AUTOLOGOUS CHONDOCYTE TRANSPLANTS & COLLAGEN MENISCUS IMPLANTS IN THE KNEE

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INSTRUCTIONS FOR USE

This protocol provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee's document (e.g., Certificate of Coverage (COC) or Evidence of Coverage (EOC)) may differ greatly. In the event of a conflict, the enrollee's specific benefit document supersedes this protocol. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Protocol. Other Protocols, Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Protocols, Policies and Guidelines as necessary. This protocol is provided for informational purposes. It does not constitute medical advice. This policy does not govern Medicare Group Retiree members.

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COMMERCIAL, MEDICARE & MEDICAID COVERAGE RATIONALE

Autologous chondrocyte transplantation (ACT) is medically necessary in patients with a single symptomatic full-thickness articular cartilage defect when all of the following are present:

- Adult patient younger than age 55,
- Defect is greater than 2 squared cm,
- Defect is caused by acute or repetitive trauma,
- Defect is in the articular cartilage of the femoral condyle (medial, lateral, or trochlea),
- Patient has had an inadequate response to a prior arthroscopic or other surgical repair procedure (e.g., debridement, microfracture, drilling/abrasion arthroplasty, or osteochondral allograft/autograft), and
• Patient has failed to respond to conservative treatment such as physical therapy, braces, and/or nonsteroidal anti-inflammatory drugs (NSAIDs.)

Autologous chondrocyte transplantation is considered **not medically necessary** for the following indications:

- Patients who have cartilage defects in locations other than the femoral condyle of the knee,
- Patients whose growth plates have not closed,
- Patients who have partial-thickness defects,
- Patients with history of multiple defects,
- Patients with history of defects of the patella,
- Patients who have osteochondritis dissecans,
- Patients who have had previous history of cancer in the bones, cartilage, fat or muscle of the treated limb,
- Osteoarthritis,
- Patients with unstable knee,
- Total meniscectomy,
- Inflammatory diseases of the joint

There is insufficient evidence to conclude that ACT is beneficial for health outcomes in patients with osteochondritis dissecans, osteoarthritis, or for cartilage defects.

**Meniscus Allograft Transplantation** with human cadaver tissue is **medically necessary** for replacement of major meniscus loss due to trauma or previous meniscectomy when ALL of the following criteria are met:

- Patient who is skeletally mature with documented closure of growth plates
- Patient has significant knee pain and limited function
- Patient is missing more than half of the meniscus due to surgery or injury or has a tear that cannot be repaired
- Radiographic criteria established by a standing anteroposterior (AP) view demonstrates all of the following:
  - Normal alignment or correctable varus or valgus deformities
  - No osteophytes or marginal osteophytes
  - No irreparable articular cartilage defects
  - No significant joint space narrowing
- Ligamentous stability has been achieved prior to surgery or achieved concurrently with meniscal transplantation (e.g., concomitant anterior cruciate ligament surgery)
- Documented minimal to absent degenerative changes in surrounding articular cartilage (Outerbridge Grade II or less)
- There is no evidence of active inflammatory arthritis or systemic arthritis
- Patient who has failed conservative treatment including physical therapy and/or bracing techniques.

**Collagen Meniscus implants** are **not medically necessary** for treating or evaluating and managing meniscus injuries or tears. There is insufficient evidence that collagen meniscus implants improve health outcomes such as reduction of symptoms and restoration of knee function in patients with meniscus injuries or tears. Additional studies with long term follow-up are needed to determine
whether implantation of a collagen scaffold is able to slow joint degeneration, delay the progression of osteoarthritis, and reduce pain for long durations.

Medicare does not have a National Coverage Determination (NCD) specifically for **meniscus allograft transplantation**. However, there is a NCD that addresses **Collagen Meniscus Implant (150.12)**.

Local Coverage Determinations (LCDs) for Nevada do not exist at this time (Accessed July 2016).

**Collagen Meniscus Implant (150.12)**

**General**
The knee menisci are wedge-shaped, semi-lunar discs of fibrous tissue located in the knee joint between the ends of the femur and the tibia and fibula. There is a lateral and medial meniscus in each knee. It is known now that the menisci provide mechanical support, localized pressure distribution, and lubrication of the knee joint. Initially, meniscal tears were treated with total meniscectomy; however, as knowledge of the function of the menisci and the potential long term effects of total meniscectomy on the knee joint evolved, treatment of symptomatic meniscal tears gravitated to repair of the tear, when possible, or partial meniscectomy.

The Collagen Meniscus Implant (also referred to as collagen scaffold (CS), CMI or MenaflexTM meniscus implant throughout the published literature) is used to fill meniscal defects that result from partial meniscectomy. The Collagen Meniscus Implant is not intended to replace the entire meniscus at it requires a meniscal rim for attachment. The literature describes the placement of the Collagen Meniscus Implant through an arthroscopic procedure with an additional incision for capture of the repair needles and tying of the sutures. After debridement of the damaged meniscus, the implant is trimmed to the size of meniscal defect and sutured into place. The Collagen Meniscus Implant is described as a tissue engineered scaffold to support the generation of new meniscus-like tissue. The Collagen Meniscus Implant is manufactured from bovine collagen and should not be confused with the meniscus transplant which involves the replacement of the meniscus with a transplant meniscus from a cadaver donor. The meniscus transplant is not addressed under this national coverage determination.

**Nationally Non-Covered Indications**
Effective for claims with dates of service performed on or after May 25, 2010, the Centers for Medicare & Medicaid Services has determined that the evidence is adequate to conclude that the Collagen Meniscus Implant does not improve health outcomes and, therefore, is **not reasonable and necessary** for the treatment of meniscal injury/tear under section 1862(a)(1)(A) of the Social Security Act. Thus, the Collagen Meniscus Implant is **non-covered** by Medicare.

**For Medicare and Medicaid Determinations Related to States Outside of Nevada:**
Please review Local Coverage Determinations that apply to other states outside of Nevada.

**Important Note:** Please also review local carrier Web sites in addition to the Medicare Coverage database on the Centers for Medicare and Medicaid Services’ Website.
DESCRIPTION OF SERVICES

Loss of the meniscus either in part or whole, can have a poor prognosis in the long term, with the possibility of future arthritis thought to be proportional to the amount of tissue that is torn or removed. There is growing consensus that meniscal allograft transplantation may be indicated in a narrowly defined subset of individuals considered too young or active for arthroplasty and who meet specific criteria. Studies have demonstrated the effectiveness of this procedure in alleviating pain and swelling and in improving knee function in select individuals.

Normal articular cartilage is a complex tissue composed of matrix, chondrocytes and water. The chondrocytes are responsible for synthesizing the matrix, which is composed primarily of collagen fibers, hyaluronate, and sulfated proteoglycans. Articular cartilage damaged through acute or chronic trauma or osteochondritis dessecans, has limited ability to regenerate, leading to the symptoms of pain, restricted mobility and locking. When a full-thickness cartilage injury occurs, the articular surface does not usually regenerate on its own. Surgical treatment options include autologous chondrocyte transplantation.

Autologous chondrocyte transplantation (ACT), also referred to as autologous chondrocyte implantation (ACI), is a form of tissue engineering that creates a graft from a patient’s own cartilage cells to repair defects in the articular cartilage.

Most patients are referred for autologous chondrocyte implantation after already having had surgery for an articular cartilage problem. If the patient remains symptomatic, and the patient and the surgeon decide that autologous chondrocyte implant is the best option, then an arthroscopic biopsy is planned.

The process involves removal, expansion (culture), and reimplantation of the patient’s own chondrocytes. The procedure involves the collection and culture of articular cartilage cells (i.e., chondrocytes). With the patient under general anesthesia, an arthrotomy is performed; the cultured cells are placed into the cartilage defect, and held in place with a periosteal patch. Repair of ligamentous or other soft tissue structures may be performed concurrently, as needed. The chondrocytes are then implanted into the defect with the goal of generating new hyaline or hyaline-like tissue which will repair the articular surface.

After the initial non-weight-bearing period immediately following surgery, an intensive physical rehabilitation program is initiated, with a gradual increase in weight bearing, and return to full activities.

Allografts are grafts of tissues made available from a live person or a human cadaver. Allografts from cadavers avoid morbidity from harvesting tissue from a different site on the person requiring meniscus repair. The goal of meniscal allograft transplantation is to restore knee function and prevent further joint degeneration by replacing the damaged or destroyed meniscus with allograft tissue having similar properties as the damaged tissue.

A meniscus is a crescent-shaped wedge of cartilage located on the proximal articulating surface of the tibia within the synovial joint of the knee. Small, unstable tears in the periphery of the meniscus may be sutured. The procedure can be performed either arthroscopically or by open technique and involves
grafting a donor meniscus into the knee of the patient. Treatment of severe meniscal injury usually involves partial excision of the damaged tissue or complete meniscectomy. The loss of tissue frequently leads to osteoarthritis and irreversible joint damage. Many different materials have been evaluated for prostheses to replace lost or damaged menisci, including artificial materials, autogenous tissue (graft tissue obtained from oneself), and allograft tissue (graft tissue obtained from another person).

Meniscal allograft transplantation is a surgical procedure that involves grafting a donor meniscus into the knee of a recipient. The procedure has been proposed as treatment for a subset of patients with irreparable meniscal tears, or who have undergone previous total meniscectomy. Patient selection criteria for meniscal allograft transplantation are not well-defined and vary across studies. However, candidates are generally young, with minimal degenerative changes, have a stable knee and normal axial alignment, and have failed to respond to conservative care.

The rationale for meniscal allograft transplant is to prevent the development of arthritis resulting from the loss of the meniscal function following trauma or meniscectomy. Donor menisci are obtained from genetically unrelated individuals, usually through organ procurement programs, coroners’ offices, hospitals, and morgues. The allografts may be implanted fresh from cadaver donor, although this presents problems regarding the timing of the surgery and also increases the risk of disease transmission. Fresh menisci can be maintained in culture for 2 weeks, which allows time for infectious disease testing while preserving cell viability. Cryopreservation, in which the graft is treated with a cryoprotectant and frozen, preserves fibrochondrocytes and does not distort the graft. Fresh freezing is another technique used in the preservation of the allograft; however, this process kills the cells and can damage the collagen net of the graft.

The Menaflex collagen meniscus implant (CMI) is a device made of a biologically derived material, primarily bovine type I collagen, which is designed to guide new tissue growth in the meniscus using the body’s own healing process. This new tissue has the potential to restore function, reduce pain, and possibly slow the degenerative process that begins with the loss of meniscus tissue. To prepare the meniscus for the implant, a partial meniscectomy or removal any loose or damaged meniscal tissue is preformed arthroscopically. The Menaflex implant is then trimmed to fit the meniscus defect and is sutured into place. Once imbedded, the implant provides a matrix into which the body’s own cells may begin to migrate. New tissue potentially forms as these cells aggregate and multiply, with the Menaflex material subsequently being absorbed by the body (ECRI, 2010). The Menaflex collagen meniscus implant is the only collagen meniscus implant with FDA clearance at this time.

**CLINICAL EVIDENCE**

**Autologous Chondrocyte Transplantation**

Harris et al. (2010) conducted a systematic review to compare autologous Chondrocyte implantation with other cartilage repair or restoration techniques. Thirteen studies (n =917) were included. Patients underwent autologous chondrocyte implantation (n = 604), microfracture (n = 271), or osteochondral autograft (n = 42). Three of 7 studies showed better clinical outcomes after autologous chondrocyte implantation in comparison with microfracture after 1 to 3 years of follow-up, whereas 1 study showed better outcomes 2 years after microfracture and 3 other studies showed no difference in these treatments after 1 to 5 years. Clinical outcomes after microfracture deteriorated after 18 to 24 months
(in 3 of 7 studies). Autologous Chondrocyte implantation and osteochondral autograft demonstrated equivalent short-term clinical outcomes, although there was more rapid improvement after osteochondral autograft (2 studies). A defect size of >4 cm(2) was the only factor predictive of better outcomes when autologous Chondrocyte implantation was compared with a non-autologous chondrocyte implantation surgical technique. The authors concluded that all of the cartilage repair/restoration techniques provide short-term success.

A systematic review of 9 different trials (n=626) by Vasiliadis et al. (2010) found that ACI is an effective treatment for full thickness chondral defects of the knee, providing an improvement of clinical outcomes. The authors note, however, that there is insufficient data to say whether ACI is superior to other treatment strategies in full thickness articular cartilage defects of the knee. Additional studies are needed before specific clinical recommendations can be made.

Vavken and Samartzis (2010) conducted a systematic review of 9 studies (n=526) to compare ACI to other methods of cartilage repair or placebo. The authors found that there was no clear recommendation concerning the efficacy of ACI compared to other treatment options such as microfracture or osteochondral grafts. There is, however, some evidence for better clinical outcomes for ACI compared with osteochondral grafts and equivalent outcomes compared with microfracture. Additional studies are needed to further assess the benefits of ACI compared to other treatments.

A systematic review conducted by authors at Vanderbilt University attempted to define the comparative effectiveness of, and indications for, ACI and osteochondral autograft transfer system (OATS) to treat full-thickness (Outerbridge stage 3 or 4) defects (Magnussen et al., 2008). The review included four trials (Bentley et al., 2003; Horas et al., 2003; Knutsen et al., 2004; Visna et al., 2004), a comparison of ACI using collagen membrane cover (ACI-C) with matrix-guided ACI (MACI), and a comparison of autologous osteochondral grafting with microfracture. The authors were not able to demonstrate a clear superiority of one procedure over the other.

A Cochrane Review by Wasiak et al. (2006) concluded that evidence was insufficient to determine whether ACI was superior to other treatment options for full-thickness cartilage lesions of the knee.

Another Cochrane Review by Vasiliadis and Wasiak (2010) concluded that there was insufficient evidence to draw conclusions on the use of ACI for treating full thickness articular cartilage defects in the knee.

Basad et al. (2010) compared the clinical outcomes of patients with symptomatic cartilage defects treated with matrix-induced autologous chondrocyte implantation (MACI) or microfracture (MF). The 60 patients included were 18 to 50 years of age with symptomatic, post-traumatic, single, isolated chondral defects (4-10 cm2) and were randomized to receive MACI (40) or MF (20). Patients were followed up 8-12, 22-26 and 50-54 weeks post-operatively for efficacy and safety evaluation. The difference between baseline and 24 months post-operatively for both treatment groups was significant for the Lysholm, Tegner, patient ICRS and surgeon ICRS scores. However, MACI was significantly more effective over time (24 months versus baseline) than MF according to the Lysholm, Tegner, ICRS patient and ICRS surgeon scores. According to the authors, MACI is superior to MF in the treatment of articular defects over 2 years.
Zeifang et al. (2010) evaluated whether matrix-associated autologous chondrocyte implantation or the original periosteal flap technique provides superior outcomes in terms of clinical efficacy and safety. Twenty-one adult patients (mean age, 29.3 +/- 9.1 years) with symptomatic isolated full-thickness cartilage defects (mean 4.1 +/- 0.9 cm2) at the femoral condyle were randomized to matrix-associated autologous chondrocyte implantation or the original periosteal flap technique. The primary outcome parameter showed improvement of patients 1 year after Autologous chondrocyte implantation, but there was no difference between the periosteal flap technique and matrix-associated ACI; 2 years after ACI, a similar result was found. The authors concluded that there was no difference in the efficacy between the original and the advanced ACI technique 12 and 24 months after surgery regarding International Knee Documentation Committee, Tegner Activity Score, and Short Form-36; however, with respect to the Lysholm and Gillquist score, better efficacy was observed in the periosteal flap technique group.

Comparative results varied according to the comparison surgery. Fu et al. (2005) observed that at 3 years, Cincinnati Knee Rating System (CKRS) scores were 2 to 3 points higher (on 10-point scales) in the ACI group than in the debridement alone group, both for overall condition and for individual symptoms. The difference in overall scores was significant. However, this was a retrospective study and CKRS data were missing for 28% to 60% of debridement patients, depending on the individual measure. Furthermore, the study did not differentiate between first- and second-line use of ACI, and several other aspects of the study design introduced bias.

In the comparisons with marrow stimulation, improvements in pain and various functional measures were either comparable between the two types of procedures or slightly better following abrasion or microfracture than following ACI (Knutsen et al., 2004; Visna et al., 2004; Knutsen et al., 2007; Saris et al., 2008). This was true of both 5-year and more short-term outcomes. These studies represented moderately strong evidence, but baseline differences in the study by Saris and colleagues created a small bias in favor of microfracture.

Saris et al. (2009) evaluated clinical outcome at 36 months after characterized Chondrocyte implantation (CCI) versus microfracture (MF). Based on the results of the trial, the authors concluded that characterized chondrocyte implantation for the treatment of articular cartilage defects of the femoral condyles of the knee results in significantly better clinical outcome at 36 months in a randomized trial compared with MF. Time to treatment and chondrocyte quality were shown to affect outcome.

Results were less consistent for comparisons with autologous osteochondral grafting. Differences between ACI procedures and a mix of single and multiple osteochondral grafting procedures slightly favored osteochondral grafting (Horas et al., 2003). This study also represented a mix of first-line and second-line applications; results were not reported separately. Mean defect size was 3.75 cm2. Bentley et al. (2003) reported results that favored ACI: 88% of ACI recipients and only 69% of mosaicplasty recipients had a good or excellent overall modified CKRS score at 19 months. However, mean defect size in this study was relatively large (4.66 cm2), and one critic suggested that some patients may not have been appropriate candidates for mosaicplasty (Kish and Hangody, 2004). In the study by Dozin et al. (2005), outcomes were considerably better in the mosaicplasty group: 68% patients had a Lysholm score of 90 or more, compared with 46% of ACI patients. Significance testing was not reported, follow-up was less than 1 year, and the study had several other significant weaknesses. This study
differed from the other two osteochondral grafting comparisons in that it involved first-line rather than second-line application and mean lesion size was smaller. Mean defect size was approximately 2 cm², consistent with guidelines for mosaicplasty reported in review articles (Clar et al., 2005; Vanlauwe et al., 2007).

A case series by Peterson et al. (2010) evaluated the clinical outcomes of Autologous chondrocyte implantation in 224 patients 10 to 20 years after implantation (mean = 12.8 years). The authors found that autologous chondrocyte implantation is an effective and durable solution for the treatment of large full-thickness cartilage and osteochondral lesions of the knee joint and clinical and functional outcomes remain high even 10 to 20 years after the implantation.

**Best Candidates for ACT**

Scientific literature reflects the following consensus regarding the best selection criteria for ACI (Clar et al., 2005; Lewis et al., 2006; Vanlauwe et al., 2007; Brittberg, 2008):

- 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 cm². (Some authors recommend ACI as an alternative to marrow stimulation if the lesion is uncontained.)
- 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.

Bony defects greater than 8 mm should be corrected with bone grafts before chondrocyte implantation.

**Adverse Events and Complications**

Studies involving 75 or more autologous chondrocyte implantation (ACI) procedures (total n=540 patients) reported failure rates of 4% to 13%, depending on how failure is defined and depending on where procedures are performed (Peterson et al., 2000; Minas, 2001; Browne et al., 2005). Adverse events were generally reported in terms of the need for arthroscopic evaluation of symptoms or for subsequent surgery. Such a need occurred in 25% to 65% of patients (nonuniform follow-up intervals). Symptomatic complications related to the periosteal flap were by far the most common adverse effects, prompting arthroscopic investigation in 20% to 26% of study participants (Peterson et al., 2000; Minas, 2001) and accounting for 10% of subsequent surgeries among ACI successes (Browne et al., 2005) or 51% of all subsequent surgeries (Henderson et al., 2006). Flap-related complications included both periosteal hypertrophy and implant extrusion.

Another review by Wood et al. (2006) found that the most common adverse events following Carticel implantation included graft failure, delamination, and tissue hypertrophy. Graft failures have been attributed to poor compliance with the rehabilitation protocol or to events such as traumatic accidents.
ACT in Adolescents
Some experts believe the use of ACI in children is not reasonable, since regenerative capacities are so much greater than in adults and due to potential interference epiphysis closure (Vanlauwe et al., 2007). However, other authors have seen the potential for faster healing to be a good reason to try ACI in athletes. A review of 37 adolescent (age 11-17) ACI procedures listed in the Cartilage Repair Registry showed an 88% rate of good/excellent outcomes (Micheli et al., 2006).

ACT for Trochlear and Patellar
Published trials comparing ACI with other surgical repair procedures for defects in the knee included relatively few patients with trochlear or patellar defects. A review of 40 Cartilage Repair Registry patients who underwent ACI for trochlear cartilage defects reported positive outcomes (Mandelbaum et al., 2007). In most cases, ACI followed previous attempts at surgical repair, often marrow stimulation. Defects were generally large (mean 4.5 cm2). A longitudinal study separately analyzed results for 45 patients who underwent ACI for defects on the patella, trochlea, patella plus trochlea, weight bearing condyle plus patella, weight bearing condyle plus trochlea, or weight bearing condyle plus patella plus trochlea (Minas and Bryant, 2005). Affected patellar surface averaged 4.86 cm2, and affected trochlear surface averaged 5.22 cm2. Most (71%) patients reported a good or excellent overall outcome. However, the rate of graft failure was rather high (18%).

In the only study that provided results according to defect type (Bentley et al., 2003), between-group differences for defects on the patella and trochlea were similar to those for femoral defects. The number of patients in those categories was very small. No results specific to osteochondritis dissecans (OCD) were presented by any study.

Additional Applications
An UpToDate review on “Surgical therapy of osteoarthritis” (Kalunian, 2013) states that “Replacing localized regions of degenerated cartilage with autologous chondrocyte grafts has not been studied in large groups of patients. It is unlikely that this technique will be helpful in patients with advanced joint degeneration because of the large surface area that needs grafting in this setting. Replacing localized regions of degenerated cartilage with autologous chondrocyte grafts may be beneficial for selected patients with less severe, localized articular cartilage defects, but it requires further study”. Additional research is needed to expand the knowledge of and develop guidelines for management of chondral injuries of the hip.

Current evidence regarding ACI largely examines cartilage restoration of the knee joint. However, two small studies and one case report were identified in the literature that evaluated the use of ACT in other joints. Investigators assessed the use of autologous chondrocytes in osteochondral lesions of the ankle joint and osteochondrosis dissecans of the ankle joint (n=8; n=8). In the first study, at 2 years of follow-up, both subjective and objective clinical improvement was observed in all patients. (Giannini, 2001) Arthroscopy and histological analysis revealed cartilaginous tissue covering the lesion area, although cell numbers were increased compared with normal cartilage. Kouialis et al. (2002) reported good to excellent results in the postoperative evaluation scores, with no complications. Arthroscopic examinations in 3 patients revealed the existence of cartilage-like tissue with complete coverage of the chondral effect. Romeo et al. (2002) reported on the use of ACT in the repair of an articular defect in the humeral head of a young patient. After 12 weeks, the patient demonstrated full range of painless motion with no complaints of rest pain or weather-related pain. Despite these early clinical results, the
available scientific evidence does not allow definitive conclusions regarding the safety and efficacy of ACT in treating focal defects of joints other than the knee, such as ankle, hip, wrist, or shoulder.

Jordan et al (2012) performed a systematic review of clinical outcomes following various treatments for chondral lesions of the hip and defined the techniques for the treatment of these cartilage defects. The full manuscripts of 15 studies were reviewed for this systematic review including case studies, case series, and clinical studies. A variety of techniques have been reported for the treatment of symptomatic chondral lesions in the hip. Although good results have been reported, most studies lacked both a control group and a large number of patients. The authors concluded that the findings in this article do provide a good foundation for treatments and stimulant for further study in an inherently difficult to treat young patient population with articular cartilage defects in the hip.

According to Hayes, there is insufficient evidence to evaluate the clinical effectiveness of autologous chondrocyte implantation compared with nonsurgical treatment. However, comparison trials of varying quality suggested that ACI provides short-term outcomes comparable to those provided by other surgical options for second-line treatment of full-thickness defects in the articular cartilage of the knee. Four moderately large noncomparison studies suggested that autologous chondrocyte implantation poses no serious safety issues. However, in its original form, autologous chondrocyte implantation often requires follow-up arthroscopic correction of hypertrophy and even high-volume centers have reported that implants can fail completely. There was no evidence from either randomized trials or observational studies regarding the long-term effectiveness of autologous chondrocyte implantation. This does not rule out the possibility of a long-term effect since most of the studies were limited by follow-up intervals of less than 2 years. Very limited and nonsystematic biopsy data suggest that most first-time autologous chondrocyte implantation procedures produce some new hyaline or hyaline-like cartilage. These data corroborate the rationale for autologous chondrocyte implantation but do not prove that long-term outcomes are enhanced compared with other surgical options. Given the typical characteristics of lesions included in the studies, the evidence more strongly supports use of ACI for lesions of the femoral condyle than for lesions in other locations. Although the FDA-approved indication for ACI is restricted to traumatic lesions, not all studies observed this restriction and results were not reported separately by etiology. Only studies with long-term follow-up, in the range of 20 years or more, will provide final answers to questions about the presumed superior ability of ACI to produce hyaline or hyaline-like cartilage and to prevent premature osteoarthritis. Such data can then also be used to clarify which patients and what types of lesions are most likely to benefit from ACI as opposed to another surgical technique (Hayes, 2013).

In a prospective cohort study, Kon et al. (2009) compared the clinical outcome of patients treated with second-generation Hyalograft C autologous chondrocyte implantation implants (n=40) with those treated with the microfracture repair (n=40). All patients had grade III to IV cartilage lesions of the femoral condyles or trochlea. Both groups demonstrated statistically significant improvement of all clinical scores from preoperative interval to 5-year follow-up. When comparing the groups, better improvement of the International Knee Documentation Committee objective (P < .001) and subjective (P = .003) scores was observed in the Hyalograft C group at 5-year follow-up. The return to sports at 2 years was similar in both groups and remained stable after 5 years in the Hyalograft C group; it worsened in the microfracture group. The investigators concluded that better clinical results and sport activity resumption were demonstrated in the group treated with second-generation autologous chondrocyte transplantation.
Zaslav et al. (2009) assessed the effectiveness of autologous chondrocyte implantation in a prospective clinical study of patients who failed prior treatments for articular cartilage defects of the knee. Follow-up was 48 months. One hundred twenty-six patients (82%) completed the study protocol. Seventy-six percent of patients were treatment successes at the end of the study and 24% were identified as treatment failures. Mean improvements were observed from baseline to all time points (P < .001) for all outcome measures. Preoperative to 48-month values, respectively, were as follows: On the Knee injury and Osteoarthritis Outcome Score subscales of pain: 48.7 to 72.2; other symptoms: 51.8 to 70.8; sports/recreation: 25.8 to 55.8; knee quality of life: 20.9 to 52.2; and activities of daily living: 58.6 to 81.0; on the Modified Cincinnati Overall Knee score: 3.3 to 6.3; on the visual analog scale: 28.8 to 69.9; and on the SF-36 Overall Physical Health: 33.0 to 44.4. Results did not differ between patients whose primary surgery had been a marrow-stimulating procedure and those whose primary procedure had been a debridement alone. The median difference in duration of benefit between autologous chondrocyte implantation and the failed non-autologous chondrocyte implantation prior procedure was at least 31 months (P < .001). Seventy-six patients (49%) had subsequent surgical procedure(s), predominantly arthroscopic. The investigators concluded that patients with moderate to large chondral lesions with failed prior cartilage treatments can expect sustained and clinically meaningful improvement in pain and function after autologous chondrocyte implantation. The subsequent surgical procedure rate observed in this study (49% overall; 40% related to autologous chondrocyte implantation) appears higher than generally reported after autologous chondrocyte implantation.

Niemeyer et al. (2008) reported the clinical results obtained in 70 patients treated with ACI for full-thickness defects of the patella. At a mean follow-up of 38.4 months, patients' subjective functional knee scores (IKDC, Lysholm) were analyzed, as were the results of objective examination (according to International Cartilage Research Society [ICRS]). The mean Lysholm score at the time of follow-up was 73.0 (+/-22.4) and the subjective IKDC score was 61.6 (+/- 21.5); normal and nearly normal clinical results according to ICRS were achieved in 67.1% of the patients, while abnormal results were achieved in 20.0% of the patients and severely abnormal results, in 12.9% of the patients.

Professional Societies/Organizations
American Academy of Orthopaedic Surgeons (AAOS) In a 2010 clinical practice guideline on the diagnosis and treatment of osteochondritis dissecans (OCD), the American Academy of Orthopaedic Surgeons (AAOS) was unable to recommend for or against a specific cartilage repair technique in symptomatic skeletally immature or mature patients with an unsalvageable osteochondritis dissecans lesion.

National Institute for Health and Care Excellence (NICE): Current NICE Guidance recommends against ACI for the treatment of articular cartilage defects of the knee joint, except in the context of ongoing or new clinical studies that are designed to generate robust and relevant outcome data, including the measurement of health-related quality of life and long-term follow-up. (NICE, 2008)

Collagen Meniscus Implants
Grassi et al (2014) performed a systematic review to summarize and evaluate the clinical outcomes of the collagen meniscus implant (CMI) and its complication and failure rates. These data were then used to evaluate the results of the CMI at different follow-up time periods and investigate possible differences in the behavior of lateral and medial CMI. All studies evaluating medial or lateral CMI using the Lysholm score, visual analogue scale (VAS) for pain, Tegner activity scale and subjective or
objective International Knee Documentation Committee (IKDC) scores were included in the systematic review. Eleven studies were included in the systematic review. The pooled number of patients involved in CMI surgery were 396. The Lysholm score and VAS for pain showed an improvement at six months up to ten years. No noticeable differences were present comparing short-term values of Lysholm score between medial and lateral CMI. The Tegner activity level reached its peak at 12 months after surgery and showed a progressive decrease through five and ten years post CMI implantation, however always remaining above the pre-operative level. Only a few knees were rated as "nearly abnormal" or "abnormal" at IKDC grading at all follow-up evaluations. The reviewers concluded the CMI could produce good and stable clinical results, particularly regarding knee function and pain, with low rates of complications and reoperations.

Rodkey et al. (2008) conducted a randomized controlled trial that included 311 patients with an irreparable injury of the medial meniscus or a previous partial medial meniscectomy. There were two study arms, one consisting of 157 patients who had had no prior surgery on the involved meniscus (the acute arm of the study) and one consisting of 154 patients who had had one, two, or three prior meniscal surgical procedures (the chronic arm). Patients were randomized either to receive the collagen meniscus implant (CMI) or to serve as a control subject treated with a partial meniscectomy only. Patients underwent frequent clinical follow-up examinations over two years and completed validated outcomes questionnaires over seven years. Patients who received the collagen meniscus implant followed a different post-op protocol, receiving a specific rehabilitation protocol and the requirement of a second-look arthroscopy with biopsy one year after implant placement. In the acute group, seventy-five patients received a collagen meniscus implant and eighty-two were controls. In the chronic group, eighty-five patients received the implant and sixty-nine were controls. The mean duration of follow-up was fifty-nine months. The 141 repeat arthroscopies done at one year showed that the collagen meniscus implants had resulted in significantly increased meniscal tissue compared with that seen after the original index partial meniscectomy. The implant supported meniscus-like matrix production and integration as it was assimilated and resorbed. In the chronic group, the patients who had received an implant regained significantly more of their lost activity than did the controls and they underwent significantly fewer non-protocol re-operations. No differences were detected between the two treatment groups in the acute arm of the study. The investigators concluded that new biomechanically competent meniscus-like tissue forms after placement of a collagen meniscus implant, and use of the implant appears safe. The collagen meniscus implant supports new tissue ingrowth that appears to be adequate to enhance meniscal function as evidenced by improved clinical outcomes in patients with a chronic meniscal injury. According to the investigators, the implant was not found to have any benefit for patients with an acute injury.

An assessment by the California Technology Assessment Forum (CTAF), (Tice, 2010) concluded that the collagen meniscus implant does not meet CTAF criteria. The CTAF assessment found that the pivotal randomized clinical trial (citing Rodkey et al, 2008) failed to demonstrate any improvement in pain or symptoms in either arm of the trial and the trial has substantial risk for selection bias, confounding, and reporting bias because of the large number of patients lost to follow-up after randomization and the lack of blinding for subjective outcomes. In addition, no data on osteoarthritis were presented. The CTAF assessment concluded that the trial "presents evidence that the collagen meniscus implant offers no important clinical benefits, requires longer and more intensive post-operative rehabilitation, and some uncertainty remains about the potential for long-term harm from the device."
The data from the Rodkey study was used by the U.S. Food and Drug Administration (FDA) in the 510(k) application process for the Menaflex collagen meniscus implant. An FDA executive summary of the Rodkey data indicated that patients who received the collagen meniscus implant followed a different post-op protocol than the control group and control patients were not required to undergo a planned second-look arthroscopy since it was assumed that there was no tissue regrowth in these patients. The FDA also indicated that more meniscal tissue was removed from the collagen meniscus implant patients than in the control patients. The FDA noted that the re-look arthroscopy results for collagen meniscus implant group showed that 16% of evaluated devices were not firmly attached to the host rim and 18% of knee compartments were determined to be worse than during the operative procedure at the time of the re-look arthroscopic procedure. According to the FDA summary, the Tegner Index is meant to complement other functional scores (Lysholm knee score) for patients with ligamentous injuries, however, the investigators reported the Tegner Index in isolation and there was no pre-specified hypothesis for its use in the study design, thus, it is unclear how this endpoint should be interpreted given that there is no defined clinical significance for the Tegner Score when used in isolation. In addition, the FDA executive summary stated that at the 3 to 7 year annual follow-up time points, there is approximately 50% of the data available. It is not clear how the missing data has impacted the presentation of the safety and effectiveness endpoints at time-points later than 24 months. The primary endpoint was a 24-month endpoint.

According to an FDA data review of the Rodkey et al. 2008 trial, of the 87 CMI patients in the chronic group, 8 (9.2%) had serious device-related adverse events. Additionally, the percentage of all serious adverse events per patient was higher for the CMI group than the control group (43% vs 33%), although it is not reported if this difference is statistically significant.

Harston et al (2012) examined collagen meniscus implant (CMI) effectiveness for improving patient function, symptoms, and activity level. Study methodologies, rehabilitation, and return to sports guidelines were also reviewed. A total of 11 studies with 520 subjects met inclusion criteria. The authors concluded that knee function, symptoms, and activity level generally improved following CMI use, but poor research report quality was common. They stated that additional well-designed long-term prospective studies are needed to better determine knee osteoarthrosis prevention efficacy and appropriate patient selection.

Zaffagnini et al. (2011) conducted a cohort study that included 33 nonconsecutive patients (men; mean age, 40 years) with meniscal injuries. Study participants received medial collagen meniscus implant (MCMI) or served as a control patient treated with partial medial meniscectomy (PMM). The choice of treatment was decided by the patient. All patients were clinically evaluated at time 0 and at 5 years and a minimum of 10 years after surgery by Lysholm, visual analog scale (VAS) for pain, objective International Knee Documentation Committee (IKDC) knee form, and Tegner activity level scores. The MCMI group, compared with the PMM one, showed significantly lower VAS for pain and higher objective IKDC, Teger index, and SF-36 for Physical Health Index scores. Radiographic evaluation showed significantly less medial joint space narrowing in the MCMI group than in the PMM group. The MRI evaluation of the MCMI patients revealed 11 cases of myxoid degeneration signal: 4 had a normal signal with reduced size, and 2 had no recognizable implant. The investigators concluded that pain, activity level, and radiological outcomes are significantly improved with use of the MCMI at a minimum 10-year follow-up compared with PMM alone. According to the investigators, randomized controlled trials on a larger population are necessary to confirm MCMI benefits at long term.
Sixty patients (19 to 68 years) with subtotal loss of the medial meniscus and varus morpotype were treated as part of a prospective, randomized, arthroscopically controlled study. The sample consisted of 30 patients with high tibial valgus osteotomy combined with implantation of a CMI, and 30 patients with correction osteotomy only. The CMI had to be removed from one patient because of a dislocation. Evaluation on the Lysholm Score, IKDC (International Knee Documentation Committee), and subjective pain data revealed only slight, nonsignificant differences for 39 patients after 24 months. According to the investigators, the chondroprotective effect of the CMI in the long term remains to be seen. This study is limited by small sample size and short-term follow-up (Linke et al. 2006).

Bulgheroni et al. (2010) investigated the clinical outcomes and any progression of knee osteoarthritis in 34 patients who underwent arthroscopic placement of a collagen meniscus implant. Lysholm and Tegner activity scores at 2 and 5 years after surgery improved significantly compared to the preoperative score. These patients showed good to excellent clinical results after 5 years from a CMI placement. In most of cases, the CMI-new tissue complex had a slight reduction in size, compared to a normal medial meniscus, but the new tissue had no apparent negative effects. According to the investigators, 5 years after the implant, the regenerated tissue still was not completely similar to a normal meniscus. This study is limited by a small sample size and lack of a control group.

Zaffagnini et al. (2007) prospectively assessed the results of bioreabsorbable collagen matrix (CMI) implantation in 8 patients (mean age 25) who were evaluated at a final observation point from 6 to 8 years after implantation. There were no complications related to the device. All patients were able to return to day activities without limitations 3 months after surgery. Both subjective Cincinnati Knee Rating Scale (CKRS) score and objective IKDC score showed improvement in all cases except one patient with an ACL re-injury. In two cases, scores were slightly worse from 2 years after surgery to the final observation point. The other five cases obtained maximum score at final follow-up. The investigators concluded that the implant may have helped reduce the deterioration of the knee joint at final observation time. The value of this study is limited by the small sample size and a lack of a comparison group.

Steadman and Rodkey (2005) reported on the five to six year follow-up of the 8 patients (reported in Rodkey and Steadman, 1999) who underwent arthroscopic placement of a collagen meniscus implant to reconstruct and restore the irreparably damaged medial meniscus. All patients returned for clinical, radiographic, magnetic resonance imaging, and arthroscopic examinations an average of 5.8 years after collagen meniscus implant placement. Lysholm scores and average Tegner activity scores improved significantly. Pain scores improved from 23 to 11 (0 = no pain, 100 = worst pain). Imaging studies confirmed that the chondral surfaces of the medial compartment had not degenerated further since the placement of the implant 5.8 years earlier. Relook arthroscopy with direct measurement of the newly generated tissue revealed 69% defect filling. The investigators concluded that the meniscus-like tissue that developed after collagen meniscus implant placement has maintained its structure and functioned without negative effects for more than 5 years. The hypothesis was affirmed that these patients were improved significantly compared with their preoperative status and unchanged compared with 2-year evaluations. This study is limited by small sample size and lack of a control group.

A technology assessment conducted by Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). (2010) concluded that the collagen meniscal implant for irreparable medical meniscus injury did not meet technology assessment criteria. The published evidence did not support
improvement in health outcomes or that clinical improvement was attainable outside of the investigational setting. Although promising, long-term data supporting safety, efficacy and improved clinical outcomes, including prevention of osteoarthritis, are not yet available to support widespread use of this bioactive scaffold for meniscal regeneration.

Furthermore, the Work Loss Data Institute's guideline on "Knee and leg (acute and chronic)” (2011; updated November 2013) does not recommend the use of CMI/Menaflex.

**Meniscus Allograft Transplantation**

Elattar et al. (2011) conducted a meta-analysis of published trials reporting outcomes of meniscal allograft transplantation to establish its safety and reproducibility. The outcomes of 678 medial and 458 lateral grafts in 613 male, 265 female and 190 non-defined patients with a mean age of 34.8 years were included in the meta-analysis. According to the authors, all studies reported a continuously satisfactory outcome with restoration of working capacity in these active patients. The authors stated that meniscal allograft transplantation can be considered as safe and reliable for the treatment of refractory post-meniscectomy symptoms in selected patients.

Hergan et al. (2011) performed a systematic review evaluating meniscal allograft transplantation (MAT). Included in the review were 14 studies with at least 2 years’ follow-up, studies with validated outcome measures, and studies in which the allograft meniscal horns were secured with bony fixation. Thirteen of the articles provided Level IV evidence, and one article (Stollsteimer et al. 2000) provided Level III evidence. The authors concluded that good early and midterm results of cryopreserved or fresh-frozen, nonirradiated MAT can be achieved in a relatively young patient with only mild chondromalacia (lower than Outerbridge grade 3) who is not overweight and has a stable, mechanically aligned lower extremity, if the allograft is sized radiographically by use of anteroposterior and lateral films and the allograft meniscal horns have bony attachments and are fixed by bony techniques. Similar results can be expected if the transplant is performed alone or with a concomitant cartilage repair procedure; however, significant cartilage defects (Outerbridge grade 2 or greater) on both the femoral and tibial sides in the same compartment requiring autologous cartilage implantation result in a high failure rate. Good outcomes of MAT can be expected when performing a concomitant ligament reconstruction or malalignment procedure on the knee, unless greater than 3 concomitant procedures are performed. There is no significant difference in outcome between medial and lateral MAT. According to the authors, despite a growing body of knowledge on the topic, there remains a lack of consensus regarding optimal allograft sizing technique, allograft fixation techniques, tissue processing, indications, and long term efficacy. The authors stated that a prospective, randomized trial comparing MAT in a meniscectomized knee with a control group is needed to determine the best technique and patient selection criteria.

Crook et al. (2009) reviewed the current literature to consolidate the evidence surrounding the use of human meniscal allograft transplantation. No Level I or II studies were identified. Many studies had small study groups with limited follow-up and patient selection and description of patient factors varied greatly. This made comparing data difficult. Four types of graft are used-- fresh, fresh-frozen, cryopreserved and freeze-dried (lyophilised) graft. Cryopreserved and fresh-frozen allografts are deemed most suitable. Most authors advocate the use of non-irradiated grafts from screened donors to reduce transmission of infection. Patients have an improved outcome if they have less severe degenerative changes within the knee prior to transplantation. The authors concluded that no
statistically significant studies looking at isolated meniscal transplantations have been found. The evidence suggests that meniscal allograft transplantation provides improvement of pain and function in the short and intermediate term. The effect on future joint degeneration is still unknown. The authors stated that the ideal patient group includes patients less than 40 years of age with knee pain, proven meniscal injury and a normally aligned, stable joint without severe degenerative changes.

The results of the reviewed studies indicate that meniscal allografts can be successfully implanted and may produce short to intermediate relief in selected patients. Many patients reported good or satisfactory results with respect to function and pain for both normal daily living and moderate sports activities (Stollsteimer et al., 2000; Rue et al., 2008; Verdonk et al., 2006; Sekiya et al., 2006; Cole et al., 2006; Noyes et al., 2005; Vundelinckx et al., 2010; LaPrade et al., 2010). Short-term functional results from clinical analysis and patient self-assessment appear to be encouraging. However, none of the studies provide strong evidence that meniscal transplantation can slow or stop the degenerative process seen in meniscectomized knees, and none provided a comparison with other treatment options. Some of the studies also reported shrinking or extrusion of the allograft with time. Results of the few long-term studies indicated deterioration of the transplants over a long-term period when compared with short-term analysis (Verdonk et al., 2005; van der Wal et al., 2009). Moreover, differences in patient selection, concomitant procedures, allograft selection and treatment, surgical technique, graft fixation, rehabilitation protocol, and length of follow-up make results difficult to interpret and compare. Issues that remain to be addressed include patient selection criteria, optimal treatment for the allografts (irradiated or non-irradiated), and long-term outcomes (Hayes 2010).

There is insufficient evidence to establish definitive patient selection criteria for meniscal allograft transplantation (Hayes, Updated 2011). Meniscal allograft transplantation is not recommended for patient’s age > 50 years, since procedures such as arthroplasty or osteotomy offer a more predictable outcome for these patients. Meniscal allograft transplantation is contraindicated in patients with large areas of significant articular degeneration (Outerbridge grade 3 or 4) or bony architectural changes, including osteophytes. The condition of the meniscus should be firmly established by previous operative reports, magnetic resonance imaging (MRI), or diagnostic arthroscopy (Hayes Updated 2011). Other contraindications include systemic inflammatory disease, obesity (body mass index > 30), immunodeficiency, previous infection of the knee, and skeletal immaturity (Crook et al., 2009; Monllau et al., 2010).

Meniscal allograft transplantation may be indicated in patients who are considered too young or active for arthroplasty if they have all of the following (Friel and Cole, 2010; Monllau et al., 2010):

- Disabling knee pain refractory to conservative treatment
- Ligamentous stability prior to surgery or achieved concurrently with meniscal transplantation
- Documented mild to moderate articular damage (Outerbridge grade I-II)
- Normal alignment without varus or valgus deformities

Society Information
American Academy of Orthopedic Surgeons
The American Academy of Orthopedic Surgeons published an advisory statement regarding the use of musculoskeletal tissue allografts (AAOS, 2011). The AAOS supports the following:

- The use of musculoskeletal allograft as a therapeutic alternative to autograft use for appropriate patients. Allograft tissues should be acquired from facilities that demonstrate compliance, use well-
accepted banking methodology and good tissue practices. The AAOS urges all tissue banks to follow rigorous national guidelines and standards.

- The AAOS strongly favors on-site inspection and recommends the use of tissue banks by the American Association of Tissue Banks (AATB). The AAOS supports informed consent, for both the donor family and the recipient of human tissue, in accordance with local, state and federal laws and regulations.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

The culturing of chondrocytes is considered by the FDA to fall into the category of manipulated autologous structural (MAS) cells, which are subject to a biologic licensing requirement.

Carticel: the culturing of chondrocytes is considered by the FDA to fall into the category of manipulated autologous structural cells (MAS), which are subject to a biologic licensing requirement. At the present time, only Carticel™ (Genzyme) has received FDA approval for the culturing of chondrocytes through a biologics license.

On August 22, 1997, the FDA granted a Biologics License for Carticel®, approving it for provision of autologous chondrocytes for the repair of clinically significant, symptomatic cartilaginous defects of the femoral condyle caused by acute or repetitive trauma. The FDA granted a supplement to the Biologics License for Carticel® on March 2, 2000. In response to a request made by Genzyme, the FDA narrowed the indication for use of autologous cultured chondrocytes to second-line therapy for patients who have failed other therapies.

The current FDA-approved indications for Carticel state that Carticel is indicated 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).

Carticel should only be used in conjunction with debridement, placement of a periosteal flap and rehabilitation.

Carticel is not indicated for:
- treatment of cartilage damage associated with generalized osteoarthritis.
- patients with total meniscectomy unless surgically reconstructed prior to or concurrent with Carticel implantation.

Prescribing information for Carticel specifies administration only by physicians who have completed Genzyme Biosurgery's Surgeon Training Program.

Pre-existing conditions, including meniscal tears, joint instability, or malalignment should be assessed and treated prior to or concurrent with Carticel implantation. Carticel should not be used in patients who have previously had cancer in the bones, cartilage, fat or muscle of the treated limb. The efficacy of ACI in young children and patients older than age 65 was not studied prior to Food and Drug Administration (FDA) approval; and the safety of ACI during pregnancy or breastfeeding has not been

Collagen meniscus implants, also known as collagen scaffold, or Menaflex, are bioresorbable, primarily bovine type 1 collagen. This product was designed as a tissue-engineered scaffold to support the generation of new meniscus-like tissue.

The Collagen Meniscal Implant (CMI), the ReGen Collagen Scaffold (CS), and the Menaflex device are different names for the same device.

Menaflex collagen meniscus implant received U. S. Food and Drug Administration (FDA) 510(k) marketing clearance on December 18, 2008 as the ReGen Collagen Scaffold (CS). According to the 510(k) summary, CS is intended for use in surgical procedures for the reinforcement and repair of soft tissue injuries of the medial meniscus. In repairing and reinforcing medial meniscal defects, the patient must have an intact meniscal rim and anterior and posterior horns for attachment of the mesh. In addition, the surgically prepared site for the CS must extend at least into the red/white zone of the meniscus to provide sufficient vascularization. See the following website for more information: http://www.accessdata.fda.gov/cdrh_docs/pdf8/K082079.pdf. Accessed July 2016.

Amid controversy about the 510(K) clearance for the ReGen Collagen Scaffold, the FDA initiated a review of the clearance process for this device. In September 2009, the FDA issued a preliminary report on the Review of the ReGen Menaflex®: Departure from Processes, Procedures, and Practices Leave the Basis for a Review Decision in Question. This preliminary report documents findings and recommendations concerning FDA’s review and clearance of Menaflex. The FDA has undertaken a reconsideration of the decision to clear ReGen’s CS device. The report states that "These findings indicate that a focused scientific reevaluation of the decision to clear the CS device is warranted, and we conclude with general recommendations for better protecting FDA’s internal processes against external pressures." See the following website for more information: http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm183745.htm. Accessed July 2016.

According to a ReGen 24-hour summary report from the FDA, the Orthopaedic and Rehabilitation Devices Panel met on March 23, 2010 to discuss and make recommendations on scientific issues relevant to FDA’s reevaluation of the ReGen Collagen Scaffold (CS) device (marketed as the Menaflex®). The panel gave scientific and clinical input on the data that was submitted in the 510(k). The Panel deliberated on the safety and effectiveness of this product as evidenced from data provided from the submitted studies. The Panel formed a consensus that due to the low number of device failures, the device can be viewed as reasonably safe, but the device’s effectiveness would need to be analyzed further. In order to determine effectiveness, the panel stated that follow-ups on participants, further imaging studies and predetermined endpoints would need to be analyzed. See the following website for more information: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/OrthopaedicandRehabilitationDevicesPanel/ucm205996.htm. Accessed July 2016.
On October 14, 2010, the FDA announced that Menaflex Collagen Scaffold should not have been cleared for marketing in the United States. “To correct this error,” the FDA said it will begin the process to rescind clearance of the device. As part of that process, the agency has requested a meeting with ReGen Biologics Inc., the manufacturer of the device, to discuss alternative marketing pathways for the device and the additional data needed for the agency to properly evaluate the safety and effectiveness of the device. According to the FDA, it has now concluded that the Menaflex device is intended to be used for different purposes and is technologically dissimilar from devices already on the market, called predicate devices. These differences can affect the safety and effectiveness of the Menaflex device. For example, instead of simply repairing or reinforcing damaged tissue like predicate devices, Menaflex is intended to stimulate the growth of new tissue to replace tissue that was surgically removed. The FDA said that because of these differences, the Menaflex device should not have been cleared by the agency. The device will remain on the market until the agency rescinds its clearance. See the following website for more information: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm229384.htm. Accessed July 2016.

The FDA has indicated that no recall is necessary. Explanting the implant is not an option because the material is resorbed and replaced with new tissue. However, the agency advised patients who received Menaflex to talk with their surgeons or other healthcare professionals about what, if any, steps should be taken. See the following website for more information: http://healthland.time.com/2010/10/14/fda-admits-it-was-wrong-to-approve-a-knee-treatment/. Accessed July 2016.

Transplantation of meniscal allografts is a surgical procedure and, as such, is not subject to regulation by the FDA. However, the FDA does regulate certain aspects of tissue banking, and tissues are subject to FDA registration and requirements for good tissue practices and infectious disease screening and testing, as well as to the good manufacturing practice requirements applicable to drugs and devices. According to current rules, FDA premarket review or marketing approval is not required for minimally processed tissues transplanted from one person to another for their normal structural functions; these criteria apply to meniscal allografts. See the following website for more information: http://www.fda.gov/BiologicsBloodVaccines/TissueTissueProducts/default.htm. Accessed July 2016.

**APPLICABLE CODES**

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

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*CPT® is a registered trademark of the American Medical Association.*
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<td>Arthroscopy, knee, surgical for harvesting of cartilage (chondrocyte cells)</td>
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REFERENCES


Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Meniscal Allograft Transplantation. TEC Assessments 1997; Volume 12


**PROTOCOL HISTORY/REVISION INFORMATION**

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Corporate Medical Affairs Committee

The foregoing Health Plan of Nevada/Sierra Health & Life Healthcare Operations protocol has been adopted from an existing UnitedHealthcare coverage determination guideline that was researched, developed and approved by the UnitedHealthcare Coverage Determination Committee.