Neuromuscular Intervention Targeted to Mechanisms of ACL Load in Athletes

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General Study Information

Principal Investigator: Nathaniel Bates, PhD

Study Title: Neuromuscular Intervention Targeted to Mechanisms of ACL Load in Athletes

Protocol version number and date: version 4.5, 08/27/2020

Research Question and Aims

Specific Aims and Hypotheses

Aim 1. Determine if prospective measures can identify patient risk profiles for second ACL injury by separation of patient groups using biomechanical and clinical risk factors.

Hypothesis 1A: Landing biomechanics (vGRF, frontal and transverse plane hip moments, frontal plane knee and hip motion, and asymmetrical sagittal plane knee moments), quadriceps and hamstrings strength and single leg postural stability will effectively identify discrete patient risk profiles for second injury based on knee abduction (KAA) and hip adduction angles (HAA), surrogates for ACL injury.

Aim 2. Determine the effects of differential rehabilitation, including the impact on biomechanical measures of ACL injury risk and return to sport readiness after ACLR.

Hypothesis 2A: Changes in hip and knee kinematics and kinetics (frontal and transverse plane hip moment, frontal plane knee motion, and sagittal plane knee motion) will vary by treatment group, with the greatest changes occurring in the Targeted neuromuscular training (TNMT) > Standard of care (STAN) > HOME groups. Hypothesis 2B: Changes in clinical performance measures (hop symmetry; quadriceps and hip abductor

and extensor strength; single limb balance and self-reported function) will vary by treatment group, with the greatest changes in the TNMT > STAN > HOME groups.

Exploratory Aim. Develop a clinical algorithm that classifies patient risk for second ACL injury.

Hypothesis EA: Clinical tests of strength (quadriceps and hamstrings), balance, 2D jump landing mechanics (frontal and sagittal plane knee angle), and knee laxity) will effectively identify patient risk for second ACL injury.

Background

Importance of the problem. Second ACL injury, whether it is an insult to the ipsilateral graft or the contralateral ligament, is a growing problem after reconstruction. Besides missing an additional year of athletic participation, increasing health care costs, and increased psychological distress, re-injury and subsequent revision surgery have significantly worse outcomes compared with those after initial reconstruction.[8-10] Second injuries have been reported to occur at a rate of 1 in 17 (6%) within the first two years of surgery.[26] However, a second tear prevalence of 29% has been reported.[5-7, 27] This is substantially higher than initial ACL injuries, reported to occur at a rate of 1 in 60 to 100.[28, 29] Risk factors for second injury include younger athletes [6] who return to high-level sporting activities early. [27, 30] Both sexes are at risk for second ACL injury, with females reported as having higher risk of contralateral injury,[15, 26] and males having an increased risk of ipsilateral injury.[8, 31, 32] Thus, it is critical to include both sexes in second ACL injury prevention programs.

Improvement in scientific knowledge and clinical practice: Patients have differential responses after ACL injury, including their functional abilities, movement biomechanics, neuromuscular performance, and quadriceps strength.[18, 19, 33-39] Building from our prior funded work, we propose to prospectively evaluate these varying patient characteristics in an attempt to identify distinct groups with differing levels of risk for second injury (Aim 1). Our previous work revealed that there were three risk groups among uninjured female athletes. The significance of identification of patient groups with distinct needs is profound. Prospective identification of at-risk patients who are the most appropriate recipients of enhanced treatment will likely reduce second ACL risk, and yield a more efficacious delivery of health care resources after ACLR. The Cincinnati group[18] described this differentiation in ACL deficient patients as the 'rule of thirds,' with one third of patients able to function without limitations and not needing to undergo surgical stabilization, one third adapting their activity level without surgery, and one third requiring surgery to perform daily activities without knee instability. A classification scheme described by the University of Delaware also differentiates ACL deficient patients into groups of thirds including copers (no limit in abilities), non-copers (unable to function without knee instability) or potential copers (individuals who have the potential to function without ACLR).[19] There is evidence these differences in functional abilities and movement characteristics persist after ACLR. A randomized clinical trial concluded individuals who exhibit poor knee stability and function after injury may require additional time to return to pre-injury functional levels.[40] In addition, some may be unable to develop appropriate quadriceps strength symmetry to support a return to high-level sports.[40] These data indicate not all patients experience the same magnitude or duration of impairments and symptoms after ACLR. Consequently, multiple post-operative rehabilitation strategies may be necessary to facilitate optimum patient care and outcomes.

Working from the rule of one-thirds, identification of distinct patient groups with unique needs after surgery is a novel approach for integration of optimum second injury prevention strategies. Primary-injury risk factors provide an important window into the underlying biomechanical and neuromuscular deficits that may persist after ACL injury and reconstruction.[25] Using a statistical analysis clustering technique, distinct groups with relative risk for first-time ACL injury have been identified, including low, moderate and high risk groups. Single limb postural stability combined with biomechanical variables including vertical ground reaction force (vGRF), frontal plane hip adduction moment minimum, and pelvis angle during drop jump landings were

identified as significant contributors to frontal plane knee loading, a surrogate for ACL injury risk. This work has demonstrated the existence of discernable groups of athletes that are more appropriate for targeted neuromuscular training (TNMT) intervention to prevent first-time ACL injury.

Factors that contribute to primary ACL injury risk provide an important window into the underlying deficits that may persist after ACL injury and reconstruction. Age and activity level are significant factors, as young active individuals are the most likely cohort to sustain a second ACL rupture. [6, 27, 30, 41] Surgical factors include decreased graft size,[42, 43] use of allograft tissue,[44] vertical graft position,[45-47] and a lax graft.[45, 48] Anatomical risk factors may also contribute to ACL injury risk and include an increase in the posterior-inferior lateral tibial plateau slope and decreased notch width.[49] Genetic factors also likely play a role. While it is encouraging that so many potential factors have been identified which may contribute to second ACL injury risk, none of these factors can be modified through non-surgical intervention. Modifiable biomechanical and neuromuscular measures associated with second ACL injury have been identified. Previous work by our laboratory included a prospective clinical trial, [56] athletes who had undergone ACLR underwent testing before a return to pivoting and cutting sports. Thirteen athletes sustained a subsequent injury.[15] Specific injury predictive parameters identified during testing included a net internal rotation moment of the uninvolved hip, an increase in total frontal plane knee movement, greater asymmetry in internal knee extensor moment at initial contact, and deficits in single-leg postural stability of the involved limb.[15] These parameters predicted second injury in this population with excellent sensitivity (0.92) and specificity (0.88).

Differences in functional abilities after ACLR may be differentiated by more than biomechanical and neuromuscular characteristics. Clinically measured muscle weakness may persist for years after ACLR. Quadriceps strength is strongly related to measurements of knee function in athletes who have undergone ACLR.[20-24] While hamstrings strength alone may not show a significant effect on knee function following ACL injury and reconstruction,[22, 50] hamstrings activation may be an important component in neuromuscular control of the reconstructed knee, especially in females, who tend to be 'quadriceps dominant'. [50, 51] In addition, deficits in the hamstrings-quadriceps torque production ratio also appear to be a key variable in the primary ACL injury risk model.[52, 53] The relationship between muscle weakness and differential risk for second injury has not been established. An understanding of the interplay may, however, be critical to the development of effective, group-specific intervention programs and reduction of second-injury risk.[25]

It is currently unknown if biomechanical and clinical measures may effectively discern groups of patients who are at greatest risk for second ACL injury. Evaluation of movement mechanics and clinical characteristics, including strength, limb stability and self-reported function, at the time a patient initiates sports-specific training may yield insight to differential responses after ACLR. If distinct patient groups are identified, this information may be used to provide differentiated interventions based on risk for second injury. In Aim 2 of this proposal, we will evaluate the effects of differential rehabilitation interventions. Our Exploratory Aim will be the initial step in translating the biomechanics-based, group algorithm into a clinical application for individualized categorization of risk. The results of this work may instigate a paradigm shift in treatment, and promote a more efficacious utilization of healthcare resources by providing enhanced care to those patients who are at greatest risk for secondary injury.

Impact on patient care. One of the factors that contributes to second ACL injury is incomplete or ineffective rehabilitation.[54] Aberrant neuromuscular and biomechanical patterns are commonly seen up to 2 years after ACLR and may help explain the high rate of second ACL injury.[11-16] Deficits in the neuromuscular control of both lower extremities following ACLR have been directly implicated in the risk for second ACL injury[15] and may not only be a result of the initial knee injury and subsequent surgery, but may also characterize the athlete's pre-injury movement patterns. Therefore, identification and subsequent targeted treatment of

aberrant post-ACLR movement patterns for both limbs are critical not only to maximize functional recovery but also to reduce the risk for second ACL injury. Though neuromuscular training programs result in a 73.4% decreased risk of a non-contact primary-ACL injury compared to those who do not participate in neuromuscular training[55], the efficacy of similar programs for reduction of second-ACL injury risk has not been examined.

An evidence-based targeted neuromuscular training (TNMT) program has been designed to reduce the incidence of second ACL injury. This training program was developed with consideration to modifiable factors related to second-injury risk, the principles of motor learning, and careful selection of the exercises that may most effectively modify aberrant neuromuscular programs. In Aims 2 and 3 of this competing renewal proposal we will evaluate the effects of differential treatment interventions. Notably, we will assess the effectiveness of TNMT, including the utilization of visual and verbal biofeedback. Validation of this evidence-based, late-phase TNMT program may significantly impact clinical practice patterns through its integration in rehabilitation settings, and serve as a critical factor in reduction of second injury risk. Ultimately, determining if less intensive HOME and STAN training programs are effective interventions for patients who are at reduced risk for second ACL injury may prove to be a tremendous time and cost savings for patients and the health-care system.

Study Design and Methods

Methods

Overall Strategy. This is a prospective, randomized, repeated measures single- blind clinical trial. The purposes of this study are to 1) stratify patient risk for second ACL injury, and 2) determine the effects of differential treatment intervention, including targeted neuromuscular training (TNMT), home program only (HOME) and standard clinical (STAN) training, on clinical, biomechanical, and neuromuscular performance measures associated with an increased secondary ACL injury risk. At this time there is no evidence to support one intervention as either superior or inferior to the other interventions proposed in this study. After the initial ACL injury and study enrollment, all patients will participate in standardized pre-operative rehabilitation. They will then undergo surgery by a fellowship-trained sports medicine surgeon at Mayo Clinic, Rochester, MN. Data for Aim 1 will be obtained from biomechanical, neuromuscular and clinical testing performed during Pre-Testing. Data for Aim 2 and the Exploratory Aim will be obtained from biomechanical and clinical test results obtained from Pre- and Post-Testing time points.

Common Rehabilitation. All study participants will follow the same rehabilitation guidelines before and immediately after surgery, until they are cleared by their attending surgeon to return to full participation in sports. After clearance, they will be randomized into the differential treatment groups. Entry into this phase is criteria-based, and represents the standards identified in the literature for entry into the final phase of rehabilitation. These criteria include: symmetrical knee range of motion; minimal or no pain and knee effusion; quadriceps strength ≥ 80% compared to contralateral limb (180°/sec and 300°/sec); self-report of function ≥ 80%; limb symmetry index during single leg hop for distance ≥ 80%. Both pre- and postoperative rehabilitation protocols are a composite of previously published, evidence-based protocols from expert researchers and clinicians.[65-67]

Differential Rehabilitation. Once study participants are cleared for full participation in sports, they will be randomized into one of three groups for differential treatment. This will include HOME, STAN and TNMT

groups. If patient lives at a distance from Mayo Clinic and cannot participate in the weekly training but is able to come to both testing session they will be randomized into the HOME and STAN programs.

HOME Program is distinguished by patients participating in a home only intervention that consists of running exercises performed twice a week for six to eight weeks. No plyometric or agility drills are performed in this study arm. This represents the minimal intervention to prepare for a return to sports. No neuromuscular training or movement training beyond the sagittal plane will be performed.

Patients in the STAN group will be used as the control group. They will receive no training. They will participate in the two testing sessions and the weekly survey updates.

Patients who are enrolled in the TNMT group will participate in 12 sessions of supervised outpatient physical therapy over a six to eight week period. The TNMT protocol is distinguished by performance of exercises designed to enhance core and hip strength, performance of neuromuscular training exercise that are designed to correct movement flaws associated with second ACL injury[25], providing verbal and visual feedback and performance of single leg drills on both legs.

Augmented feedback is a key treatment feature for the TNMT group. Feedback will be provided for appropriate exercises, including dynamic jumping, stepping and lunging activities. Structured feedback has been shown to promote positive changes in jump landing biomechanics.[57-61] Specific feedback will be provided regarding toe to heel landing, landing on both feet at the same time, landing with feet hip width apart, knees over the midfoot, landing with knee flexion > 30°, trunk in front of hips, and no lateral trunk flexion.[57] Real time and delayed movement feedback will be provided using a commercially available system (Dartfish, Alpharetta, GA) to capture two-dimensional kinematics, and a force plate (Bertec Corp., Columbus, OH) to capture vertical ground reaction forces. The use of expert video feedback utilizing a standardized movement checklist has been shown to improve lower extremity dynamics during jump landing activities including a reduction in vertical ground reaction forces and increases in sagittal plane angular knee displacement.[92] Evidence based techniques will be utilized to aid patients in the TNMT group to master optimal dynamic movement strategies,[17, 18] which will include the use of a standardized movement evaluation performed by the subject's physical therapist.[63] Therapists will instruct patients in the desired movement quality, review presence of high risk movement patterns, and cue the patient for correct movement performance. The therapist will determine if an anterior or lateral video view is appropriate for providing the visual necessary feedback. For each of the TNMT exercises there will be four phases. The three treatment sessions in each phase will match the three phases of motor learning (cognitive, associative and autonomous).

aNMT (augmented NeuroMuscular Training) training. A 12-session, return to sport training program were modified from prior investigations to include real-time aNMT biofeedback. aNMT biofeedback training will consist of 2 sets of 10 repetitions per session with a progression in volume as exercise intensity increases (Squat: 40 repetitions during weeks 1-2; Pistol Squat, 40 repetitions during week 3-4, Overhead Squat, 80 repetitions during weeks 5-6) over the 6-week training period. aNMT biofeedback maps the values of key biomechanical variables, computed continuously in real-time, to a geometric shape that athletes view via a heads-up display consisting of a high-resolution screen fixed in a constant position in the eye's field of view. The biomechanical variables—selected based on our prior NIH-funded research that identified them as contributing injury risk factors—include: 1) Lateral trunk flexion (optimal = 0°), 2) Knee to hip sagittal plane moment ratio (<1), 3) Knee abduction moment (≤0 Nm), 4) Foot placement (1:1 ratio to hip width) 5) VGRF ratio (1:1 ratio between limbs) and 6) Landing position.

The desired outcome for athletes to achieve while performing each intervention exercise is to move so as to produce a rectangular shape and make the shape as large as possible. This is achieved when each targeted

biomechanical variable is at the desired value. Deviations of the variables from desired values result in specific and systematic changes to the feedback shape: 1) Lateral trunk flexion causes the object to lean to the respective side, 2) Inverse dynamics will determine the hip to knee sagittal plane moment ratio; reduced relative hip moment contributions shrink the shape and larger ratios make it bigger, 3) Knee abduction moment changes cause the stimulus to pinch (excessive valgus) or expand (excessive varus) at the middle, 4) Foot position changes the width of the stimulus base; feet too close together causes the base to be narrower than the top and too far apart causes it to be wider than the top, 5) VGRF asymmetry causes the corner of increased load to drop, and 6) The stimulus translates left or right if landing position deviates laterally from a target on the floor. After receiving basic instruction about how to accomplish the exercises, athletes must discover the movement pattern that produces a stimulus shape as close to the desired rectangle as possible and maintain the stimulus in a large rectangular shape as best as she can on each repetition. No explicit directions will be provided to athletes on their movement other than to achieve the goal shape. Based on our preliminary studies, we expect that the aNMT protocol will be especially beneficial to an athlete who can respond to self-guided, implicit learning strategies to correct multiple deficits that are likely cumulative in the exacerbation of injury risk. Given the automated, objectively prescribed mapping between the athlete and the stimulus, there is no interaction between the technician and the stimulus during aNMT delivery. This ensures blinding of the technician.

Biomechanical Testing Protocol Testing will be conducted at Mayo Clinic, prior to clinical testing. This portion of the data collection session will last approximately one hour. Testing will include collection of three-dimensional kinematic data with a high-speed, 10-camera motion capture system collected at 240 Hz (Motion Analysis, Santa Clara CA). Kinetic data will be collected at 1200 Hz from two force plates (Bertec, Columbus, OH) embedded into the floor and synchronized with motion data. We have demonstrated excellent reliability in our sagittal- and frontal-plane hip and knee mechanics both within and between testing sessions. We have excellent intraclass correlations in knee flexion angles and moments (0.933; 0.926 respectively), knee abduction angles and moments (0.993; 0.931 respectively), knee internal rotation (0.971; 0.666 respectively).[3] Reflective markers will be placed on the anatomical landmarks of the lower limbs, pelvis, trunk, neck, arms, and hands. The digital cameras will record the 3D coordinates of each marker first during a static pose (standing calibration) to define neutral alignment. Subjects will complete a trial to identify the functional hip joint center[73] on both limbs for post-processing of joint center calculations. Subsequent kinematic measures will be referenced in relation to this position.

Dynamic task descriptions

Drop vertical jump (DVJ): Subjects will begin the protocol by standing on top of a box (height of 31cm) with their feet 35 cm apart. Subjects will then drop off the box (without jumping) and land with their feet on the floor below, followed immediately by a maximum vertical jump with an overhead target. Both of the subject's feet must land separately on the two adjacent platforms, and a staggered foot fall to initiate the drop jump must be avoided. Five acceptable trials will be collected and post-processed.

Single cross-over drop (COD): To test the right lower extremity, subjects will stand on the right side of the top of box (height of 31cm) with their left foot. Subjects will be asked 'hop' off the box, crossing the midline of their body and landing with their right foot on the force plate to their left, holding the position for 3 seconds. A double hop on the landing (where the foot loses contact with the force plate) or the lack of a 3-second hold following the jump will not be utilized in the analysis. Five acceptable trials will be collected.

Single leg drop (SLD): Subjects will stand on a box (height of 31cm) on one foot. Subjects will be asked to drop off the box (without jumping), landing with their foot on the force plate below, and hold the position for 3

seconds. A double hop on the landing (where the foot loses contact with the force plate) or the lack of a 3-second hold following the jump will not be utilized in the analysis. Five acceptable trials will be collected.
Countermovement jump (CMJ): Subjects will stand on the floor with feet shoulder width apart. Subjects will be asked to squat down and execute a maximal vertical jump in one fluid movement. Five acceptable trials will be collected.
Single leg postural balance will be assessed using force plates. Two force plates (Bertec, Columbus, OH) will be used to measure static and dynamic bilateral and unilateral postural stability under eyes open and eyes closed conditions. During testing subjects will stand on one foot on the force plate sensor for 30 seconds with opposite knee flexed to 90° and the hands positioned on the hips. During the trial, COP path length, COP path velocity, and mean COP sway (limit of stability) will be recorded. Each task will be performed three times and the average of the three scores will be utilized for statistical analysis.

These movements are common sport activities and ones that can be completed safely in a controlled laboratory environment, posing no more risk than would be assumed during normal sports participation.

Data Analysis: Standard International Society of Biomechanics (ISB) conventions for calculating Euler angles will be used to describe lower extremity motions (Figure 2B).[74] From the standing trial, a kinematic model comprised of twelve skeletal segments and 36 degrees of freedom will be defined using commercial software (Visual 3D, C-Motion, Inc. Germantown, MD). The tracked 3D marker coordinate data recorded for the movement trials will be processed with custom software (MATLAB, MathWorks, Inc. Natick, MA) environment through the Visual3D pipeline to solve the generalized coordinates for each frame. These data will be low-pass filtered with a cubic smoothing spline at a 12 Hz cut-off frequency. The ground reaction force (GRF) data recorded for each limb will be used to normalize the kinematic data to 100% of stance at 1% increments (N=101), with initial contact defined as the instant when vertical GRF first exceeds 10N. From the 3D kinematic and force plate data, 3D moments at hip and knee will be computed using inverse dynamic analysis within Visual3D. The 3D moment vector in each joint will be decomposed in three components, each oriented along one of the axes of a standard joint coordinate system. The resulting variables represent the total moment due to muscle, ligament, and contact forces with respect to each axis. The moment arm and the horizontal distance from the resultant GRF to the knee joint center and COM will be calculated using Visual3D and MATLAB. These variables will be collected simultaneously and imported into the database with the kinematic and kinetic measures. Center of pressure (COP) and the anterior/ posterior, medial/lateral and vertical components of the force platform will be used to estimate the lateral distance between the resultant GRF vector and virtual knee joint center. Visual3D utilizes the geometrical approach to the inertial properties in order that segments are more generalizable to multiple models. The mass proportions of the segments were derived by Dempster[75] and the inertial properties were derived by Hanavan.[76]

The force platform data will be synchronized with the motion data to ensure accuracy of the representative model. The marker set and the segment coordinate systems are already constructed and have been found to be reliable.[3] In the frontal plane if the GRF, reacting to the COM, passes lateral to the center of the head of the femur, that results in an external hip abduction moment, which is counter balanced by an internal hip adductor torque.[77, 78] These concepts assume static equilibrium and neglect the inertia of the body segments between hip and ground. The inverse dynamic analysis performed will include all inertial effects.

Two-dimensional video collection of jump landing mechanics will be collected concurrent to three-dimensional drop jump (DVJ, SLD, COD, CMJ) testing. Continuous two-dimensional data will be collected with two digital video cameras (Bosch LLC, Farmington Hills, MI) at 60 Hz. Cameras will be positioned

anteriorly and laterally to the subject at 90 degree angles, and placed on tripods at a height of 0.3 m. Data analysis will be performed using commercially available software (Dartfish, Alpharetta, GA). Motions to be evaluated include frontal plane knee and hip angles at initial contact and at peak knee flexion, and knee flexion angle at initial contact.

Clinical Testing Protocol. This portion of the data collection session will last approximately two hours.

A. Subjects will be required to complete self-report questionnaires specific to their current knee function. The data will be collected using OBERD (Outcome Based Electronic Research Database), a software system integrated into the Mayo Clinic infrastructure to facilitate collection and consolidation of data. Questionnaires include the Marx Activity Scale (ICC of 0.97 for test-retest reliability)[79], Tegner scale (ICC of 0.82 for test-retest reliability)[80], International Knee Documentation Committee (IKDC) Subjective Knee Evaluation (ICC test-retest reliability of 0.95)[81], Knee Osteoarthritis Outcome Score (KOOS) (ICC test-retest reliability of 0.61-0.95)[82], Knee Outcome Survey-Activities of Daily Living (KOS-ADLS) and Sports (KOS-ADL Sports) (ICC test-retest reliability of 0.94) [83] Global Rating score (GRS) (ICC test-retest reliability of 0.88) [84] and the Anterior Cruciate Ligament Return to Sport after Injury (ACL-RSI) (Cronbach's Alpha= 0.92)[91].

B. Strength will be measured on both limbs using a clinical dynamometer (either Humac, CSMi, Stoughton, MA, or Biodex System, Biodex, Shirley, NY).

1. Isokinetic quadriceps and hamstrings strength: Subjects will be seated on the dynamometer with the hip and knee flexed to 90°. Prior to testing, they will undergo a short warm-up. A test session will consist of 10 repetitions at slow (180°/sec) and fast (300°/sec) speeds through a knee range of motion of 0-100°. Peak flexion and extension torques will be recorded.

2. Isokinetic hip abduction strength: Subjects will stand in front of the rotating arm of the dynamometer. A test session will consist of two test sets of 5 repetitions at 120°/second moving into abduction. Peak abduction torque will be recorded.

3. Isometric hip abduction strength: Isometric abduction strength will be collected using a custom force sensing strap. Subjects will stand with their feet placed shoulder-width apart, their knees aligned directly above each foot, and hips and knees slightly flexed. A non-stretchable athletic wrap will be secured around the subject's thighs, superior to the femoral condyles and patella, and secured with tape or Velcro. Three practice repetitions will be conducted in which the subjects will maximally abduct their thighs and push out against the wrap. [5] maximum efforts will be conducted and recorded. A strain gauge will measure induced voltage and display force output on a monitor. Maximum abduction force in all 5 trials will be recorded.

C. Patient functional performance will be evaluated with a battery of hop tests. Reliability of the unilateral hop tests is good, with ICC coefficients ranging from .[92-.96.85, 86]

1. Single leg hop for distance tests: The limb symmetry indexes (LSIs) for the single hop, cross-over hop, and triple hop tests are all based on the maximum distance jumped with a controlled landing, and performance will be calculated by dividing the distance hopped on the involved leg by the distance hopped on the uninvolved leg. Hop distance will be measured to the nearest centimeter on a standard measuring taped secured to the floor. The maximum hop distance of two trials will be used for analysis.

2. Single leg timed hop: The 6-meter timed hop is a measure of how fast it takes the athlete to hop 6-meters on one leg. A handheld or digital timing system will be used by a trained tester. The 6-meter timed hop LSI will be calculated by dividing the time recorded for the uninvolved (or dominant leg) divided by the time recorded for the involved leg.

D. Skeletal maturity will be evaluated with a modified Pubertal Maturation Observational Scale (PMOS). Maturational categories will include prepubertal (equivalent to Tanner[87, 88] Stage 1), early pubertal (equivalent to Tanner Stages 2 and 3) or late or postpubertal (equivalent to Tanner Stages 4 and 5). The categories are

based on several indicators of pubertal maturation (growth spurt, menarchal status, body hair, sweating, and muscular definition).[89] The scale reliably classifies subjects into developmental stages and is based on parental/participant report, and investigator observations.[90] The reliability of the scale has been demonstrated to be high.[89]

F. Passive anterior knee laxity will be captured with a GNRB arthrometer (Genourob, Laval, France) or a Blue Bay arthrometer (Blue Bay Research Inc, Navarre, FL, USA) using an automated 134 N anterior push on the posterior aspect of the tibia or a Blue Bay arthrometer (Blue Bay Research Inc, Navarre, FL, USA) using a 134 N anterior pull on the tibia.

Tracking

During the six weeks of training, patients will be contacted weekly via email or text message. The surveys will include questions of compliance and involvement of sport activities. If the patient prefers, the surveys can be conducted over the phone rather than on the computer. The coordinator will call the patient/guardian if the survey has not been filled out after two notices. Post training, the patient will receive monthly surveys of injury surveillance for two years. Then yearly follow up for 4 years. Patients will be followed a total of 6 years.

Check all that apply. If none apply, leave blank:

☐ This is a multisite study involving Mayo Clinic and non-Mayo Clinic sites.
When checked, describe the research procedures/activities being conducted **only** at Mayo Clinic:

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☒ The research involves contact or interaction with subjects, for example, surveys, questionnaires, observation, blood draw.

☒ The study involves photographing, audiotaping or videotaping subjects (and guests).

CITED REFERENCES

1. Smith HC, Johnson RJ, Shultz SJ, Tourville T, Holterman LA, Slauterbeck J, et al. A prospective evaluation of the Landing Error Scoring System (LESS) as a screening tool for anterior cruciate ligament injury risk. Am J Sports Med. 2012;40(3):521-6.
2. Krosshaug T, Steffen K, Kristianslund E, Nilstad A, Mok KM, Myklebust G, et al. The Vertical Drop Jump Is a Poor Screening Test for ACL Injuries in Female Elite Soccer and Handball Players: A Prospective Cohort Study of 710 Athletes. Am J Sports Med. 2016;44(4):874-83.
3. Ford KR, Myer GD, Hewett TE. Reliability of landing 3D motion analysis: implications for longitudinal analyses. Med Sci Sports Exerc. 2007;39(11):2021-8.
4. Swart E, Redler L, Fabricant PD, Mandelbaum BR, Ahmad CS, Wang YC. Prevention and screening programs for anterior cruciate ligament injuries in young athletes: a cost-effectiveness analysis. J Bone Joint Surg Am. 2014;96(9):705-11. PMCID: 4001460.

5. Pinczewski L, Morgan M, Salmon LJ, Waller A, Thompson S, Roe J. 15 year survival of endoscopic anterior cruciate ligament reconstruction in patients aged 18 years and under. Orthopaedic J Sports Med. 2015;3(3):Suppl 1.
6. Webster KE, Feller JA, Leigh WB, Richmond AK. Younger patients are at increased risk for graft rupture and contralateral injury after anterior cruciate ligament reconstruction. Am J Sports Med. 2014;42(3):641-7.
7. Webster KE, Feller JA. Exploring the High Reinjury Rate in Younger Patients Undergoing Anterior Cruciate Ligament Reconstruction. Am J Sports Med. 2016.
8. Failla MJ, Arundale AJ, Logerstedt DS, Snyder-Mackler L. Controversies in knee rehabilitation: anterior cruciate ligament injury. Clin Sports Med. 2015;34(2):301-12. PMCID: 4379426.
9. Gifstad T, Drogset JO, Viset A, Grontvedt T, Hortemo GS. Inferior results after revision ACL reconstructions: a comparison with primary ACL reconstructions. Knee Surg Sports Traumatol Arthrosc. 2013;21(9):2011-8.
10. Wright RW, Gill CS, Chen L, Brophy RH, Matava MJ, Smith MV, et al. Outcome of revision anterior cruciate ligament reconstruction: a systematic review. J Bone Joint Surg Am. 2012;94(6):531-6. PMCID: 3298683.
11. Hart JM, Ko JW, Konold T, Pietrosimone B. Sagittal plane knee joint moments following anterior cruciate ligament injury and reconstruction: a systematic review. Clin Biomech (Bristol, Avon). 2010;25(4):277-83.
12. Hartigan E, Axe MJ, Snyder-Mackler L. Perturbation training prior to ACL reconstruction improves gait asymmetries in non-copers. J Orthop Res. 2009;27(6):724-9. PMCID: 3597104.
13. Myer GD, Schmitt LC, Brent JL, Ford KR, Barber Foss KD, Scherer BJ, et al. Utilization of modified NFL combine testing to identify functional deficits in athletes following ACL reconstruction. J Orthop Sports Phys Ther. 2011;41(6):377-87. PMCID: 3439811.
14. Paterno MV, Ford KR, Myer GD, Heyl R, Hewett TE. Limb asymmetries in landing and jumping 2 years following anterior cruciate ligament reconstruction. Clin J Sport Med. 2007;17(4):258-62.
15. Paterno MV, Schmitt LC, Ford KR, Rauh MJ, Myer GD, Huang B, et al. Biomechanical measures during landing and postural stability predict second anterior cruciate ligament injury after anterior cruciate ligament reconstruction and return to sport. Am J Sports Med. 2010;38(10):1968-78.
16. Roewer BD, Di Stasi SL, Snyder-Mackler L. Quadriceps strength and weight acceptance strategies continue to improve two years after anterior cruciate ligament reconstruction. J Biomech. 2011;44(10):1948-53. PMCID: 3124616.
17. Hewett TE, Ford KR, Xu YY, Khoury J, Myer GD. Utilization of ACL Injury Biomechanical and Neuromuscular Risk Profile Analysis to Determine the Effectiveness of Neuromuscular Training. Am J Sports Med. 2016.
18. Noyes FR, Matthews DS, Mooar PA, Grood ES. The symptomatic anterior cruciate-deficient knee. Part II: the results of rehabilitation, activity modification, and counseling on functional disability. J Bone Joint Surg Am. 1983;65(2):163-74.
19. Hurd WJ, Axe MJ, Snyder-Mackler L. A 10-year prospective trial of a patient management algorithm and screening examination for highly active individuals with anterior cruciate ligament injury: Part 1, outcomes. Am J Sports Med. 2008;36(1):40-7. PMCID: 2891099.
20. Eitzen I, Holm I, Risberg MA. Preoperative quadriceps strength is a significant predictor of knee function two years after anterior cruciate ligament reconstruction. Br J Sports Med. 2009;43(5):371-6.

21. Keays SL, Bullock-Saxton J, Keays AC, Newcombe P. Muscle strength and function before and after anterior cruciate ligament reconstruction using semitendonosus and gracilis. Knee. 2001;8(3):229-34.
22. Keays SL, Bullock-Saxton JE, Newcombe P, Keays AC. The relationship between knee strength and functional stability before and after anterior cruciate ligament reconstruction. J Orthop Res. 2003;21(2):231-7.
23. Lewek M, Rudolph K, Axe M, Snyder-Mackler L. The effect of insufficient quadriceps strength on gait after anterior cruciate ligament reconstruction. Clin Biomech (Bristol, Avon). 2002;17(1):56-63.
24. Morrissey MC, Hooper DM, Drechsler WI, Hill HJ. Relationship of leg muscle strength and knee function in the early period after anterior cruciate ligament reconstruction. Scand J Med Sci Sports. 2004;14(6):360-6.
25. Di Stasi S, Myer GD, Hewett TE. Neuromuscular training to target deficits associated with second anterior cruciate ligament injury. J Orthop Sports Phys Ther. 2013;43(11):777-92, A1-11. PMCID: 4163697.
26. Wright RW, Dunn WR, Amendola A, Andrish JT, Bergfeld J, Kaeding CC, et al. Risk of tearing the intact anterior cruciate ligament in the contralateral knee and rupturing the anterior cruciate ligament graft during the first 2 years after anterior cruciate ligament reconstruction: a prospective MOON cohort study. Am J Sports Med. 2007;35(7):1131-4.
27. Paterno MV, Rauh MJ, Schmitt LC, Ford KR, Hewett TE. Incidence of Second ACL Injuries 2 Years After Primary ACL Reconstruction and Return to Sport. Am J Sports Med. 2014;42(7):1567-73. PMCID: 4205204.
28. Gomez E, DeLee JC, Farney WC. Incidence of injury in Texas girls' high school basketball. Am J Sports Med. 1996;24(5):684-7.
29. Messina DF, Farney WC, DeLee JC. The incidence of injury in Texas high school basketball. A prospective study among male and female athletes. Am J Sports Med. 1999;27(3):294-9.
30. Laboute E, Savalli L, Puig P, Trouve P, Sabot G, Monnier G, et al. Analysis of return to competition and repeat rupture for 298 anterior cruciate ligament reconstructions with patellar or hamstring tendon autograft in sportspeople. Ann Phys Rehabil Med. 2010;53(10):598-614.
31. Bourke HE, Salmon LJ, Waller A, Patterson V, Pinczewski LA. Survival of the anterior cruciate ligament graft and the contralateral ACL at a minimum of 15 years. Am J Sports Med. 2012;40(9):1985-92.
32. Shelbourne KD, Gray T, Haro M. Incidence of subsequent injury to either knee within 5 years after anterior cruciate ligament reconstruction with patellar tendon autograft. Am J Sports Med. 2009;37(2):246-51.
33. Chmielewski TL, Rudolph KS, Fitzgerald GK, Axe MJ, Snyder-Mackler L. Biomechanical evidence supporting a differential response to acute ACL injury. Clin Biomech (Bristol, Avon). 2001;16(7):586-91.
34. Di Stasi SL, Hartigan EH, Snyder-Mackler L. Unilateral stance strategies of athletes with ACL deficiency. J Appl Biomech. 2012;28(4):374-86. PMCID: 3610327.
35. Fitzgerald GK, Axe MJ, Snyder-Mackler L. A decision-making scheme for returning patients to high-level activity with nonoperative treatment after anterior cruciate ligament rupture. Knee Surg Sports Traumatol Arthrosc. 2000;8(2):76-82.
36. Rudolph KS, Eastlack ME, Axe MJ, Snyder-Mackler L. 1998 Basmajian Student Award Paper: Movement patterns after anterior cruciate ligament injury: a comparison of patients who compensate well for the injury and those who require operative stabilization. J Electromyogr Kinesiol. 1998;8(6):349-62.
37. Rudolph KS, Snyder-Mackler L. Effect of dynamic stability on a step task in ACL deficient individuals. J Electromyogr Kinesiol. 2004;14(5):565-75.
38. Chmielewski TL, Ramsey DK, Snyder-Mackler L. Evidence for differential control of tibial position in perturbed unilateral stance after acute ACL rupture. J Orthop Res. 2005;23(1):54-60.

39. Chmielewski TL, Stackhouse S, Axe MJ, Snyder-Mackler L. A prospective analysis of incidence and severity of quadriceps inhibition in a consecutive sample of 100 patients with complete acute anterior cruciate ligament rupture. J Orthop Res. 2004;22(5):925-30.
40. Hartigan EH, Axe MJ, Snyder-Mackler L. Time line for noncopers to pass return-to-sports criteria after anterior cruciate ligament reconstruction. J Orthop Sports Phys Ther. 2010;40(3):141-54. PMCID: 3613129.
41. Brophy RH, Schmitz L, Wright RW, Dunn WR, Parker RD, Andrish JT, et al. Return to play and future ACL injury risk after ACL reconstruction in soccer athletes from the Multicenter Orthopaedic Outcomes Network (MOON) group. Am J Sports Med. 2012;40(11):2517-22. PMCID: 3692367.
42. Magnussen RA, Lawrence JT, West RL, Toth AP, Taylor DC, Garrett WE. Graft size and patient age are predictors of early revision after anterior cruciate ligament reconstruction with hamstring autograft. Arthroscopy. 2012;28(4):526-31.
43. Park SY, Oh H, Park S, Lee JH, Lee SH, Yoon KH. Factors predicting hamstring tendon autograft diameters and resulting failure rates after anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc. 2013;21(5):1111-8.
44. Pallis M, Svoboda SJ, Cameron KL, Owens BD. Survival comparison of allograft and autograft anterior cruciate ligament reconstruction at the United States Military Academy. Am J Sports Med. 2012;40(6):1242-6.
45. Bourke HE, Gordon DJ, Salmon LJ, Waller A, Linklater J, Pinczewski LA. The outcome at 15 years of endoscopic anterior cruciate ligament reconstruction using hamstring tendon autograft for 'isolated' anterior cruciate ligament rupture. J Bone Joint Surg Br. 2012;94(5):630-7.
46. Hui C, Salmon LJ, Kok A, Maeno S, Linklater J, Pinczewski LA. Fifteen-year outcome of endoscopic anterior cruciate ligament reconstruction with patellar tendon autograft for "isolated" anterior cruciate ligament tear. Am J Sports Med. 2011;39(1):89-98.
47. Leys T, Salmon L, Waller A, Linklater J, Pinczewski L. Clinical results and risk factors for reinjury 15 years after anterior cruciate ligament reconstruction: a prospective study of hamstring and patellar tendon grafts. Am J Sports Med. 2012;40(3):595-605.
48. Pinczewski LA, Lyman J, Salmon LJ, Russell VJ, Roe J, Linklater J. A 10-year comparison of anterior cruciate ligament reconstructions with hamstring tendon and patellar tendon autograft: a controlled, prospective trial. Am J Sports Med. 2007;35(4):564-74.
49. Sturnick DR, Vacek PM, DeSarno MJ, Gardner-Morse MG, Tourville TW, Slauterbeck JR, et al. Combined anatomic factors predicting risk of anterior cruciate ligament injury for males and females. Am J Sports Med. 2015;43(4):839-47.
50. Bryant AL, Clark RA, Pua YH. Morphology of hamstring torque-time curves following ACL injury and reconstruction: mechanisms and implications. J Orthop Res. 2011;29(6):907-14.
51. Hewett TE, Paterno MV, Myer GD. Strategies for enhancing proprioception and neuromuscular control of the knee. Clin Orthop Relat Res. 2002(402):76-94.
52. Myer GD, Ford KR, Barber Foss KD, Liu C, Nick TG, Hewett TE. The relationship of hamstrings and quadriceps strength to anterior cruciate ligament injury in female athletes. Clin J Sport Med. 2009;19(1):3-8.
53. Myer GD, Ford KR, Khoury J, Succop P, Hewett TE. Biomechanics laboratory-based prediction algorithm to identify female athletes with high knee loads that increase risk of ACL injury. Br J Sports Med. 2011;45(4):245-52. PMCID: 4019975.
54. Wilk KE. Anterior Cruciate Ligament Injury Prevention and Rehabilitation: Let's Get It Right. J Orthop Sports Phys Ther. 2015;45(10):729-30.

55. Sugimoto D, Myer GD, McKeon JM, Hewett TE. Evaluation of the effectiveness of neuromuscular training to reduce anterior cruciate ligament injury in female athletes: a critical review of relative risk reduction and numbers-needed-to-treat analyses. Br J Sports Med. 2012;46(14):979-88. PMCID: 4164156.
56. Salmon L, Russell V, Musgrove T, Pinczewski L, Refshauge K. Incidence and risk factors for graft rupture and contralateral rupture after anterior cruciate ligament reconstruction. Arthroscopy. 2005;21(8):948-57.
57. Cronin JB, Bressel E, Fkinn L. Augmented feedback reduces ground reaction forces in the landing phase of the volleyball spike jump. J Sport Rehabil. 2008;17(2):148-59.
58. McNair PJ, Prapavessis H, Callender K. Decreasing landing forces: effect of instruction. Br J Sports Med. 2000;34(4):293-6. PMCID: 1724204.
59. Mizner RL, Kawaguchi JK, Chmielewski TL. Muscle strength in the lower extremity does not predict postinstruction improvements in the landing patterns of female athletes. J Orthop Sports Phys Ther. 2008;38(6):353-61.
60. Parsons JL, Alexander MJ. Modifying spike jump landing biomechanics in female adolescent volleyball athletes using video and verbal feedback. J Strength Cond Res. 2012;26(4):1076-84.
61. Prapavessis H, McNair PJ. Effects of instruction in jumping technique and experience jumping on ground reaction forces. J Orthop Sports Phys Ther. 1999;29(6):352-6.
62. Myer GD, Stroube BW, DiCesare CA, Brent JL, Ford KR, Heidt RS, Jr., et al. Augmented feedback supports skill transfer and reduces high-risk injury landing mechanics: a double-blind, randomized controlled laboratory study. Am J Sports Med. 2013;41(3):669-77. PMCID: 4166501.
63. Etnoyer J, Cortes N, Ringleb SI, Van Lunen BL, Onate JA. Instruction and jump-landing kinematics in college-aged female athletes over time. J Athl Train. 2013;48(2):161-71. PMCID: 3600918.
64. Krych AJ, Woodcock JA, Morgan JA, Levy BA, Stuart MJ, Dahm DL. Factors associated with excellent 6-month functional and isokinetic test results following ACL reconstruction. Knee Surg Sports Traumatol Arthrosc. 2015;23(4):1053-9.
65. Adams D, Logerstedt DS, Hunter-Giordano A, Axe MJ, Snyder-Mackler L. Current concepts for anterior cruciate ligament reconstruction: a criterion-based rehabilitation progression. J Orthop Sports Phys Ther. 2012;42(7):601-14. PMCID: 3576892.
66. Wilk KE, Macrina LC, Cain EL, Dugas JR, Andrews JR. Recent advances in the rehabilitation of anterior cruciate ligament injuries. J Orthop Sports Phys Ther. 2012;42(3):153-71.
67. Wright RW, Haas AK, Anderson J, Calabrese G, Cavanaugh J, Hewett TE, et al. Anterior cruciate ligament reconstruction rehabilitation: MOON guidelines. Sports Health. 2014;7(3):239-43.
68. Zazulak BT, Hewett TE, Reeves NP, Goldberg B, Cholewicki J. The effects of core proprioception on knee injury: a prospective biomechanical-epidemiological study. Am J Sports Med. 2007;35(3):368-73.
69. Ford KR, DiCesare CA, Myer GD, Hewett TE. Real-time biofeedback to target risk of anterior cruciate ligament injury: a technical report for injury prevention and rehabilitation. J Sport Rehabil. 2015;Technical Notes.
70. Fraley C, Raftery AE. Model-based clustering, discriminant analysis, and density estimation. J Am Statistical Assoc. 2002;97:611-31.
71. Kim S, Tadesse MG, Vannucci M. Variable selection in clustering via Dirichlet process mixture models. Biometrika. 2006:877-93.
72. Raftery AE, Dean N. Variable selection for model-based clustering. J Amer Statistical Assoc. 2006:168-78.

73. Bell AL, Pedersen DR, Brand RA. A comparison of the accuracy of several hip center location prediction methods. J Biomech. 1990;23(6):617-21.
74. Wu G, Siegler S, Allard P, Kirtley C, Leardini A, Rosenbaum D, et al. ISB recommendation on definitions of joint coordinate system of various joints for the reporting of human joint motion--part I: ankle, hip, and spine. International Society of Biomechanics. J Biomech. 2002;35(4):543-8.
75. Dempster W. Space requirements of the seated operator. Wright-Patterson Air Force Base, Ohio: WADC Technical Report; 1955.
76. Hanavan EP, Jr. A Mathematical Model of the Human Body. Amrl-Tr-64-102. Amrl Tr. 1964:1-149.
77. Winter DA. Biomechanics and Motor Control of Human Movement. 3rd ed. ed. New York: John Wiley & Sons, Inc.; 2005.
78. Andriacchi TP, Natarajan RN, Hurwitz DE. Musculoskeletal Dynamics, Locomotion, and Clinical Applications. In: Mow VC, Hayes WC, editors. Basic orthopaedic biomechanics. 2nd ed. Philadelphia: Lippincott-Raven; 1997. p. 37-68.
79. Marx RG, Stump TJ, Jones EC, Wickiewicz TL, Warren RF. Development and evaluation of an activity rating scale for disorders of the knee. Am J Sports Med. 2001;29(2):213-8.
80. Briggs KK, Lysholm J, Tegner Y, Rodkey WG, Kocher MS, Steadman JR. The reliability, validity, and responsiveness of the Lysholm score and Tegner activity scale for anterior cruciate ligament injuries of the knee: 25 years later. Am J Sports Med. 2009;37(5):890-7.
81. Crawford K, Briggs KK, Rodkey WG, Steadman JR. Reliability, validity, and responsiveness of the IKDC score for meniscus injuries of the knee. Arthroscopy. 2007;23(8):839-44.
82. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. J Orthop Sports Phys Ther. 1998;28(2):88-96.
83. Marx RG, Jones EC, Allen AA, Altchek DW, O'Brien SJ, Rodeo SA, et al. Reliability, validity, and responsiveness of four knee outcome scales for athletic patients. J Bone Joint Surg Am. 2001;83-A(10):1459-69
84. McGuine TA, Leverson G, editors. The reliability and responsiveness of the SANE knee score in high school athletes. National Athletic Trainers Association Annual Meeting; 2008; St. Louis, MO.
85. Bolgla LA, Keskula DR. Reliability of lower extremity functional performance tests. J Orthop Sports Phys Ther. 1997;26(3):138-42.
86. Bandy WD, Ruschke KR, Tekulve FY. Reliability and symmetry for five unilateral functional tests of the lower extremity. Isokinetics and Exercise Science. 1994;4:108-11.
87. Biro FM, Lucky AW, Huster GA, Morrison JA. Pubertal staging in boys. J Pediatr. 1995;127(1):100-2.
88. Biro FM, McMahon RP, Striegel-Moore R, Crawford PB, Obarzanek E, Morrison JA, et al. Impact of timing of pubertal maturation on growth in black and white female adolescents: The National Heart, Lung, and Blood Institute Growth and Health Study. J Pediatr. 2001;138(5):636-43.
89. Davies PS. Assessment of cognitive development in adolescent motor performance by a means of neuropsychological assessments. Laramie, WY: University of Wyoming; 1995.
90. Davies PL, Rose JD. Motor skills of typically developing adolescents: awkwardness or improvement? Phys Occup Ther Pediatr. 2000;20(1):19-42.
91. Webster KE, Feller JA, & Lambros, C. Development and preliminary validation of a scale to measure the psychological impact of returning to sport following anterior cruciate ligament reconstruction surgery. Physical therapy in sport, 2008; 9(1), 9-15.

Resources:
Space. The research methodology described in this application will primarily be conducted in the Biodynamics Laboratory. Patient care and rehabilitation will be provided in Mayo Clinic Sports Medicine Centers (SMCs).

Mayo Clinic has recently built two state of the art outpatient Sports Medicine Centers (SMCs) in Rochester and Minneapolis, MN. The offices and facilities of the SMCs are dedicated to creating an atmosphere of clinical, research and academic excellence. All facilities and resources are readily available to Dr. Bates, and include everything necessary for the successful completion of this proposal. The availability of two sports medicine rehabilitation centers within the Mayo Clinic system that provide standardized care enhances the ability to provide patient services to a large geographic region. Both clinics occupy more than 20,000 square feet. Eleven physical therapists, seven athletic trainers, and three performance coaches provide rehabilitation services. Physician treatment rooms are housed on the same floor at each site. Five sports medicine, fellowship-trained physicians comprise the surgical team, including Dr. Aaron Krych (PI). All of the surgery providers are participating in the investigation.

This project will utilize the dual clinical spaces available at Mayo Clinic Sports Medicine housed within the Dan Abraham Healthy Living Center (DAHLC) in Rochester, MN, as well as Mayo Clinic Square in downtown Minneapolis, MN. The DAHLC houses approximately 25,000 square feet of clinical sports medicine treatment space, which includes exam rooms, radiology suite with access to MRI, strength and mobility training equipment, an enclosed turf field, reception area, open office space for staff that is in close proximity to the clinical treatment space. In addition, there is another approximately 13,000 feet of clinical sports medicine space housed in the Charlton Building for a total of approximately 38,000 feet of clinical treatment space in Rochester, MN. Mayo Clinic Square is comprised of approximately 25,000 square feet of clinical sports medicine treatment space, which includes exam rooms, radiology suite with access to MRI, strength and mobility training equipment, isokinetic/isometric dynamometers, an enclosed turf field, reception area, open office space for staff that is in close proximity to the clinical treatment space. These state of the art facilities will be the site of patient care and rehabilitation following ACL reconstruction surgery.

The Biodynamics Laboratory is located within the SMC in Minneapolis, MN. It contains approximately 1,800 square feet dedicated to the latest state-of-the art, cutting edge technology motion capture and neuromuscular control assessment currently available.

Equipment.
1. 14 Camera Motion Analysis System (Raptor Cameras, Motion Analysis Corp., Santa Rosa, CA) with assorted height mounting rails and 14 mounting brackets for flexible camera placement (Figure FE1).
2. Cortex software (v3, Motion Analysis Corp., Santa Rosa, CA) including Skelton Builder, Calcium, BioFeedTrak, and Kintools RT.
3. Four (4) 60 x 90 centimeter, 6-component force plates (Bertec, Columbus, OH)
4. Motion analysis data acquisition computer workstation: Dell Precision T7500, 6-core Xeon X5690 3.47 GHz CPU, 12 GB ECC RAM, 3 Hitachi 15k SAS hard drives (250GB boot drive and 2x 500GB drives in a RAID 0 array), dual Nvidia Quadro 2000 video cards, and 3 30” Dell monitors, Windows 7. UPS battery backup on all motion capture equipment.

5. Three (3) Microsoft Lifecam Studio HD webcams (Higher quality cameras are needed for this study, please see the budget justification for the proposed make and model of purchase)
6. One (1) static digitizing probe for creating calibration marker locations on hard-to-reach anatomical landmarks.
7. Two (2) Visual 3D motion analysis software licenses (C-motion inc., Germantown, MD)
8. Two (2) Microsoft Kinect 3D cameras (Microsoft Corp., Redmond, WA)
9. Two (2) Wii Balance boards (Nintendo of America, Inc., Redmond, WA)
10. Two HumacNORM isokinetic and isometric dynamometers with accompanying software (Figure FE2, CSMi, Stoughton, MA).
11. Two Humac balance devices with accompanying software (CSMi, Stoughton, MA.
12. One GNRB arthrometer (Genourob, Laval, France)
13. Two (2) complete Simi Aktisys marker-based and marker-less motion analysis systems with associated cameras, hardware, and software (Simi Reality Motion Systems GmbH, Unterschleissheim, Germany).
14. Thirteen (13) Dartfish Motion Pro Premium licenses with fourteen (14) associated cameras and necessary hardware split between Mayo Clinic Rochester and Mayo Clinic Square facilities (Dartfish USA, Inc., Alpharetta, GA).

Computer/Office

Adequate dedicated office space and computing capabilities already exists within the laboratories and clinical facilities to meet the needs of all personnel included in this project. Each listed clinical and laboratory space also has designated multimedia conference room space with teleconferencing capabilities. All key personnel have office space in both Minneapolis and Rochester SMCs.

☐ (1a) This is a multisite study involving Mayo Clinic and non Mayo Clinic sites. *When checked, describe in detail the research procedures or activities that will be conducted by Mayo Clinic study staff.*

☐ (1b) Mayo Clinic study staff will be engaged in research activity at a non Mayo Clinic site. *When checked, provide a detailed description of the activity that will be conducted by Mayo Clinic study staff.*

Subject Information

Target accrual: This study will enroll 150 subjects. Anticipating a 30% dropout rate, this will yield a final accrual of 120 subjects.

Subject population (children, adults, groups): All subjects will be patients who undergo primary ACL reconstruction, and will be recruited from the practices of the sports medicine surgical team at Mayo Clinic, Rochester, MN, as well as the practices of the surgeon affiliates of the sports medicine team at Cincinnati Children's Hospital Medical Center, Cincinnati, OH. Recruitment will also include primary ACL reconstruction patients from the sports medicine surgical team at the University of Minnesota, Minneapolis, MN, and primary ACL reconstruction patients from the sports medicine surgical team at Mayo Clinic Health System, La Crosse, WI. This will include male and female patients between the ages of 13 and 30 years in age

at the time of injury. The University of Minnesota and Mayo Health System locations will serve only as referral sites as no research activity will occur there.

Inclusion Criteria:

1. Age, 13 ≥ 30 years, 2. Acute, first-time, isolated ACL injury, 3. No history of previous knee surgery to either extremity, 4. No low back or lower extremity injury in the year prior to ACL injury necessitating medical care, 5. Pre-injury participation in cutting, jumping or pivoting sports for ≥ 50 hours/year, 6. Plan to return to full participation in sports following ACL reconstruction.
7. Mechanism of injury did not involve a direct blow to the knee

Patients who sustain a medial collateral ligament (MCL) injury are eligible for study participation if medial knee instability is resolved prior to surgery.

This age range is selected secondary to the majority of ACL injuries occurring in young, active individuals who participate in jumping, cutting and pivoting sports on a regular basis.

Patients with simple meniscus tears (i.e., 2 cm vertical longitudinal tear) that do not necessitate alterations in rehabilitation will be eligible for study participation.

Exclusion Criteria:

Patients with complex, repairable meniscus tears (i.e., radial or root repair), multi-ligment repair, and patients with full thickness articular cartilage lesions will not be eligible for participation.

Research Activity

Check all that apply and complete the appropriate sections as instructed.

1. ☐ **Drug & Device**: Drugs for which an investigational new drug application is not required. Device for which (i) an investigational device exemption application is not required; or the medical device is cleared/approved for marketing and being used in accordance with its cleared/approved labeling. (Specify in the Methods section)

2. ☐ **Blood**: Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture.

3. ☐ **Biological specimens other than blood**: Prospective collection of human biological specimens by noninvasive means that may include: urine, sweat, saliva, buccal scraping, oral/anal/vaginal swab, sputum, hair and nail clippings, etc.

4. ☒ **Tests & Procedures:** Collection of data through noninvasive tests and procedures routinely employed in clinical practice that may include: MRI, surface EEG, echo, ultrasound, moderate exercise, muscular strength & flexibility testing, biometrics, cognition testing, eye exam, etc. (Specify in the Methods section)

5. ☒ **Data** (medical record, images, or specimens): Research involving use of existing and/or prospectively collected data.

6. ☒ **Digital Record**: Collection of electronic data from voice, video, digital, or image recording. (Specify in the Methods section)

7. ☐ **Survey, Interview, Focus Group:** Research on individual or group characteristics or behavior, survey, interview, oral history, focus group, program evaluation, etc. (Specify in the Methods section)

☐ NIH has issued a *Certificate of Confidentiality* (COC). *When checked, provide the institution and investigator named on the COC and explain why one was requested*. _____

Biospecimens – Categories 2 and 3

(2) Collection of blood samples. When multiple groups are involved copy and paste the appropriate section below for example repeat section b when drawing blood from children and adults with cancer.

a. **From healthy, non-pregnant, adult subjects who weigh at least 110 pounds**. For a minimal risk application, the amount of blood drawn from these subjects may not exceed 550ml in an 8 week period and collection may not occur more frequently than 2 times per week.
   Volume per blood draw: _____ml
   Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

b. **From other adults and children considering age, weight, and health of subject.** For a minimal risk application, the amount of blood drawn from these subjects may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than 2 times per week.
   Volume per blood draw: _____ml
   Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

(3) Prospective collection of biological specimens other than blood: _____

Review of medical records, images, specimens – Category 5

For review of existing data: provide a date range or an end date for when the data was generated. The end date can be the date this application was submitted to the IRB. Example: *01/01/1999 to 12/31/2015* or all records through *mm/dd/yyyy*.

Date Range:

Check all that apply (data includes medical records, images, specimens).

☐ (5a) Only data that exists before the IRB submission date will be collected.

☐ (5b) The study involves data that exist at the time of IRB submission **and** data that will be generated after IRB submission. Include this activity in the Methods section.
Examples

- The study plans to conduct a retrospective chart review and ask subjects to complete a questionnaire.
- The study plans to include subjects previously diagnosed with a specific disease and add newly diagnosed subjects in the future.

☐ (5c) The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol*.

Enter one IRB number per line, add more lines as needed

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ (5d) This study will obtain data generated from other sources. Examples may include receiving data from participating sites or an external collaborator, accessing an external database or registry, etc. Explain the source and how the data will be used in the Methods section.

☒ (6) Video audio recording: *Describe the plan to maintain subject privacy and data confidentiality, transcription, store or destroy, etc.*
Files will be stored on a secured server to which only authorized study personnel may access. Files will be names according to the subject's research study ID. Files will be used for research analysis only and not distributed.

HIPAA Identifiers and Protected Health Information (PHI)

Protected health information is medical data that can be linked to the subject directly or through a combination of indirect identifiers.

Recording identifiers (including a code) during the conduct of the study allows you to return to the medical record or data source to delete duplicate subjects, check a missing or questionable entry, add new data points, etc. De-identified data is medical information that has been stripped of all HIPAA identifiers so that it cannot be linked back to the subject. De-identified data is **rarely** used in the conduct of a research study involving a chart review.

Review the list of subject identifiers below and, if applicable, check the box next to each HIPAA identifier being recorded at the time of data collection or abstraction. Identifiers apply to any subject enrolled in the study including Mayo Clinic staff, patients and their relatives and household members.

Internal refers to the subject's identifier that will be recorded at Mayo Clinic by the study staff.
External refers to the subject's identifier that will be shared outside of Mayo Clinic.

Check all that apply:	INTERNAL	EXTERNAL
Name		
Mayo Clinic medical record or patient registration number, lab accession, specimen or radiologic image number	X	
Subject ID, subject code or any other person-specific unique identifying number, characteristic or code that can link the subject to their medical data	X	
Dates: All elements of dates [month, day, and year] directly related to an individual, their birth date, date of death, date of diagnosis, etc. **Note:** Recording a year only is not a unique identifier.	X	
Social Security number		
Medical device identifiers and serial numbers		
Biometric identifiers, including finger and voice prints, full face photographic images and any comparable images	X	
Web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, email address	X	
Street address, city, county, precinct, zip code, and their equivalent geocodes	X	
Phone or fax numbers	X	
Account, member, certificate or professional license numbers, health beneficiary numbers		
Vehicle identifiers and serial numbers, including license plate numbers		
Check 'None' when none of the identifiers listed above will be recorded, maintained, or shared during the conduct of this study. (exempt category 4)	☐ None	☒ None

Data Analysis

Power analyses and study endpoints are not required for minimal risk research, pilot or feasibility studies.

☐ No statistical information. *If checked, please explain*:

Power Statement:

We expect that the minimal clinically significant effect size of TNMT on knee biomechanics is 0.17 or above. Using an a priori power analysis based on repeated measures ANOVA, we expect that to achieve 80% power with $\alpha = 0.05$, this study will require a final accrual of 87 subjects. This assumes a correlation coefficient of 0.3 among the repeated measures, which is likely conservative. Thus, an accrual of 116 (with an estimated 30% dropout rate) subjects will be sufficient to determine if a clinically significant reduction in uninvolved limb transverse plane hip net moment impulse, frontal plane knee joint ROM, initial contact sagittal plane knee moment asymmetry, and deficits of involved limb postural stability has occurred as a result of TNMT. This sample size provides adequate power for all variables of interest for Aims 1 and 2. Mayo Clinic averages more than 120 ACLR per year in the Minneapolis/Rochester region on individuals under age 25. Thus, the available patient pool is more than adequate to meet study requirements.

Data Analysis Plan:
Aim 1: We will utilize normal mixture based clustering analysis70 to identify groups with distinguished risks based on a priori covariates (i.e., demographics and biomechanical variables). Our previous work used a similar approach to effectively cluster subjects into three distinct risk groups. We intend to confirm disparate risk for injury by assessment of the magnitude of differences across groups using knee and hip abduction angles, surrogates for ACL injury.

The normal mixture model approach works by assuming the density of the covariates for a subject $\boldsymbol{x}$, can be described as:

$$f(\boldsymbol{x}) = \sum_{k=1}^{K} \pi_k \phi(\boldsymbol{x}; \boldsymbol{\mu_k}, \boldsymbol{\Sigma_k}),$$

where (i) K is the number of mixture components (groups), (ii) π_k is the unconditional probability that a subject fall into the kth group, and (iii) $\phi(\cdot; \boldsymbol{\mu}, \boldsymbol{\Sigma})$ is the multivariate normal density with mean $\boldsymbol{\mu}$ and covariance $\boldsymbol{\Sigma}$. Estimates of the parameters, $\pi_k, \boldsymbol{\mu_k}, \boldsymbol{\Sigma_k}$, are typically obtained using maximum likelihood. The number of groups is most commonly chosen to optimize the Bayesian Information Criterion (BIC). Often assumptions such as a common covariance matrix for all k, or common shape (i.e., correlation) matrix, are made to make estimation feasible, depending on the size of data, and these decisions are also commonly made on the basis of BIC. In this work we intend to assume a common $\boldsymbol{\Sigma}$, and assess the validity of this assumption via model diagnostics. Once parameter estimates are obtained, clustering is performed by calculating the probability of group membership m for a given subject, conditional on his/her covariate values, i.e.,

$$P(m = k \mid \boldsymbol{x}) = \frac{\pi_k \phi(\boldsymbol{x}; \boldsymbol{\mu_k}, \boldsymbol{\Sigma_k})}{\sum_{l=1}^{K} \pi_l \phi(\boldsymbol{x}; \boldsymbol{\mu_k}, \boldsymbol{\Sigma_k})}.$$

The subject will then be assigned to the group k that results in the largest conditional group membership probability $P(m = k \mid \boldsymbol{x})$. This approach has been shown to perform very well in the presence of a large number of variables with the inclusion of a variable selection mechanism.[71, 72] We will leverage such an approach in our analysis to identify a reduced set of biomechanical variables that most informatively differentiate the subjects.

Aim 2:

Aim 2 will utilize a prospective, single blind, randomized clinical trial design. Subjects from Aim 1 will comprise the study sample. Subjects will undergo testing twice.

We will use a repeated-measures ANOVA model with between-subjects factors that include interactions, to determine the effect of TNMT compared to HOME or STAN treatment on clinical performance after ACLR. Specifically, for a response of interest *y*, e.g., hip abductor strength, for the i^{th} subject in the k^{th} treatment group, with $l = 0$ indicating before intervention and $l = 1$ indicating after,

$$y_{ikl} = \alpha + \delta_l + (\gamma\delta)_{kl} + \tau_{i(k)} + \epsilon_{ikl},$$

with (i) intercept α, (ii) subject random effect $\tau_{i(jk)} \sim N(0, \sigma_\alpha^2)$, (iii) pure error (or noise) $\epsilon_{ijkl} \sim N(0, \sigma_\epsilon^2)$, (iv) δ_l is the main effect due to intervention, and (vi) $(\gamma\delta)_{kl}$ is the interaction effect allowing intervention efficacy to vary with intervention type. The fixed effects are constrained such that $\delta_0 = (\gamma\delta)_{k0} = 0$. In this model, the baseline (i.e., pre-treatment) response for an individual is:

$$y_{ikl} = \alpha + \tau_{i(k)} + \epsilon_{ikl}.$$

Thus, the pre- intervention response for a given subject is the same regardless of which intervention group k they were assigned to, since nothing would have happened yet within their intervention group to distinguish them from other groups. Under the formulation in (1), the difference between observations before and after intervention is:

$$d_{ijk} = y_{ijk1} - y_{ijk0} = \delta^* + \gamma_k^* + \epsilon_{ijk}^*,$$

where $\delta^* = \delta_1$, $\gamma_k^* = (\gamma\delta)_{k1}$, and $\epsilon_{ijk}^* = (\epsilon_{ijk1} - \epsilon_{ijk0}) \sim N(0, 2\sigma_\epsilon^2)$. The primary inference of interest is with respect to the relative efficacy of rehabilitation type γ_k^* and the effect of risk group on intervention efficacy, along with their interaction $(\beta\gamma)_{jk}^*$. Thus, this inference could equivalently be conducted using the pairwise differences in a straightforward one-way ANOVA model. We will assess model assumptions (e.g., normality and constant variance) via residual diagnostics and apply transformations if needed. Where appropriate, we will also utilize Tukey HSD post hoc analysis to further determine significance between groups on intervention effect.

Endpoints

There will be no known direct medical benefits to subjects from participating in this study.

Primary: Completion of all study activities
Secondary: Second injury