Meniscal Allografts and Other Meniscal Implants

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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions is addressed separately in medical policy 00006.

Note: Autografts and Allografts in the Treatment of Focal Articular Cartilage Lesions is addressed separately in medical policy 00091.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider meniscal allograft transplantation (MAT) when performed in combination, either concurrently or sequentially, with autologous chondrocyte implantation (ACI), osteochondral allografting or osteochondral autografting for focal articular cartilage lesions to be **eligible for coverage**.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider MAT in patients who have had a prior meniscectomy and have symptoms related to the affected side to be **eligible for coverage.**

Patient Selection Criteria
Coverage eligibility may be considered for MAT in patients who have had a prior meniscectomy and have symptoms related to the affected side when ALL of the following criteria are met:

- Adolescent patients should be skeletally mature with documented closure of growth plates (e.g., 15 years or older). Adult patients should be too young to be considered an appropriate candidate for total knee arthroplasty (TKA) or other reconstructive knee surgery (e.g., younger than 55 years); AND
- Disabling knee pain with activity that is refractory to conservative treatment, i.e., physical therapy and analgesic medications; AND
- Absence or near absence (more than 50%) of the meniscus, as documented by previous operative reports, MRI, or diagnostic arthroscopy; AND

- Documented minimal to absent diffuse degenerative changes in the surrounding articular cartilage (Outerbridge grade II or less, < 50% joint space narrowing); AND
- Normal knee biomechanics, or alignment and stability either prior to surgery or achieved concurrently with meniscal transplantation.

Note:
MAT may be considered medically necessary when performed in combination, either concurrently or sequentially, with treatment of focal articular cartilage lesions using autologous chondrocyte implantation, osteochondral allografting or osteochondral autografting. Additional procedures, such as repair of ligaments or tendons or creation of an osteotomy for realignment of the joint may be performed at the same time.

Note: Grade Description of Outerbridge scale:
Grade 0 normal articular cartilage
Grade I softening or blistering of joint cartilage
Grade II cartilage fragmentation or fissuring on the surface <1cm diameter
Grade III cartilage fragmentation or fissuring > 1cm diameter
Grade IV cartilage erosion down to subchondral bone

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers MAT when the patient selection criteria are not met to be **investigational.***

Based on review of available data, the Company considers the use of other meniscal implants incorporating materials such as collagen and polyurethane to be **investigational.***

Background/Overview

MENISCAL CARTILAGE
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 (OA). The integrity of the menisci is particularly important in knees in which the anterior cruciate ligament (ACL) has been damaged. In these situations, the menisci act as secondary stabilizers of anteroposterior and varus-valgus translation.

Treatment
MAT has been investigated in patients with a previous meniscectomy, or in patients who require a total or near total meniscectomy for irreparable tears. There are 3 general groups of patients who have been treated with MAT:

- Young patients with a history of meniscectomy who have symptoms of pain and discomfort associated with early OA 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 OA. 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 4 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 (Marietta, GA) 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.

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).

Tissue engineering that grows new replacement host tissue is also being investigated. For example, the Collagen Meniscus Implant (Ivy Sports Medicine, formerly the ReGen Collagen Scaffold (CS) 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 CS that is replaced by the patient's own 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. For example, Actifit (Orteq) is a biodegradable polyurethane scaffold that currently has market approval in Europe. 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Collagen Meniscus Implants

In 2008, the ReGen CS was cleared for marketing by the U.S. FDA through the 510(k) process. FDA determined that this device was substantially equivalent to existing absorbable surgical mesh devices. The ReGen CS (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 it decision. In October 2010, 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®, is manufactured by Ivy Sports Medicine. CMI®‡ is the only FDA-approved collagen meniscus product currently on the market. FDA product code: OLC.

Polyurethane Meniscal Implant

There are no FDA-approved polyurethane meniscal implants (PMIs) currently on the market in the United States. Actifit®‡ is approved for marketing in Europe.

Centers for Medicare and Medicaid Services (CMS)

In May 2010, the CMS issued a national noncoverage determination for the CMI. A number of concerns regarding the efficacy and safety were raised in the CMS analysis that compared data reported to the FDA and published data. Concerns included an increased number of reoperations and a higher serious adverse event rate than in the control group. CMS concluded that the CMI does not improve health outcomes in the Medicare population and determined that the CMI is not reasonable and necessary for the treatment of meniscal injury or tear.

Rationale/Source

MAT is considered a salvage procedure, reserved for patients with disabling knee pain following meniscectomy who are considered too young to undergo TKA. As a result, the population intended to receive these transplants is relatively limited. Using a large database of privately insured non-Medicare patients, a 2015 report estimated an annual incidence of MAT in the United States of 0.24 per 100,000. 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. 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.

The primary literature consists of retrospective case series and systematic reviews of these case series. Two main issues are investigated: (1) Does MAT improve pain and function? and (2) Does this procedure

reduce joint degeneration? Following is a summary of key references to date, focusing on graft survival and health outcomes with longer term follow-up.

MENISCAL ALLOGRAFT TRANSPLANTATION

Systematic Reviews

Several systematic reviews of available case series have found improvements in pain and function at mid-term follow-up, with failure rates at the time of follow-up that range from 7% to 35% (see Table 1). Elattar et al (2011) published a large systematic review with a total of 1136 allografts. Twelve different clinical scoring systems were described, which generally showed an improvement in pain and function. Hergan et al (2011) conducted a systematic review of the literature to evaluate characteristics of patients, graft survival, and clinical outcomes. Analysis found that patients with Outerbridge scores of 2 or less in any area had significantly improved posttreatment Lysholm Knee Score (LKS) and Tegner Activity Scale (TAS) scores, whereas patients with Outerbridge grade 3 or more in any area (not repaired) did not experience significant improvements in pain and function. Studies that analyzed patients undergoing concomitant procedures did not detect a difference between the subgroup compared with MAT alone. Functional outcomes were considered generally good where reported. In 2015, Rosso et al published a systematic review including 55 studies (total N=1623 patients). 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 (see Table 1).

Table 1. Summary of Key Systematic Reviews of MAT

Variables	Elattar et al (2011)	Hergan et al (2011)	Rosso et al (2015)
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)	53.8 mo (24-167 mo)	53.6 mo (12-168 mo)
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%-35%	Fresh frozen: 9.9% Cryopreserved: 18.2%
Complication rate	21.3%		10.6%
Review conclusion	Meniscal allograft improves pain and function	Improvements in objective and subjective outcome measures shown in relatively young patients without significant chondromalacia who underwent concomitant	Agreement in literature on MAT indications: • All studies showed clinical improvement at short- and mid-term follow-ups • Complication and failure

		repair for cartilage defects, limb malalignment, and/or limb instability	rates acceptable • 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.

Case Series
Several case series with longer term follow-up are discussed next. Series characteristics and results are provided in Tables 2 and 3. 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. 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 ACL reconstruction or revision (n=10), high tibial osteotomy (n=2), and lateral retinaculum release (n=3).

At a mean follow-up of 16 years, van der Wal et al (2009) reported graft survival decreased to 52.5%, while most failures in the study by Vundelinckx et al (2010) occurred approximately 10 years postoperatively. That said, at an average of 105-month follow-up, the 34 remaining patients assessed in the Vundelinckx study showed significant improvements in pain and function relative to preoperative levels. Radiographic evidence reported by van der Wal et al also showed a slight or moderate increase in 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 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 2. Summary of Key Case Series Characteristics for MAT

Variables	Verdonk et al (2005)	Van der Wal et al (2009)	Vundelinckx et al (2010)
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 3. Summary of Key Case Series Results for Meniscal Allograft Transplantation

Outcomes	Verdonk et al (2005)			Van der Wal et al (2009)			Vundelinckx et al (2010)		
	Base	FU	p	Base	FU	p	Base	FU	p
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
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. 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 10 years and beyond. 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.

MAT PLUS ARTICULAR CARTILAGE REPAIR
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.

The evidence available for the efficacy of MAT in knees with chondral damage consists of 1 prospective comparative study, case series, most of which are retrospective, and systematic reviews of case series.

Harris et al (2011) published a systematic review of MAT plus cartilage repair or restoration (see Table 4). Patients underwent MAT with 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 4. Summary of Key Systematic Reviews

Variables	Harris et al (2011)
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 that by Stone et al who reported mean allograft survival of 9.9 years (see Table 5). Other prospective studies have reported on graft survival and functional outcomes when MAT has been combined with articular cartilage repair.

The following studies are those published more recently and subsequent to the systematic review (see Table 5). Kempshall et al (2015) looked at MAT concomitant with cartilage repair procedures on (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). 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 ACI and MAT. 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 6 procedures considered failures, 4 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). 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 [CI], 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 5. Series of MAT with Articular Cartilage Repair

Variables	Stone et al (2010)	Kempshall et al (2015)	Ogura et al (2016)	Zaffagnini et al (2016)
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; OAT: osteochondral autograft transplantation; 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 a limited amount of 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

A CMI is sutured into place on a meniscal rim and is intended for use with a partial meniscectomy. Therefore, the literature search focused on controlled trials comparing health outcomes for CMI versus partial meniscectomy alone. The literature to date consists of case series, a large randomized controlled trial (RCT) sponsored by a CMI manufacturer, a smaller RCT from Germany, and a small prospective comparative cohort study.

Systematic Reviews

Two systematic reviews, 1 published in 2012 (Harston et al) and 1 published in 2015 (Warth et al) are summarized in Table 6. A third, by Zaffagnini et al (2015), focused only on studies assessing postoperative magnetic resonance imaging evaluations, which included 6 studies, none was an RCT and all which were included in the Warth review. We do not discuss the Zaffagnini review further.

Table 6. Summary of Key Systematic Reviews for CMI

Variables	Harston et al (2012)	Warth et al (2015)
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 7 and 8 summarize select studies (2 RCTs, 2 cohort) included in the systematic reviews. A large RCT from the manufacturers of MenaFlex (Rodkey et al, 2008) was conducted under a FDA 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.

An independent research group published results from an RCT comparing high tibial valgus osteotomy alone and osteotomy plus CMI (Linke et al, 2006). 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.

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. 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.

Retrospective Studies
A retrospective review by Bulgheroni (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.

Table 7. Summary of Key Study Characteristics for CMI

Variables	Rodkey et al (2008)	Linke et al (2006)	Zaffagnini et al (2011)	Bulgheroni et al 2014)
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 8. Summary of Key Study Results for CMI

Outcomes	Rodkey et al (2008)			Linke et al (2006)			Zaffagnini et al (2011)			Bulgheroni et al (2014)		
	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	79[a]	78[a]	*NS*	93.6	91.0	*NS*	≈86	≈80	*NS*	94.1	95.5	*NS*
IKDC						*NS*			<0.001[b]	85.7	88.1	*NS*
TAS	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
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.

POLYURETHANE MENISCAL IMPLANT
A PMI (Actifit) is currently on the market in Europe. There are no FDA-approved PMIs to date.

Evidence on the PMI includes a multicenter series from the Actifit Study Group, an independently conducted pragmatic trial, and a case series (see Tables 9 and 10). Verdonk et al (2011, 2012) reported positive results in 2-year clinical outcomes in patients who received a PMI at the time of partial meniscectomy (34 medial, 18 lateral). In 2016, Dhollander et al presented updated data on 44 patients in this cohort. Significant improvements in VAS pain, International Knee Documentation Committee, and Knee Injury and Osteoarthritis Outcome Score were maintained through 5-year follow-up (see Table 10). Interpretation of these results is limited by the absence of a control group undergoing partial meniscectomy without the scaffold.

Another report from the Actifit Study Group, by Bouyarmane et al (2014), evaluated the Actifit biodegradable polyurethane scaffold for the lateral meniscus in patients with postmeniscectomy syndrome Using last observation carried forward for missing data, clinical outcomes were found to improve during the study. This study also lacked a control group.

In contrast with the results from the Actifit Study Group, a controlled pragmatic trial (2015) found no benefit of inserting an Actifit at the time of high tibial osteotomy compared with those left with a meniscus defect.

A case series by Schuttler et al (2016) evaluated the use of Actifit to treat patients with symptomatic segmented medial meniscus deficiency (N=18). Results from a subset of these patients followed for 4 years (n=16) showed that significant reductions in pain and improvements in function were maintained.

Table 9. Summary of Key Study Characteristics for PMI

Variables	Verdonk et al (2012) Dhollander et al (2016)	Bouyarmane et al (2014)	Gelber et al (2015)	Schuttler et al (2016)
	Actifit Study Group			
Study design	Prospective multicenter series	Prospective multicenter series	Pragmatic comparative trial	Case series
Sample size	52	54	60	18
Inclusion	Undergoing partial meniscectomy	Postmeniscectomy syndrome	Symptomatic varus knees with defect >25 mm	Symptomatic segmented medial meniscus deficiency
Intervention	FU of subjects from Verdonk et al (2011)	PMI of the lateral meniscus	HTO with PMI	FU of subjects from Efe et al (2012)
Control	None	None	HTO without PMI	None

Outcome measures	Clinical outcomes	Clinical outcomes	Clinical outcomes	Clinical and radiographic outcomes
Length of FU	5 y	24 mo	31.2 mo	48 mo

FU: follow-up; HTO: high tibial osteotomy; PMI: polyurethane meniscal Implant.

Table 10. Summary of Key Study Results on for PMI

Outcomes	Verdonk et al (2012) Dhollander et al (2016)		Bouyarmane et al (2014)		Gelber et al (2015)		Schuttler et al (2016)	
	Actifit Study Group							
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
VAS pain	56.2/100	19.3/100[a]	5.5/10	2.9/10[a]	5.9	4.7[b]	5.2	1.0[a]
IKDC	38.7	66.9[a]	47.0	67.0[a]	56.7	50.3[c]		
KOOS pain	48.3	77.2[a]					47	89[a]
KOOS ADLs	54.4	80.2					53	94[a]
KSS function							61	98[a]
KSS knee							65	90[a]

ADLs: activities of daily living; IKDC: International Knee Documentation Committee; KOOS: Knee Injury and Osteoarthritis Outcome Score; KSS: Knee Society Score; VAS: visual analog score.
[a] p<0.001.
[b] p<0.006.
[c] Not significant.

Section Summary: Polyurethane Meniscal Implant
Evidence for the use of PMIs for patients undergoing meniscectomy consists of several case series. Long-range follow-up have shown significant improvements in pain and functional outcomes maintained up through 5 years. There are currently no PMIs approved for marketing in the United States, though these products are available in Europe.

SUMMARY OF EVIDENCE
For individuals who are undergoing partial meniscectomy who receive MAT, the evidence includes systematic reviews of mostly case series. 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 MAT can delay or prevent the development of knee OA. A limitation of the evidence is its reliance primarily on case series. The evidence is sufficient to determine that the technology results in a meaningful 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 MAT, the evidence includes 1 systematic review of case series as well as case series published after the systematic review. 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 a meaningful improvement in the net health outcome.

For individuals who are undergoing partial meniscectomy who receive collagen meniscal implants, the evidence includes 2 systematic reviews primarily of case series. Relevant outcomes are symptoms, functional outcomes, and quality of life. The reviews reported overall positive results with the CMI, but the quality of the included studies (RCTs, observational studies) is low. Radiologic evaluations have shown reduced size of the implant in a large portion of patients. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are undergoing partial meniscectomy who receive PMIs, the evidence includes a multicenter case series from the Actifit Study Group, an independently conducted pragmatic trial, and a small case series. Relevant outcomes are symptoms, functional outcomes, and quality of life. Overall improvements in pain and function have been seen following the implantation. The longest follow-up among these studies is 5 years. The studies had small sample sizes and were of low quality. Currently, no PMIs have been approved by the FDA for use in the United States. The evidence is insufficient to determine the effects of the technology on health outcomes.

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Policy History

Original Effective Date: 06/05/2002
Current Effective Date: 05/16/2018

05/16/2002	Medical Policy Committee review
06/05/2002	Managed Care Advisory Council approval
06/24/2002	Format revision. No substance change to policy
06/01/2004	Medical Director review
06/15/2004	Medical Policy Committee review
06/28/2004	Managed Care Advisory Council approval
07/12/2006	Medical Director review
07/19/2006	Medical Policy Committee review. Format changes and FDA information added.
07/02/2008	Medical Director review
07/16/2008	Medical Policy Committee review. Coverage eligibility unchanged.
07/02/2009	Medical Director review
07/22/2009	Medical Policy Committee review. Coverage changed from investigational to eligible with criteria.
07/01/2010	Medical Policy Committee approval
07/21/2010	Medical Policy Implementation Committee approval. Policy statement added; collagen implant considered investigational; collagen meniscus implant added to policy title.
07/07/2011	Medical Policy Committee review.
07/20/2011	Medical Policy Implementation Committee approval. Meniscal allograft transplantation when performed in combination, either concurrently or sequentially, with autologous chondrocyte implantation, osteochondral allografting or osteochondral autografting for focal articular cartilage lesions is now considered eligible for coverage instead of investigational.
06/28/2012	Medical Policy Committee review.
07/27/2012	Medical Policy Implementation Committee approval. No change to coverage.
06/27/2013	Medical Policy Committee review
07/17/2013	Medical Policy Implementation Committee approval. Title and investigational statement changed from “collagen” to “other” and included polyurethane as an example of other meniscal implants in the investigational statement.
07/10/2014	Medical Policy Committee review
07/16/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/25/2015	Medical Policy Committee review
07/15/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Updated rationale and references.
08/04/2016	Medical Policy Committee review
08/17/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
08/03/2017	Medical Policy Committee review
08/23/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/03/2018	Medical Policy Committee review

Meniscal Allografts and Other Meniscal Implants

Policy # 00083
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05/16/2018 Medical Policy Implementation Committee approval. Coverage section adopts both BCBSA and AIM Guidelines.
Next Scheduled Review Date: 05/2019

Coding

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Code Type	Code			
CPT	29868			
HCPCS	G0428			
ICD-10 Diagnosis	M23.000-M23.009	M23.011-M23.069	M23.200-M23.269	M23.300-M23.369
	Q68.6	S83.200A-S83.209A	S83.211A-S83.219A	S83.221A-S83.229A
	S83.231A-S83.239A	S83.241A-S83.249A	S83.251A-S83.259A	S83.261A-S83.269A
	S83.271A-S83.279A	S83.281A-S83.289A	S83.30XA-S83.32XA	

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

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B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);

2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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