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Commentary and Perspective, data tables, additional images, video clips and/or translated abstracts are available for this article. This information can be accessed at <http://www.ejbjs.org/cgi/content/full/90/7/1413/DC1>

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Comparison of the Collagen Meniscus Implant with Partial Meniscectomy

A Prospective Randomized Trial

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Investigation performed at the Steadman Hawkins Research Foundation, Vail, Colorado

Background: Loss of meniscal tissue leads to increased pain and decreased clinical function and activity levels. We hypothesized that patients receiving a collagen meniscus implant would have better clinical outcomes than patients treated with partial medial meniscectomy alone.

Methods: Three hundred and eleven patients with an irreparable injury of the medial meniscus or a previous partial medial meniscectomy, treated by a total of twenty-six surgeon-investigators at sixteen sites, were enrolled in the study. There were two study arms, one consisting of 157 patients who had had no prior surgery on the involved meniscus (the “acute” arm of the study) and one consisting of 154 patients who had had one, two, or three prior meniscal surgical procedures (the “chronic” arm). Patients were randomized either to receive the collagen meniscus implant or to serve as a control subject treated with a partial meniscectomy only. Patients underwent frequent clinical follow-up examinations over two years and completed validated outcomes questionnaires over seven years. The patients who had received a collagen meniscus implant were required by protocol to have second-look arthroscopy at one year to determine the amount of new tissue growth and to perform a biopsy to assess tissue quality. Reoperation and survival rates were determined.

Results: In the acute group, seventy-five patients received a collagen meniscus implant and eighty-two were controls. In the chronic group, eighty-five patients received the implant and sixty-nine were controls. The mean duration of follow-up was fifty-nine months (range, sixteen to ninety-two months). The 141 repeat arthroscopies done at one year showed that the collagen meniscus implants had resulted in significantly ($p = 0.001$) increased meniscal tissue compared with that seen after the original index partial meniscectomy. The implant supported meniscus-like matrix production and integration as it was assimilated and resorbed. In the chronic group, the patients who had received an implant regained significantly more of their lost activity than did the controls ($p = 0.02$) and they underwent significantly fewer non-protocol reoperations ($p = 0.04$). No differences were detected between the two treatment groups in the acute arm of the study.

Conclusions: New biomechanically competent meniscus-like tissue forms after placement of a collagen meniscus implant, and use of the implant appears safe. The collagen meniscus implant supports new tissue ingrowth that appears to be adequate to enhance meniscal function as evidenced by improved clinical outcomes in patients with a chronic meniscal injury. The collagen meniscus implant has the utility to be used to replace irreparable or lost meniscal tissue in patients with a chronic meniscal injury. The implant was not found to have any benefit for patients with an acute injury.

Level of Evidence: Therapeutic Level I. See Instructions to Authors for a complete description of levels of evidence.

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Well-documented studies have confirmed the importance of the menisci to the health of the knee joint¹⁻⁶. Loss of meniscal tissue leads to decreased clinical function and activity levels^{4,6}. To date, only meniscal allografts and the collagen meniscus implant (CMI [now called Menaflex]; ReGen Biologics, Hackensack, New Jersey) have been shown to replace lost or damaged meniscal tissue successfully in patients⁷⁻¹⁷. The use of a meniscal allograft is indicated when all or nearly all of the native meniscus has been destroyed or removed. The collagen meniscus implant, however, can be used to fill meniscal defects that result from partial meniscectomy, and it is unique in that, as a tissue-engineered scaffold, it enables the body's own tissue to fill the meniscal defect¹⁴⁻¹⁷. Unlike a meniscal allograft, the collagen meniscus implant is not intended to replace the entire meniscus as it requires a meniscal rim for attachment¹⁵⁻¹⁷.

The collagen meniscus implant has been tested extensively *in vitro* and in laboratory animal trials¹⁸⁻²¹. An initial Phase-I clinical feasibility study was completed successfully¹⁴. On the basis of that study, the collagen meniscus implant was modified in size and shape to be more meniscus-like for use in a Phase-II feasibility trial in which patients were followed for two years¹⁵. The same patients were reevaluated clinically and with a second-look arthroscopic examination at five to six years to assess clinical outcomes and to determine if the newly generated tissue had persisted within the original meniscal defect and remained functional¹⁷.

The initial results of the Phase-II feasibility study were used to support U.S. Food and Drug Administration (FDA) approval of a multicenter clinical trial of the collagen meniscus implant, which is the subject of this report. Under an FDA Investigational Device Exemption (IDE), a prospective, randomized, multicenter, controlled clinical trial was conducted to confirm the safety and establish the efficacy of the collagen meniscus implant. Our hypothesis was that patients who receive the collagen meniscus implant will have an improved clinical outcome two years or more after the index surgery compared with their preoperative status and compared with control patients who undergo only partial medial meniscectomy.

Materials and Methods

This trial was conducted at sixteen sites involving twenty-six surgeon-investigators. All sites received institutional review board approval for participation, and all subjects provided informed consent prior to participation. This study included patients eighteen to sixty years of age who had an irreparable injury to or previous partial loss of one medial meniscus, with an intact rim. The involved knees had to be in neutral alignment with the weight-bearing axis falling within the limits of the tibial eminences on a standing anteroposterior radiograph. Patients with a full-thickness (Outerbridge²² Grade-IV) chondral lesion were excluded from the study as were patients with posterior cruciate ligament insufficiency. We also excluded patients who had concurrent pathological involvement of the lateral meniscus that required repair or

excision of >25% of the lateral meniscus. Injuries of the anterior cruciate ligament could be treated concurrently or in a staged manner, within twelve weeks either before or after the index meniscal surgery.

The trial was designed with two study arms performed concurrently but separately. Each arm was separately controlled and analyzed. One arm of the trial included patients with no prior surgery on the involved meniscus (designated as the "acute" arm of the study), and the second arm included patients who had undergone one, two, or three prior surgical procedures on the involved meniscus (designated as the "chronic" arm). All patients had symptoms of a meniscal lesion. The patients in the chronic group experienced signs and symptoms such as medial joint line pain, swelling, locking, clicking, and catching.

Patients enrolled in the study were randomized either to receive the collagen meniscus implant or to serve as controls. The randomization schedule was computer-generated, and the sealed randomization envelopes were maintained in a centralized location for all sites. After the informed consent form was signed and before the surgery, the results of the randomization were made known to the patient and the surgeon so that both could be prepared in detail for the procedure and the aftercare and rehabilitation. Four hundred and ninety-four patients consented to participate in the study and were randomized to a treatment group. Of these patients, 132 were excluded at the time of surgery for reasons such as the surgeon finding that the meniscus was repairable, that >25% of the lateral meniscus also required repair or removal, or that there was a Grade-IV chondral defect or other exclusionary factors that were clearly defined prospectively in the original study protocol. Of the remaining 362 patients, forty-nine voluntarily withdrew prior to or at the time of surgery for a host of personal reasons. In two additional cases, serious protocol violations, in terms of the patient not meeting the inclusion and exclusion criteria, were found, and those patients were withdrawn from the study immediately on discovery of the violations and all of their data were excluded from the analyses. The remaining 311 patients represent the intention-to-treat group that is described in this report. Figure 1 illustrates the flow of participants through the trial. This study could not be blinded because of the extensive differences in the surgical procedures and the rehabilitation protocols. The control patients underwent an appropriate partial meniscectomy and joint débridement (if indicated). The patients randomized to receive the collagen meniscus implant underwent the identical treatment plus the implantation of the collagen meniscus implant. All procedures were performed arthroscopically. The patients who received the collagen meniscus implant, but not the controls, were required by protocol to have a second-look arthroscopy and biopsy one year after placement of the implant, a condition mandated by the FDA.

At the time of the index surgery, the length and width of the meniscal defect after the partial meniscectomy were measured with use of specific instrumentation (Fig. 2). If the patient had been randomized to the control group, nothing

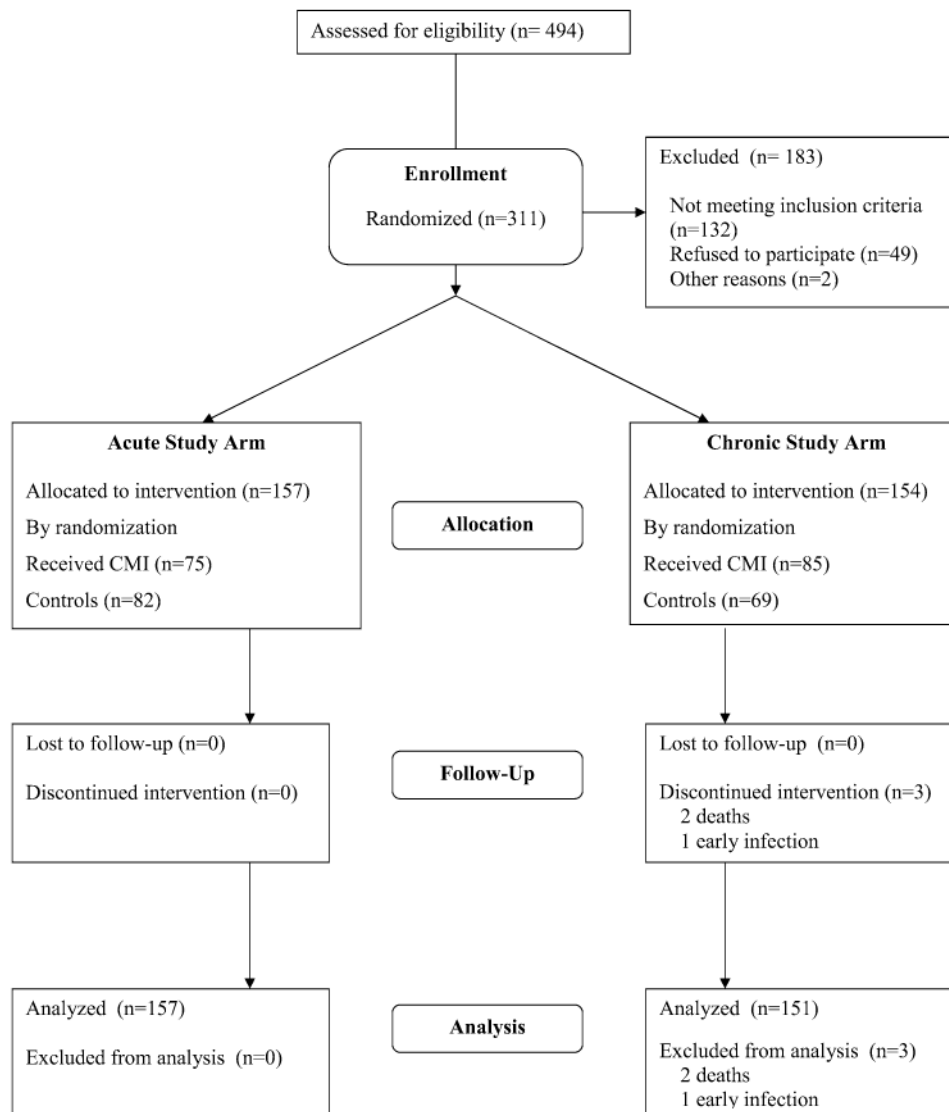


Fig. 1

Diagram illustrating the flow of participants through the trial. CMI = collagen meniscus implant.

further was done to the meniscus. If the patient had been randomized to the collagen meniscus implant group, a collagen meniscus implant was trimmed to the appropriate size to fill the meniscal defect. After delivery of the implant into the joint, it was sutured to the host meniscus remnant with non-absorbable sutures and an inside-out technique (Fig. 3). A detailed description of the surgical technique has been published previously^{15,17}. Additionally, at the time of the index surgery, the status of the chondral surfaces was assessed with use of the Outerbridge score²², which was recorded for all patients.

The postoperative rehabilitation program was specific to each treatment group. The control patients (partial meniscectomy only) were prescribed standard physical therapy, which included full weight-bearing, an unrestricted range of motion, quadriceps and hamstring strengthening, and re-

sumption of activity as tolerated. When the patient had received a collagen meniscus implant, a knee brace was applied and locked in full extension immediately postoperatively. The brace was worn for six weeks, but the patient removed it three or four times per day to perform self-assisted passive range-of-motion exercises. Typically, each patient did at least 500 range-of-motion repetitions three times a day. During the first four weeks, the range of motion was limited from 0° to 60°, and then it was increased to 90° for the fifth and sixth weeks. After the sixth week, the brace was unlocked and worn for comfort only. Unlimited active and passive range-of-motion exercises were initiated at this time. During the initial two postoperative weeks, patients remained non-weight-bearing with crutches. Starting on the third week, they were transitioned to partial weight-bearing, on the basis of evidence derived from basic-science and preclinical studies¹⁸⁻²¹. Patients were allowed to

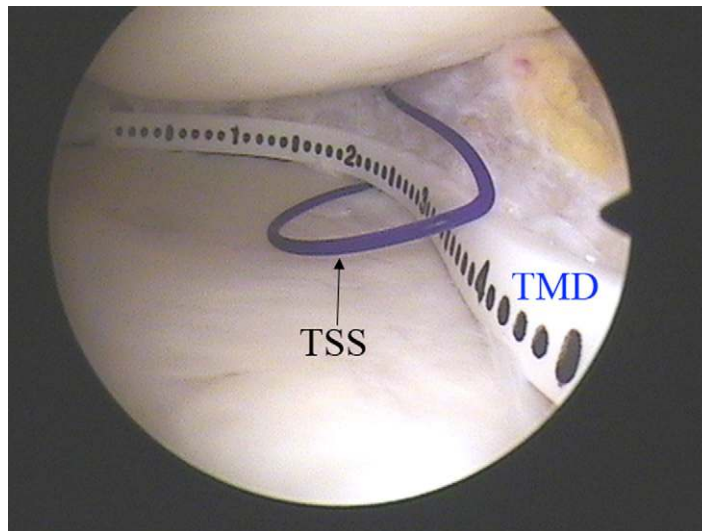


Fig. 2

Following the partial meniscectomy, the size of the meniscal defect was measured with use of specific instrumentation. The numbers on the Teflon measuring device (TMD) represent centimeters, and the hash marks represent millimeters. The temporary stay suture (arrow, TSS) can be used to guide the Teflon measuring device and to stabilize the collagen meniscus implant during suture fixation. The temporary stay suture is removed after the collagen meniscus implant has been sutured to the meniscus rim.

stand with the knee loaded in extension. After the sixth week, they were allowed full weight-bearing while walking but were encouraged to use one or both crutches for at least two more weeks until they were able to walk without a limp. After the sixth week, rehabilitation exercises progressed on a weekly

basis until the patient had returned to full, unrestricted activity at six months after placement of the collagen meniscus implant.

Postoperatively, all patients underwent frequent and extensive clinical follow-up examinations. At each visit, they

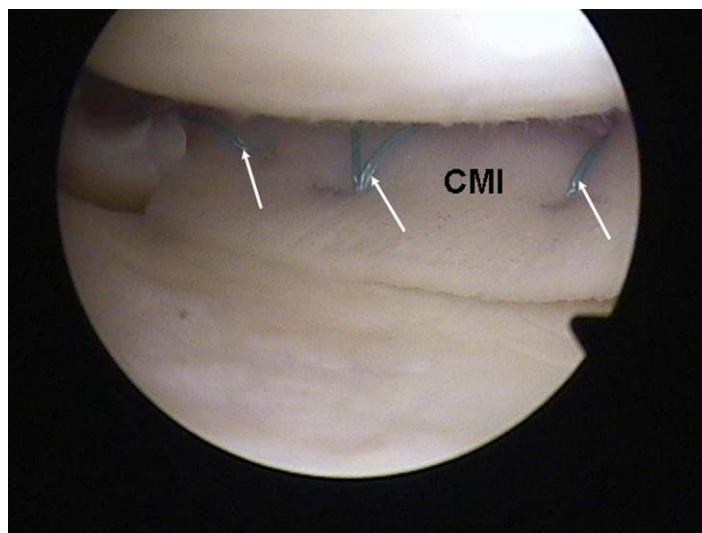


Fig. 3

After the collagen meniscus implant (CMI) was delivered into the joint, it was sutured to the host meniscus remnant with nonabsorbable sutures (white arrows) and an inside-out technique.

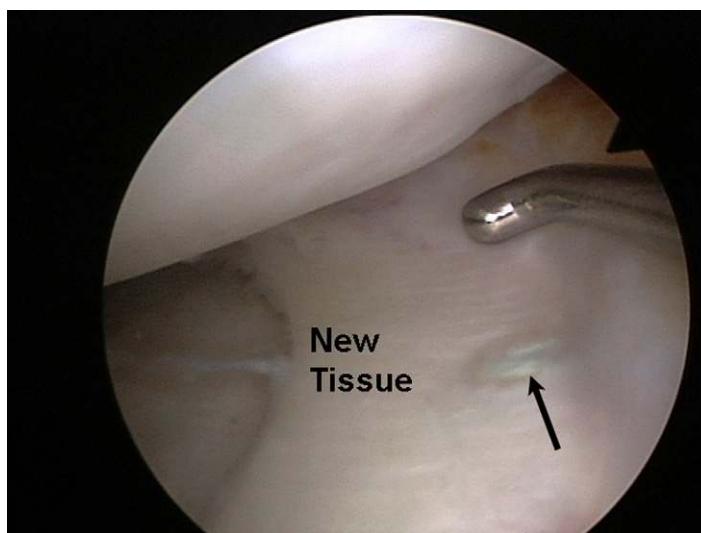


Fig. 4
One-year second-look arthroscopy showed that the collagen meniscus implant had been replaced by new tissue. One of the sutures can still be seen (arrow), although it is covered by synovial tissue. The probe demonstrates the approximate interface between the new tissue generated by the collagen meniscus implant and the host meniscus rim.

completed validated outcome measures, including the Lysholm functional score and Tegner activity scale²³. Pain levels were measured with use of a visual analog scale in which 0 indicated no pain and 100, the worst possible pain. Pain was assessed during rest, activities of daily living, and at the highest levels of activity. The change in pain status between the preoperative and latest follow-up evaluations was also determined for all patients. Patients filled out identical forms at each evaluation.

Tegner activity scores were obtained preinjury (retrospectively, on the basis of patient recall), preoperatively, and postoperatively. Thus, we could calculate the percentage of the lost activity level that was regained as a result of the treatment intervention. This measurement is the Tegner index, and it normalizes the return to activity across a diverse patient population. For example, a Tegner index of 1.0 indicates that the patient regained 100% (all) of the activity level that had been lost as a result of the injury, whereas a Tegner index of 0.25 shows that the patient regained only 25% of lost activity.

Patient satisfaction was measured by asking patients how satisfied would they be if they had to live with the current condition of their knee. The response choices were very dissatisfied, somewhat dissatisfied, neutral, somewhat satisfied, or very satisfied. This evaluation provided patients the opportunity to assess their outcome after meniscal treatment.

All complications and adverse events were documented at each follow-up visit. The surgeon-investigator at each site solely determined the severity of each complication and whether it was related to the implant.

At one year after the index surgery (the first surgical procedure performed as part of this trial), patients who had received a collagen meniscus implant underwent second-look

arthroscopy for direct observation of the new tissue and measurement of defect filling. At the same time, a specimen of the new tissue was obtained with a 14 or 15-gauge-needle biopsy for histological examination and analysis as required by the FDA. The biopsy needle was introduced through the contralateral portal and was maintained parallel to the tibial plateau as it penetrated the new tissue and the host meniscal rim. At the time of the index surgery, the length and width of the meniscal defect were measured, and the percentage of the meniscus that had been lost was calculated. At the one-year second-look arthroscopy, the same or similar instrumentation was used to measure or estimate the amount of meniscal defect that was now filled with new tissue that had replaced the resorbed collagen meniscus implant (Fig. 4). Additionally, the status of the chondral surfaces was assessed with use of the Outerbridge score²². Control patients were not required to undergo a planned second-look arthroscopy. On the basis of published literature¹⁻⁴, it was assumed that no new functional meniscal tissue would form in the control patients. The postoperative status of the chondral surfaces of the control patients was not determined.

Histological evaluation of the biopsy specimens was conducted by an independent pathologist. A second pathologist then performed an independent evaluation of each biopsy specimen without knowledge of the first pathologist's assessment. Histological evaluations were based on specific criteria prospectively set forth in the original protocol, including cellular growth into the implant, vascularity, extracellular matrix organization, integration at the implant-host interface, separation of the host-implant interface, and inflammatory response.

TABLE I Demographic Data*

	Acute Group (N = 157)		Chronic Group (N = 154)	
	Collagen Meniscus Implant	Control	Collagen Meniscus Implant	Control
Patients enrolled and evaluated (no.)	75	82	85	69
Concurrent ant. cruciate lig. reconstruction (no.)	22	16	25	22
Follow-up time (mo)				
Range	23-89	16-85	23-90	23-92
Mean	64	60	60	57
Mean age (yr)	40	40	38	39
Sex distribution (no.)				
Male	65	67	61	50
Female	10	15	24	19

*There were no significant differences between the treatment groups within the study arms.

Radiographs were made in most cases at one and two years after the index surgery; however, there was so much variability in the views and techniques used at the sixteen different study sites that the consulting radiologist was unable to make any definitive statements. Therefore, we elected not to address radiographic findings.

Reoperation and survival rates were determined through five years of follow-up of all patients. A reoperation was defined as an unplanned additional operation (outside of the protocol) on the study knee as a result of disabling or persistent pain and/or mechanical symptoms that could possibly involve the meniscus. A reoperation was done when it was the surgeon-investigator's professional judgment that such an intervention at that time was in the patient's best interest. Survivorship analysis was done to assess the durability of the result of the index surgical procedure, with the end point defined a priori as no unplanned (outside-the-protocol) second operation on the study knee as a result of disabling or persistent pain and/or mechanical symptoms that could possibly involve the meniscus.

Statistical Methods

A priori sample sizes for this study were determined with use of formulae and methods for comparing two independent population means (Lysholm scores and visual analog scale pain scores) and for estimating a population proportion (tissue regrowth). It was determined that, at a level of significance of $p = 0.05$ and with 80% power, a minimum of 128 evaluable patients were needed for each study arm (sixty-four patients treated with the collagen meniscus implant and sixty-four control patients). With an expected 20% drop-out rate, it was determined that a minimum of 154 patients needed to be enrolled in each study arm. Thus, at least 308 patients needed to be enrolled.

All data were recorded on standardized case report forms and submitted to a third-party data management firm contracted by the manufacturer of the collagen meniscus implant. This firm prepared the data analyses presented herein,

and then all analyses were confirmed by one of us (K.K.B.). The accuracy of data entries was verified and certified for submission to the FDA by an independent third party at the expense of the manufacturer of the collagen meniscus implant. For all statistical analyses and values described below, significance was set at $p \leq 0.05$. The data reported were obtained at the latest (most recent) follow-up evaluation.

Associations between normally distributed continuous variables were assessed with use of the Pearson correlation coefficient. The Spearman rho was used to compare ranks between continuous nonparametric variables. Comparisons of continuous variables between groups were performed with post hoc independent-samples t tests. Improvements in continuous variables between the preoperative and postoperative evaluations were analyzed with use of a paired t test. Cox regressions, with use of the outcomes variables, were performed at the time of the latest follow-up with covariates of treatment (collagen meniscus implant or control), duration of follow-up, and whether or not the patient had undergone concurrent reconstruction of the anterior cruciate ligament. The Kaplan-Meier method was used to analyze time to an end point (a reoperation) to assess the durability of the result of the index surgical procedures. This method provides an estimate of the probability of the proportion of patients with a reoperation at a particular time. Because of the low number of patients at risk after five years of follow-up, survival results were estimated at five years. Patients for whom follow-up had not been completed were censored because of the unavailability of information. A log-rank test was used to compare the Kaplan-Meier curves between the controls and the patients who had received a collagen meniscus implant.

Results

Demographic data are provided in Table I. A total of 311 patients met all inclusion and exclusion criteria and were enrolled and treated under the clinical protocol. The average

TABLE II Meniscus Remaining and Defect Filling

	Acute Group		Chronic Group	
	Collagen Meniscus Implant	Control	Collagen Meniscus Implant	Control
Percent meniscus remaining				
No. studied	75	82	85	69
Mean and stand. dev. (%)	51 ± 20	59 ± 19	37 ± 20	40 ± 22
Percent defect filled				
No. studied	65		76	
Mean and stand. dev.* (%)	45 ± 28	0†	58 ± 27	0†
Percent tissue surface area				
No. studied	65	82	76	69
Mean and stand. dev.* (%)	73 ± 17	59 ± 19	73 ± 20	40 ± 22

*There was a significant difference ($p < 0.05$) between the treatment groups within the study arms. †The zero value was assumed on the basis of values for historical controls.

age, sex distribution, and follow-up times within the study arms were not significantly different ($p > 0.05$) between the treatment groups. Of the 160 patients who received the collagen meniscus implant, 141 (88%) underwent the one-year second-look arthroscopy in accordance with the protocol. Concurrent anterior cruciate ligament reconstruction was carried out in eighty-five (27%) of the 311 patients. The most recent follow-up evaluation of seventeen patients (5.5%) was carried out less than two years postoperatively.

At the second-look arthroscopy, the new tissue generated by the collagen meniscus implant appeared to be grossly meniscus-like and was well integrated with the host meniscus rim. The tissue was soft and supple to probing, with a feel similar to that of a normal meniscus. The new tissue was stable in location, and it maintained the shape of the meniscus without apparent shrinkage. No failures due to a lack of healing of the collagen meniscus implant to the host meniscus rim or as a result of gross tearing of the collagen meniscus

implant were observed. When defect filling was not complete, it was a result of inner rim fraying or partial resorption of the implant. No exuberant tissue growth was observed in any of the 141 patients who underwent second-look arthroscopy. No chondral damage caused by the collagen meniscus implant or the new tissue was observed.

The second-look arthroscopy procedures showed that the collagen meniscus implant had resulted in a significant ($p = 0.001$) increase in total tissue surface area¹⁷. The increased tissue surface area included the area of the new tissue plus the existing meniscus rim. For example, in the chronic group, a mean of 37% of the total tissue surface area remained at the index surgery and a mean of 73% of the total tissue surface area was seen one year after insertion of the collagen meniscus implant. These data are summarized in Table II. Cox regression analysis did not show concurrent anterior cruciate ligament reconstruction to have any influence on the amount of new tissue growth in either group.

TABLE III Clinical Outcomes Data at Time of Most Recent Follow-up

	Acute Group		Chronic Group	
	Collagen Meniscus Implant (N = 75)	Control (N = 82)	Collagen Meniscus Implant (N = 82)	Control (N = 69)
Visual analog scale pain score (<i>points</i>)				
Mean change from preop. score	16	21	18	18
Mean score at time of last follow-up	5	6	19	21
Lysholm score (<i>points</i>)				
Mean change from preop. score	26	28	16	22
Mean score at time of last follow-up	90	87	79	78
Patient self-assessment score (<i>points</i>)				
Mean change from preop. score	0.9	1.1	0.7	0.9
Mean score at time of last follow-up	1.6	1.6	1.9	2.1

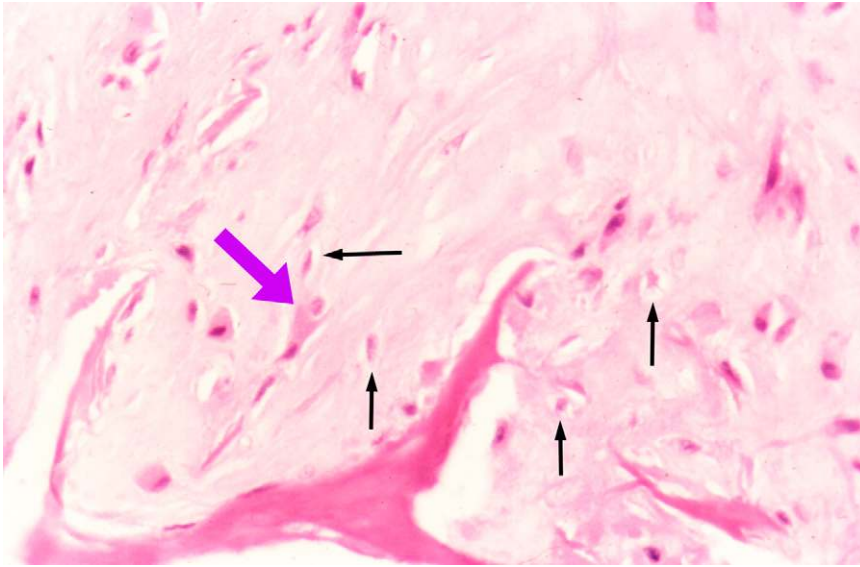


Fig. 5

In this biopsy specimen, obtained at one year, the collagen meniscus implant appears to provide a scaffold for meniscus-like fibrochondrocytic matrix production by the host. The collagen meniscus implant was integrated into this tissue as it was assimilated and/or resorbed (large purple arrow). Cells that appear to be meniscus fibrochondrocytes (small black arrows) are noted to be surrounded by lacunae, suggesting that they are viable and active cells (hematoxylin and eosin; original magnification, $\times 100$).

At the index surgery, the mean Outerbridge score was 1.3 points for the patients in the acute group who had received a collagen meniscus implant, 1.5 points for the patients in the chronic group who had received a collagen meniscus implant,

1.2 points for the control patients in the acute group, and 1.7 points for the controls in the chronic group. None of these differences were significant. At the time of the one-year second-look arthroscopy, the mean Outerbridge score was 1.3 points

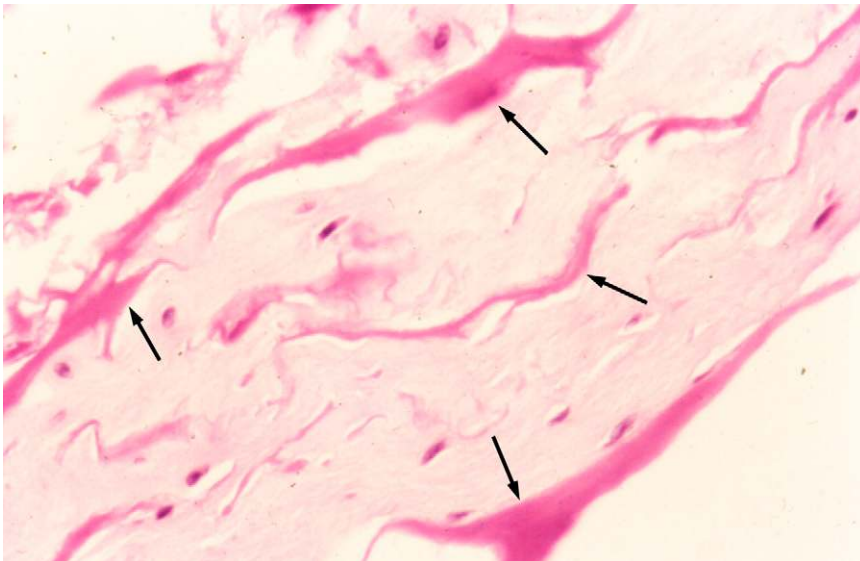


Fig. 6

In this biopsy specimen, obtained at one year, it can be seen that most of the collagen meniscus implant has been resorbed or assimilated into the new matrix. The arrows point to darker-staining structures that are remnants of the collagen meniscus implant (hematoxylin and eosin; original magnification, $\times 100$).

**TABLE IV Serious or Clinically Relevant Complications
in the Study Knee***

Complication	Collagen Meniscus Implant (no.)	Control (no.)
Pain	2	7
Swelling/effusion/redness	4	1
Instability	1	0
Infection/fever	1	1
Nerve injury/numbness	1	1
Deep vein thrombosis	1	1
Wound-related/other	1	0
Patellofemoral symptoms	1	0
Total	12	11

*These complications were classified as serious or clinically relevant by the surgeon-investigator and required some form of treatment.

for the patients who had received a collagen meniscus implant in both the acute and the chronic group. With the numbers studied, the slight improvement in the patients in the chronic group who had received a collagen meniscus implant was not significant. Since the control patients did not undergo second-look arthroscopy, similar comparisons are not possible.

The latest mean pain scores, Lysholm scores, and patient self-assessment scores as well as the change in these scores between the preoperative and latest follow-up evaluations are presented in Table III. The mean pain, Lysholm, and self-assessment scores were not significantly different between treatment groups. The Cox regression analysis did not show concurrent anterior cruciate ligament reconstruction to have any effect on any of these outcomes at the latest follow-up evaluation.

As demonstrated by the Tegner index, patients in the chronic group who had received a collagen meniscus implant regained significantly more of their lost activity than did the control patients in that group, thus returning closer to their preinjury activity levels. The patients in the chronic group who had received a collagen meniscus implant regained, on the average, 42% of their lost activity level at nearly five years whereas the controls in the chronic group regained only 29% ($p = 0.02$). Over the same period of time, the patients in the acute group (no prior surgery on the involved meniscus), regardless of whether they had been treated with a partial meniscectomy only or with the collagen meniscus implant, regained an average of 41% of their lost activity level. According to the regression analysis, the Tegner index was not affected by whether or not the patients had undergone concurrent anterior cruciate ligament reconstruction.

In the chronic group, 66% of the patients treated with a collagen meniscus implant and 49% of the controls were very or somewhat satisfied with the outcome ($p = 0.09$). In the

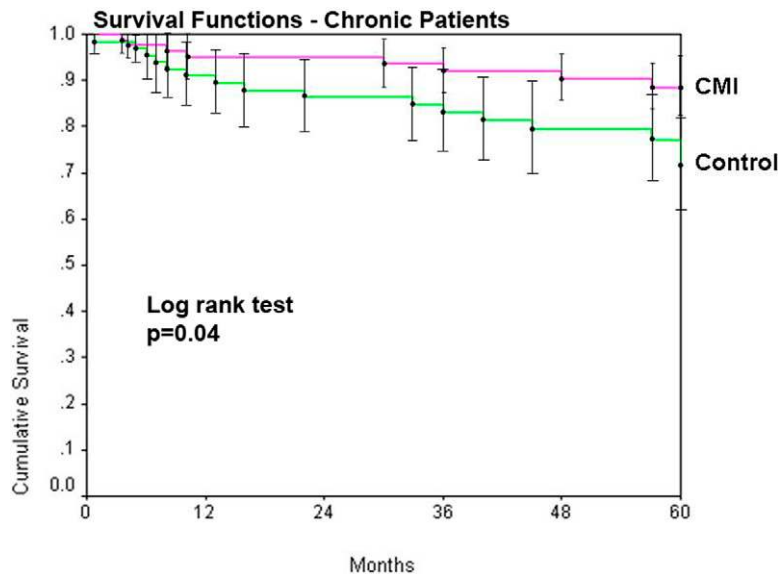


Fig. 7
Kaplan-Meier curve with 95% confidence intervals illustrating a significantly greater survival rate at five years for patients in the chronic group who had received a collagen meniscus implant (CMI) compared with the controls in the chronic group. The majority of reoperations in the control patients were done prior to twenty-four months, but only four unplanned reoperations were done prior to twenty-four months in patients who had received a CMI.

TABLE V Reoperations

	Acute Group		Chronic Group	
	Collagen Meniscus Implant (N = 5)	Control (N = 5)	Collagen Meniscus Implant (N = 8)	Control (N = 15)
Primary presenting symptom				
Pain	2	4	5	11
Swelling/effusion	1	0	2	1
Stiffness/decreased motion	1	0	0	0
Locking/catching/popping	0	0	1	2
Instability	1	1	0	1
Primary surgical procedure performed				
Explant of collagen meniscus implant	1	0	2	0
Repeat partial meniscectomy	0	3	1	3
Allograft meniscus transplant	0	0	0	1
High tibial osteotomy	0	0	1	1
Joint débridement/synovectomy/loose body removal	3	1	4	9
Ligament stabilization	1	1	0	1

acute group, 82% of the patients treated with a collagen meniscus implant and 75% of the controls were very or somewhat satisfied with the outcome ($p > 0.05$). Cox regression analysis did not show a concurrent anterior cruciate ligament reconstruction to have any effect on patient satisfaction at the latest follow-up evaluation.

On the basis of the histological evaluations, the collagen meniscus implant appears to provide a scaffold for the formation of meniscus-like fibrochondrocytic matrix by the host. In nearly all cases in which remnants of the collagen meniscus implant could be identified, there was evidence of infiltration into the interstices of the collagen meniscus implant with maturing fibrous connective tissue differentiating toward meniscus-like fibrochondrocytic tissue. All of these cases demonstrated some degree of assimilation of the collagen meniscus implant into a newly developing fibrochondrocytic matrix. Most often, the collagen meniscus implant became embedded in a benign fashion and was resorbed or assimilated without obvious surface cellular resorption (Fig. 5). Typically, cells could be seen directly apposed to the collagen meniscus implant surfaces, suggesting that the collagen meniscus implant acts as a scaffold for new tissue deposition. When an interface between the collagen meniscus implant and the host meniscus rim could be identified, incorporation of the new tissue generated by the implant into the host tissue was consistently present and characterized by an angiogenic track connecting the implant matrix into the host tissue. Visual estimates indicated that about 10% to 25% of the collagen meniscus implant remained at one year (Fig. 6). An incidental, rare finding (observed in <5% of the cases) was inflammation of the synovium in the biopsy specimen of the collagen meniscus implant, but none of these cases were associated with any clinical findings of synovitis at the time of the second-look arthroscopy. There were no clinically relevant negative findings such as severe inflamma-

tion or a giant-cell response in any of the biopsy specimens examined at twelve months postoperatively. With new tissue ingrowth and new matrix production considered markers of success, the collagen meniscus implant was found to be successful in 97% of the patients in the chronic group and 70% of the patients in the acute group. The new tissue was not pure fibrocartilage; rather, it consisted of hybrid repair tissue. The findings of the two independent pathologists were consistently in agreement.

Table IV lists the number of patients who experienced a serious or clinically relevant complication in the study knee and required some form of treatment. The severity of each event and whether it was related to the implant was determined by the surgeon-investigator. A serious or clinically relevant complication was identified in twelve patients (7.5%) who had received a collagen meniscus implant and eleven (7.3%) in the control group. Of the twelve documented serious complications in patients with a collagen meniscus implant, seven were classified as probably or at least possibly related to the collagen meniscus implant. A skin infection developed at a portal site at one week and later penetrated into the joint in one patient with a collagen meniscus implant. At about three weeks, joint irrigation with débridement was carried out and the collagen meniscus implant was removed. It was the surgeon-investigator's assessment that the original skin infection was not related directly to the collagen meniscus implant.

Reoperation and survival rates were calculated, to assess the durability of the result of the index procedure, through five years for the chronic study group. As noted above, the a priori definition of a reoperation was an additional surgical procedure on the study knee, outside the protocol, as a result of disabling or persistent pain and/or mechanical symptoms that could possibly involve the meniscus. The follow-up rate was

96%. The reoperation rate was 9.5% for the patients who had received a collagen meniscus implant and 22.7% for the control patients. Thus, the risk (odds) of a reoperation, at five years, in the patients who had had a partial meniscectomy only was 2.7 times greater than that for the patients who had received a collagen meniscus implant (95% confidence interval = 1.2 to 6.7; $p = 0.04$). At five years, with a reoperation as the end point, the survival rate was 89% for the patients who had received a collagen meniscus implant and 74% for the controls, which was a significant difference ($p = 0.04$). The Kaplan-Meier survivorship curve (Fig. 7) illustrates that, in the chronic group, the majority of the reoperations in the controls occurred prior to twenty-four months but only four of the reoperations in the patients treated with a collagen meniscus implant occurred prior to twenty-four months. In the acute study group, there was no difference in the reoperation and survival rates between the two types of treatment (five reoperations following each). One acute collagen meniscus implant was explanted early because of mechanical failure, and that explantation is included as a reoperation. As demonstrated by Cox regression analysis, the reoperation and survival rates at five years did not appear to be influenced by concurrent anterior cruciate ligament reconstruction. Table V lists both the primary presenting symptoms that precipitated the reoperations and the types of reoperations that were performed.

Discussion

Contemporary thinking related to the meniscus focuses on preservation, restoration, and reconstruction^{24,25}. The literature is replete with studies that cite the important biomechanical roles that the menisci play in shock absorption, force transmission, and load distribution across the knee in addition to contributing to stability, joint congruence, nutrition of the articular cartilage, protection of the articular cartilage, joint lubrication, and proprioception^{6,26-31}. Published data support the theory that meniscal attrition after partial or subtotal meniscectomy may be associated with degenerative processes in adjacent articular cartilage surfaces^{30,32-36}. Despite this extensive fund of knowledge about the potential negative effects of removing part or all of the meniscus, arthroscopic partial meniscectomy remains the most commonly performed orthopaedic procedure in the United States. The development of a more sophisticated and scientific understanding and approach to knee problems and, in particular, the natural history of the meniscectomized knee has raised substantial concern about the risk of late degenerative osteoarthritis^{24,25}. Hence, it seems more logical to repair or reconstruct injured menisci whenever possible rather than just resecting the damaged portion.

Many different materials, including artificial materials, autogenous tissue, and allograft tissue, have been evaluated for replacement of the meniscus. Our work with the collagen meniscus implant has confirmed that this device supports the growth of new repair tissue^{15,17}. The new tissue replaces the collagen meniscus implant as it is resorbed, or the collagen meniscus implant is assimilated into the new tissue over time¹⁵⁻¹⁷.

We hypothesized that this form of meniscus replacement would meet the body's need and, compared with partial meniscectomy, lead to better clinical knee function, without causing any harm and while potentially protecting the articular cartilage in the involved compartment.

This randomized clinical trial is unique in that all patients who received the collagen meniscus implant were required by protocol to undergo second-look arthroscopy and biopsy of the new tissue at one year.

A recent cadaver study confirmed that the greater the amount of meniscus that is retained, the more normal are the biomechanical stresses experienced by the knee joint³¹. In our study, patients who received the collagen meniscus implant had significantly more tissue, and thus more tissue surface area, at one year than they had immediately after the meniscectomy. Although we could not measure in situ joint forces in our patients, this finding of an increased amount of tissue surface area suggests that it is possible that a joint with new tissue generated by the collagen meniscus implant will experience biomechanical forces that are closer to normal than those experienced by a joint following partial meniscectomy.

Pain scores, Lysholm scores, and patient self-assessment scores improved between the preoperative and latest follow-up evaluations in all treatment groups, and they were similar regardless of treatment or chronicity. These outcome measures may not be sensitive enough to detect differences in a meniscus treatment study of this type, or it is possible that any differences between treatment groups in the acute arm of the study may not have been great enough to matter clinically. Alternatively, it is possible that the follow-up time, although it was about five years, was insufficient for significant changes to develop. Limited follow-up may have been more of a factor in the acute group than in the chronic group. Long-term follow-up of all patients in this study is necessary to determine if treatment with the collagen meniscus implant will eventually prove superior to partial meniscectomy alone or if both treatments will remain equivalent.

One of the goals of meniscal replacement is to permit patients to regain activity levels that they had lost as a result of the meniscal injury and/or partial meniscectomy. As demonstrated by the Tegner index, patients with a chronic meniscal injury treated with the collagen meniscus implant regained significantly more of their lost activity than did controls, thus returning more closely to their preinjury activity levels. It therefore appears that the control patients in the chronic group had to reduce their activity levels in order to maintain pain levels similar to those in the patients in the chronic group who had received a collagen meniscus implant. In the acute arm of the study, the patients in the two treatment groups regained equal amounts of their lost activity and essentially the same amount as the patients in the chronic arm who had received a collagen meniscus implant. Thus, the new tissue generated by the collagen meniscus implant allowed the patients with a chronic injury that had been treated with multiple operations to regain as much of their preinjury activity level as the patients with an acute injury, who had lost much less of the meniscus at

the time of the index surgery (63% loss in the chronically injured patients who received the collagen meniscus implant compared with 41% and 49% loss in the acutely injured controls and patients who had received a collagen meniscus implant, respectively, as noted in Table II).

Patient satisfaction has gained important attention in recent years as a major outcome measure of the success of orthopaedic procedures, especially those involving the knee^{37,38}. In this study, we cannot draw any firm conclusions with regard to patient satisfaction. The limited follow-up time of five years might be a factor, especially for the patients in the acute group. Only longer follow-up will determine if there is a true clinical difference between the outcomes of the two treatments studied.

The ultimate goal of any knee treatment is to prevent, or at least delay, further degenerative joint disease and, hence, the necessity for additional surgical procedures. In this study, patients in the chronic group who had received a collagen meniscus implant had about half as many unplanned reoperations on the involved knee for the treatment of disability or persistent pain and/or mechanical meniscus symptoms as did the controls. The odds of such a reoperation being performed were 2.7 times greater for the controls than for the patients in the chronic group who had received a collagen meniscus implant. Although the patients who had received a collagen meniscus implant were required to have second-look arthroscopy with a biopsy at one year, the reported nonprotocol reoperations for the patients who had received a collagen meniscus implant were a result of clinically relevant pathological conditions (Table V); hence, we do not believe that the repeat arthroscopic procedures required by the protocol biased the overall survival and reoperation rates. These findings suggest that, in the patients in the chronic group, the new tissue generated by the collagen meniscus implant appears to have replaced or reproduced at least some of the functions of the original meniscal tissue. Thus, we speculate that the new tissue, the function of which was similar to that of the native meniscal tissue, may slow the progression of degenerative joint changes that otherwise would lead to decreased functional capacity and require additional surgical intervention. We were unable to demonstrate any differences between the acutely injured patients who had received the collagen meniscus implant and those treated with partial meniscectomy alone.

As demonstrated by the Outerbridge scores, the status of the chondral surfaces in the patients in either the acute or the chronic group who had received a collagen meniscus implant did not change significantly during the first year. Thus, it appears that the collagen meniscus implant and the new tissue did not damage the chondral surfaces during the first year after implantation in either the acute or the chronic group. We are unable to speculate on whether there were further changes of the chondral surfaces beyond one year in the patients who had received a collagen meniscus implant.

The rates of serious complications were essentially equal for the patients treated with the collagen meniscus implant and the control patients. Although seven of the twelve complica-

tions in the group with the collagen meniscus implant were classified as being probably or at least possibly related to the implant, it appears that placement of the collagen meniscus implant did not lead to any more serious complications than did partial meniscectomy, the current standard of care. We believe that this finding is noteworthy especially because the patients who had received a collagen meniscus implant were required to undergo a second surgical procedure with a biopsy of the meniscal tissue but the controls were not.

One of the major strengths of this study is the relatively high percentage of second-look arthroscopic procedures and biopsies performed in the patients with the collagen meniscus implant. Theoretically, the tissue replacing the lost meniscal tissue does not have to recapitulate the normal meniscus exactly. It must, however, function enough like normal meniscal tissue so that patients will regain their lost activity level and it will not cause damage to the joint, and hopefully it will function biomechanically so that further degenerative changes are lessened. The histological analysis confirmed that the collagen meniscus implant supports the growth of a new hybrid repair tissue—that is, not pure fibrocartilage like the normal meniscus, but rather a composite of repair tissues. The new tissue is meniscus-like, fills the meniscal defect, and remains stable and survives for at least one year as demonstrated by direct observation in this study. Because approximately 10% to 25% of the collagen meniscus implant scaffold was still present at one year, presumably the maturation process was ongoing. It is noteworthy that, in the Phase-II feasibility study, no remnants of the collagen meniscus implant were observed in the biopsy specimens taken at five to six years and the new tissue appeared to be mature and had survived in place¹⁷. There was no arthroscopic or histological evidence that the collagen meniscus implant or the new tissue had any significant untoward effects on the joints; thus, it appears safe.

As noted, one of the covariates in the data analysis was the presence or absence of a concurrent anterior cruciate ligament reconstruction. In no instance did we observe such a reconstruction to have an apparent effect on clinical outcomes at the latest (five-year) follow-up evaluation, regardless of whether the patient had been treated with the collagen meniscus implant or partial meniscectomy alone. This finding suggests that all effects observed at the latest follow-up evaluations were likely a result of the meniscal procedure, not the secondary procedure of anterior cruciate ligament reconstruction.

A weakness of our study is that it could not be blinded, and lack of blinding could lead to patient reporting bias. The postoperative rehabilitation protocols were very different between the collagen meniscus implant and control groups, but we speculate that those differences would not have any profound effects on the five-year outcomes. Additionally, the control patients did not have second-look arthroscopy to confirm that they had not regenerated competent meniscal tissue. However, on the basis of the literature and historical controls, we are confident that there was no meaningful spontaneous regeneration of meniscal tissue in the patients treated with partial meniscectomy alone^{1-6,28-36}. Another weakness of the study is that

the follow-up period may have been insufficient to observe some of the chronic or long-term changes known to occur following meniscectomy. A follow-up period of only five years may have been more important in the acute group since significant changes and diminished clinical results would not be expected that soon in that group^{2,32,34-36}. Alternatively, it may be that the collagen meniscus implant does not provide any positive benefits over partial meniscectomy in acutely injured patients.

An additional weakness of this study is the possibility of recall bias in the scoring of preinjury activity levels to calculate the Tegner index. However, if patients overestimated their preinjury activity level, in most instances this overestimation would have resulted in an underestimation of the Tegner index. Another weakness is that, although radiographs were made at one and two years in most cases, there was so much variability in the views and techniques used at the sixteen different study sites that the consulting radiologist was unable to make any definitive statements. Finally, the duration of follow-up for seventeen patients (5.5% of the original enrollment) was less than two years.

In conclusion, the collagen meniscus implant supports new tissue ingrowth that appears to be adequate to enhance meniscal function as evidenced by improved clinical outcomes in patients with a chronic meniscal injury. This new tissue generated by the collagen meniscus implant is stable and appears safe and biomechanically competent. Consistent with our study hypothesis, we believe that the collagen meniscus implant has the utility to be used to replace irreparable or lost meniscal tissue and improve the quality of life in patients with a chronic meniscal injury. ■

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