

RESEARCH ARTICLE

Predictors of clinical outcome following revision anterior cruciate ligament reconstruction

MARS Group

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Abstract

The underlying theme throughout this series of studies authored by the Multicenter anterior cruciate ligament (ACL) Revision Study consortium has been to determine the modifiable predictors or risk factors of long-term outcomes of revision ACL reconstruction. The observational studies described and summarized in the manuscript are both clinically relevant and of great interest in finding out the long-term consequences of the intervention and its relationship to the original injury. The successful completion of these studies has important implications for both therapy and future clinical trials. The identification of modifiable risk factors will play an important role in secondary prevention, while the identification of nonmodifiable risk factors will aid us in counseling our patients and making surgical decisions. Thus, we expect a profound clinical impact on patients' care. More importantly, this project represents an important step forward in bringing evidence to bear in clinical decision making in orthopedic surgery.

KEYWORDS

ACL, clinical outcomes, knee, ligament, osteoarthritis

1 | BACKGROUND

Anterior cruciate ligament (ACL) reconstruction remains the treatment of choice for ACL-deficient active individuals involved with sports or activities that involve quick start/stop, cutting, jumping, and abrupt change of direction activities. On the basis of the insurance, industry, and implant evidence, there are approximately 200 000 ACL reconstructions per year in the United States.¹ Fortunately, primary reconstructions typically do well, but can fail at a low but significant rate.²⁻⁴ While highly successful in the short term there can be problems with primary reconstructions including loss of motion, extensor dysfunction with certain grafts, arthritis, and graft failure. This treatise will address graft failure and the multicenter, multi-surgeon group (Multicenter ACL Revision Study [MARS]) assembled to study the issues surrounding revision ACL reconstruction.

A variety of studies have evaluated graft failure in the primary ACL reconstruction setting and have found the failure rates to range from approximately 1% to 8% in the standard patient and graft

setting.^{2,4,5} In the Multicenter Orthopedic Outcomes Network (MOON), the graft failure rate in primary reconstructions was 3% in the ipsilateral knee and 3% in the contralateral knee at 2-year follow-up.⁴ In a systematic review evaluating hamstring vs patellar tendon autografts, Spindler et al³ reported a 3.7% overall failure rate. Wright et al,² in a systematic review of the minimum 5-year follow-up of ACL reconstructions, found an ipsilateral ACL graft failure rate of 5.8% and a contralateral native ACL failure rate of 11.8%.

These are reasonably low levels of failure, but the question confronting us was what happens in cases of failure. What expectations of current and future knee health should these patients have? Can they return once again to the activities that resulted in ACL failure? A better understanding of revision results would allow us to better counsel patients as to expected outcomes.

Defining the outcomes patients can expect and the outcomes that truly matter in the ACL revision setting was the impetus for the development of the MARS group. There was a consensus amongst the MARS surgeons that revision ACL reconstruction typically

resulted in worse outcomes compared to primary reconstructions. Revision ACL reconstruction was the strongest predictor for a worse Knee injury and Osteoarthritis Outcome Score (KOOS) in a mixed ACL reconstruction cohort early in the MOON experience.⁶ In a series of ACL reconstructions reported at minimum 5-year follow-up, the revision was the strongest predictor for worse outcome across the board, but in the editing process the journal reviewers and Editor requested that the revision ACL reconstructions be removed from the published manuscript due to the small number and percentage of revision reconstructions.⁶

Unfortunately, little level 1 or 2 evidence existed at the time to help us confirm this discrepancy in outcomes that we observed between primary and revision ACL reconstructed patients. In a mixed model meta-analysis of 21 studies with minimum 2-year follow-up after revision reconstruction, these worse results were demonstrated after revision reconstruction.⁷ Of the 21 studies, however, only 4 were level 1 or 2, while 1 was level 3, and 16 were level 4 studies. Objective failure (defined as a rerevision, KT-1000 side-to-side difference of >5 mm, or a positive pivot shift) occurred in $13.7\% \pm 2.7\%$ —a much higher rate of failure than typically reported in primary ACL reconstruction. Patient-reported outcomes were worse than expected compared with primary ACL results and usually exceeded the known clinically important difference for these outcome scores.

On the basis of these findings, the MOON Group reviewed their prospectively collected cohort, which began as a mixed primary and revision patient ACL reconstruction cohort.^{8,9} Their working hypothesis was that revision ACL reconstruction results in worse outcomes compared with primary reconstruction, as measured by validated patient-based outcome measures, including the Marx activity rating scale, KOOS, and International Knee Documentation Committee (IKDC) subjective form. Out of 487, 408 (84%) were available at a minimum 2-year follow-up with 39 of 47 (83%) revisions available at a 2-year follow-up. At 2 years, the median Marx activity level scores had dropped from 12 to 9 points in the primary reconstructions vs 10 to 6 points in revisions ($P = .009$). While the minimally clinically important difference (MCID) is not known for the Marx score, it is assumed on a 16-point scale that 2 points (representing more than a 10% change or difference) would be clinically significant. The IKDC at 2 years was 85.6 for primary ACL reconstructions and 79.6 for revisions, which was statistically different ($P = .005$), but not clinically significant (MCID: 11.5 points).^{10,11} For the five KOOS subscales, a difference of 8 to 10 points is clinically significant. In this study, the KOOS knee-related quality of life subscale was lower in revisions at 2 years (75 vs 62.5; $P < .001$). The KOOS sports and recreation subscale also was worse for revisions at 2 years (85 vs 75; $P = .004$). KOOS Pain was lower in revisions and potentially clinically significant (91.7 vs 83.3). KOOS Symptoms (85.7 vs 78.6) and ADLs (98.7 vs 97.1) did not demonstrate a clinically significant difference between primary and revision reconstructions.

Thus, the data represented a prospectively collected cohort of primary and revision ACL reconstructions that used identical validated patient-reported outcome measures. While worse scores across the board were observed for revisions, the factors

contributing to these worse outcomes were unknown. Unfortunately, revisions represented only 10% of the cohort. We sought to identify predictors for these worse results. To identify predictors, multi-variable analysis requires approximately 10 to 15 subjects per variable assessed and with the multiple factors (50-75 or more) potentially contributing to revision ACL reconstruction outcomes, we realized that a comprehensive assessment of important factors in revision ACL outcomes would require a cohort with 750-1000 patients. It became apparent that the MOON group, with less than 20 members, could not enroll an adequate number of patients quickly enough for this type of study. A simple moon could not get it done, as we needed a planet. With this in mind, we set out to establish a larger group of interested sports medicine surgeons.

2 | METHODS

2.1 | Study design

We felt that the basic approach utilized by the MOON group would be appropriate for evaluating the revision patient but realized there were different factors involved in revision surgeries that would need to be captured. A small group developed a standard operating procedure (SOP) manual that outlined rules of engagement for surgeons and patients. Very early on, we engaged the American Orthopedic Society for Sports Medicine (AOSSM), through Bart Mann, the AOSSM research director. He, the AOSSM Research Committee, and the AOSSM society were enthusiastic about the opportunity to engage their members in an important research question. Based on this collaboration, we had access to the AOSSM website and email systems and were able to solicit broad surgeon participation. Interested AOSSM members participated in three training meetings to learn how the study would proceed. Participants were also engaged in designing forms and determining the variables that would be collected and analyzed. Over 100 members originally expressed interest and we currently have 83 surgeons participating at 52 IRB-approved sites. The surgeons are a near 50/50 mix of academic and private practice surgeons, adding to the generalizability of our results.¹²

In determining study design, we debated over a prospective cohort design versus a randomized trial. Ultimately, we believed we did not know a single critical variable to randomize and felt a cohort to determine predictors would best serve a revision series with its rich number of potential factors. We, thus, chose a prospective longitudinal cohort similar to the classic Framingham study for a cardiovascular disease many years ago.¹³

2.2 | Surgeon involvement

Surgeon inclusion was based on AOSSM membership, attendance at one of our training meetings, and a willingness to follow the procedural issues identified in the SOP. This included utilizing a

Musculoskeletal Transplant Foundation (MTF) graft if an allograft was chosen for the subsequent revision. Training videos were reviewed for consensus on meniscal and chondral injury classification and treatment and were based upon similar studies performed by members of the group.^{14,15} We studied the group's ability to agree on etiology of failure for ACL reconstructions utilizing intra-articular videos and radiographs and found fair agreement on most items measured.¹⁶

2.3 | Study logistics

After obtaining informed consent, the patients filled out a 13-page questionnaire prior to their revision ACL surgery that included questions regarding demographics, sports participation, injury mechanism, comorbidities, and knee injury history. Within this questionnaire, each participant also completed the KOOS, the IKDC Subjective form, and the Marx activity rating scale. Contained within the KOOS was the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Surgeons filled out a 49-page questionnaire at the time of the revision surgery that included the impression of the etiology of the previous failure, physical exam findings, the surgical technique utilized, the intra-articular findings, and surgical management of meniscal and chondral damage.

Patient follow-up was completed by mail with readministration of the same questionnaire like the one they completed at baseline. Patients were also contacted by phone or email to determine whether any subsequent surgery had occurred to either knee since their initial revision ACL reconstruction. If so, operative reports were obtained, whenever possible, in order to document pathology and treatment.

Completed data forms were mailed from each participating site to the data coordinating center. Data from both the patient and surgeon questionnaires were scanned with Teleform software (OpenText, Waterloo, Ontario, Canada) utilizing optical character recognition, and the scanned data was verified and exported to a master database.

Teleform paper forms were utilized so data was available in real-time. If starting today we would utilize electronic data capture, but in 2006 this was best practice for us and our coordinating center. Data were housed at Vanderbilt. Our data capture was outstanding;

greater than 99% of all patient and surgeon data points were completed when assessed on our first 900 patients (Table 1).

Once a 2-year follow-up began, we added a full-time central follow-up coordinator whose responsibility was to contact all patients to send out and obtain questionnaires and perform phone/email follow-up. Each site manages their site with their personal healthcare personnel or research personnel. An electronic newsletter (Figure 1) was developed that arrived monthly to all surgeons and coordinators and acted as an impetus to stimulate patient enrollment listing total and monthly enrollment figures for surgeons. Participating surgeons all had the goal of appearing on the top 10 list.

Keys that helped us early on were frequently based on our experience with the MOON and included the use of conference calls and the ability to communicate by email. The group's experience with IRB helped new sites get approval and the knowledge regarding grants helped immensely in obtaining funding.

We developed a Scientific Advisory Board for advice. This eight-member Board meets at least annually and provides advice and oversight for the study. This has included what studies should be performed via an application form by members. This has been critical for governance issues. The makeup is balanced by geography, gender and practice type.

2.4 | Unique aspects of MARS

The MARS group and study offer many unique aspects for orthopedics and even for medical research in general. The recruitment of surgeon participants from the broad population of the AOSSM allowed private practice surgeons to participate and make intellectual contributions that might otherwise not be possible in their practice setting. In fact, the final MARS study surgeon breakdown included more private than academic surgeons (55% vs 45%). Moreover, the inclusion of private practice surgeons improves the generalizability of the results for the entire orthopedic surgeon population. We were able to accomplish this broad demographic of participants by leveraging the strength of the coordinating center personnel and minimizing local site and surgeon burden. This included assistance with IRB preparation and submission with no central site multicenter IRB available in 2006 when this study was

TABLE 1 Data completeness within a subset of variables (n = 900 cases)

Outcome variable	Questionnaire source form	No. variables	No. missing/observations (%)	% Complete
Marx activity level	Patient	4	23/3600 (0.6%)	99.4%
IKDC	Patient	19	38/17 100 (0.2%)	99.8%
KOOS	Patient	42	259/37 800 (0.7%)	99.3%
Current graft type	Surgeon	1	1/900 (0.1%)	99.9%
Surgical technique	Surgeon	1	2/900 (0.2%)	99.8%
Rehabilitation factors	Surgeon	6	35/5400 (0.7%)	99.3%

Abbreviations: IKDC, International Knee Documentation Committee; KOOS, Knee injury and Osteoarthritis Outcome Score.



The Rover

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What's New?

- This newsletter! The new MARS newsletter will be sent out on the first working day of each month. We are still in the process of working on content and layout, so comments and suggestions will be welcomed at the AOSSM MARS meeting. For those of you who will not be in attendance, please submit any comments or suggestions using the hyper-link at the bottom of the page.
- Dr. Bob Giffin and Dr. Matt Matava are developing a study to determine our ability to agree on modes and mechanisms of failure of ACL reconstruction at the time of ACL revision reconstruction. Dr. Matava will be presenting a short presentation about this study at the MARS meeting in July.
- Please welcome newly IRB approved MARS surgeons:
Robert Arciero, Keith Baumgarten, Jeffery Bechler, J. Brad Butler, Brian Cole, Charles Gatt, Tim Hosea, G. Peter Maiers II, Arun Ramappa, Arthur Rettig, and Orrin Sherman.

Upcoming Events

- AOSSM MARS Meeting Saturday July 12th, 12:30-2:30 Mediterranean Ball room of the JW Marriott. Lunch will be provided. Please RSVP to haasa@wudosis.wustl.edu if you have not already done so.
- We are in the planning stages of organizing research coordinator phone conferences. More details to come.



Bright Blue Newly Formed Stars. (NASA)

Upcoming IRB Renewals

Vermont IRB– Expires 7/5/08
HSS IRB– Expires 7/15/08
Lenox Hill IRB– Expires 7/22/08
Booth, Bartolozzi, Balderston Ortho. IRB– Expires 7/31/08
Colorado IRB– Expires 8/1/08
Connecticut Children's IRB– Expires 8/31/08

Need New IRB Approval Letters From:

COR-Arlington, VA
University of North Carolina
Case Western

Reminders



• XRAYs

As a reminder, everyone should be obtaining x-rays **Pre-OP** for MARS patients.

The following views are **required**:

- 1) Standing bilateral AP in full extension
- 2) Lateral view in maximum extension

The following views are **recommended** and would allow additional analysis for predictors of outcome:

- 3) Bilateral flexion weightbearing views at 45° (Rosenberg)
- 4) Bilateral 45° Merchant views
- 5) Standing Alignment (hip-knee-ankle)

• New Surgeons

Continue to work on getting your IRB approval. It is all downhill from there!

Questions or Comments? E-mail us at haasa@wudosis.wustl.edu or call (314) 362-3768

FIGURE 1 Example of the monthly Multicenter ACL Revision Study electronic newsletter which was emailed to all site investigators and coordinators [Color figure can be viewed at wileyonlinelibrary.com]

initiated. In addition, central coordinating site control of phone and questionnaire follow-up provided outstanding follow-up for a population that is sometimes difficult to follow due to changing patient locations. The 52 sites represent the largest number of sites utilized for a single orthopedic surgery research study and one of the largest number of sites involved in any multicenter medical studies.

The size and prospective nature of our study is unique for this topic. As we designed the study, we were uncertain of the critical factors leading to the worse outcome observed following revision ACL

reconstructions. Thus, we felt a randomized controlled trial of one or two variables might be misguided and inappropriate. We believed a prospective longitudinal cohort design would allow us to recruit adequate subjects and allow leeway for the surgeons to appropriately manage what can be challenging technical cases. This has been borne out by examining one key issue—graft choice for the revision reconstruction. This was the most critical issue for many surgeons performing these reconstructions. Our study design allowed accumulation of a large number of subjects that ended up (unintentionally) equally divided between the four main graft

options with approximately 25% for each choice (BPTB autograft, soft tissue autograft, BPTB allograft, soft tissue allograft). More details of the graft choice study are discussed in the results section.

The size of this study dwarfs all previous revision ACL reconstruction studies. We performed a meta-analysis of the 21 previous studies with a minimum 2-year follow-up. In that meta-analysis, it was noted that the 21 studies involved follow-up results for 863 patients in total with predominantly level 4 retrospective case series represented. Thus, in one study (with over 1200 enrolled patients), we have eclipsed the entirety of the previous result reporting for this important orthopedic problem. The strength of the size of our cohort becomes even more apparent when moving beyond the 2-year follow-up. Recently, we performed a systematic review of the minimum 5-year follow-up of revision ACL reconstructions.¹⁷ Wright et al demonstrated there are only four studies involving 148 patients with 121 followed. We have completed a minimum 6-year follow-up and have more than 800 patients followed at that time point. We have begun analysis (see Section 3) of our 6-year results and will have information for surgeons that no other cohort can accomplish. Using this approach, we have simultaneously collected the largest cohort ever assembled prospectively of the multiply revised ACL patient: 150 patients (157 of 1234; 13%) of the cohort had two or more revisions of their ACL reconstructions.

We performed an analysis that represents a unique approach to orthopedic research. Propensity analysis was performed after our graft choice analysis demonstrated improved results and decreased failure rates if an autograft was utilized.¹⁸ Propensity analysis can determine factors that predict decision making for factors when they are not controlled by study design. Propensity analyses flourish when there are more variables so a study of revision ACL reconstructions is a rich milieu to perform this in and would address the concern that graft choice is a fait accompli and that it is predetermined by patient age, sport, previous graft, and so on and cannot be impacted by the surgeon choice. Our propensity analysis proved this belief wrong as the surgeon was five times the strongest determinant of the graft utilized for the patient (Figure 2).

Thus, if the surgeon wanted to use an autograft, they could typically find a way to accomplish this. We were encouraged by this that our study actually has an impact because educating surgeons through manuscripts, reviews and podium presentations is an easier,

cheaper approach than any other approach for broadcasting these results, that is, educating patients.

3 | RESULTS

3.1 | Epidemiology

Follow-up has been very successful despite the challenge of coordinating 52 sites. Our use of central follow-up for this study has been a successful model and provides consistency across the study. The demographics and epidemiology of our cohort were first described in our original MARS publication as well as subsequent publications.^{12,19} A total of 1234 patients have been enrolled in the study. The median age was 26 with a range from 12 to 63 years. Of the total, 518 (42%) were female. For 87% it was their first revision,¹² while 13% were undergoing their second or higher revision ACL reconstruction. Seventy-three percent were injured while playing a sport. The most common sports involved both genders and were soccer and basketball. Associated surgeries included high tibial osteotomies (n = 21), medial meniscus transplants (n = 34), and lateral meniscus transplants (n = 10).

Modern ACL reconstruction with appropriate grafts and well-positioned tunnels realistically began in the 1980s. In the 1990s, case series of revision ACL surgery began to appear. In the vast majority of these cases, it was felt the etiology of the original ACL graft failure was due to technical issues.²⁰⁻²² However, in the MARS cohort trauma was more commonly reported as a cause of graft failure (Table 2; Figure 3).

This reflects two potential considerations for this finding: (a) improved technical ability with improved training and education; and (b) surgeons self-reporting on their own failures in this cohort: 30% (367 of 1234) of the patients were the surgeons' own failures. The cause of technical failure in the MARS study was most commonly felt to be due to femoral tunnel malposition (Table 3) with the tibial tunnel the second most common cause. Varus and valgus malalignment were seldom felt to be an issue (Table 3).

Prior graft utilized was autograft 68% of the time, allograft 29%, and a combination (autograft + allograft) 3%. The most common

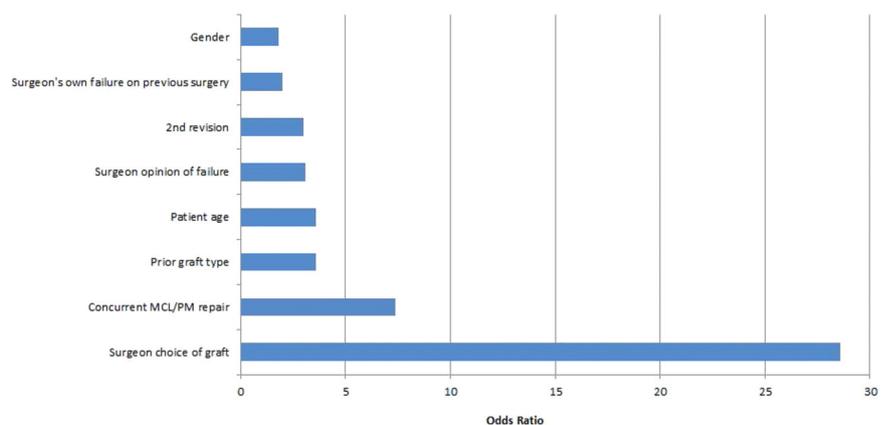


FIGURE 2 Variables that significantly influence graft choice in a revision anterior cruciate ligament reconstruction [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Cause of failure in the Multicenter ACL Revision Study cohort

	No.	Percentage ^a
Traumatic	697	56%
Technical	616	50%
Biologic	329	27%
Other	35	3%
Blank	2	<1%

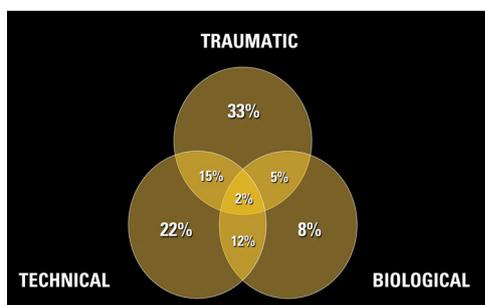
Note: n = 426 (35%) of these responses listed a combination of these components as the reason for failure.

^aThe denominator is >100% due to the multiple-choice options of this question (surgeons were instructed to “check all that apply”).

previous autograft was a patellar tendon, utilized 52% of the time. Patellar tendon was the most common allograft utilized previously for the primary ACL reconstruction (11%). The current graft utilized was 26% patellar tendon autograft, 20% soft tissue autograft, 23% patellar tendon allograft, and 25% soft tissue allograft.

Radiographs were obtained for enrolled patients. MARS had required (bilateral standing anterior-posterior, full-extension lateral) and recommended (Rosenberg, sunrise/merchant, and bilateral long leg standing alignment) radiographs. These radiographs were analyzed for the group and findings collated.^{23,24} Sagittal views of the femur demonstrated that 42% of femoral tunnels were more than 40% anterior to the posterior cortex. On the tibia sagittal view, 49% demonstrated some form of roof impingement on full extension. On longstanding alignment films, the average limb alignment was 43% from the medial edge of the tibia.

Interesting use of the cohort involved assessment of osteoarthritis rating scales utilizing the radiographs obtained as part of the study.²⁵ The reliability of different radiographic views as correlated with arthroscopic findings were analyzed. In addition, a multirater osteoarthritis scale study was performed analyzing the Kellgren-Lawrence, IKDC, Albrecht, Fairbank, Brandt and Jäger-Wirth grading scales. 45° flexion posterior-anterior weight-bearing radiographs demonstrated the best interobserver reliability as compared to anteroposterior straight standing radiographs. The IKDC grading scale correlated best with the arthroscopic findings of cartilage damage.

**FIGURE 3** Cause of failure Venn diagram [Color figure can be viewed at wileyonlinelibrary.com]**TABLE 3** Cause of technical failure

	No.
Femoral tunnel malposition	595
Tibial tunnel malposition	228
Varus/valgus malalignment	23
Femoral fixation	38
Tibial fixation	18
Autograft source	17
Allograft source	66
Posteromedial laxity	16
Posterolateral laxity	4

3.2 | Graft choice

The choice of graft is a major issue for revision ACL reconstructions. Obviously, the patient's previous graft will alter and potentially bias future choices. Many surgeons prefer allografts due to the complexity of the revision ACL reconstructions. Previous studies in the last few years have demonstrated failure rates for allograft in primary ACL reconstructions to be higher than those noted for autograft reconstructions.^{26,27} This is especially true in the young active patient. Despite these findings, there was no evidence that these higher failure rates would be present in the different clinical situations of a revision ACL reconstruction. In addition, many surgeons believed that processing was the key to the higher failure rates in allograft reconstructions and that a fresh frozen allograft with no irradiation would perform similarly to an autograft. For that reason, we knew that controlling the source and preparation for our allografts was key. We limited our allograft source to MTF and were able to track the demographics and preparation history for each individual graft utilized in the MARS study. This has given increased validity to our findings outlined later in this review.

We analyzed graft choice as a predictor for the outcome as one of the specific aims of our NIH funded grant.¹¹ The demographics of patients that received autograft and allograft can be seen in Table 4. Allografts were placed in older, less active patients on average.

TABLE 4 Graft choice demographics

	Autograft group (n = 598)	Allograft group (n = 599)	Auto + allo group (n = 37)
Age	24 (19, 32)	28 (21, 36)	21 (18, 28)
Gender			
Males (%)	361 (60%)	338 (56%)	17 (47%)
Females (%)	237 (40%)	261 (44%)	19 (53%)
Marx activity level			
Baseline	12 (5, 16)	10 (3, 15)	12 (8, 16)
2-y follow-up	8 (2, 12)	5 (1, 11)	10 (3, 13)
6-y follow-up	6 (2, 10)	4 (0, 8)	8 (3, 10)

Note: Continuous variables are reported as medians (25%, 75% interquartiles). Frequencies are reported as number (%).

TABLE 5 Allograft treatment

Sterilization method	Allograft cohort (n = 636)	Allograft failure cohort at 6 y
Aseptic	257 (40%)	15 (42%)
Whole-body (1.2-1.8 mRad)	343 (54%)	18 (50%)
Terminal (0.7-1.0 mRad)	36 (6%)	3 (8%)

The form of treatment was known for each allograft and included no radiation (aseptic), light total whole-body irradiation (< 1.8 mrad), or rarely terminal radiation (Table 5).

The overall rerupture rate at two years was 3.3% (37 of 1112): 2.2% (12 of 545) in autografts, 4.5% (24 of 534) in allografts, and 3% (1 of 33) in combination autograft + allografts. Autograft use was 2.78 times less likely to rerupture ($P = .047$; 95% confidence interval [CI] = 1.01, 7.69). No difference in rerupture rate was found in soft tissue vs bone-patellar tendon-bone (BTB) in either autograft or allograft. IKDC scores improved with autograft reconstruction with an odds ratio (OR) of 1.33 (95% CI, 1.01-1.7; $P = .045$). KOOS Sports and Recreation subscale significantly improved with autograft (OR = 1.33; 95% CI, 1.02-1.73; $P = .037$), as did the KOOS Quality of Life (OR = 1.33; 95% CI, 1.03-1.73; $P = .031$). The KOOS ADL and Symptoms subscales were not affected by graft choice.

Many people believed that graft choice was a predetermined fate in a revision setting and that the surgeon truly had no choice in determining what graft the patient obtained. To analyze this belief we performed a propensity analysis for graft choice (Figure 2).¹⁸ Our analysis demonstrated that the surgeon performing the procedure was far and away the biggest factor on what graft type was chosen for the revision reconstruction, approximately five times more impactful than the second most common predictor (which was prior graft). Thus, surgeons truly did have a choice in what graft they utilized. This allows us to modify clinical practice by educating surgeons through publications and podium presentations at major meetings such as the American Academy of Orthopedic Surgeons (AAOSs) or AOSSM.

Subsequent 6-year follow-up for the MARS group has strengthened the graft choice conclusions.²⁸ In an analysis presented at the 2019 AAOS Annual Meeting and currently in manuscript preparation we noted the following. Questionnaire follow-up was obtained on 810 subjects (65%), while phone follow-up was obtained on 949 subjects (76%). Graft choice proved to be a significant predictor of 6-year Marx activity level scores ($P = .024$). Specifically, the use of a BTB autograft for revision reconstruction predicted improved activity levels compared with a BTB allograft (OR = 1.92; 95% CI = 1.25, 2.94). Graft choice was not significant in predicting 6-year IKDC, WOMAC, or KOOS outcome scores.

Graft rerupture was reported in 5.8% (55 of 949) of patients by their 6-year follow-up: 3.4% (16 of 472) in autografts, 8.3% (37 of 448) in allografts, and 6.9% (2 of 29) in combination allograft + autografts. Use of a BTB autograft for revision resulted in patients 4.2 times less likely to sustain a subsequent graft rupture than if a BTB allograft was utilized ($P = .011$; 95% CI = 1.56; 11.27). Thus, graft choice has increased in significance in predicting rerupture and sports performance.

3.3 | Meniscus and articular cartilage

Compared with primary reconstructions the revision patient has a much higher chance of having meniscus or articular cartilage damage at the time of revision reconstruction. In our cohort, only 9% of the patients did not have a meniscus tear or grade 2 or worse articular cartilage damage, 90% had at least meniscus or articular cartilage damage and 59% had both at the time of revision (Table 6).

We analyzed the impact of these meniscus tears and articular cartilage damage on patient outcomes at 2 years.²⁹ Previous lateral meniscectomy prior to the time of revision significantly resulted in worse patient-reported outcomes (Table 7); previous medial meniscectomy less so. Interestingly, current meniscal pathology variables documented at the time of the index revision surgery had no significant predictor effect on any 2-year patient outcome measure (Table 7).

Grade 2 or worse articular cartilage damage grade negatively impacted patient-reported outcomes at 2 years. The most significant finding was the consistent negative impact of trochlear groove chondrosis across outcome measures (Table 8).

MARS analyzed the impact of the previous meniscectomy on the presence of chondral damage noted at the time of revision ACL reconstruction. Previous partial meniscectomy was associated with chondral damage ($P < .0001$). Meniscus repair appeared to be chondral protective as there was no statistically significant increase in chondral damage noted in the setting of meniscus repair. There was no difference between knees that had not had previous meniscus surgery and those with repair.³⁰

The association of meniscus status, lower extremity alignment and body mass index (BMI) with chondrosis at the time of revision ACL reconstruction was also analyzed.³¹ The medial compartment had more chondrosis than the lateral compartment (grade 2/3, 42% vs lateral grade 2/3, 26%). The mean weight-bearing line was 0.43 as measured from the medial edge of the tibia. Medial compartment chondrosis was associated with higher BMI ($P = .025$), alignment ($P = .002$), and "disrupted" medial meniscus status (ie, a tear that required a repair or a partial meniscectomy; $P = .001$). No patient with a weight-bearing line greater than or

TABLE 6 Overall meniscal and articular cartilage integrity in the Multicenter ACL Revision Study cohort at the time of enrollment

		Articular cartilage pathology		
		Normal	Abnormal	Total
Meniscal pathology	Normal	9%	12%	21%
	Abnormal	19%	59%	78%
Total		28%	71%	

TABLE 7 Meniscus impact on 2-y patient-reported outcomes (significant *P* values only)

Structure	Marx	KOOS					IKDC	WOMAC		
		Symptoms	Pain	ADL	Sports/Rec	QOL		Stiffness	Pain	ADL
Previous meniscal pathology										
Medial			.002				.035			
Lateral		.008	.042			<.001	.038	.03		.032
Current meniscal pathology										
Medial										
Lateral										

Note: Wald χ^2 test used to compute overall predictor variable significance. Blank cells indicate nonsignificant $P > .05$. ADL, activities of daily living; Rec, recreation; QOL, quality of life.

Abbreviations: ADL, activities of daily living; IKDC, International Knee Documentation Committee; KOOS, Knee injury and Osteoarthritis Outcome Score; QOL, quality of life; Rec, recreation; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

lateral to 0.625 had grade 4 medial compartment chondrosis. Lateral compartment chondrosis was significantly associated with higher age ($P = .013$) and “disrupted” lateral meniscus status (ie, a tear which required a repair or a partial meniscectomy; $P < .001$). Subjects with intact menisci were found to decrease their odds of associated chondrosis by 64% to 84%.³¹

Predictors of significant chondral surface damage from primary reconstruction to revision reconstruction were analyzed utilizing the MARS and MOON databases.³² One hundred thirty-four patients had been enrolled in the MOON cohort and subsequently underwent revision and were enrolled in MARS. Progression of articular cartilage damage was noted in 25.4% (34 of 134) of patients in the lateral compartment, 23.9% (32 of 134) in the medial compartment, and 23.1% (31 of 134) in the patellofemoral compartment. For the lateral compartment, patients who had undergone a greater than 33% partial lateral meniscectomy at the time of primary ACL reconstruction had 16.9 times greater odds of progression of articular cartilage injury than those with an intact lateral meniscus ($P = .001$). Patients that underwent a less than 33% partial medial meniscectomy at the time of primary ACL reconstruction had 4.8 times greater odds of progression of articular cartilage injury than those with an intact medial meniscus at the time of primary reconstruction ($P = .02$). For each increase in age by one year there was a 6% increase in

the onset of significant chondral damage in the medial compartment and 5% in the lateral compartment ($P \leq .02$). For the patellofemoral compartment use of an allograft reconstruction at the time of primary ACL reconstruction resulted in a 15 times increase in the risk of progression of articular cartilage injury as compared with a patellar tendon autograft ($P < .001$). At the time of revision ACL reconstruction, a one-unit increase in BMI was associated with a 10% increase in the risk of progression of articular cartilage damage ($P = .046$).

Meniscus repair success at two years was analyzed for the cohort.³³ In total, 218 patients from 1205 revision ACL reconstructions underwent concurrent meniscal repairs (18% of the cohort). There were 235 repairs performed: 153 medial, 48 lateral and 17 medial + lateral. The vast majority of these repairs ($n = 178$; 76%) were performed with all-inside techniques. Two-year surgical follow-up was obtained on 90% (197 of 218) of the cohort. Overall, the meniscal repair failure rate was 8.6% (17 of 197) at 2 years. Of the 17 failures, 15 were medial (13 all-inside, 2 outside-in) and 2 were lateral (both all-inside). Four of the medial failures were treated in conjunction with a subsequent repeat revision reconstruction. Thus, meniscus repair is overall very successful in the revision setting approaching that of repair results in isolated or primary ACL reconstruction settings.

TABLE 8 Articular cartilage impact on 2-y patient-reported outcomes (significant *P* values only)

Structure	Marx	KOOS					IKDC	WOMAC		
		Symptoms	Pain	ADL	Sports/Rec	QOL		Stiffness	Pain	ADL
Previous AC pathology (yes/no)										
Current AC pathology										
MFC			.018							.012
LFCA				.048						.048
MTP					.004					
LTP										
Patella										
Trochlea			.034	<.001	.011		.01			<.001

Note: Wald χ^2 test used to compute overall predictor variable significance. Blank cells indicate nonsignificant $P > .05$.

Abbreviations: AC, articular cartilage; ADL, activities of daily living; IKDC, International Knee Documentation Committee; KOOS, Knee injury and Osteoarthritis Outcome Score; LFC, lateral femoral condyle; LTP, lateral tibial plateau; MFC, medial femoral condyle; MTP, medial tibial plateau; QOL, quality of life; Rec, recreation; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

3.4 | Surgical factors

Surgical factors were analyzed to determine the impact on patient-reported outcome measures at 2 years.³⁴ A variety of factors were analyzed and in many cases, it is difficult to determine intuitively why certain factors impacted outcome. With regards to the surgical approach, having undergone a prior arthrotomy decreased IKDC scores ($P = 0.037$; $OR = 2.43$) and decreased all KOOS subscales ($P < .05$; OR range = 2.38-4.35). A double femoral tunnel resulted in worse KOOS QOL scores ($P = .027$; $OR = 3.13$). An ideal tibial position that was not enlarged resulted in worse KOOS, WOMAC, and IKDC scores ($P = .001-.03$; OR range = 1.19-2.68). Using a femoral tunnel declared “optimum” vs drilling an entirely new femoral tunnel resulted in worse KOOS QOL scores ($P = .025$; $OR = 1.79$). Undergoing a notchplasty decreased KOOS, IKDC, and WOMAC scores ($P = .013-.034$; OR range = 1.40-1.49). Factors that did not impact the outcome included blended tunnels and knee position at the time of graft fixation.

Graft fixation as a surgical factor impacting outcome was also analyzed. Femoral fixation with a metal screw had better 2-year outcomes in KOOS and WOMAC scores ($P = .01-.05$; OR range = 1.41-1.96) when compared with using a bioabsorbable screw, cross-pin, or combination. Tibial fixation other than metal screw resulted in worse IKDC ($P = .017$; $OR = 1.67$) and WOMAC stiffness ($P = .013$; $OR = 1.72$) scores.

The use of biologics and bone grafting was analyzed. The use of biologic enhancement in the revision setting resulted in lower 2-year MARX activity level scores ($P = .025$; $OR = 1.79$). Utilizing femoral bone grafts resulted in lower MARX activity scores at 2 years ($P = .048$; $OR = 2.04$). Conversely, not bone grafting the tibia resulted in worse KOOS Pain scores ($P = .046$; $OR = 1.95$) and WOMAC Pain scores ($P = .004$; $OR = 3.31$).

Reoperations following revision ACL reconstruction were analyzed.³⁵ Eleven percent of patients underwent subsequent reoperation by 2-year follow-up: 27% were meniscal procedures (69% meniscectomy, 26% repair), 19% were revision ACL reconstructions, 17% were cartilage procedures (61% chondroplasty, 17% microfracture, 13% osteochondral

autograft), 11% hardware removal, and 9% were performed for arthrofibrosis reasons. Multivariate analysis demonstrated that age less than 20 years old resulted in a doubling of the risk for reoperation as compared with the patient's age range between 20 and 29 years old. The use of an allograft at the time of revision was a significant predictor for the need for reoperation within 2 years ($OR = 1.79$; $P = .007$). Patients with grade 4 chondral damage noted at the time of revision ACL reconstruction were 78% less likely to undergo a reoperation within 2 years. Gender, BMI, smoking history, Marx activity scale, and meniscal treatment (repair, meniscectomy) did not impact the need for reoperation within 2 years.

3.5 | Rehabilitation factors

Rehabilitation factors were analyzed regarding their potential impact on revision ACL reconstruction outcomes.³⁶ Two rehabilitation factors predicted outcome: (a) use of an ACL derotation brace for return-to-sport had better KOOS sports/rec scores at 2 years ($OR = 1.50$; 95% $CI = 1.07-2.11$; $P = .019$), and (b) use of an ACL derotation brace for postoperative rehabilitation period were 2.3 times more likely to have a subsequent surgery by 2 years ($OR = 2.26$; 95% $CI = 1.11-4.60$; $P = .024$). The use of an ACL derotation brace at the time of return to the sport could not be determined to improve or decrease the graft rupture rate. Restricting or allowing of all other factors did not predict outcomes including active range of motion, passive range of motion, immediate weight-bearing, and the use of rehabilitative postoperative bracing.

3.6 | Patient-reported outcomes

Predictors both positive and negative for patient-reported outcomes measured at 2 years were studied.³⁷ Patient-reported outcomes for 2 and 6 years remained stable except steadily decreasing Marx activity level scores (Table 9). Scores for KOOS Quality of Life and Sports/Recreation and IKDC were 15 to 20

TABLE 9 Median (IQR) of KOOS, IKDC, and Marx outcomes over time of the MARS cohort

	Score range	Baseline	2-Y	6-Y
IKDC	0-100	52 (38, 63)	77 (60, 86)	75 (60, 87)
KOOS				
Symptoms	0-100	68 (54, 82)	79 (64, 89)	79 (64, 89)
Pain	0-100	75 (58, 86)	89 (75, 94)	89 (75, 97)
Activities of daily living	0-100	87 (69, 96)	97 (88, 100)	97 (87, 100)
Sports & recreation	0-100	45 (25, 65)	75 (55, 90)	75 (50, 90)
Quality of life	0-100	31 (19, 44)	56 (38, 75)	62 (44, 75)
WOMAC				
Stiffness	0-100	75 (50, 88)	75 (62, 100)	75 (63, 100)
Pain	0-100	85 (70, 95)	95 (80, 100)	95 (80, 100)
Activities of daily living	0-100	87 (69, 96)	97 (88, 100)	97 (87, 100)
Marx activity level	0-16	11 (4, 16)	7 (2, 12)	5 (1, 9)

Abbreviations: IKDC, International Knee Documentation Committee; IQR, interquartile range; KOOS, Knee injury and Osteoarthritis Outcome Score; MARS, Multicenter ACL Revision Study; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

points below those for the same time point in historical primary ACL reconstruction series (Table 9; Figure 4).

The most significant positive predictors of 2-year IKDC scores were having a high baseline IKDC score, high baseline Marx activity level, male gender, and having a longer time between a patient's last ACL reconstruction, while negative predictors included having a previous lateral meniscectomy, grades 3/4 trochlear groove or medial tibial plateau chondrosis. For KOOS, having a high baseline score and having a longer time between their last ACL reconstruction were significant positive predictors for having better (ie, higher) 2-year KOOS scores, while having a previous lateral meniscectomy prior to the revision ACL reconstruction was a consistent predictor for having significantly worse (ie, lower) 2-year KOOS scores. Statistically significant positive predictors for 2-year Marx activity levels included higher baseline Marx activity levels, younger age, male gender, and being a nonsmoker. Negative 2-year activity level predictors included having an allograft and a biologic enhancement.

3.7 | Other databases

The size and strength of this cohort have encouraged comparison to other registries and cohorts. Our first analysis in this area was to

compare it to a prospectively collected primary cohort. During identical enrollment times using a similar collection approach we compared MARS and MOON intra-articular findings.³⁸ Demographics were similar for both populations. Prevalence of medial meniscus tears was fundamentally equivocal (40%) in both populations. New untreated lateral meniscus tears were less common in the revision setting (46% in primaries vs 34% in revisions; OR = 0.54; $P < .01$). Outerbridge grades 3 and 4 chondrosis was more common in the patellofemoral joint of revision ACL reconstructions (3%-7% in primaries vs 11%-13% in revisions; OR = 1.70; $P = .04$) and the lateral femoral condyle (5% in primaries vs 11% in revisions; OR = 1.73; $P = .04$). No other compartments demonstrated statistically significant differences between revision and primary ACL reconstructions. Both revision and primary ACL reconstructions demonstrated an increased risk of the medial and lateral femoral condyle and medial and lateral tibial plateau grades 3 and 4 chondrosis in the setting of a previous medial or lateral meniscectomy, respectively.

The MARS cohort was compared with the Norwegian revision registry and a revision database for the French Arthroscopic Society.³⁹ Patient demographics were very similar. Allograft was more frequently chosen in the United States MARS cohort (29% vs <1%). Hamstring autograft was most commonly used in Norway (74%) and the most common French graft was a BTB autograft (70%).

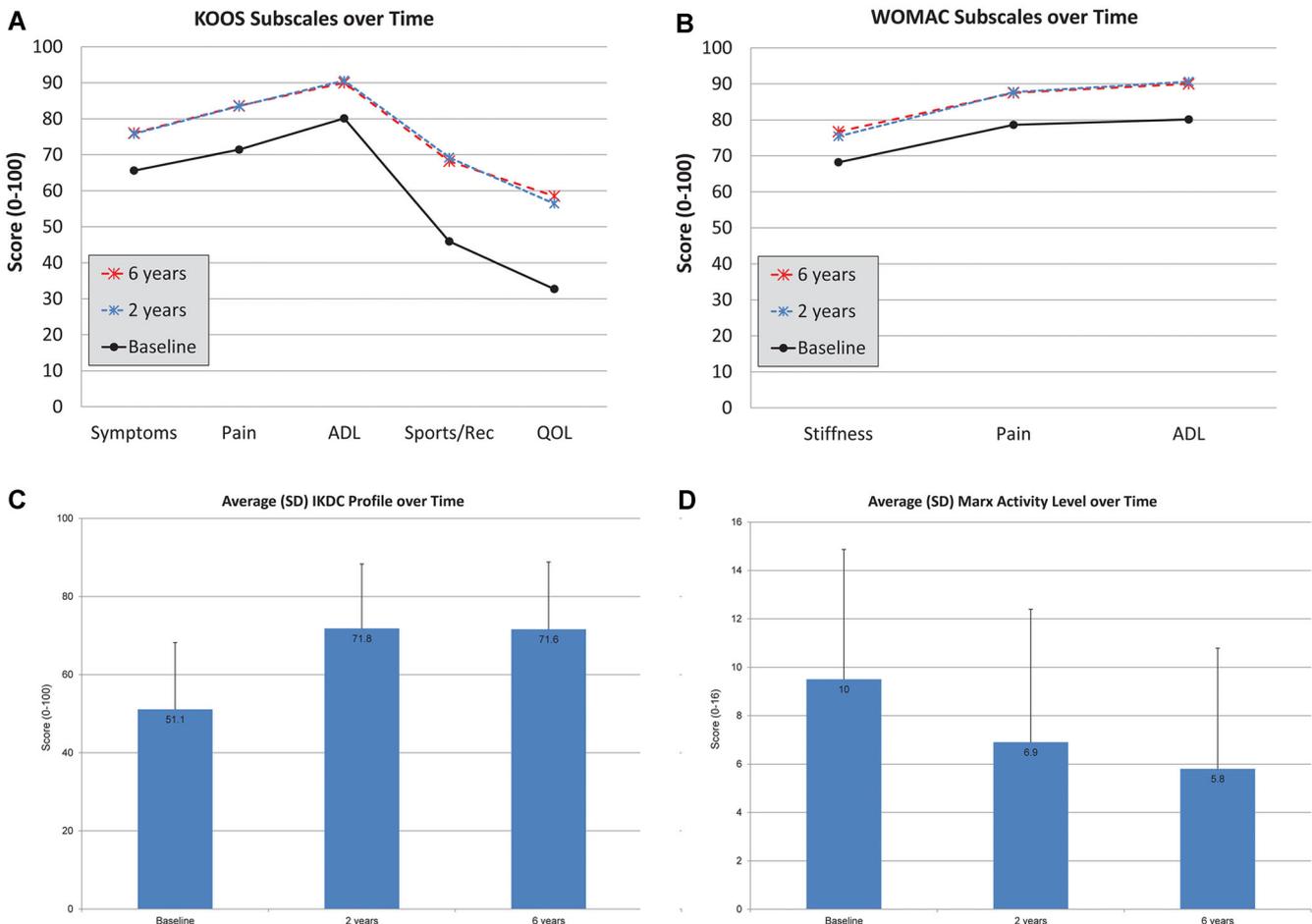


FIGURE 4 Global patient-reported outcomes over time [Color figure can be viewed at wileyonlinelibrary.com]

Significant articular cartilage injuries were most commonly noted in the MARS cohort. Patient-reported outcomes at baseline were statistically significantly different for KOOS and IKDC for the different patient groups but were only clinically significantly different for the KOOS sports and recreation subscale where the MARS group was more than eight points better at baseline.

4 | CONCLUSIONS

The MARS group was formed over 10 years ago, with the aim of assessing both the short and long-term progression of outcomes following revision ACL reconstruction, and to determine how the initial factors at the time of revision surgery may influence and predict disease progression. This consortium is unique in its size, scope, and demographics. The MARS group comprises the most sites involved in a single orthopedic study with 83 members at 52 sites, covering both academic (44%) and private practice (56%) settings. The study design involves a longitudinal prospective cohort of over 1200 patients, for whom we have a baseline, 2- and 6-year follow-up on, and which has allowed us to assess modifiable surgical factors in a fashion previously never contemplated. While there have been multiple challenges encountered in the MARS study, they have for the most part been surmountable. The level of research and the questions that can be asked and answered in a cohort of this size and type is unmatched by any other approach. We believe the study design and scaffolding we have developed for this type of truly multisurgeon, multicenter research can be a model for future orthopedic research groups.

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All authors contributed to the study design, data collection, or data interpretation. SN and JSP contributed to the statistical analyses. RWW, LJH, and AKH were involved in the manuscript drafting and editing and assume responsibility for the overall content and manuscript integrity. All authors have read and approved the final submitted manuscript.

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