Prognosis and Predictors of ACL Reconstructions using the MOON Cohort: A Model for Comparative Effectiveness Studies

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ABSTRACT: Injury to the anterior cruciate ligament (ACL) threatens an active lifestyle and exposes the patient to risk of early osteoarthritis (OA). ACL reconstruction is typically chosen by individuals to allow a return to their previous work and sports activities. Primary ACL reconstruction (ACLR) has in general been effective at restoring functional stability, but patients' modifiable predictors of both short- and long-term validated outcomes and OA are largely unknown. The Multicenter Orthopaedic Outcomes Network (MOON) consortium was established in 2002 to enroll and longitudinally follow a population cohort of ACL reconstructed patients. The objective was to establish patient-specific predictive models of clinically important outcomes. Over the past 10 years, the overarching aims of this NIAMS-funded prospective multicenter cohort of ACL reconstructions has been threefold: (1) to identify both short- and long-term prognosis and predictors of sports function, activity level, and general health through validated patient-reported outcomes, (2) to identify the symptoms and signs of OA, and (3) to quantify the incidence of ACL reconstruction graft and/or contralateral ACL failures and additional surgical procedures. This manuscript summarizes the Kappa Delta Ann Doner Vaughan Award paper and presentation at the 2012 ORS/AAOS Annual Meeting. © 2012 Orthopaedic Research Society. Published by Wiley Periodicals, Inc. J Orthop Res 31:2–9, 2013

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Reconstruction of a ruptured anterior cruciate ligament in the United States is considered the standard of care for patients who experience giving way and recurrent swelling, and who participate in high-demand activities, particularly cutting and pivoting sports. Anterior cruciate ligament (ACL) reconstruction (ACLR) prevents future knee joint instability, reduces future knee injuries, and is the most reproducible treatment available to individuals who wish to return to cutting and pivoting sports. Comprehensive evidence based medicine (EBM) reviews of the clinical practice of ACL injured patients have been published by Beynnon et al.[1,2] and Spindler and Wright.[3] The recent knee, anterior cruciate ligament, non-surgical versus surgical treatment (KANON) randomized controlled trial (RCT) comparing rehabilitation versus ACLR observed in the nonoperative/rehab group that 37% crossed over to ACLR, 20% had partial meniscectomy, and 36% had signs and symptoms of meniscus tear at 2 years,[4] thus confirming a majority of patients would benefit from early ACLR. Patients and physicians are not particularly interested in population effects; they want the best possible patient-specific information about what to expect after an ACLR and how different pre-, intra-, and postoperative treatment options and lifestyle can change the expected outcome of that individual, based on his/her own specific characteristics. These patient-specific risk factors for prognosis are largely unknown.

A prospective longitudinal cohort is the preferred study design to provide the prognosis after ACLR using the particular predictors (risk factors) unique to the patient. The multivariable analysis performed on the MOON cohort will identify which of the many factors, especially modifiable predictors related to the injury, intraoperative treatment, postoperative care, physical, and behavioral patient characteristics contribute to clinically relevant outcomes.

The longer-term impact of this research is the modifiable predictors will guide basic science research,[5] and future clinical studies including comparative effectiveness studies will focus on these predictors propelling research toward developing and assessing better ACLR techniques and treatments. Finally, this research will have more general population benefits. An ACL injured knee, even with reconstruction, is at extremely high-risk for developing OA.[6] Thus, the reconstructed knee is an ideal model in which to study the initiation and progression of this degenerative disease, and information about modifiable predictors of OA gathered through this research on ACLR may impact the vast portion of the population who develop post-traumatic or idiopathic OA.

The outline of this article will include: evidence-based clinical literature, why is the MOON study

design unique to orthopaedics? development of the MOON consortium, maintaining definition uniformity (inter-rater agreement studies), inclusion/exclusion study criteria, outcome measures, 2-year results of ACLR outcomes, ACLR outcomes at 6 years, onsite comprehensive follow-up utilizing a nested cohort, MOON's impact on orthopaedics nationally and internationally, and conclusions.

EVIDENCE-BASED CLINICAL LITERATURE REVIEW AND STUDY DESIGN

Over the past decade 11 systematic reviews/meta-analyses on autograft choice and one review summarizing these 11 have been published.[7] A systematic review on fixation methods,[8] one systematic review evaluating one- versus two-incision approach ACLR,[9] and one meta-analysis on single versus double bundle grafts,[10] have been performed. However, no clinically relevant differences have been reported when evaluating fixation methods, surgical approaches, or number of ACL bundles using validated outcome measures, clinical assessment, graft failure criteria, or OA measures. In contrast, meniscus tears are associated with poor outcomes and increased incidence of radiographic OA in univariate models.[6] No Framingham-like cohort study has ever been performed to evaluate baseline patient characteristics, mechanism, concurrent injuries to meniscus and articular cartilage with their treatments, and surgical decisions on clinically relevant outcomes until the development of MOON.

A systematic review of 31 manuscripts (seven prospective) evaluating knee OA after ACL tear found that concomitant meniscus tears were associated with radiographic OA by univariate analysis.[6] They observed a 21–48% incidence with meniscus tears and 0–21% without meniscus tear. However, Øiestad's review concluded that, "A meta-analysis could not be performed as a result of heterogeneous classification systems of OA, lack of inter-rater agreement and lack of multivariable analysis."[6] They recommended that future studies to define both the prognosis and predictors of OA after ACLR be prospective with clearly defined aims and endpoints, utilize a common radiographic classification system with reliability data and an independent blinded examiner, the rehabilitation protocol should be reported, and regression analysis should be performed to evaluate risk factors. This defines the established MOON ACLR nested cohort initiated in 2005 which returns "onsite" for comprehensive evaluation, including standardized radiographs. Since both meniscus tears and articular cartilage injuries are suddenly induced at the time of ACLR (not under patient control and could not be randomized) a "natural experiment" has occurred and is the ideal opportunity to use a prospective cohort to evaluate how these intra-articular injuries affect validated patient-reported outcomes and signs of OA.

Finally, we conducted a systematic review and meta-analysis on Level I (RCT) and Level II (prospective cohort) studies on minimum 5-year ACLR outcomes for patient-reported outcomes, clinical assessments, and failure.[11] There were no clinically relevant differences by autograft choice (patellar tendon vs. hamstring) for any outcomes, no multivariable analysis was performed to identify modifiable risk factors for worse outcomes, and each study's sample size was insufficient to model the major risk factors. There have been two meta-analyses performed on allograft versus autograft choice for ACLR[12,13] in which the total allograft failures identified were under 10 events in both studies; therefore, the failure rate difference between allograft and autograft remains unknown. Conversely, our cohort was designed to provide sufficient sample size to answer this critical question regarding failure. Evaluating the highest evidence in the field has found that autograft choice, graft fixation method, and surgical technique had no clinically relevant outcome effects. However, a paucity of studies evaluating allograft choice and meniscus tears found they contribute to clinically relevant outcomes differences. Thus, the study design of the MOON prospective longitudinal cohort was set up to identify risk factors or predictors of patient relevant outcomes that impact physician and patient decision making and to guide future studies in order to improve outcomes.

Rehabilitation was believed to be an important variable. Two systematic reviews performed by the MOON group of Level I and II evidence regarding ACL reconstruction rehabilitation were used to design, in conjunction with physical therapists' input, a standardized rehabilitation protocol used by the group.[14,15]

To summarize, in the past decade the MOON team and/or individual members have published two papers on how to review the literature and conduct systematic reviews,[16,17] three inter-rater agreement studies, and 10 systematic reviews and/or meta-analyses. Thus MOON has been a driving force for EBM literature review and patient and physician evidence-based decision-making in sports medicine and orthopaedics.

WHY IS THE MOON STUDY DESIGN UNIQUE TO ORTHOPAEDICS?

Our enrolled cohort of 2,340 ACLRs has established the largest prospective ACLR outcomes cohort in the U.S. Our results are changing clinical practice paradigms by providing the best evidence for physicians to use when discussing with patients their prognosis, decisions about graft source, treatment options for meniscus, and/or articular cartilage injuries, as well as lifestyle choices that affect the knee in order to improve a patient's validated outcomes. To the field of orthopaedics and sports medicine, our study design and statistical modeling is novel and it challenges current experience-based physician decision-making.

The choice of preferred study design is dependent on the leading clinical question. If a single specific question regarding treatment efficacy is desired such as autograft choice, hamstring versus patellar tendon ACLR, then a randomized clinical trial is ideal. The results are applicable in the setting of all other factors being equal (BMI, activity level, age, meniscus tears, articular cartilage injuries, etc.). However, to define prognosis and risk factor analysis for worse outcomes in a given patient, then a prospective longitudinal cohort is preferred. Perhaps the most famous cohort was the Framingham study. Further, in the case of ACLR outcomes meniscus and articular cartilage injuries are presumed based on univariable models to influence outcome, yet those injuries cannot be randomized. This is an ideal setting to investigate by cohort as it is a "natural experiment."

A nested cohort is a specific subset of a larger cohort with unique features for a particular question. For our purpose to study the initiation of and risk factors for both symptomatic and structural (radiographic) OA we only included our younger patients without prior knee injuries to follow by returning onsite for physical examination, functional testing, and radiographs to detect developing OA. Many experts feel that a prospective longitudinal cohort is an ideal study design for comparative effectiveness research.

There are many contributing factors to these outcomes, some modifiable (e.g., weight, activity level, graft choice, treatment of meniscus and/or articular cartilage injuries, smoking) and some not (concurrent injuries, such as occurrence of meniscus tears and damage to articular cartilage; gender, race, and hearing a pop at injury). A cohort design is a novel way to deal with the multitude of factors known and unknown that cannot be independently randomized (e.g., meniscus tears and articular cartilage injuries which occur at the time of an ACL tear).[18,19]

Finally a longitudinal cohort study design is ideally suited for comparative effectiveness studies in the "real world" for the following reasons. First, enrollment is simpler and nearly 100% of patients participate since the physician is not altering the current treatment. Second, the preferred outcomes can be patient-reported validated questionnaires which can be self-administered either online or on paper pretreatment. Third, the designated follow-up can be web or mail based making 80% follow-up attainable at minimum costs.

DEVELOPMENT OF THE MOON CONSORTIUM

The concept for MOON was first conceived in 1991 when Spindler and two co-investigators from the Cleveland Clinic (Parker and Andrish) began to enter the demographics, mechanism of injury (e.g., contact/non-contact, jumping, sport), meniscus and articular cartilage injury/treatment, and technical details of the ACLR surgeries prospectively into a registry database. The Orthopaedic Research and Education Foundation (OREF) subsequently funded a cross-sectional follow-up outcome study. This prospective ACLR registry preceding MOON resulted in several publications documenting the statistical relationship between gender, weight, and sports with intra-articular injuries,[20,21] the success of two meniscal repair techniques,[22] and identified independent predictors (e.g., "pop" heard at time of injury, a weight increase of 15 pounds or greater, and years of education) for poor patient-oriented outcomes 5 years following ACLR.[23]

MAINTAINING DEFINITION UNIFORMITY (INTER-RATER AGREEMENT STUDIES)

The ability to perform multicenter studies involving multiple surgeons is dependent on close agreement in classification of intra-articular pathology, such as articular cartilage injury (ACI) and meniscal pathology, since these are believed to be associated with long-term outcome. As such, one of the first agenda items for the newly formed MOON group was to come to consensus on pathology definitions, and to perform a series of inter-rater agreement tests related to articular cartilage and meniscal pathology.[24,25] For articular cartilage lesions (modified Outerbridge chondromalacia grading I–IV) the range of observed agreement was from 81% to 94%. There was almost perfect agreement on an overwhelming majority of the lesions seen on the femoral condyles where the majority of lesions occur. Classification of meniscal pathology (normal, partial vs. complete tear) also has high inter-rater reliability for treatment (84% agreement, $\kappa = 0.66$) which is the final common pathway to meniscus status.[24] Excellent agreement was observed (between 71% and 87%) except for location of tear with respect to the periphery. The kappa indicated substantial agreement for type, length, and treatment. Moderate agreement was observed for sagittal location, depth, degenerative component, and location with reference to the popliteus. Thus MOON demonstrated sufficient reproducibility to pool data amongst sites.[24,25]

INCLUSION/EXCLUSION STUDY CRITERIA

The inclusion/exclusion criteria for the two MOON prospective cohorts (a population cohort and a nested cohort) are shown in Table 1. The nested cohort is a subset focused on the initiation and risk factors for OA, therefore, more selective criteria to limit the population to younger patients injured in sports with a previously normal (uninjured) knee without any preexisting risk factors for degenerative OA.

Note: since the ability to perform standard ACLR is limited to closed distal femoral and proximal tibial physes, the youngest age is defined by skeletal maturity.

OUTCOME MEASURES

In both cohorts (population and nested) we measure a series of five validated outcome instruments at

Table 1. Inclusion Criteria: Population Versus Nested Cohort

	Ages	Gender	Minorities	Mechanism of injury	Prior knee surgery		Opposite knee status
					Same	Opposite	
Population	All	Both	All	Any	Any	Any	Recorded
Nested 2-year cohort	12–33	Both	All	Injured in sport	No	No	Normal

baseline and at follow-up, along with recording the incidence of subsequent ipsilateral ACLR graft failure or contralateral normal ACL tear and any subsequent knee surgery at the time of our 2- and 6-year follow-up time points. The five validated patient-reported outcome questionnaires are administered in their original form within 2 weeks preoperatively and at minimum 2 and then 6 years after ACLR. These outcome instruments are self-administered to eliminate evaluator bias. These are the *KOOS* [26] and *IKDC* [27] (*Sports Function*), *Marx* (*Activity level*),[28] *SF-36* (*General Health*),[29] and *WOMAC* (*Symptoms of Osteoarthritis*).[26] All additional surgical procedures on either knee as well as the incidence of subsequent ACLR graft failure and contralateral ACL tears are longitudinally followed.

Further, a nested cohort evaluation for signs and symptoms of OA is evaluated uniquely by return on-site to undergo a comprehensive clinical assessment and specialized radiographic imaging[30] for OA along with the same validated patient-reported outcome measures. The nested cohort of ACLRs is focused on the initiation, predictors, and progression of symptoms and signs of OA.

TWO-YEAR RESULTS OF ACLR OUTCOMES
Overall, the 2-year follow-up rate for the 2,340 MOON enrollees reached 85% for the validated patient-reported outcome measures (via questionnaire) and 93% for phone confirmation of ACLR graft failure or contralateral ACL tear. A summary of clinical questions, answers to these questions with subsequent predictors (risk factors), both modifiable and non-modifiable, and manuscripts published are presented in Table 2. All studies were Level I prognostic studies except the return-to-play study concentrating on football players. Our study with the highest clinical impact thus far was cause of ACLR failure by Kaeding et al.[31] This study had 95% follow-up of 988 ACLRs where failure for the first time was predicted by age and graft choice. A graphic display is shown in Figure 1.

This figure clearly displays that for both graft choices the younger the age the greater the failure but failure rate difference between autograft and allograft increases the younger the patient. For example, an 18-year-old with autograft has a risk of failure equaling 6%, where if an allograft is used in this same 18-year-old, the risk of failure jumps to 20%. That is a 14% difference or a number needed to harm by choosing allograft of ~7. As a result of this study, all MOON surgeons now use autograft for high school, college, and competitive athletes in their primary ACL reconstructions. For the multivariable analysis in our publications (displayed as a nomogram in publications), these can be converted to interactive computer/web based programs for patients and health care providers so that the highest evidence of ACLR outcomes can be accessed. For example, in the Kaeding manuscript depicted in Figure 1, patients could determine their future failure risk by knowing their age and expected graft choice, which could easily be an application available via web.

Table 2. Two-Year Outcomes and Predictors—How MOON Has Changed Clinical Practice

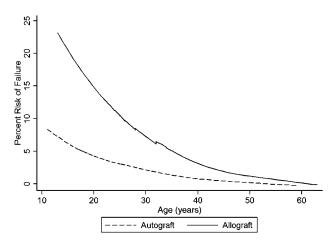| Question	Answer	Predictors	Reference
Bone bruise causes pain	No	Higher BMI, female	Dunn et al.[38]
Activity level	Decreased by 4 pts	Revision, age, female	Dunn et al.[39]
Contralateral ACL tear rate	3%	Unknown (requires greater sample size)	Wright et al.[40]
ACLR graft failure	1–20%	Allograft, younger age, higher activity	Borchers et al.[41]; Kaeding et al.[31]
Success of meniscal repair	94%	Unknown	Toman et al.[42]
KOOS outcomes	Improved, but not normal	Revision, smoking, grade 2 LCL	Spindler et al.[32]
Does hop test correlate with IKDC and KOOS at 2 years	Yes	Explains a minority of variation	Reinke et al.[34]
Return to play (high school and college football players)	~70%	Fear of re-injury ~50% reason do not continue in high school, college	McCullough et al.[43]

Figure 1. Probability of ACLR graft failure by age and choice of autograft versus allograft. This represents 95% of 2-year follow-up of 2002 and 2003 MOON cohort. ACLR graft failure was defined as revision ACLR.[31]

ACLR OUTCOMES AT 6 YEARS

We have completed follow-up for the first 3 years (2002–2004) and analyzed the first enrollment year (2002) of our cohort at a minimum of 6 years. We have maintained an average follow-up rate similar to our 2-year rate: ~84% for the validated patient-reported outcomes and over 90% for phone confirmation of ACLR graft failure or contralateral ACL tear. Table 3 (rows 1–3) shows our results of multivariable analysis on the first MOON enrolled cohort year (2002) for sports function (KOOS and IKDC) and activity (Marx).[32] Figure 2 depicts the population results. An unanticipated positive outcome was the stable population outcomes seen at 6 years as compared to 2 years. Figure 3 depicts a nomogram on the relative contributions of each of the aforementioned predictors on the KOOS knee-related quality of life subscale. Note, however, that a lateral meniscus tear that was not treated at the time of ACLR was a predictor of better outcome. This Level I prognostic study is the most comprehensive analysis of ACLR outcomes performed at 2 and 6 years. However, we still lacked sufficient sample size (i.e., power) to assess the role of partial meniscectomy and repair as well as articular cartilage injuries on these outcomes. This problem will be solved as 3 more years of data are accrued. The description of additional

arthroscopic surgery and hardware removals in the first 2 years' cohort at 6 years ($n = 988$ with 93% follow-up) were presented at the 2011 annual meeting of the American Orthopaedic Society for Sports Medicine (AOSSM) (Table 3). Additional surgeries are costly, significantly problematic for patients, and the effect on outcomes is unknown. On the ipsilateral ACLR 19.2% have had additional surgery 6 years following their index surgery. The ipsilateral ACLR graft failure was 5.6% with the contralateral normal ACL tear rate 6.5%. Thus the incidence of combined recurrent ligament disruption was 12.1%.

ONSITE COMPREHENSIVE FOLLOW-UP UTILIZING A NESTED COHORT

Our MOON nested cohort (ACLRs who return onsite for comprehensive testing), initiated in 2005, includes all Øiestad's systematic review guidelines for the preferred study design (OA after ACL tear). Current enrollment is 196 ACLRs at minimum 2-year follow-up and will expand to over 400 at completion of our competitive renewal. Finally, several experts in the field of OA have found that post-ACL injury OA closely mimics degenerative OA which affects 60 million Americans.[33] Thus, insights into the initiation, progression of, and modifiable predictors for OA will advance both scientific knowledge and clinical treatments for millions of individuals with OA. In a preliminary analysis of the cohort we published a significant correlation between the hop tests with IKDC patient-reported questionnaire.[34] However, the hop test accounted for <25% of the IKDC variation.

MOON'S IMPACT ON ORTHOPAEDICS NATIONALLY AND INTERNATIONALLY

One of the strongest predictors of poor ACLR outcomes within the MOON cohort is revision ACLR. Since only ~10% of MOON's ACLR are revisions, a much broader and larger multicenter study was needed to determine the predictors or risk factors for worse outcome in an effort to identify ways to improve results. This was done by Rick Wright (original MOON member) and sponsored by the AOSSM and is called the Multicenter ACLR Revision Study (MARS). The MARS group[35] (which includes all the original MOON sites) has 85 surgeons at 51 sites with approximately half the

Table 3. Six-Year Outcomes and Predictors—How MOON Has changed Clinical Practice

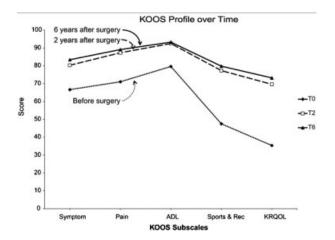| Question	Answer	Predictors	Reference
KOOS outcomes	Same as 2-year	Revision, allograft, smoking, lateral meniscus status	Spindler et al.[32]
IKDC outcomes	Same as 2-year	Revision, allograft, smoking, lateral meniscus status, BMI	Spindler et al.[32]
MARX activity level	Same as 2-year	Revision, female	Spindler et al.[32]
SF-36	Modeling	Modeling	
WOMAC	Modeling	Modeling	
Additional surgeries	19% @ 6 years	Modeling	Hettrich et al.[44]

Figure 2. KOOS population results. The five subscales of KOOS are displayed on horizontal axis and preoperative, 2-year, and 6-year follow-up population results are labeled.

participating surgeons in private practice. MARS completed enrollment June 30, 2011, with ~1,200 revision ACLRs and is now funded by the NIH/NIAMS.

NIH/NIAMS also has funded Meniscal Tear and Osteoarthritis Research (MeTeOR), a multicenter randomized trial comparing operative versus nonoperative treatment for mild to moderate OA with concomitant meniscus tears. This study also utilizes either MOON

or MARS sites for six of its seven centers. All these clinical sites in MeTeOR were enrolling in either MOON or MARS, and thus had built the culture and infrastructure to participate in an RCT.

One of the primary outcome measures, the KOOS, is identical to the outcome instrument the Norwegian and Swedish ACL database registries use, making predictor comparisons possible.[36] Thus these three separate cohorts will be analyzed to discover common modifiable predictors of poorer patient-reported outcomes; however, only MOON has demonstrated the ability to maintain Level I follow-up of their cohort at >80. Therefore for validated patient-reported outcomes MOON will be the gold standard or Level I study.

Collectively, the development and function of MOON has served as a template and framework for clinical research and will continue to collaborate with colleagues for discovery of common modifiable predictors to improve ACLR outcomes.

CONCLUSIONS

MOON's research will (1) identify modifiable predictors to provide guidance to future basic science and translational research; (2) perform and influence clinical trials and comparative effectiveness studies as they choose a proven modifiable risk factor (i.e., predictor) identified in our prospective longitudinal
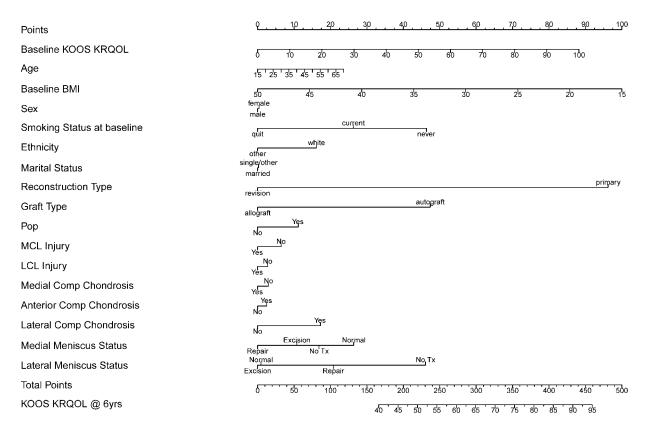

Figure 3. KOOS knee-related quality of life patient-specific predictive nomogram at 6 years. The nomogram is used to predict a patient-specific outcome score at 6 years based on summing the individual point total for each variable on the left. For each variable the patient's result is indicated and the points based on the top point scale are recorded. Then the sum of points is placed on the total points line on the bottom. After the total points are marked, you read the outcome score predicted at 6 years below.

cohort; (3) support the MARS group[37] which will identify modifiable predictors for revision ACLR; (4) collaborate by understanding common outcomes within the MOON, Sweden, and Norway ACLR databases; and (5) perform RCTs on early intervention to mitigate the initial proteoglycan loss from articular cartilage from the initial ACL tear to delay OA and improve outcomes of ACLR.

Our results have had and will continue to have direct impact on both physician and patient decision making for the individual patient considering ACLR. This will improve ACLR outcomes by altering the modifiable predictors of worse outcome. Ideally the overall impact of our prospective longitudinal cohort for orthopaedics will be analogous to Framingham's impact on the field of cardiology.

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