



The MOON and Marsteam based Research: Formation, Challenges, and Success

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Abstract

Anterior Cruciate Ligament (ACL) Reconstruction (ACLR) is widely considered as the standard of care for patients with a torn ACL who participate in high-demand activities such as pivoting or cutting sports, or who experience continued instability despite conservative measures.

Introduction

An estimated 200,000 ACLR are performed annually in the United States [1]. With such high volume, it is paramount to obtain evidence-based analyses of the predictors and outcomes of the procedure. Patients and physicians are particularly interested in the expected patient-specific outcomes after ACLR and how pre-, intra-, and postoperative treatment decisions or lifestyle changes may affect these outcomes. The Multicenter Orthopedic Outcomes Network (MOON) and the Multicenter ACL Revision Study (MARS) were established in response to the growing need for high-quality studies in ACLR. This review highlights the team-based designs, challenges, and achievements of these two multicenter prospective cohorts, which may serve as a model for future research collaborations.

Formation and Design of MOON

The concept for MOON originated in 1993 when the Vanderbilt Sports Medicine – Cleveland Clinic Foundation ACL Reconstruction Registry was formed [2]. The success of these initial efforts evolved into the creation of a true multicenter network of seven institutions (Cleveland Clinic Foundation, Vanderbilt Orthopedic Institute, The Ohio State University, University of Iowa, Washington University in St. Louis, Hospital for Special Surgery, and University of Colorado). The goal of this network was to allow for quality multicenter prospective research in orthopedic sports medicine. The MOON group initially sought to target three identifiable gaps in ACLR knowledge to date. First, no large, prospective cohort study existed to understand how baseline patient characteristics, concurrent pathology, and surgical decisions affect clinical outcomes after ACLR. Second, existing studies lacked the power to identify the impact of ACLR graft choice on clinical outcome. And third, high-quality research was needed to define both the prognosis and predictors of osteoarthritis after ACLR: necessitating well-defined aims and endpoints, a common radiographic classification system with reliability data and blinded examiner, a defined rehabilitation protocol, and regression analysis [3]. To address this final aim, a nested cohort was developed within MOON to specifically study the progression of osteoarthritis. A longitudinal prospective cohort is the ideal study design to define prognosis and risk factor analysis for outcomes in a specific patient. It allows for a “natural experiment” to study how intra-auricular injuries affect validated patient-reported outcomes and signs of osteoarthritis. There are many predictors of outcome in ACLR, including modifiable (e.g. weight, smoking status, graft choice) and non-modifiable (sex, concurrent injury, race). The cohort design easily handles factors which cannot be independently randomized (such as concurrent injury) and multivariable analysis allows these predictors to be individually understood. The cohort design thus allows for the study to be quite inclusive and generalizable (Table 1). The design also allows for high rates of patient enrollment because the physician is not altering standard treatment decisions.

Challenges of MOON: how to measure outcome, record outcome and achieve follow-up

Higher levels of follow-up may be achieved with remote rather than on-site follow-up. Thus the preferred outcomes for the MOON cohort study were validated patient-Reported Outcome Measures (PROMs), which are self-administered and could be completed electronically. Five validated PROMs were selected for use in the MOON cohort: KOOS [4] and IKDC [5] (function),

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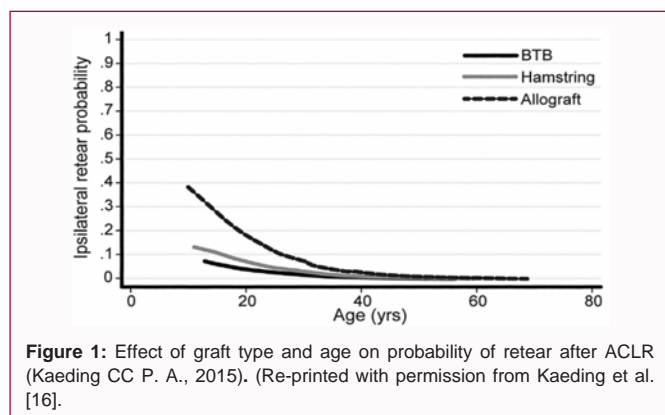
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Marx [6] (activity level), *SF-36* [7] (general health), and *WOMAC* [4] (symptoms of osteoarthritis). These PROMs were recorded at baseline and then administered at regular follow-up intervals (2, 6, and 10 years). Failure of ACLR graft or contralateral knee ACL injury, as well as any subsequent knee surgery, was discovered via phone call. To reliably administer follow-up questionnaires and phone calls, a full-time employee was hired. Additionally, about 25% of calls were made by surgeons. On-site follow-up is a much more difficult task, and was only reserved for the nested osteoarthritis cohort. This smaller group was asked to return for radiographic imaging and comprehensive clinical assessment. With over 3,500 enrolled patients, the amount of data created by the cohort has been massive. Thus it was imperative to efficiently organize and recall data. For example, at Vanderbilt alone, there were 6.6 million items recorded at baseline for patients between 2002-2009. Initial enrollment from 2002-2003 found 98% surgeon compliance and 98% patient PROM compliance with completing all components of the questionnaires. The MOON cohort has a follow-up rate of 85% for PROM questionnaire completion and 93% with the addition of phone confirmation of ACLR graft failure, contralateral ACL tear, or subsequent knee surgery at 2-year follow-up. A total of 425 patients in the nested cohort have completed 2-year follow-up onsite. The follow-up at 6-years is similar, with 82% of patients completing PROMs and >90% reached by phone. MOON has completed >80% of 10-year follow-up on the first half of the cohort to date.

Challenges of MOON: multicenter design

A multicenter design was selected as it offered several advantages. Most obvious was the benefit of greater patient enrollment in a limited amount of time. A large sample size to study ACLR was necessary as many outcome events (e.g. graft rupture, infection) occur infrequently and clinically significant differences may be undetected in a small, underpowered cohort. Furthermore, multiple surgeons and sites increased the generalizability of the study's findings. However, establishing standardization across sites was an initial challenge. To ensure close agreement regarding identification and management of intra-auricular pathology - such as meniscus and auricular cartilage injury - a series of surveys and arthroscopic videos were distributed among the MOON group's surgeons. Classification of meniscal pathology had a high level of inter-rater reliability, with observed agreement of type of tear (73%, $k=0.63$), location of tear (87%, $k=0.67$), and treatment (84%, $k=0.66$) [8]. Agreement for classification of auricular cartilage lesions was also reliable and ranged from 81%- 94% ($k=0.34 - 0.87$), higher for lesions on the femoral condyle and patella [9]. Additionally, there has been found a high level of inter-surgeon reproducibility for ACL tunnel placement

as well [10]. This is significant as tunnel placement is considered to be a crucial modifiable determinant of outcome after ACLR [11]. Regardless of tunnel technique (medial portal, transtibial, 2-incision), MOON surgeons were relatively consistent in tunnel placement compared to each other (with tunnel location ranging from 4% to 22%) and very consistent among themselves [10]. A more difficult challenge for the multicenter group has been the standardization of the onsite follow-ups for the nested osteoarthritis cohort. These are performed at three separate institutions by an independent, blinded orthopedic surgeon and a physical therapist at each site. In addition to the 5 PROMs, patients complete a physical exam, radiographs, and MRI of both knees. Each site requires a dedicated research coordinator as well as radiology technicians trained in a standardized technique. Thus, these on-site visits require much more funding, labor, and patient compliance.

Success of MOON

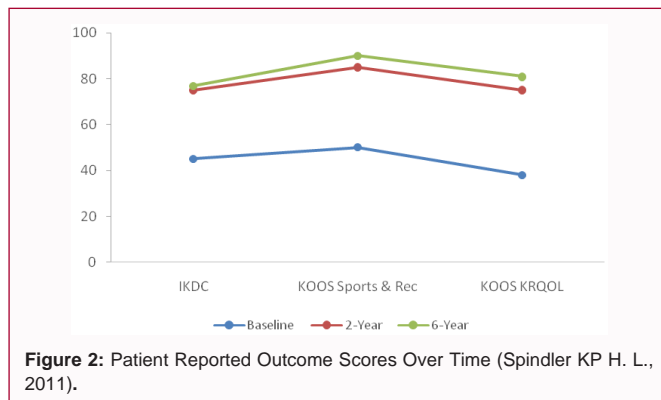
MOON cohort consists of 3,547 ACLR, making it the largest prospective ACLR outcomes cohort with 80% follow-up maintained at 2, 6, and 10 years in the United States. Enrollment for the MOON cohort began in 2002 and ended in 2008. The MOON group has published over 40 publications with primarily grade 1-2 level of evidence. The following sections highlight the main findings of the group.

Baseline data

After multivariate analysis of preoperative factors, increased pain and symptoms at time of index ACLR were associated with higher Body Mass Index (BMI), female sex, and concurrent lateral collateral ligament injury [12]. Bone bruise on MRI was found in 80% of patients but had no effect on pain or symptoms. In another study, incidence and management of meniscus tears at time of index ACLR was evaluated [13]. Thirty-six percent of knees had medial meniscus tears and 44% had lateral meniscus tears; only 30% of medial meniscal tears and 12% of lateral meniscus tears were repairable. A more recent study evaluated the factors associated with high-grade laxity on examination under anesthesia, finding that chronic ACL tears compared to tears <6 months had the greatest association with high grade laxity, with OR 2.71-3.99 for Lachman, pivot shift, and anterior drawer testing (all $p<0.001$) [14]. Other significant predictors were generalized ligamentous laxity and presence of a meniscus tear.

Modifiable and non-modifiable predictors of failure after ACLR

The effect of graft choice on failure rate after ACLR has been one of the most important findings of the MOON cohort. Kaeding et al. initially investigated predictors of graft failure in a cohort of approximately 1000 ACLRs with 2-year follow-up, first with a single surgeon's data (281 ACLR) and then with the rest of the group [15]. Younger age and use of allograft were significant predictors of failure in both models. For each 10-year decrease in age the odds of graft rupture increased 2.3 times, and holding age constant, the odds of tearing an allograft ACLR were 4 times higher than the odds of tearing an auto graft ACLR. These findings were later corroborated with the entire MOON cohort of primary ACLR with 93% follow-up at 2-years (2488 patients) [16]. Overall there were 4.4% graft failures and 3.5% contralateral ACL tears. Odds of allograft failure were 5.2 x odds of auto graft failure, and there was no difference between BTB and hamstring auto grafts. Odds of graft failure or contralateral knee ACL tear were increased with younger age and higher Marx activity level. The pooled effects of age and graft selection are shown in (Figure 1).



Regarding subsequent surgery after ACLR, a 6-year follow-up study found an 19% rate in the ipsi lateral leg (7.7% revision ACL, 13.3% for cartilage, 5.4% for arthrofibrosis, 2.4% for hardware) and a 10% rate in the contralateral leg (6.4% primary ACLR) [17]. Younger age and use of allograft were risk factors for subsequent surgery. Transtibial drilling has also found to be a predictor of subsequent ipsilateral knee surgery (OR 2.49) [18]. And a 0.8% infection rate has been found in the cohort, significantly higher for patients with diabetes (OR 18.8) and non- bone-tendon-bone auto graft (i.e. hamstring auto graft, allograft, or combined; OR 4.6) [19].

Predictors of activity, quality of life, and pain after ACLR

At 2-year follow-up after ACLR, the most significant predictor of higher Marx activity level was baseline activity level (OR 3.84) and lower BMI (OR 1.37) [20]. Lower activity level was more likely found in women (OR 0.60), smokers (OR 0.55), and cases of revision ACLR (OR 0.41). At 6-year follow-up, revision ACLR and use of allograft predicted worse outcomes on the IKDC and KOOS [21]. Lateral meniscus treatment, smoking status, and BMI were also predictors of worse PROMs. Lower activity level was again seen in women and revision ACLR. It was also seen that while IKDC and KOOS scores were similar from 2 to 6 years (both improved from baseline, (Figure 2)), Marx activity level declined from baseline median of 12 (out of 16 points) to 9 points at 2 years and 7 at 6 years. When studying intra-auricular pathology specifically, both auricular cartilage injury and meniscus tears/treatment (found at the time of ACLR) were significant predictors of reduced IKDC and KOOS scores at 6-years after surgery, and a grade 4 cartilage lesion on the medial femoral condyle was predictive of a lower Marx activity score [22]. Improvements from preoperative IKDC and KOOS scores were maintained 6 years after surgery. *IKDC* and *KOOS* subscales are rated out of 100, with higher scores indicating improved function. Median scores are presented. (Rec=recreation; *KRQOL*=knee-related quality of life.) General quality of life (SF-36) improved after ACLR and was maintained from 2 to 6 years after surgery, with mean gain of 5.3 quality-adjusted life years (QALYs, calculated from SF-6D) [23]. Fewer years of education, smoking, and revision ACLR were significant predictors of a lower quality of life. A separate study investigated the prevalence of significant knee pain after ACLR as well as predictors of a painful knee at 2- and 6-years postoperatively [24]. The investigators used three previously published KOOS models for clinically significant knee pain and found that between 9% to 43% of patients has clinically significant pain, depending on the model used and time point. The strongest independent risk factor for pain across all models was ipsilateral knee surgery. Other important predictors were baseline KOOS score, BMI, activity level, and cartilage damage.

Meniscus and ACLR

The MOON cohort also has captured data on meniscus treatment. In a 6-year follow-up of 1440 patients from the MOON cohort, 286 underwent concurrent repair [25]. Meniscal repair failure rate was 14%. Upon multivariate analysis, medial meniscus repair was found to be a predictor of inferior outcomes, and lateral meniscus tears left alone portended improved outcomes [22]. In another study, out of 208 meniscus tears left in situ without treatment at time of ACLR, 98% of lateral and 94% of medial meniscus tears did not require subsequent reoperation – risk factors for reoperation were younger age and tear >1 cm [26].

Return to play after ACLR

Return to play after ACLR is known for football and soccer and can be used for patient counseling. Of 114 high school and college football players from the MOON cohort, 63 and 69% (respectively) were able to return to the same self-described level of sport [27]. Fear of reinjury was cited by half of those who did not return to play. Of 100 soccer athletes in the cohort, 72% returned to play at an average of 1 year after surgery (85% of which returned to same level of sport), and at 7-year follow-up 36% were still playing [28]. Older athletes and women were less likely to return to play (OR 0.38 and 0.31, respectively).

Societal and economic impact of ACLR

With rising cost of healthcare, economic models are becoming increasingly important in orthopedic surgery. Six-year follow-up comparing the MOON database to the Knee Anterior cruciate ligament, NON-surgical versus surgical treatment (KANON) study has shown that ACLR is both less costly (reduction of \$4503) and more effective with a Quality-Adjusted Life Years (QALY) gain of 0.18 compared to rehabilitation [29]. Extrapolation to long term shows a mean lifetime cost savings of \$50, 417 and QALY gain of 0.72. Based on these and quality of life data previously mentioned [23], healthcare expenditures are justified for ACLR.

Nested osteoarthritis cohort findings

Minimum Joint Space Width (mJSW) at 2-3 years after ACLR was evaluated in patients within the nested cohort [30]. Out of 476 patients invited to participate, 285 agreed and could be analyzed within the appropriate time interval. Patients with meniscectomy at time of ACLR had significantly narrower mJSW compared to their contralateral normal (control) knee (difference of 0.64 mm). Older age and meniscus repair also resulted in significantly narrower mJSW compared to control. Interestingly, isolated ACLR had a 0.35 mm wider mJSW than the contralateral knee.

Formation and Design of MARS

Recurrent instability after primary ACLR has a significant impact on a patient and often requires revision ACLR. Revision ACLR can be technically difficult and patients can present with increased intra-auricular damage to the knee compared to their original injury [31]. Patient outcomes in revision ACLR are consistently inferior to outcomes after primary surgery [2,32,33]. Thus revision is an independent risk factor for worse outcome after ACLR. Prior to the development of MARS, studies on revision ACLR were limited by small sample size and low level of evidence. The goal of MARS was to use a sufficiently large sample of revision ACL patients to identify predictors of graft failure and outcomes after revision surgery. The successes and early findings of the MOON study led to the initiation of MARS in 2006. Like MOON, a multicenter model was employed

Table 1: Inclusion Criteria for MOON cohort and nested osteoarthritis (OA) cohort (Spindler et al. [3]).

	Age ^a	Sex	Race	Mechanism of Injury	Prior Knee Surgery		Contralateral Knee Status
					Ipsilateral	Contralateral	
Main Cohort	Any	Both	Any	Any	Any	Any	Any
Nested OA Cohort	<34	Both	Any	Injured in sport	No	No	Normal

a) All patients had to have reached skeletal maturity in order to allow for standard ACLR techniques.

b) The nested OA cohort requires more selective criteria to limit the population to younger patients without prior knee injury.

in order to obtain a sufficient sample size. The MOON group (8-10 surgeons) had enrolled 1040 unilateral ACLRs in its first two years, of which 10% were revision ACLRs. It was concluded that a minimum of 50 surgeons (1000 patients) would be needed to acquire the power needed to analyze the 75 independent variables in the MARS study. This is based on 10-15 ACLR per independent variable for analysis. Feasibility studies for MARS were paramount given the large multicenter nature of the cohort. The successful infrastructure of MOON laid the groundwork for the MARS feasibility analysis. MOON established examples of inter-rater reliability, well-organized infrastructure, and validated PROMs as described above. Additionally, the feasibility of attaining follow-up was also known from the 2-year data of MOON. And finally, early Level 1 evidence from the MOON group (that revision ACLR is an independent risk factor for worse outcome compared to primary ACLR) provided additional momentum to the development of a group such as MARS which could analyze the predictors for poor outcome after revision ACLR [34].

Challenges of MARS: how to enroll enough patients

Given the estimate of 50 surgeons needed to meet the necessary patient volume to provide meaningful analysis, the MARS group enrolled surgeons through the American Orthopedic Society for Sports Medicine. In 2006, three individual 6-hr training sessions for MARS were held and attracted over 125 surgeons. Participating surgeons had to be active members of AOSSM, obtain Institutional Review Board approval from their own research oversight authority, and complete the required training sessions. They could perform revision ACLR per their own practice but allograft tissue had to be obtained from a single vendor (the Musculoskeletal Transplant Foundation) to ensure standardization of graft processing. Final study participation included 83 surgeons from 52 sites, with an equal representation of private and academic practices.

Challenges of MARS: how to obtain radiographic data

While the MARS study employed most of the same data collection techniques as the MOON study (same PROMs, demographic data, similar intra operative data, etc.), the study did add an additional factor of radiographic findings prior to revision surgery. A standard radiographic series was obtained on all patients and sent to three independent readers. Inter observer agreement for most measurements was higher than 0.7, and intra observer agreement (4 weeks apart) was 0.7 for most measurements [35]. In terms of radiographic classification systems, inter observer reliability was moderate to good, with medium correlation to arthroscopic findings – the Rosenberg views had the most favorable reliability and correlation [36].

Challenges of MARS: surgeon assessment of cause of failure

As part of the data collection, surgeons in the MARS group were required to select their reasoning as to the cause of failure in ACLR. In order to validate these opinions, a study within MARS has looked

at multirater agreement for graft failure, using 20 randomly-selected cases from the MARS database [37]. The study exposed a challenge for the group, as there was wide variability in agreement among these experts as to cause of ACL graft failure and also poor agreement for ideal tunnel placement. More objective criteria are needed to accurately define cause of primary ACLR graft failure and identify the ideal tunnel position.

Success of MARS

With enrollment concluding in June 2011, the MARS study consisted of 1205 patients, making it easily the largest revision ACL cohort in the United States and the world. At 2-year follow-up, 82% of patients have completed PROM questionnaires [38]. There are over 14 publications from the cohort, with main findings detailed below.

Baseline characteristics of patients with revision ACLR

One of the earliest studies from the MARS cohort, prior to completion of enrollment, looked at overall epidemiology of the patients who undergo revision ACLR [39]. Of 460 patients, the most common mode of failure was deemed traumatic by the revising surgeon (32%), followed by technical (24%). Most patients were at least 2 years out from their last operation. Meniscal or chondral damage was found in 90% of patients. Allograft graft choice was more commonly used for the revision procedure (54% allograft versus 45% auto graft, 1% combined). Propensity analysis of the MARS group demonstrated that the revising surgeon's preferences had the largest impact on graft choice - five times which of the other significant factors, prior graft and age [40]. Comparing intra-auricular findings of the revision ACLR to those of primary ACLR (MARS versus MOON cohorts), the main difference between the groups was increased lateral and patella femoral chondral damage in the revision cohort, even after controlling for meniscus status (OR 1.7-1.73) [41].

Predictors of cartilage loss at time of revision ACLR

Studies from the MARS group have looked at predictors of cartilage loss at time of revision ACLR. Controlling for patient age, prior partial meniscectomy was associated with a higher rate of chondrosis in the same compartment than meniscus repair or no prior meniscus surgery [42]. However, knees with meniscus repair had no increased rate compared to knees without prior meniscus surgery, suggesting that meniscus repair may be preferable if possible at time of ACL reconstruction. Interestingly, this is consistent in the MOON cohort as well – investigators found that both MOON and MARS patients had a significantly increased odds ratio of chondral damage if they had undergone prior meniscectomy (OR 1.44- 1.65) [41]. Having an “intact” meniscus is strongly predictive of improved cartilage status in the MARS group. Evaluating meniscus status, BMI, and overall limb alignment as they related to chondral damage, investigators found medial and lateral chondrosis were significantly associated with disruption (tear or previously debridement) of the corresponding meniscus ($p=0.001$, $p<0.001$ respectively) – an intact meniscus decreased odds of chondrosis by 64-84% [42]. Additionally,

varus alignment and increased BMI were associated with increased medial compartment chondrosis while older age was associated with increased lateral compartment chondrosis.

Outcomes after revision ACLR and effect of graft type

At 2-year follow-up after revision ACLR, patients had significantly improved IKDC, KOOS, and WOMAC scores, but significantly decreased Marx activity scores (decrease from median 11 to 7 on a 16 point scale) [43]. Use of auto graft for revision predicted improved scores on the IKDC and the KOOS Sports and Recreation and Quality of Life subscales. Higher baseline PROM scores, male gender, and younger age also predicted improved outcome scores at follow-up. Prior lateral meniscectomy and current trochlear auricular cartilage damage resulted in poorer PROMs (OR 1.52-2.70) in all scales except for Marx activity [38]. Three percent of patients have experienced graft re-rupture at 2-year follow-up. Similar to the MOON primary ACL findings, auto grafts had improved performance, with 2.78 decreased odds of re-rupture [36].

Single revision ACLR vs. multiple revisions ACLR

Predictors of multiple revisions ACLR were compared to single revision ACLR within the entire MARS cohort [44]. Thirteen percent of the cohort was undergoing a second or subsequent revision. As expected, Marx activity levels were significantly lower in the multiple revision patients, and they were more likely to have chondral damage in medial and patella femoral compartments. Also, while non-contact trauma was the most common mechanism of injury for re-rupture in the single revision group (55%), non-traumatic gradual-onset recurrent injury was cited as the most common mechanism of injury for multiple revision ACLR patients (47%). Surgeons were more likely to cite an isolated technical error as the primary cause of failure in the multiple revision ACLR group compared to the single revision group (29% vs. 21%).

Conclusion

Overcoming design and implementation challenges, the MOON and MARS studies have made dramatic contributions to knowledge regarding ACLR. Their significant findings have already impacted practice among orthopedic surgeons and a wealth of information remains to be gained as follow-up continues within the nested osteoarthritis cohort of MOON. Results from both MOON and MARS will continue to impact clinical-decision making and improve ACLR outcomes by altering the modifiable predictors of worse outcome. They may be seen as a model to base future prospective longitudinal cohort studies within sports medicine and orthopedic surgery.

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