Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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(See policy history boxes for previous effective dates)

Title: Meniscal Allografts and Other Meniscal Implants

Description/Background

MENISCAL CARTILAGE DAMAGE

Meniscal allografts and other meniscal implants (e.g., collagen) are intended to improve symptoms and reduce joint degeneration in patients who have had a total or partial meniscus resection.

Meniscal cartilage is an integral structural component of the human knee, functioning to absorb shocks and providing load sharing, joint stability, congruity, proprioception, and lubrication and nutrition of the cartilage surfaces. Total and partial meniscectomy frequently result in degenerative osteoarthritis. The integrity of the menisci is particularly important in knees in which the anterior cruciate ligament has been damaged. In these situations, the menisci act as secondary stabilizers of anteroposterior and varus-valgus translation.

Treatment

Meniscal allograft transplantation (MAT) is considered a salvage procedure, reserved for patients with disabling knee pain following meniscectomy who are considered too young to undergo total knee arthroplasty or in patients who require a total or near total meniscectomy for irreparable tears. As a result, the population intended to receive these transplants is relatively limited. Using a large database of privately insured non-Medicare patients, Cvetanovich et al (2015) estimated an annual incidence of MAT in the United States of 0.24 per 100,000.(1) It is not expected that clinical trials will be conducted to compare meniscal allografts with other orthopedic procedures, although trials comparing allograft transplant with medical therapy are possible.

There are 3 general groups of individuals who have been treated with MAT:

- young patients with a history of meniscectomy who have symptoms of pain and discomfort associated with early osteoarthrosis that is localized to the meniscus-deficient compartment
- patients undergoing ACL reconstruction in whom a concomitant meniscal transplant is intended to provide increased stability
- young athletes with few symptoms in whom the allograft transplantation is intended to deter the development of osteoarthritis. Due to the risks associated with this surgical procedure, prophylactic treatment for this purpose is not frequently recommended

Issues under study include techniques for processing and storing the grafts, proper sizing of the grafts, and appropriate surgical techniques. The four primary ways of processing and storing allografts are fresh viable, fresh frozen, cryopreserved, and lyophilized. Fresh viable implants, harvested under sterile conditions, are less frequently used because the grafts must be used within a couple of days to maintain viability. Alternatively, the harvested meniscus can be fresh frozen for storage until needed. Cryopreservation freezes the graft in glycerol, which aids in preserving the cell membrane integrity and donor fibrochondrocyte viability. CryoLife is a commercial supplier of such grafts. Donor tissues may also. be dehydrated (freeze-dried or lyophilized), permitting storage at room temperature. Lyophilized grafts are prone to reduced tensile strength, shrinkage, poor rehydration, post transplantation joint effusion, and synovitis; they are no longer used in the clinical setting. Several secondary sterilization techniques may be used, with gamma irradiation the most common. The dose of radiation considered effective has been shown to change the mechanical structure of the allograft; therefore, nonirradiated grafts from screened donors are most frequently used. In a survey conducted by the International Meniscus Reconstruction Experts Forum, when surgeons were asked about allograft preference, 68% preferred fresh frozen nonirradiated allografts, with 14% responding fresh viable allografts.(2)

There are several techniques for MAT; most are arthroscopically assisted or all-arthroscopic. Broadly, the techniques are either all-suture fixation or bone fixation. Within the bone fixation category, the surgeon may use either bone plugs or a bone bridge. Types of bone bridges include keyhole, trough, dove-tail, and bridge-in-slot. The technique used depends on laterality and the need for concomitant procedures. Patients with malalignment, focal chondral defects, and/or ligamentous insufficiency may need concomitant procedures (osteotomy, cartilage restoration, and/or ligament reconstruction, respectively).(3)

Tissue engineering that grows new replacement host tissue is also being investigated. For example, the Collagen Meniscus Implant (CMI®) (by Stryker, formerly the ReGen Collagen Scaffold® by ReGen Biologics), is a resorbable collagen matrix composed primarily of type I collagen from bovine Achilles tendons. The implant is provided in a semilunar shape and trimmed to size for suturing to the remaining meniscal rim. The implant provides an absorbable collagen scaffold that is replaced by the patient’s soft tissue; it is not intended to replace normal body structure. Because it requires a meniscal rim for attachment, it is intended to fill meniscus defects after a partial meniscectomy. Other scaffold materials and cell-seeding techniques are being investigated. Nonabsorbable and nonporous synthetic implants for total meniscus replacement are in development. One total meniscus replacement that is in early phase clinical testing is NUsurface® (Active Implants); it is composed of a polyethylene reinforced polycarbonate urethane.

Outcome Measures
The outcomes of this treatment (i.e., pain, functional status) are subjective, patient-reported outcomes that are prone to placebo effects. On the other hand, the natural history of a severely damaged meniscus is predictable, with progressive joint damage, pain, and loss of function.

Regulatory Status

Collagen Meniscus Implants
In 2008, the ReGen Collagen Scaffold was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. The FDA determined that this device was substantially equivalent to existing absorbable surgical mesh devices. The ReGen Collagen Scaffold (also known as MenaFlex™ CMI) was the only collagen meniscus implant (CMI) with FDA clearance at that time. Amid controversy about this 510(k) clearance decision, FDA reviewed its decision. In October 2010, the FDA rescinded the approval, stating that MenaFlex is intended for different purposes and is technologically dissimilar from the predicate devices identified in the approval process. The manufacturer appealed the rescission and won its appeal in 2014. The product, now called CMI, was manufactured by Ivy Sports Medicine (now Stryker). CMI is the only FDA-approved collagen meniscus product currently on the market.

FDA product code: OLC.

Medical Policy Statement

The safety and effectiveness of meniscal *allograft* transplants have been established for individuals who meet specific criteria. It may be considered a useful therapeutic option when indicated.

Meniscal *allograft* transplantation has been shown to be safe and effective when performed in combination, either concurrently or sequentially, with autologous chondrocyte implantation, osteochondral allografting or osteochondral autografting for focal articular cartilage lesions. It may be considered a useful therapeutic option when indicated.

Other meniscal implants incorporating materials such as collagen and polyurethane have not been shown to be an effective treatment for repairing meniscal defects and are considered experimental/investigational.

Inclusionary and Exclusionary Guidelines

Inclusions:
Meniscal *allograft* transplantation is established in individuals who have had a prior meniscectomy and have symptoms related to the affected side, when **ALL** of the following criteria are met:

- Disabling knee pain with activity that is refractory to conservative treatment
- Adult patients should be too young to be considered an appropriate candidate for total knee arthroplasty or other reconstructive knee surgery (e.g., younger than 55 years)
- Surgeon attests that the knee joint has normal or near normal ligamentous stability, or that treatment will result in restoration of ligamentous stability to normal.
- Absence or near absence (more than 50 percent) of the meniscus, established by imaging or prior surgery
- Surgeon attests that the knee joint is in normal alignment or near normal alignment, or that treatment will include restoration of alignment to normal
- Documented minimal to absent degenerative changes in the surrounding articular cartilage

Meniscal *allograft* transplantation has been shown to be safe and effective when performed in combination, either concurrently or sequentially, with treatment of focal articular cartilage lesions using any of the following procedures:
- autologous chondrocyte implantation, or
- osteochondral allografting, or
- osteochondral autografting.

Exclusions:
- Use of other meniscal implants incorporating materials such as collagen and polyurethane
- Limited knee range of motion (more than 10 degrees loss of extension; flexion less than or equal to 110 degrees)
- Loss of strength (must have at least 50% extension strength relative to body weight or other side)
- Osteoarthritis on radiographs (joint space narrowing, osteophytes)

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

29868

Other codes (investigational, not medically necessary, etc.):

G0428

Note: The above code(s) may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition

improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

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

MENISCAL ALLOGRAFT TRANSPLANTATION

Clinical Context and Therapy Purpose

The purpose of meniscal allograft transplantation (MAT) is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as partial meniscectomy without MAT, in patients who are undergoing partial meniscectomy.

The following PICOs were used to select literature to inform this review.

Populations

The relevant population of interest are individuals who are undergoing partial meniscectomy.

Interventions

The therapy being considered is MAT. Meniscal allografts and other meniscal implants (e.g., collagen) are intended to improve symptoms and reduce joint degeneration in patients who have had a total or partial meniscus resection.

Comparators

Comparators of interest include partial meniscectomy without MAT.

Outcomes

The general outcomes of interest are symptoms, functional outcomes, and quality of life. (Table 1).

Table 1. Outcomes of Interest for Individuals Undergoing Partial Meniscectomy

Outcomes	Details	Timing
Symptoms	Outcomes of interest include pain measured using various scales and questionnaires	1-10 years
Functional outcomes	Outcomes of interest include knee function and range of motion	1-10 years

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;

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

Review of Evidence

Systematic Reviews

Several systematic reviews of available case series have reported reductions in pain and improvements in function at mid-term follow-up, with failure rates at the time of follow-up ranging from 7% to 35% (see Table 2). Elattar et al (2011) published a large systematic review with a total of 1136 allografts.(4) Twelve different clinical scoring systems were described; which generally showed reductions in pain and improvements in function. Hergen et al (2011) conducted another systematic review of the literature to evaluate characteristics of patients, graft survival, and clinical outcomes.(5) Analysis found that patients with Outerbridge scores of II or less in any area had significantly improved post treatment Lysholm Knee Score (LKS) and Tegner Activity Scale (TAS) scores, whereas patients with Outerbridge grade III or more in any area (not repaired) did not. Studies that analyzed patients undergoing concomitant procedures did not detect a difference between the subgroup in comparison with MAT alone. Functional outcomes were considered generally good where reported. Rosso et al (2015) published a systematic review including 55 studies (n=1623 patients).(6) Data from 37 studies were included in demographic and outcome analyses. These systematic reviews, which are based primarily on level IV evidence, summarize the short- to medium-term outcomes of MAT (Table 2).

Table 2. Summary of Key Systematic Reviews of MAT

Variables	Elattar et al (2011)[4]	Herganet al (2011)[5]	Rosso et al (2015)[6]
No. and study type	44 cohort and case series	14 cohort and case series with minimum 2-y follow-up	55 (2 level II, 7 level III, 46 level IV)
Population	1136 knees (1068 patients)	196 knees	1623 patients
Follow-up (range)	4.6 y (8 mo to 20 y)	4.5 mo (2 y – 14 y)	4.5 y (1 y -14 y)
Outcome measures	Pain and function	Pain and function	Pain and function
Review synthesis			
Pain and function	All showed clinical improvement	Alleviation of knee pain and improvement in function noted	Weighted pre-/postmeasures[a]: • VAS pain score decreased from 6.4 to 2.4 • LKS increased from 55.5 to 82.7
Failure rate	10.6%	7% to 35%	Fresh frozen: 9.9% Cryopreserved: 18.2%
Complication rate	21.3%		10.6%
Review conclusion	MAT improves pain and function	Improvements in objective and subjective outcome measures shown in relatively young patients without significant chondromalacia who underwent concomitant repair for cartilage defects, limb	Agreement in literature on MAT indications: • All studies showed clinical improvement at short- and mid-term follow-ups • Complication and failure rates acceptable

		malalignment, and/or limb instability	• Potential chondro-protective effect of MAT remains unclear
Review limitations	Based primarily on case series	Based primarily on case series and qualitative review only	Based primarily on case series

LKS: Lysholm Knee Score; MAT: meniscal allograft transplantation; VAS: visual analog scale.
[a] Data from 37 of the 55 studies in the systematic review.

Randomized Controlled Trials

Smith et al (2018) reported on the results of a small RCT that randomized 21 patients with symptomatic meniscal deficient knee to MAT (n=10) or personalized physical therapy (n=11).(7) Another 15 patients who were screened for the RCT decided instead to choose their treatment (referred to as the preference group), receiving MAT (n=6) or personalized physical therapy (n=9). The Knee Injury and Osteoarthritis Outcome Score (KOOS), International Knee Documentation Committee (IKDC) score, Lysholm Knee Scoring Scale score, and complications were collected at baseline, four and eight months, and one year after the interventions. Trialists reported pooled results from the RCT and preference group, with statistically significant differences in favor of the MAT group for KOOS composite score (mean difference, 12; p=0.03) and KOOS subscales of pain (mean difference, 15; p=0.02) and activities of daily living (mean difference, 18; p=0.005). However, pooling data from the RCT and preference group precluded meaningful interpretation of data.

Case Series

The characteristics and results of several case series with longer term follow-up are provided in Tables 3 and 4. Verdonk et al (2005) published a large case series with long-term follow-up from 95% of their first 105 fresh cultured (viable) meniscal allografts.(8) The indication for transplantation was moderate-to-severe pain in patients who had undergone previous total meniscectomy, not old enough to be considered for a knee joint replacement, and with good alignment of the lower limb and a stable joint (some were corrected concomitantly). In the study by Hommen et al (2007), concomitant procedures were performed in 75% of the patients, including anterior cruciate ligament reconstruction or revision (n=10), high tibial osteotomy (n=2), and lateral retinaculum release (n=3).(9)

At a mean follow-up of 16 years, van der Wal et al (2009) (10) reported graft survival decreased to 52.5%, while most failures in the study by Vundelinckx et al (2010) (11) occurred approximately 10 years postoperatively. That said, at an average of 105 months of follow-up, the 34 remaining patients assessed in the Vundelinckx et al (2019) study showed significant reductions in pain and improvements in function relative to preoperative levels. Radiographic evidence reported by van der Wal et al (2009) also showed a slight or moderate increase in osteoarthritis (OA) in 42% of patients (1 or 2 points), and no increase in the other 58%. Of 15 patients with follow-up radiographs in the Hommen et al (2007) study, 10 (67%) had joint space narrowing and 12 (80%) had progression of the Fairbank degenerative joint disease score in the transplanted tibiofemoral compartment.

Table 3. Summary of Key Case Series Characteristics for MAT

Variables	Verdonk et al (2005)[8]	Van der Wal et al (2009)[10]	Vundelinckx et al (2010)[11]
Sample size	105	57	34/49
Mean age (range), y	35 (16-50)	39 (26-55)	33 (14-47)
Population	Previous total meniscectomy	Previous total meniscectomy	Patients with intact allograft
Intervention	MAT	MAT	MAT
Control	None	None	None
Length of FU (range)	3-15 y	14 y (9-18 y)	105 mo

FU: follow-up; MAT: meniscal allograft transplantation.

Table 4. Summary of Key Case Series Outcomes for Meniscal Allograft Transplantation

Outcomes	Verdonk et al (2005)[8]			Van der Wal et al (2009)[10]			Vundelinckx et al (2010)[11]		
	Base	FU	p-value	Base	FU	p-value	Base	FU	p-value
VAS score							7.0	3.4	<0.001
LKS score				36	61	<0.05	39.7	71.8	<0.001
KOOS score							35.8	60.2	<0.001
Graft survival rate		70%			• 11 y: 71% • 16 y: 52.5%			90%	
Mean survival		11.6 y							

Base: baseline; FU: follow-up; KOOS: Knee Injury and Osteoarthritis Outcome Score; LKS: Lysholm Knee Score; VAS: visual analog scale.

Section Summary: Meniscal Allograft Transplantation (MAT)

Evidence for the use of MAT in patients with disabling knee pain and a prior meniscectomy, consists of systematic reviews of a large number of case series and an RCT. The reviews have found that MAT is associated with reductions in pain and improvements in function. Longer term studies have indicated that these improvements are maintained in a substantial percentage of patients, up to ten years and beyond. Because the results of a single RCT, which enrolled a very small number of patients, pooled data from randomized and nonrandomized groups, results cannot be interpreted in a meaningful way. Adverse events, such as graft failure and the need for additional procedures, occur frequently. The strength of the evidence, including accurate estimates of the magnitude of benefit and the complication rates, are limited by the type of data available (case series and systematic reviews of these case series) as well as the heterogeneity in surgical techniques and patient characteristics across the studies.

MENISCAL ALLOGRAFT TRANSPLANTATION PLUS ARTICULAR CARTILAGE REPAIR

Clinical Context and Therapy Purpose

The purpose of MAT is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as partial meniscectomy without MAT, in patients who are undergoing partial meniscectomy and repair of malalignment, focal chondral defects and/or ligamentous insufficiency.

The following PICOs were used to select literature to inform this review.

Populations

The relevant population of interest are individuals who are undergoing partial meniscectomy and repair of malalignment, focal chondral defects and/or ligamentous insufficiency.

Interventions

The therapy being considered is MAT. Patients with malalignment, focal chondral defects, and/or ligamentous insufficiency may require additional surgery combined with MAT. When MAT is combined with osteotomy or articular cartilage repair in a single procedure, MAT should be performed first.

Comparators

Comparators of interest include partial meniscectomy without MAT.

Outcomes

The general outcomes of interest are symptoms, functional outcomes, and QOL.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Systematic Reviews

Harris et al (2011) published a systematic review of MAT plus cartilage repair or restoration (Table 5).(12) Patients underwent MAT with autologous chondrocyte implantation (ACI; n=73), osteochondral allograft (n=20), osteochondral autograft (n=17), or microfracture (n=3). All studies showed improvement in clinical outcomes at final follow-up compared with the preoperative condition. Outcomes were similar to historical outcomes, extracted from mid-term and long-term follow-up studies, of procedures performed in isolation. Additional surgeries are common (nearly 50%) after MAT plus cartilage repair or restoration procedures.

Table 5. Summary of Key Systematic Reviews for MAT Plus Articular Cartilage Repair

Variables	Harris et al (2011)[12]
No. and study type	6 case series
Population	110
Intervention	MAT combined with cartilage repair or restoration
Control	• Baseline to posttreatment • Historical controls of procedures performed in isolation
Outcome measures	Pain and function
Review synthesis	• Outcomes improved from baseline to posttreatment • 4/6 studies found outcomes equivalent to procedures performed in isolation • 2/6 studies found combined surgery not as good as historical controls
Review conclusion	MAT can improve pain and function when combined with cartilage repair or restoration procedures
Review limitations	Based on case series with historical controls

MAT: meniscal allograft transplantation.

The largest and longest study to report on MAT in patients with significant (grade III and IV) chondral damage is by Stone et al (2010) who reported mean allograft survival of 9.9 years.

(Table 6).(13) Other prospective studies have reported on graft survival and functional outcomes when MAT has been combined with articular cartilage repair.(14,15)

Case Series

The following studies were published subsequent to the systematic review (Table 6). Kempshall et al (2015) looked at MAT concomitant with cartilage repair procedures in (1) patients with more knee cartilage damage (grade 3b >1 cm^2) and (2) patients with less knee cartilage damage (grade 3b <1 cm^2).(16) Functional outcomes following the procedures were similar between the 2 groups. However, implant survival (using graft failure as an end point) was lower among those with greater cartilage damage.

Ogura et al (2016) retrospectively reviewed patients who had undergone autologous chondrocyte implantation and MAT.(17) Seventeen patients were followed for a mean of 7.9 years. Significant improvements in clinical outcomes (visual analog scale for pain, Western Ontario and McMaster Universities Arthritis Index, 36-Item Short-Form Health Survey, and modified Cincinnati Knee Rating Scale scores) were reported in 65% of the patients. Of the six procedures considered failures, four underwent TKA and 2 underwent revision surgery.

Zaffagnini et al (2016) reviewed 147 patients undergoing arthroscopic bone plug-free MAT, with 48% of patients having concomitant procedures (mostly high tibial osteotomy and ACL reconstruction).(18) Two survival analyses were conducted, one with the end point of surgical failure (need for revision procedures related to initial MAT) and the other with the end point of clinical failure (same revision procedures as surgical failure or LKS less than 65 at final follow-up). Mean overall survival time with the surgical failure end point was 9.7 years (95% confidence interval, 9.1 to 10.3 years) and mean overall survival with the clinical failure end point was 8.0 years (95% CI, 7.1 to 8.8 years). Logistic regression analysis did not reveal any variables (including concomitant procedures) affecting the surgical or clinical failure end points.

Table 6. Case Series of MAT Plus Articular Cartilage Repair

Variables	Stone et al (2010)[13]	Kempshall et al (2015)[16]	Ogura et al (2016)[17]	Zaffagnini et al (2016)[18]
Sample size	115	99	17	147
Population	Consecutive patients with grade III-IV chondral damage	Prospective series • Grade 3b <1 cm^2 • Grade 3b >1 cm^2	Retrospective series	Retrospective series
Intervention	MAT	MACI and microfracture more common if chondral damage was 3c >1 cm^2	ACI with MAT	MAT
Control	None	None	None	None
Outcome measures	MAT survival	• MAT survival • KOOS, TAS, LKS, IKDC scores	• MAT survival • MCKRS, WOMAC, VAS, SF-36	• MAT survival • KOOS, LKS, VAS
Length of FU	5.8 y	2 y	5-10 y	4 y
Results	• Mean MAT survival, 9.9 y • 47% required additional surgery	• Similar outcomes on KOOS, TAS, LKS, IKDC scores for 2 groups • MAT survival 97.9% if 3b <1 cm^2 and 78% if 3c >1 cm^2	• Mean MAT survival rate, 75% at 5- and 10-y follow-up • 67% (12/18) required additional surgery	• Mean MAT survival range, 8-9.7 y • 17% required additional surgery

ACI: autologous chondrocyte implantation; FU: follow-up; IKDC: International Knee Documentation Committee; KOOS: Knee Injury and Osteoarthritis Outcome Score; LSK: Lysholm Knee Score; MACI: matrix-assisted autologous chondrocyte implantation; MAT: meniscal allograft transplantation; MCKRS: modified Cincinnati Knee Rating Scale; SF-36: 36-Item Short-Form Health Survey; TAS: Tegner Activity Scale; VAS: visual analog scale; WOMAC: Western Ontario and McMaster Universities Arthritis Index.

Section Summary: MAT Plus Articular Cartilage Repair

There is limited low-quality evidence on combined MAT and articular cartilage repair. The available literature has reported reductions in pain and improvements in functioning following these procedures, though studies have reported graft failures and the need for additional surgeries.

COLLAGEN MENISCUS IMPLANTS

Clinical Context and Therapy Purpose

The purpose of collagen meniscal implants (CMIs) is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as partial meniscectomy without a meniscal implant, in patients with who are undergoing partial meniscectomy.

The following PICOs were used to select literature to inform this review.

Populations

The relevant population of interest are individuals who are undergoing partial meniscectomy.

Interventions

The therapy being considered is CMIs. A CMI is sutured into place on a meniscal rim and is intended for use with a partial meniscectomy.

Comparators

Comparators of interest include partial meniscectomy without a meniscal implant.

Outcomes

The general outcomes of interest are symptoms, functional outcomes, and QOL.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Systematic Reviews

Two systematic reviews, 1 by Harston et al (2012) (19) and the other by Warth et al (2015),(20) are summarized in Table 7. A third systematic review, by Zaffagnini et al (2015),(21) focused only on studies assessing postoperative magnetic resonance imaging evaluations, which included 6 studies, none of which was an RCT and all which were included

in the Warth review. We do not discuss the Zaffagnini et al (2015) review further. Houck et al (2018) published the results of a systematic review that included multiple scaffold implantations including CMI.(22) No studies in addition to those previously summarized by Warth et al 2015 (20) were cited in this systematic review and Houck et al (2018) is not discussed further.

Table 7. Summary of Systematic Reviews for CMI

Variables	Harston et al (2012)[19,]	Warth et al (2015)[20,]
Search date	May 2011	March 2014
No. of studies	11	13
Population	520	674
Intervention	• 321 patients received a CMI • 41.1% patients had concomitant procedures	• 439 patients received CMI • 32.3% patients had concomitant procedures
Control	Partial meniscectomy alone	
Outcome measures	• LKS, TAS, pain scales • 8/11 studies provided postoperative imaging data	• LKS, TAS, pain scales • 11/13 studies provided postoperative imaging data
Length of FU	6-135 mo	3-152 mo
Review synthesis	• 66%-70% patients receiving CMI had satisfactory outcomes • Outcomes in studies with control or comparison groups reported improvements in both groups • Reduced CMI size at last follow-up reported in 6 (54.5%) of 11 studies	• CMI showed superior clinical outcomes vs partial meniscectomy alone • Several studies reported that meniscus scaffold decreased in volume over time • Second-look arthroscopy showed presence of newly formed meniscus-like tissue in area of the scaffold
Review limitations	• Based on low-quality evidence	• Mostly level IV evidence • No meta-analysis due to differing methodologies and data reporting across studies

CMI: collagen meniscus implant; FU: follow-up; LSK: Lysholm Knee Score; TAS: Tegner Activity Scale.

The quality of the studies included in the systematic reviews was generally rated as low. Tables 8 and 9 summarize select studies (two RCTs, two cohort) included in the systematic reviews. A large RCT from the manufacturers of MenaFlex (Rodkey et al, 2008 [23]) was conducted under a Food and Drug Administration investigational device exemption (IDE). Only TAS scores in the chronic arm (but not the acute arm) differed significantly between the CMI and partial meniscectomy only groups. Kaplan-Meier analysis suggested a modest 10% increase in survival in the chronic CMI group.

Randomized Controlled Trials

An independent research group published results from an RCT reported by Linke et al (2006), comparing high tibial valgus osteotomy alone and osteotomy plus CMI.(24) Arthroscopy in the CMI group showed 35% complete healing, 30% partial healing requiring resection of the posterior part of the implant, and 35% with only small remains of the CMI left. Complications included implantation in insufficiently vascularized tissue, sutures cutting into the implant, inadequate fixation to the rim, destruction of the implant in an unstable knee joint or with premature loading postoperatively, allergic reaction to the xenogenic collagen implant, avulsion of the implant with joint blocking, and infection. Pain and function scores did not differ significantly between the CMI and control groups.

Observational Studies

Zaffagnini et al (2011) compared outcomes of 18 patients who chose to CMI with 18 patients who chose partial medial meniscectomy, with a minimum 10-year follow-up.(25) The 2 groups were comparable at baseline. No significant differences were found in the LKS and Yulish scores. Independent and blinded radiographic evaluation showed significantly less medial joint space narrowing in the CMI group (0.48 mm) than in the partial meniscectomy group (2.13 mm). This study had a potential for selection bias.

A retrospective review by Bulgheroni et al (2015) of 34 patients (17 CMI, 17 partial medial meniscectomy) found no significant difference between the groups for pain and function scores at an average of 9.6 year-follow-up.(26)

Table 8. Summary of Study Characteristics for CMI

Variables	Rodkey et al (2008)[23]	Linke et al (2006)[24]	Zaffagnini et al (2011)[25]	Bulgheroni et al 2015)[26]
Study design	RCT	RCT	Controlled cohort	Retrospective cohorts
Sample size	311	60	36	34
Population	Acute and chronic partial meniscectomy		Patient choice	Matched controls
Intervention	CMI	Osteotomy plus CMI	CMI	CMI
Control	Partial meniscectomy alone	Osteotomy alone	Partial meniscectomy alone	Partial meniscectomy alone
Length of FU (range)	59 mo (16-92 mo)	8-18 mo	133 mo (120-152 mo)	9.6 y

CMI: collagen meniscus implant; FU: follow-up; RCT: randomized controlled trial.

Table 9. Summary of Study Results for CMI

Outcomes	Rodkey et al (2008)[23]			Linke et al (2006)[24]			Zaffagnini et al (2011)[25]			Bulgheroni et al (2015)[26]		
	CMI	Ctrl	p	CMI	Ctrl	p	CMI	Ctrl	p	CMI	Ctrl	p
Survival rate	90%[a]	80% [a]		65%			89%					
VAS pain	19/100[a]	21/100[a]		2.2/10	1.5/10	*NS*	1.2/10	3.3/10	<0.004	14.7/100	13.5/100	*NS*
LKS score	79[a]	78[a]	*NS*	93.6	91.0	*NS*	»86	»80	*NS*	94.1	95.5	*NS*
IKDC score						*NS*			<0.001[b]	85.7	88.1	*NS*
TAS score	42%[a]	29%[a]	<0.02				75	50	<0.026	6 5-6	6 5-6	*NS*

CMI: collagen meniscus implant; Ctrl: control; IKDC: International Knee Documentation Committee; LSK: Lysholm Knee Score; TAS: Tegner Activity Scale; VAS: visual analog scale.

[a] Chronic only.

[b] Higher scores reported by CMI group vs control group.

Section Summary: Collagen Meniscus Implants (CMI)

Evidence for the use of CMI in patients undergoing partial meniscectomies consists of 2 systematic reviews, the most recent including 674 patients. The reviews reported overall positive results with CMI, but the quality of the included studies (RCTs and observational studies) was low. Radiologic evaluation showed destruction and/or absorption of the implant in a very large portion of patients.

SUMMARY OF EVIDENCE

For individuals who are undergoing partial meniscectomy who receive meniscal allograft transplantation, the evidence includes systematic reviews of mostly case series and a randomized controlled trial. The relevant outcomes are symptoms, functional outcomes, and quality of life. The systematic reviews concluded that most studies have shown statistically

significant improvements in pain and function following the procedure. The benefits have also been shown to have long-term effect (>10 years). Reviews have also reported acceptable complication and failure rates. There remains no evidence that meniscal allograft transplantation can delay or prevent the development of knee osteoarthritis. A limitation of the evidence is its reliance primarily on case series. Because of the single RCT, which enrolled a very small number of patients, pooled data from randomized and nonrandomized groups, results cannot be interpreted in a meaningful way. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are undergoing partial meniscectomy and concomitant repair of malalignment, focal chondral defects, and/or ligamentous insufficiency who receive meniscal allograft transplantation, the evidence includes a systematic review of case series as well as case series published after the systematic review. The relevant outcomes are symptoms, functional outcomes, and quality of life. The systematic review concluded that pain and function improved following the procedure. One of the series published after the review showed that patients with more severe cartilage damage experienced favorable outcomes similar to patients with less cartilage damage. Another series published subsequently reported an overall 9.7-year survival of the implant. A limitation of the evidence is its reliance primarily on case series. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are undergoing partial meniscectomy who receive collagen meniscal implants, the evidence includes two systematic reviews primarily of case series. The relevant outcomes are symptoms, functional outcomes, and quality of life. The reviews reported overall positive results with the collagen meniscus implant, but the quality of the selected studies (randomized controlled trials, observational studies) was low. Radiologic evaluations have shown reductions in size of the implant in a large portion of patients. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

CLINICAL INPUT RECEIVED THROUGH PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2011 Input

In response to requests, Blue Cross Blue Shield Association received input from 1 physician specialty society (3 reviewers) and 3 academic medical centers while this policy was under review in 2011. The input considered combined meniscal allograft transplantation and focal cartilage repair procedures to be medically necessary in patients younger than 55 years of age who have failed conservative treatment. The reviewers agreed that the collagen meniscus implant is investigational, although some considered the implant to be both investigational and medically necessary for some patients.

2008 Input

In response to requests, Blue Cross Blue Shield Association received input from 1 physician specialty society and 3 academic medical centers while this policy was under review in 2008. Although long-term effects on joint space narrowing were unknown, all of the reviewers considered meniscal allograft to be beneficial in selected patients, with evidence of short to intermediate pain relief when performed in younger patients with a prior meniscectomy who have disabling knee pain. Contraindications were noted as uncorrected instability, uncorrected mal-alignment, and the presence of significant articular disease.

PRACTICE GUIDELINES AND POSITION STATEMENTS

International Meniscus Reconstruction Experts Forum

The International Meniscus Reconstruction Experts Forum (2015) published consensus statements on the practice of meniscal allograft transplantation (MAT) (Table 10).(2) The Forum's statements included guidance on indications, graft procurement and preparation, surgical technique, and rehabilitation.

Table 10. Select Consensus Statements on the Practice of MAT

Statements
Indications for MAT: • Unicompartmental pain post-meniscectomy • In combination with anterior cruciate ligament reconstruction when meniscus deficient • In combination with articular cartilage repair if meniscus deficient
MAT not recommended for asymptomatic meniscus deficient patient.
Potentially poorer outcomes expected in patients with moderate to severe OA (Kellgren-Lawrence grade ≥3).
Non-irradiated fresh frozen or fresh viable grafts are recommended.
Mechanical axis alignment should be performed prior to MAT; if mechanical axis deviation present, consider realignment osteotomy.
Based on current evidence, the superiority of 1 surgical technique over another (all-suture vs bone) is not established.
Outcome scores should include: • Disease-specific: Western Ontario Meniscal Evaluation Tool • Region-specific: Knee injury and Osteoarthritis Outcome Score • Activity: Marx Activity Rating Scale • Quality of life/utility: EuroQoL 5 dimensions questionnaire

MAT: meniscal allograft transplantation; OA: osteoarthritis.

National Institute for Health and Care Excellence

The guidance from the National Institute for Health and Care Excellence (2012) stated that the evidence on "partial replacement of the meniscus of the knee using a biodegradable scaffold raises no major safety concerns," but evidence for any advantage of the procedure over standard surgery was limited.(27)

American Academy of Orthopaedic Surgeons

The American Academy of Orthopaedic Surgeons (2009) updated its position in 2014, still recommending MAT for active people younger than 55 years-old, with the goal of replacing the meniscus cushion before the articular cartilage is damaged.(28) The website also notes that "synthetic (artificial) meniscal tissue has been tried, but there is conflicting information at this time".

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Currently ongoing and unpublished trials that might influence this review are listed in Table 11.

Table 11. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02483988	The SUN Clinical Trial (Safety Utilizing NUsurface Meniscus Implant). A Multi-Center, Single-arm, Prospective, Open-label, Non-randomized, Observational Clinical Study	115	Dec 2023 (Unknown)
Unpublished			
NCT02108496[a]	The VENUS Clinical Study (Verifying the Effectiveness of the NUSurface® System): A Multi-centered, Prospective, Randomized, Interventional Superiority Clinical Study	127	May 2022 (completed)
NCT01712191[a]	Treatment of the Medial Meniscus with the NUSurface® Meniscus Implant	150	Mar 2016 (completed)

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

Government Regulations

National:

Collagen Meniscus Implant Pub 100-3. Manual 150.12. Version 1. Effective 5/25/10
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.

Local:

There is no local coverage determination.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Autografts and Allografts in the Treatment of Focal Articular Cartilage Lesions

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 11/22/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/5/06	1/5/06	1/17/06	Joint medical policy established
3/1/07	12/28/06	1/14/07	Routine maintenance
11/1/08	8/19/08	10/30/08	Routine maintenance
5/1/09	3/6/09	2/10/09	Status change from experimental/investigational to established; Omitted Outerbridge criteria from 4th inclusion bullet
11/1/10	9/15/10	8/17/10	Expanded policy to address collagen meniscus implant (HCPCS code G0428), which is considered experimental/investigational. Policy title changed from "Meniscal Allografts" to "Meniscal Allograft Transplants and Collagen Meniscal Implants;" Omitted, "(e.g., Outerbridge grade II or less, <50% joint space narrowing)" from inclusion bullet
11/1/11	8/16/11	8/16/11	Removed from exclusions "Meniscal allograft transplantation is considered experimental and investigational when performed in combination, either concurrently or sequentially, with *autologous* chondrocyte implantation or osteochondral allografting" and added to "Inclusions" and to the Medical Policy Statement; removed "Adolescent patients should be skeletally mature with documented closure of growth plates (e.g., 15 years or older)" from inclusion criteria.
1/1/13	10/16/12	10/16/12	Routine maintenance; omitted word "transplants" from title; background, rationale and reference sections revised.
7/1/14	4/8/14	4/15/14	Routine maintenance Expanded policy exclusion and medical policy statement to include

			meniscal implants incorporating materials such as collagen and polyurethane. Previously the statement addressed only collagen meniscal implants. Policy title changed from “Meniscal Allografts and Collagen Meniscus Implants” to “Meniscal Allografts and Other Meniscal Implants.” Rationale and references updated.
9/1/15	6/19/15	7/16/15	Routine maintenance
9/1/16	6/21/16	6/21/16	Routine maintenance
9/1/17	6/20/17	6/20/17	Routine maintenance
9/1/18	6/19/18	6/19/18	Routine maintenance
9/1/19	6/18/19		Routine maintenance
5/1/20	2/18/20		Routine maintenance
5/1/21	2/16/21		Routine maintenance
5/1/22	2/15/22		Inclusions and exclusions updated
5/1/23	2/21/23		Routine maintenance (slp) Vendor: Turning Point
5/1/24	2/20/24		Routine maintenance (slp) Vendor: Turning Point
5/1/25	2/18/25		Routine maintenance (slp) Vendor: Turning Point

Next Review Date: 1st Qtr, 2026

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: MENISCAL ALLOGRAFTS AND OTHER MENISCAL IMPLANTS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.