of symptoms
    - Isolated lesions
    - Full-thickness lesions
    - Excluded participants with ligamentous deficiency, malalignment or knee instability."

  A review of comparative studies and case series indicated that most outcomes had significant levels of improvement when allografting was compared to other treatments. Outcomes such as

Tegner activity score and SF-12 quality of life scores were among the outcomes reported as significantly favoring allografting over other procedures.

- In 2018, the WA HCA updated their 2011 recommendations based on an updated literature search, including two recent systematic reviews that reported on functional outcomes and safety of allografting.[8,9] Both of these systematic reviews reported that functional outcomes between 5-20 years post-allograft still showed improvement over pre-treatment baseline measures. The new evidence did not change the recommendations from the 2011 report.

- In addition, in 2015 De Caro et al. published the results of a systematic review that included 11 studies (N=374 knees in 358 patients) of patients predominantly treated with fresh osteochondral allografts.[10] The size of the lesions ranged from 1- 27 cm^2 (mean area of 6.4 cm^2). The age of patients ranged from 15 to 68 years. The majority of procedures were performed on femoral condyles, but patellar lesion were treated in one study. Overall results showed improvement in objective and subjective clinical scores and functional scores at long-term follow-up, and graft survival rates of 82% at 10 years and 66% at 20 years. Although cartilage integration was limited, bony integration was usually achieved, demonstrating that allografting is a reasonable cartilage restorative treatment for larger lesions.

Pediatric and Adolescent Populations

- In 2018, Valtanen et al. also published results of a systematic review that evaluated clinical outcomes in patients ranging from 11 to 18 years following various surgical procedures to repair articular cartilage, including osteochondral allografting and autografting.[11] This review only identified and included one small case series on allografting and two studies (one small RCT and one small case series) on autografting. Results were conflicting regarding the benefit of each of these procedures in this population regarding outcomes from various scoring systems used. The authors concluded that outcome data on cartilage repair in pediatric and adolescent populations was limited. Limitations of this review included:

    - Limited number of studies, thereby limiting the ability to perform statistical analysis and the ability to draw subjective conclusions regarding the safety and efficacy of OATS and allografting in adolescents.
    - Relatively high use of concurrent procedures during allografting in the one included study, making it difficult to draw definitive conclusions about the efficacy of allografting.
    - There is a paucity of RCTs published evaluating OATS and allografting 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.

<u>Randomized Controlled Trials (RCTs)</u>

No additional RCTs evaluating osteochondral allografts were identified after the publication of the systematic reviews described above.

<u>Evidence Summary: Osteochondral Allografts</u>

The body of evidence regarding osteochondral allografting of the knee indicates that this procedure has demonstrated acceptable long-term benefit in terms of pain reduction, improved physical function, and sustained osteochondral graft viability. Several long-term studies have demonstrated long-term donor osteochondral grafts viability up to 10 years or longer, with a success rate reported over 60%. Since donor site complications and morbidity are not an issue with allografting, this procedure is consistently reported as being more appropriate than other restorative procedures in patients with larger cartilage lesions of the knee. Lastly, the literature has consistently emphasized the importance adequate joint stability and alignment.

Osteochondral Autografts

Systematic Reviews

- In 2017 (updated 2020), ECRI published a systematic review evaluating the safety and efficacy of osteochondral autologous and allogeneic grafts for repairing knee cartilage.[6] In total, 2 systematic reviews addressing osteochondral autologous graft transfer (OAT), osteochondral allogeneic graft (OCA) transplantation, microfracture and autologous chondrocyte implantation were included for review. OATS failure rates were not significantly different from microfracture and autologous chondrocyte implantation. Of these studies, 2 were RCTs on OATs and reported 10-year failure rates of 55% and 14%. A meta-analysis of 19 OCA studies reported a 10-year graft survival rate of 78.7% (range 39.0% to 93.0%) and a weighted mean failure rate of 18.2% (range 0% to 31%). OATs patients also experienced a higher return-to-activity rate than microfracture after 10 years. Authors concluded that evidence was insufficient to determine how these procedures compare to autologous chondrocyte implantation or microfracture. Limitations included variation in study designs and conduct, which led to mixed results across studies, making comparisons difficult. Additional RCTs were judged necessary to determine how well OAT and OCA work compared with autologous chondrocyte implantation or microfracture.

- In the 2011 WA HCA technology assessment described above,[7] conducted a systematic review of the literature regarding the efficacy of OATs, including three technology assessments, 12 systematic reviews and five RCTs. Regarding autografts, the assessment indicated that the patient inclusion criteria for autografting were as follows:

    - "Mention of symptoms including pain, locking of the joint, swelling
    - Isolated defects, usually on a weight-bearing surface of the femoral condyle
    - Full thickness cartilage lesions; lesions classified as ICRS 3 or 4 or Outerbridge III or IV lesions
    - Mean lesion sizes ≤ 4 cm^2
    - Less than 45 years old
    - Stability of the knee and/or absence of alignment, ligament or meniscus problems.
    - Excluded individuals with degenerative or rheumatoid joint changes."

  Of note, two of the included RCTs reported that functional outcomes were comparable among patients who received OAT regardless of defect size, but among patients who received microfracture, those with defects larger than 2 cm^2 had worse functional outcomes. In addition, based on data from the included RCTs, OAT was consistently associated with statistically better patient-reported and

clinician-reported outcomes compared to microfracture, and longevity of treatment (up to 48 months follow-up) for OATS was found to be equal to or better than that of any comparator treatment.

- In 2018, the WA HCA updated their 2011 recommendations based on an updated literature search, including three recent systematic reviews and five RCTs that reported on the efficacy of autografting compared to other treatments.[12-15] Of note, pooled data including new trials suggested no difference between OAT and either microfracture or ACI at ≥5 years for pain/symptom, function, or activity scores. The new evidence did not change the recommendations from the 2011 report.

- Of note, in 2016, Gracitelli et al. published the results of a Cochrane review (also included in the WA HCA updated assessment above) that evaluated the benefits and harms of different surgical interventions for treating cartilage defects of the knee, including three of the four RCTs included in the WA HCA review above, that compared OAT to microfracture.[15] The review included studies with the following inclusion criteria:

    - Adults (typically older than 18 years)
    - Lesions:
        - symptomatic, isolated cartilage lesions on the medial or lateral femoral condyle, trochlea, or patella.
        - Grade 3 or 4 cartilage lesions (International Cartilage Repair Society (ICRS) classification).
    - Defect area ranged from 1.0 cm^2 to 6.0 cm^2; the mean area in all three trials was 2.8 cm^2

    Trials focusing primarily on the treatment of people with multiple cartilage lesions, moderate or severe osteoarthritis, rheumatoid diseases, and osteonecrosis were excluded. Pooled results in this review indicated that patients who underwent OAT had less symptom recurrence at long-term follow-up (mean 6.3 to 10.4 years)(Relative risk [RR] 0.47, 95% CI 0.24 to 0.90) than those underwent microfracture.

    Also in 2016, one of the reviews included in the WA HCA review described above, by Pareet et al., compared microfracture (MFX) and OAT with regards to postoperative activity level, subjective patient outcomes, failure rates, and lesion characteristics.[13] The six studies included were all prospective studies and included 249 patients (186 male, 120 female) with an average age of 26.4 years and follow-up of 67.2 months. Tegner activity scores were superior in patients treated with OAT compared with MFX ($p = 0.005$). Failure rates of MFX were higher than OAT (OAT = 11%, MFX = 32%, risk ratio = 2.42, $p < 0.036$). OAT was superior to MFX at three years regarding subjective outcome scores ($p = 0.008$). When assessing OAT lesions larger than 3 cm^2, OAT was superior to MFX with respect to activity level ($p = 0.001$). The reviewers concluded that depending on lesion size, OAT might achieve similar or better activity levels and risk of failure when compared with MFX.

- In 2017 (updated in 2020), Hayes published a review mosaicplasty compared to other treatments, including 17 studies on the knee.[16] Seven studies compared mosaicplasty to microfracture and, overall, suggested that mosaicplasty is somewhat more effective than microfracture, statistically significant increases in mean knee score and greater return to preinjury level of sports 5- to 10-year post mosaicplasty. The significant improvement in outcomes resulting from OATS compared to

microfracture was also reported by a 2018 systematic review of six RCTs, conducted by Haien et al., who also reported lower failure rates for OATS.[17] In addition, five RCTs comparing mosaicplasty to autologous chondrocyte implantation (ACI) found similar improvements in outcomes scores between the two treatments. Regarding patient selection criteria for autografting, the review stated:

> "Definitive patient selection criteria have not been established for mosaicplasty for articular cartilage injuries of the knee or ankle joint.
> In the knee, results may be more favorable for younger patients with sufficient knee stability and when used to treat focal areas of cartilage damage.
>
> In malaligned or unstable joints (varus or valgus, patellar-subluxation), restoration or joint mechanics needs to be addressed separately or at the time of the mosaicplasty procedure. Patellar realignment, anterior cruciate ligament, posterior cruciate ligament, meniscal repair, and osteotomies can be done concurrently.
>
> Contraindications: OC grafting (with the Smith & Nephew Mosaicplasty System) include the following:
>
> - Infectious or tumor defects
> - Generalized arthritis, rheumatoid and/or degenerative in type
> - Patients younger than 50 years with early unicompartmental arthritis where the donor site cartilage is thin and the cartilage surrounding the defect is of poor quality."

Randomized Controlled Trials (RCTs)

No additional RCTs evaluating autografting, including OATS and mosaicplasty, were identified after the publication of the systematic reviews described above.

Evidence Summary: Osteochondral Autografts

The body of evidence regarding osteochondral autograft transplant (OATS) and mosaicplasty of the knee consists mostly of single-institution case series that include heterogeneous populations of individuals, some of whom are undergoing concurrent treatment for additional abnormalities such as ligament or meniscal repair. There are very few studies currently available comparing the results of autografting with other established therapies. However, there is a large collection of small studies demonstrating that autografting procedures confer significant benefit in terms of both functional improvement and pain relief. Several long-term studies report finding stable hyaline cartilage at the operative site at >3 years post-autograft. In the majority of studies, individuals with misalignment, arthritis, unstable knees, and missing or compromised meniscus, were excluded from the studies due to concerns regarding suitability for the procedures. Lastly, there is little agreement on any limitations regarding the size of chondral defects that are appropriate for these procedures. While the literature suggests that mosaicplasty might be appropriate for lesions ranging as large as 16 cm^2, most recent evidence supports the position that the larger the chondral defect, the higher the rates of complications and donor site morbidity. Therefore, at this time it may be appropriate to limit these procedures to small- to moderate-sized lesions (1.0 - 2.5 cm^2), until further evidence is available to clarify this issue.

Hybrid Autologous Chondrocyte Implantation (ACI) and OATS

- In 2019, ECRI conducted a systematic review evaluating the safety and efficacy of combined autologous chondrocyte implantation and osteochondral autograft for repairing osteochondral knee defects.[18] In total, 2 case series and 3 case reports were included for review. The combined sample size was 33 patients. One case series (n = 17) reported 3 treatment failures after 5 years. Lysholm Knee Scoring Scale (a 100-point self-report functional assessment scale) significantly improved from 45 to 77 at 1 year and was 70 at 5 years. One case series (n = 13) reported Knee Society Scores significantly improved from 63.6 to 84.6 at 6 months, 90.2 at 1 year, and 90.6 at 2 years. Three case reports reported patient symptom improvement and implant integration into the defect site. Limitations include the extremely small sample sizes of studies available for review, and lack of control groups, randomization and blinding.

- In 2005, Sharpe et al. published the results of a small case series that evaluated the treatment of large osteochondral lesions (lateral femoral condyle, medial femoral condyle and patella) using a combination of ACI and OAT in 13 patients.[19] The mean age of the patients was 42 years (range: 24 to 48 years). The mean size of the lesions was 4.84 ± 3.45 cm^2 (range: 2.2 to 15.3 cm^2). After one year, the patients reported significant improvement in symptoms and after three years, this level of improvement was maintained in ten of the 13 patients. Arthroscopic examination revealed that the osteochondral cores became well integrated with the surrounding cartilage. However, the actual contribution of each of the elements used in this procedure is unknown. The authors concluded that the hybrid ACI/OATS technique was a promising surgical approach for the treatment of patients with large degenerative osteochondral defects, but this combination treatment may not be superior to ACI alone for the treatment of smaller traumatic defects.

Investigational Procedures and Implants

Minced Autograft Cartilage

In 2011, Cole et al. reported on a small RCT of patients with focal defects of articular cartilage, randomized in a 1:2 ratio to microfracture (n=9) or application of minced cartilage via the Cartilage Autograft Implantation System (CAIS) (n=20).[20] Patients enrolled were heterogeneous in terms of cause of injury, speed of onset of symptoms, and defect size and severity. In addition, there were differences between treatment groups with respect to these baseline characteristics. At 12- and 24- month follow up, subjective outcomes including stiffness, pain, activities of daily living, sports and recreation, knee-related quality of life, quantified using two different knee-specific assessment tools, were significantly higher in the CAIS group compared with the microfracture group. However, objective qualitative analysis of structural changes using MRI at 3 weeks and 6-, 12-, and 24-month follow-up showed no differences in the fill of the graft bed, tissue integration, or presence of subchondral cysts between treatments.

Juvenile Minced Cartilage

Evidence on the efficacy of DeNovo NT is limited to case reports and small case series. The largest series identified was an industry-sponsored prospective study by Farr et al. in 2014, which included 25 patients with cartilage lesions of the femoral condyle or trochlea.[21] Patients reported significantly improved

subjective outcomes at 2-years post-treatment compared to baseline, and MRI results suggested the development of normal cartilage and integration of transplanted tissue. Additional small case series (n=13 -45) have also been published.[22-24]

These case series are limited by one of more of the following:

- small sample size
- lack of a control group
- retrospective study design
- inadequate powered for anything other than an analysis of safety
- relatively short follow-up time
- large proportion (20-30%) of the treated knees had evidence of graft hypertrophy
- use of a single radiologist and a single pathologist prevents intra-rater reliability measurements
- large proportion of patient in each study underwent concomitant procedures, limiting the ability to determine the efficacy of minced juvenile cartilage as a stand-alone treatment for cartilage defects[22,24]

Randomized trials with larger patient populations comparing minced cartilage repair with standard methods of cartilage repair are needed to establish long-term efficacy and safety.

In 2015, Bonasia et al., published the results of a systematic review that evaluated the Cartilage Autograft Implantation System (CAIS) or particulated juvenile allograft cartilage (PJAC) and the use of minced chondral fragments for one-stage cartilage repair.[25] Only one clinical study was included regarding CAIS system (the Cole et al. study described above) and only three case series were included regarding PJAC (all three described above). The review stated that the clinical studies for both treatments were preliminary in nature, and the data was limited. However, further studies are necessary to precisely determine the indications, surgical techniques, and long-term outcomes for PJAC and CAIS.

Decellularized Osteochondral Allograft Plugs

In 2017, Johnson et al., published the results of a case series that evaluated the short-term clinical and radiographic outcomes following the use of decellularized osteochondral (OC) allograft plugs in the treatment of distal femoral OC lesions, including 34 patients.[26] MRIs obtained at 1-year postoperatively demonstrated significantly improved osseous integration ($p = 0.0086$) and opposing cartilage ($p = 0.019$). However, the failure rate was unacceptable high, with ten patients (29%) requiring revision surgery with removal of the implant. Implant survivorship was 61% at 2 years. Even higher failure rates were reported in a 2016 case series by Farr et al., who found a 72% failure rate (32 knees) at a mean follow-up of 1.29 years.[27]

Reduced Osteochondral Allograft Discs

No clinical studies were identified that evaluated Prochondrix, Cartiform, or any other reduced osteochondral allograft discs.

Synthetic Products

- In 2014, Hindle et al. published the results of a nonrandomized comparative cohort study that evaluated mosaicplasty versus TruFit synthetic grafts for knee repair in 66 patients.[28] The authors found that mosaicplasty provided a statistically significantly increase in return to sports (69% versus 29% of patients) and decrease in mean pain score (23 versus 34). There were no significant differences in revision rates or overall quality of life between the two treatments.

- In 2015, Verhaegen et al. published the results of a systematic review that examined clinical, radiological, and histological effectiveness of the TruFit plug in restoring osteochondral defects primarily in the kneejoint.[29] The review included four small case series and one comparative study (Hindle et al.[28], described above). Although all five studies reported improvement at 12-month follow-up compared to baseline, two studies reporting longer follow-up showed deterioration of early improvement. MRI findings regarding defect filling and incorporation with adjacent cartilage indicated improvement at 24 months follow-up, but conflicting evidence existed on the properties of the newly formed overlying cartilage surface. None of the included studies showed evidence for bone ingrowth. The authors concluded that "there are no data available that support superiority or equality of TruFit compared to conservative treatment or mosaicplasty/microfracture. Further investigation is needed to improve synthetic biphasic implants as therapy for osteochondral lesions. RCTs comparing TruFit plugs with an established treatment method are needed before further clinical use can be supported."

Evidence Summary: Investigational Procedures and Implants

There is insufficient clinical evidence that the following treatments confer long-term benefits to patients suffering from cartilage defects of the knee. For all of the indications below there is a paucity of comparative studies, including RCTs, as well as studies of large enough sample size to be appropriately powered to detect significant treatment-specific effects:

- *Hybrid ACI/OATS procedure*: only one small case series was identified.
- *Minced cartilage (including autograft, allograft and juvenile)*: The majority of studies identified were case series. All studies suffered from small sample size, lack of sufficient power, short-term follow-up, and large proportions of patients undergoing a variety of concomitant procedures.
- *Decellularized Osteochondral Allograft Plugs*: Two small case series identified, both of which reported high failure rates (29-72%) at approximately one-year follow-up.
- *Reduced Osteochondral Allograft Discs*: no clinical studies were identified that evaluated Prochondrix, Cartiform, or any other reduced osteochondral allograft discs.
- *Synthetic Products*: Clinical evidence was only identified for TruFit plugs. No RCTS were identified and all studies suffered from small sample size, short-term follow-up and inconsistencies regarding improvement of outcomes post-treatment.

CLINICAL PRACTICE GUIDELINES

National Institute for Health and Care Excellence (NICE)

The 2018 NICE guidance on mosaicplasty as a treatment for symptomatic articular cartilage defects of the knee, stated the following:[30]

- "Current evidence on the safety and efficacy of mosaicplasty for knee cartilage defects is adequate to support the use of this procedure.
- Earlier mobilization may lead to better outcomes.
- Most of the evidence was from patients aged between 16 years and 30 years.
- Outcomes are better and donor-site morbidity is less when the procedure is used to treat smaller defects."

American Academy of Orthopaedic Surgeons (AAOS)

In 2015, the AAOS published appropriate use criteria addressing the management of osteochondritis dissecans of the femoral condyle.[1] These appropriate use criteria were developed from a list of 288 patient scenarios for which 13 treatments were evaluated for appropriateness, including osteochondral allograft transplantation. Sixty-four clinical scenarios are outlined with treatments presented as "Rarely Appropriate," "May Be Appropriate," and "Appropriate." These scenarios may be accessed at the following link. The 9-point appropriateness scale is defined as follows:

Rating	Explanation
7-9	**Appropriate** Appropriate for the indication provided, meaning treatment is generally acceptable and is a reasonable approach for the indication and is likely to improve the patient's health outcomes or survival.
4-6	**May Be Appropriate**: Uncertain for the indication provided, meaning treatment may be acceptable and may be a reasonable approach for the indication, but with uncertainty implying that more research and/or patient information is needed to further classify the indication.
1-3	**Rarely Appropriate:** Rarely an appropriate option for management of patients in this population due to the lack of a clear benefit/risk advantage; rarely an effective option for individual care plans; exceptions should have documentation of the clinical reasons for proceeding with this care option (i.e. procedure is not generally acceptable and is not generally reasonable for the indication).

CENTERS FOR MEDICARE & MEDICAID

As of 8/5/2021, no Centers for Medicare & Medicaid (CMS) coverage guidance was identified which addresses osteochondral allografting, autografting or similar procedures for cartilage defects of the knee.

POLICY SUMMARY

Osteochondral Allografting

The body of evidence regarding osteochondral allografting of the knee has limitations. However, overall the evidence indicates that this procedure has demonstrated acceptable long-term benefit in terms of pain reduction, improved physical function, and sustained osteochondral graft viability. Several long-term studies have demonstrated long-term donor osteochondral grafts viability up to 10 years or longer, with a success rate reported over 60%. Since donor site complications and morbidity are not an issue with allografting, this procedure is consistently reported as being more appropriate than other restorative procedures in patients with larger cartilage lesions of the knee. Lastly, the literature has consistently emphasized the importance adequate joint stability and alignment.

Osteochondral Autografting (Mosaicplasty and OATS)

The body of evidence regarding osteochondral autograft transplant (OATS) and mosaicplasty of the knee has limitations. The evidence consists mostly of single-institution case series that include heterogeneous populations of individuals, some of whom are undergoing concurrent treatment for additional abnormalities such as ligament or meniscal repair. There are very few studies currently available comparing the results of autografting with other established therapies. However, there is a large collection of small studies demonstrating that autografting procedures confer significant benefit in terms of both functional improvement and pain relief. Several long-term studies report finding stable hyaline cartilage at the operative site at >3 years post-autograft. In the majority of studies, individuals with misalignment, arthritis, unstable knees, and missing or compromised meniscus, were excluded from the studies due to concerns regarding suitability for the procedures. Lastly, there is little agreement on any limitations regarding the size of chondral defects that are appropriate for these procedures. While the literature suggests that mosaicplasty might be appropriate for lesions ranging as large as 16 cm^2, most recent evidence supports the position that the larger the chondral defect, the higher the rates of complications and donor site morbidity. Therefore, at this time it may be appropriate to limit these procedures to small- to moderate-sized lesions (1.0 - 2.5 cm^2), until further evidence is available to clarify this issue.

Investigational Procedures and Implants

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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 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)

The FDA regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research. Tissues such as cartilage and bone, and the tissue products derived from them, are included in these regulations. Under these regulations, these tissues are exempt and therefore, do not follow the traditional FDA regulatory pathway.[31]

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. 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.

MEDICAL POLICY CROSS REFERENCES

- Knee: Autologous Chondrocyte Implantation (ACI) for Cartilaginous Defects
- Knee: Meniscal Allograft Transplantation and Other Meniscal Implants
- Knee: Ablative Procedures of Peripheral Nerves to Treat Knee Pain

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