

TITLE: Collagen meniscus implant for repair of medial meniscus injury of the knee

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DRAFT

COLLAGEN MENISCUS IMPLANT FOR REPAIR OF MEDIAL MENISCUS INJURY OF THE KNEE

A Technology Assessment

INTRODUCTION

The California Technology Assessment Forum (CTAF) was asked to assess the evidence for the use of collagen meniscus implants for the treatment of medial meniscus injuries. The US Food and Drug Administration (FDA) approval of the collagen meniscal implants (CMI) has generated controversy about whether external lobbying influenced the final approval decision. In September 2009, the FDA took the extraordinary step of publishing a report “ReGen Menaflex: Departure from the Processes, Procedures, and Practices Leave the Basis for a Review Decision in Question” and are currently reconsidering the decision to approve the medical device.

BACKGROUND

Meniscal injuries

The medial and lateral meniscus are crescent-shaped fibrous pads of the knee joint located between the femur and tibial head.¹ They provide shock absorption, pressure redistribution, joint stability, proprioception and contribute to the smooth motion of the knee joint. Meniscal injury is the most common adult acute musculoskeletal injury.² There are two types of meniscus injuries: acute tears or degenerative tears. The first typically occurs in young athletes and the latter in older patients often associated with degeneration of the meniscus, often in association with osteoarthritis. The most common cause is a twisting injury with the foot planted during sports like soccer or football. In the setting of degenerative tears, the amount of trauma may be much less significant and the onset of pain may be insidious. Depending on the severity of the damage to the meniscus and other associated injuries (anterior cruciate ligament tear), pain and swelling can develop slowly over 24 hours or there can be immediate pain and limitation to knee movement. Patients usually present complaining of vague pain along the medial or lateral joint line with the knee clicking, catching or locking. They may also report that the knee is not moving normally. Patients with large meniscus tears may complain of loss of range of motion

The diagnosis of a meniscal tear is made by a combination of history, physical exam, and magnetic resonance imaging (MRI) findings. In some studies, the physical exam was more sensitive and specific than MRI for the diagnosis of meniscal tears.^{3, 4} The presence of an effusion, tenderness along the knee joint line, and a positive McMurray's test are all signs of a meniscal tear.⁵⁻⁸ The most sensitive test is tenderness along the medial or lateral joint line, although this has relatively low specificity. Other tests, such as the McMurray's test, attempt to trap the torn portion of the meniscus under the femoral condyle. These tests are more specific, but less sensitive, especially for clinician's with limited experience.⁹

MRI findings are also sensitive, but not specific. In one study of asymptomatic volunteers, MRI evidence of a meniscus tear was present in 13% of patients younger than 45 years and in 36% of older patients.¹⁰ In another study, 56% of men over 70 years old had MRI evidence of a meniscal tear.¹¹ Thus asymptomatic meniscal tears are common and do not require treatment. When used appropriately, MRI has reasonable good sensitivity and specificity.¹²

Non-operative treatment is appropriate in many patients. These options include icing the knee, analgesics, and limiting activities. Once the pain is controlled, the patient can begin quadriceps-strengthening exercises with straight leg raises. If symptoms do not improve within two to four weeks, surgery may be indicated. Patients with immediate pain and swelling that limits activity after a twisting injury and those with significant restriction in the range of motion of the knee are more likely to require surgery.

Surgical treatment

Surgical options include removal of part or all of the injured meniscus or repair of the meniscus tear. The trend over time has been to repair tears whenever possible and to limit the amount of meniscus tissue that is removed in order to minimize the risk of subsequent osteoarthritis.^{13, 14} However, an old Cochrane review found little evidence in support of one option over another.¹⁵ There was a trend in randomized trials towards improved outcomes with partial rather than total meniscectomy, but the number of patients in the studies was too small for definitive conclusions. No large randomized trials have been published since the review. One small observational study in older patients suggested that good long-term outcomes were more common for traumatic tears (~90%) than for degenerative tears (~20%).¹⁶ One small randomized trial found that partial meniscectomy followed by a supervised exercise program was no better than the supervised exercise program alone.¹⁷ Despite the paucity of well done randomized trials, the current treatment is to repair the meniscus in cases where there is a peripheral tear in younger patients, and to perform a partial

meniscectomy in cases where there are degenerative tears or tears in the central avascular region of the meniscus.

Meniscal Allografts

In cases where there is complete loss of the meniscus in younger (less than 50 years old) patients, a meniscal allograft is considered an option. The indications for meniscal allograft transplantation are patient with unicompartmental pain, limited degenerative changes, normal alignment and normal knee stability. The outcomes from meniscal allograft transplantation are generally good in studies with several years follow-up. A recent study¹⁸ reviewed the outcomes for 63 meniscal allografts after a mean follow-up of 13.8 years. There were significant improvements in function overall, though there was a 29% long-term failure rate. The authors recommend meniscal allograft as a salvage operation for patients who have symptomatic degenerative arthritis in a knee that has had the meniscus removed.

Collagen meniscus implants (Menaflex, ReGen Collagen Scaffold)

Collagen meniscus implants were developed to mimic the function of an intact meniscus in order to reduce pain, restore function, and prevent the accelerated osteoarthritis thought to be a result of partial or total meniscectomy. The Menaflex implant is primarily made from bovine type I collagen from the Achilles tendon enriched with chondroitin sulfate and hyaluronic acid. It is designed to provide a scaffold for new tissue growth in the meniscus. The implant is intended to be reabsorbed by the body as the meniscus regenerates. In the porcine animal model, the implant was rapidly reabsorbed, but human data suggests that the implant is reabsorbed more slowly. The current device is designed to repair the medial meniscus.

The implants can fill defects in the meniscus after partial meniscectomy, but can't replace the entire meniscus because they require an intact meniscal rim in order to be sutured into place. They are usually placed during arthroscopic surgery following partial meniscectomy when a large amount of the meniscus is removed. The implant is trimmed to match the size of the meniscal defect following partial meniscectomy and sutured into place.

TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.

The FDA gave 510(K) approval for the ReGen Collagen Scaffold on December 18, 2008. The approved indication is for reinforcement and repair of soft tissue injuries of the medial meniscus in patients with an intact meniscal rim.

Approval through the 510(k) process requires the manufacturer to show substantial equivalence to predicate devices. A few of the devices noted in the 510(k) application for this device are:

- Restore Orthobiologic Implant (DePuy Orthopaedics, Inc.)
- SIS Fistula Plug (Cook Biotech, Inc.)
- TissueMend, OrthoMend (TEI Biosciences, Inc.)
- Surgisis Mesh (Cook Biotech, Inc.)

There were several more listed.

The FDA is currently reevaluating the clearance of this device.

TA Criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The Medline database, Cochrane clinical trials database, Cochrane reviews database and the Database of Abstracts of Reviews of Effects (DARE) were searched using the key words “collagen meniscus implant,” “CMI,” “Menaflex,” and “collagen scaffold.” The search was performed for the period from 1966 through May 2010. The bibliographies of systematic reviews and key articles were manually searched for additional references. References were also solicited from the manufacturers and local experts. The abstracts of

citations were reviewed for relevance and all potentially relevant articles were reviewed in full. This review focuses on the essential patient oriented outcomes: knee pain and function. Progression of osteoarthritis and rates of reoperation are additional outcomes of interest.

The search identified 72 potentially relevant trials. After elimination of duplicate and non-relevant references, 24 articles were reviewed in full. The remaining eight references describe one randomized trial of 311 patients¹⁹ and six case-series²⁰⁻²⁶ describing 104 patients; one case series had two reports on the same eight patients.^{23, 24} Unpublished data available from the FDA website and from the Centers for Medicare and Medicaid Services (CMS) were reviewed, but not included.

We excluded an additional small randomized trial that used the implant in conjunction with tibial osteotomy to correct varus deformity of the knee as this procedure is not part of the FDA indication for the device.²⁷ In brief, the investigators in the study randomized 60 patients with partial loss of the medial meniscus and a varus morphology of the knee to high tibial osteotomy plus collagen meniscus implant or the osteotomy alone. During two years of follow-up 35% of the patients were lost to follow-up. At that time there were no significant differences on the Lysholm Knee Scoring Scale, the International Knee Documentation Committee scale, or pain scores. It was too early to assess whether the implant slowed down progression of osteoarthritis by reducing cartilage loss.

Level of Evidence: 1 and 5.

TA Criterion 2 is met.

TA Criterion 3: The technology must improve net health outcomes.

There are several well validated scales that are commonly used to evaluate response to therapy following knee injury. The most important for patients is usually pain.²⁸⁻³¹ Pain is most commonly assessed using either a ten point visual analog scale (VAS) with zero indicating no pain and ten indicating the worst possible pain. This is sometimes assessed in a variety of activities including at rest, during usual daily activities, and during exercise. The Lysholm scale uses eight items to assess knee function on a 100 point scale with higher numbers corresponding to better function.²⁸⁻³¹ The questions assess knee stability, pain, locking, swelling, stair climbing, limping, squatting, and use of a knee support. The Tegner activity scale assesses global activity on a ten-point scale with zero indicating a patient on disability because of the injury and ten

indicating participation in competitive sports.²⁸⁻³¹ Finally, one of the major motivations for the development of the collagen meniscus implant was to prevent osteoarthritis of the knee (loss of cartilage) that is thought to be accelerated when the meniscus is partially or completely removed. This is most commonly assessed by measuring the distance between the tibia and fibula on weight-bearing radiographs of the knee, although the degree of radiographic disease does not always correspond to patient symptoms.³² There is also a four-point visual grading of cartilage performed during arthroscopic surgery, the Outerbridge scale.^{33, 34} Grade I corresponds to softening or blistering of the surface of the cartilage while grade IV corresponds to exposure of subchondral bone. Patients with Outerbridge grade IV osteoarthritis were excluded from participation in the trials of the collagen meniscus implant.

Case Series

The six published case series²⁰⁻²⁶ of the collagen meniscus implant are described in the Table below. A total of 104 patients were studied with follow-up ranging from six months to eight years. Almost all of the patients were younger than 50 years of age and the majority was male. The indications for surgery were knee symptoms in the setting of either an acute tear of the medial meniscus that could not be repaired or prior partial meniscectomy. Many of the studies included biopsies to evaluate the histology of the implant between six months and five years after implantation. All of the biopsy studies showed infiltration of the implant by cells similar to fibroblasts as well as the development of a blood supply and secretion of an appropriate extracellular matrix. The device appeared to be well tolerated – there was no evidence of an inflammatory infiltrate on histology, though one patient did require debridement for excessive scar tissue formation. Average pain scores decreased significantly and knee symptoms, measured by the Lysholm scale also improved significantly. Finally patients' activity level, as measured by the Tegner scale, also increased. Many of the trials also looked for evidence of new osteoarthritis using weight bearing knee radiographs. None found evidence suggesting progressive osteoarthritis, though the studies were too small to detect significant changes in this young patient population.

The case series suggest that the collagen meniscus implant can safely replace tissue removed from the medial meniscus and promote new cell growth in the region of the implant. Symptomatically patients improve and there was no evidence of new osteoarthritis. However, without controls, it is unclear whether the symptomatic improvements are due to the implant or the partial meniscectomy. The manufacturer of the implant has supported a large, randomized trial to address this question. The results are described below.



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Table 1: Case series describing patients receiving collagen meniscal implants

Study	N	Patients	Follow-up (years)	Lost to follow-up	Age (years) Female (%)	Pain VAS (0-10)	Lysholm Scale (0-100)	Tegner Activity Scale (0-10)	Biopsy	Reoperations	Progression of osteoarthritis
Stone 1997	10	Irreparable tear or major loss of meniscus ≤ 50 years	3	10%	39 20%	2.2 to 0.6 on a 0 to 3 point scale	NR	3.0 to 1.9 on a 1-5 point scale	Fibrocartilaginous tissue similar to meniscal cartilage	2/9 (22%)	No change in joint space on plain films over 3 years
Rodkey 1999	8	Irreparable tear medial meniscus or prior medial meniscectomy 18 - 50 years	2-3	0%	38 0%	2.3 to 0.2	75 to 93	3.4 to 5.3	CMI replaced by cells similar to meniscus fibrochondrocytes	1 excessive scar formation responded to debridement	No progression.
Reguzzoni 2005	4	Irreparable tear medial meniscus 18 - 50 years	0.5	0%	38 NR	NR	62 to 94	2.2 to 4.5	6 months: implant not reabsorbed, ingrowth of blood vessels, fibroblast-like cells, and extracellular matrix	0%	Not evaluated
Steadman 2005	8*	Irreparable tear medial meniscus or prior medial meniscectomy 18 - 50 years	5.8	0%	38 0%	2.3 to 1.1	75 to 88	3.4 to 6.0	3 patients: fibrocartilage with uniform extracellular matrix. Implant completely reabsorbed.	0	None (3 no change in joint height, 3 decreased less than 0.5 mm, 2 increased less than 0.5 mm)
Genovese 2007	40	Irreparable tear medial meniscus or prior medial meniscectomy	1	0%	41 33%	NR	NR	NR	NR	12/40 (30%)	2/40 (5%) with new chondral lesions on MRI at 2 years.
Zaffagnini 2007	8	Irreparable tear medial meniscus or prior medial meniscectomy 20 - 51 years	6.8	0%	31 0%	5.1 to 1.8	NR	NR	NR	NR	2/8 with 1 mm loss of joint height at 6 years. The other 6 unchanged.
Bulgheroni 2010	34	Irreparable tear medial meniscus or prior medial meniscectomy	5	0%	39	NR	58 to 94 2 year results	2 to 5 2 year results	At 5 years – not completely reabsorbed; not completely similar to normal meniscus	7/34 (21%)	No progression of osteoarthritis at 5 years, although no baseline films for comparison.

* Same 8 patients as in Rodkey 1999

Randomized trial

Rodkey et al reported on an FDA sponsored randomized trial using 26 surgeons at 16 sites.¹⁹ The study included patients 18 to 60 years old who had irreparable injury to the medial meniscus or prior partial resection of a medial meniscus with an intact rim. Patients were excluded if they had full thickness cartilage damage (Outerbridge Grade IV), posterior cruciate ligament insufficiency, or concurrent lateral meniscus disease. Patients with anterior cruciate ligament injuries were eligible if they were repaired within 12 weeks of the study surgery. The investigators divided patients into two arms: an acute arm of patients who had no prior surgery on the involved meniscus (n=157) and a second chronic arm of patients with between one and three prior meniscal surgeries (n=154).

Originally 494 patients were randomized, but 132 were excluded at the time of surgery because the meniscus was able to be repaired, there was significant lateral meniscus disease, or significant cartilage damage. In addition, 49 patients voluntarily withdrew before or at the time of surgery for personal reasons. Finally, two patients were found to have serious protocol violations. Thus, 183 of the randomized patients (37%) were not followed. The investigators described their analysis of the remaining 311 patients as “intention to treat.” Three additional patients from the chronic arm of the trial who were randomized to receive the device were excluded from analyses due to one early infection and two deaths.

Post-operatively, patients in the control arm received standard physical therapy with full weight bearing, unrestricted range of motion, and muscle strengthening exercises as tolerated. Patients who received the collagen meniscus implant were put in a knee brace locked in extension for six weeks that was removed only for daily range of motion exercises. After six weeks, unlimited range of motion exercises were started, but the patients were encouraged to continue to use crutches for an additional two weeks. After six weeks, rehabilitation exercises increased weekly for a total of six months. All patients randomized to the collagen meniscus implant group were required to have a repeat arthroscopy one year after the original surgery.

The mean age of patients in the trial was 39 years and 22% were female. Anterior cruciate ligament repair was performed at the same time as the meniscus surgery in 27% of patients. 88% of patients who received the collagen meniscus implant had a second-look arthroscopy at one year. No failures or shrinkage of the implant were observed and at one year there was a significant increase in total tissue surface area covered by the regenerated meniscus ($p<0.001$). The meniscus defect area filled in by 45% in the acute arm of the study and by 58% in the chronic arm. Historical data suggest that patients in the control arm would have 0% filling²⁴, although they did not have repeat arthroscopy performed in this study.

According to the power calculations and the study protocol submitted to the FDA, the primary outcomes of the study were the VAS for pain and the Lysholm score. There were no significant differences between treatment groups on pain scores or the Lysholm scores. For the acute arm of the study, the 10-point VAS pain score improved by 1.6 points in the implant arm and by 2.1 points in the control arm. For the chronic arm of the study, the 10-point VAS pain score improved by 1.8 points in the implant arm and by 1.8 points in the control arm. For the acute arm of the study, the Lysholm score improved by 26 points in the implant arm and by 28 points in the control arm. For the chronic arm of the study, the Lysholm score improved by 16 points in the implant arm and by 22 points in the control arm. Thus, there was no trend towards benefit with the collagen meniscus implant in the two primary outcomes of the study.

Equivalent pain and functional outcomes would be acceptable if the implant prevents osteoarthritis – the outcome it was designed to improve. The Outerbridge scores in the patients receiving implants who also had repeat arthroscopies at one year demonstrated no change. However, there was no comparison with the control group. More importantly, no long-term comparative outcomes were presented on preservation of joint cartilage or other measures of osteoarthritis. The value of the study would have improved greatly if data on radiographic or MRI changes were presented.

The investigators reported two outcomes in favor of the implant. The first was the Tegner index – this is a novel index used in this study. The Tegner activity scale is a standard, validated measure often used in studies of knee surgery. Data on changes in the Tegner activity scale were not presented in the published article. The Tegner index is a novel statistic representing the percentage of lost activity that is regained post-operatively based on changes in the Tegner activity scale from the preinjury period to the preoperative period and from the preoperative period to the postoperative period. As the authors state, a Tegner index of 1.0 indicates that the patient has regained 100% of the activity level that was lost because of the injury while a Tegner index of 0.25 indicates that only 25% of the lost activity level has been regained. In the acute arm, the Tegner index was 0.41 for both the implant and control groups. However, in the chronic arm of the study, the Tegner index was 0.42 for the implant group and 0.29 for the control group ($p=0.02$). According to FDA documents, the Tegner index was not one of the 15 primary or secondary outcomes in the original study protocol. Since the two arms of the study were analyzed separately, this implies that more than 30 statistical tests were performed without any adjustment for multiple comparisons.

In the acute arm there were no differences in the re-operation rate (five in each group). In the chronic arm, the non-protocol re-operation rate was 9.5% for patients who received an implant compared with 23% in the

control patients ($p=0.04$). However, this discounts the 76 arthroscopies (93%) performed at one year in the 82 patients receiving implants because those patients were required by the study protocol to have a repeat arthroscopy.

Serious complications occurred in about 7% of patients and the rate was similar in the two arms of the study. Seven of the twelve documented serious complications in patients receiving a collagen meniscus implant were classified as possibly or probably related to the implant. A joint infection classified as not related to the implant resulted in removal of the implant in one patient.

In summary, in this relatively large randomized trial, the collagen meniscus implant appeared safe through five years. However, there were no differences on the two primary outcomes of the study (pain, Lysholm score) in either arm. In both the acute and chronic arms, trends in these outcomes favored the control groups. In the chronic arm, patients who received the collagen meniscus implant had a significantly greater improvement in the Tegner index and fewer non-protocol re-operations in patients randomized to receive the collagen meniscus implant. However, the differences in re-operation rates may in part be due to the large number of protocol re-operations in the implant group. There were also several important methodological issues with the trial. A remarkably high number of patients (37%) were excluded from the study after randomization. There was also post-hoc exclusion of three patients randomized to the device who had serious adverse events. There was no blinding of staff or patients in a trial with primary outcomes that were subjective: self-reported pain and function. There were also major differences in co-interventions: the control group received standard physical therapy while the collagen meniscus implant group received a knee brace locked in extension for six weeks followed by a graduated exercise plan for six months and repeat arthroscopy at one year. The recovery period following surgery appears to be much longer than would be expected following partial meniscectomy alone. There were also multiple statistical tests performed without any adjustment for multiple comparisons. Finally, there were no data on any careful assessment for progression in osteoarthritis – a reduction in osteoarthritis is supposed to be the primary benefit from use of the implant.

TA Criterion 3 is not met.



TA Criterion 4: The technology must be as beneficial as any established alternatives.

The established alternative for meniscal injury when repair is not possible is partial meniscectomy. The large randomized trial described above used partial meniscectomy as the appropriate comparator. There were no clear benefits in patient symptoms, function, or subsequent osteoarthritis. It appears that the recovery and rehabilitation time following the implant is longer than that following partial meniscectomy alone. Finally, the clinical impact of any remnant implants or the regenerated tissue beyond five to eight years remains uncertain.

TA Criterion 4 is not met.

TA Criterion 5: The improvement must be attainable outside of the investigational setting.

To date, clear improvements in patient outcomes compared with standard surgery have not been demonstrated in or out of the investigational setting.

TA Criterion 5 is not met.

CONCLUSION

The medial meniscus cushions and redistributes force in the knee joint. Injuries to the medial meniscus are one of the most common soft tissue injuries presenting to the orthopedic surgeon. Many patients' injuries can be managed conservatively. When surgery is required, every attempt is made to repair the meniscus as removal of meniscus tissue is thought to increase the risk for osteoarthritis in the affected knee. However, five and ten year outcomes after partial meniscectomy are good: the majority of patients return to their prior

level of activity. The collagen meniscus implant was developed to help prevent osteoarthritis in patients whose injuries require partial meniscectomy. The implant is intended to serve as a scaffold to promote growth of meniscus-like tissue in place of tissue removed during surgery.

Six case series reporting on 104 patients with up to eight years follow-up suggest that the implant can be safely placed during arthroscopy and that it encourages some new tissue growth without eliciting a significant inflammatory response. Improvements in pain, knee symptoms, and overall patient activity were consistently reported, though it is unclear whether this was due to the surgery on the meniscus or placement of the collagen meniscus implant.

One multi-center trial, unblinded randomized 494 patients with medial meniscus injury to partial meniscectomy and the collagen meniscus implant or to partial meniscectomy alone. The investigators reported follow-up data through five years. Patients were analyzed in two arms: an acute arm including patients who had not had prior meniscal surgery and a chronic arm of patients who had undergone between one and three prior surgeries. After randomization, 183 patients were excluded and an additional three patients who received the implant were excluded from outcome analyses because of one early infection and two deaths. There were no differences between the two groups on the primary outcomes: pain measured by a visual analog scale and symptoms measured by the Lysholm scale. The investigators reported a significant improvement in the Tegner index for patients in the chronic arm of the study who were randomized to receive the implant, but this was not one of the two primary outcomes, nor one of the thirteen secondary outcomes, according to FDA documents. The investigators also noted fewer repeat arthroscopies for patients in the chronic arm who were randomized to the implant, but this discounts the arthroscopies required of all patients in the chronic arm at the one year follow-up. No data on osteoarthritis outcomes were reported in the published article. In summary, the trial 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. Finally, no data on osteoarthritis were presented. 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.



DRAFT RECOMMENDATION

It is recommended that use of a collagen meniscus implant for the treatment of irreparable medial meniscus injury does not meet CTAF TA Criterion 3 through 5 for improvement in health outcomes.

June 2, 2010

This is the first review of this technology by the California Technology Assessment Forum

The California Technology Assessment Forum Panel voted to accept the recommendation as presented.

RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

The BCBSA Technology Evaluation Center (TEC) has not conducted an assessment of this technology.

Centers for Medicare and Medicaid Services (CMS)

On February 24, 2010 the CMS posted a Proposed Decision Memo noting:

“The Centers for Medicare and Medicaid Services (CMS) proposes that the evidence is adequate to conclude that the collagen meniscus implant does not improve health outcomes. Therefore, CMS has determined that the collagen meniscus implant is not reasonable and necessary for the treatment of meniscal injury/tear and we propose to issue a national non-coverage determination.”

California Orthopaedic Association (COA)

The COA has been invited to provide an opinion regarding this technology and to have a representative attend the meeting.

Arthroscopy Association of North America (AANA)

The AANA has been invited to provide an opinion regarding this technology and to have a representative attend the meeting.



ABBREVIATIONS

CTAF	California Technology Assessment Forum
FDA	US Food and Drug Administration
CMI	Collagen meniscal implants
MRI	Magnetic resonance imaging
DARE	Database of Abstracts of Reviews of Effects
CMS	Centers for Medicare and Medicaid Services
VAS	Visual analog scale
NR	Not reported

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