

# Anterior Cruciate Ligament Research Retreat VIII Summary Statement: An Update on Injury Risk Identification and Prevention Across the Anterior Cruciate Ligament Injury Continuum, March 14–16, 2019, Greensboro, NC

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The Anterior Cruciate Ligament (ACL) Research Retreat VIII was held March 14–16, 2019, in Greensboro, North Carolina. The retreat brought together clinicians and researchers to present and discuss research advances in ACL injury risk, outcomes, and prevention. Prior retreats (2001–2012)<sup>1–6</sup> largely focused on advances in primary injury risk-factor identification and prevention (ie, preventing the initial trauma). Despite our improved understanding of ACL injury risk and the success of primary prevention efforts, ACL injuries continue to occur and lead to short-term and long-term consequences that have substantial effects on joint health and quality of life for years to come. To address these additional challenges, the ACL Research Retreat expanded in scope to include secondary ACL injury risk and prevention in 2015<sup>7</sup> and the short-term and long-term sequelae of early-onset osteoarthritis that results from the initial trauma (herein, *posttraumatic osteoarthritis* or *PTOA*) in 2019. The ACL Research Retreat VIII therefore considered ACL injury risk and prevention along a continuum that includes primary, secondary, and tertiary risk identification and prevention strategies as described by Palmieri-Smith et al (Table 1).<sup>8</sup>

To illustrate this continuum, consider a soccer team comprising 13-year-old girls. We know the ACL injury risk increases dramatically from ages 13 to 16,<sup>9–11</sup> such that girls have a 2 to 4 times greater risk than similarly trained males.<sup>12,13</sup> Thus, our first goal for this age group, especially

among maturing girls, is to prevent the initial trauma from occurring (ie, primary prevention). We pursue injury risk reduction by leveraging 2½ decades of research to screen for known risk factors and deliver evidence-based neuromuscular-training programs to reduce the ACL injury risk. Despite these interventions, 1 or more of these active, young girls may still go on to sustain an ACL injury, which has both short-term and long-term secondary consequences. In the short term (first year after injury), we know that 50% of injured athletes do not return to their prior levels of sport.<sup>14</sup> Of the young athletic patients who do return to high-risk sport, nearly 1 in 4 will sustain another ACL injury, often within the first few months of their return.<sup>15–19</sup> Therefore, once an injury has occurred, our goals are to deliver therapeutic interventions to optimally restore joint function and reduce that individual's potential for experiencing a second ACL injury while at the same time preventing further joint damage (ie, secondary prevention). This includes intervening in both the primary risk factors that contributed to the initial injury (assuming they are still present) and the neuromechanical deficits that resulted from the injury. This also includes establishing evidence-based biopsychosocial benchmarks to safely return the athlete to sport. Still, more than 30% of these athletes have been reported<sup>20</sup> to develop early evidence of PTOA within 10 years of the initial injury, which has the potential to significantly alter joint function and quality of life. Long-term prevention strategies are

**Table 1. Prevention Levels and Definitions<sup>a</sup>**

Levels of Prevention	Definition
Primary prevention	Interventions are designed to prevent an injury or disease condition from occurring in the first place. The focus is generally on policies, practices, and behaviors that mitigate risk.
Secondary prevention	Initiatives attempt to recognize or identify an injury or a disease at its earliest stage so that prompt and appropriate management can be implemented to mitigate the secondary effects of the injury or disease and restore function. Successful secondary prevention reduces the effect of the disease in the short term and perhaps also in the long term. The focus is generally on emergency management and initial medical care.
Tertiary prevention	Initiatives focus on reducing or minimizing the long-term consequences of an injury or a disease once it has occurred. The goal is to eliminate or delay the onset of complications, morbidity, and long-term disability due to the injury or disease. Most medical interventions fall into this category. The focus is generally on chronic management and health-behavior change.

<sup>a</sup> Reprinted with permission.<sup>8</sup>

therefore geared at identifying the factors that hasten the development and progression of PTOA and developing appropriate therapeutic interventions to delay or mitigate these complications (ie, tertiary prevention).

The ACL Research Retreat VIII featured 3 keynote presentations and 32 peer-reviewed abstract presentations highlighting advances in risk identification and prevention strategies across the ACL injury continuum. Keynote speakers presented cutting-edge research on ACL injury biomechanics and the motions that elevate in vivo ACL strains during dynamic activities that place individuals at high risk for ACL injury (Louis DeFrate, ScD, Duke University, Durham, NC), innovative augmented neuromuscular-training approaches to more effectively reduce the biomechanical risk factors for ACL injury (Gregory Myer, PhD, Cincinnati Children's Hospital Medical Center, OH), and the identification of early markers of PTOA and directions for therapeutic interventions to prevent joint degeneration and promote joint rejuvenation earlier in the clinical course after ACL injury (Constance Chu, MD, Stanford University School of Medicine, Redwood City, CA). Free communication sessions were organized around the themes of primary risk identification (ACL morphology and brain contributions) and intervention strategies, secondary risk identification and prevention (neuromechanical deficiencies and return-to-play considerations after ACL reconstruction [ACLR]), and tertiary risk identification and prevention (chronic sequelae of PTOA progression). Substantial time was provided for group discussion to summarize the recent advances and emerging trends from each thematic session and identify strategic initiatives for future research. We then considered risk factors that were common targets across primary, secondary, and tertiary prevention efforts and the potential for developing a collaborative, multicenter ACL injury research network that could span the time course of ACL injury from primary injury prevention to the secondary and tertiary prevention of PTOA after injury. The summary of these discussions follows. We also present the summaries<sup>21,22</sup> of 2 keynotes and the research abstracts<sup>23</sup> on which these discussions were based. (Note: As Dr DeFrate's keynote focused primarily on recently completed yet unpublished data, a written summary is not included. Please watch for forthcoming publications from his work.)

## PRIMARY RISK ASSESSMENT

It is widely accepted that multifactorial mechanisms contribute to the risk of primary ACL injury. Much of the

discussion during the meeting centered on the concept that at-risk biomechanics known to strain the ACL could be considered an intersection of overlapping contributions from anatomic/structural, biological, neurologic, and psychosocial factors. These at-risk biomechanics have been correlated with joint actions ascertained from modeled and direct ACL-loading biomechanics,<sup>24–32</sup> video observation of actual injury events,<sup>33–36</sup> and prospective ACL injury risk-factor studies.<sup>37,38</sup> The mechanistic studies presented by Dr DeFrate indicated that a relatively extended knee at foot contact may be a high-risk position due to the relatively larger ACL strain values in this position.<sup>39–41</sup>

Research on primary risk assessment presented at the ACL Research Retreat VIII focused on structural and neurologic risk factors. This summary is therefore limited to those areas. The reader is referred to the 2015 ACL Research Retreat VII consensus statement<sup>7</sup> for an in-depth discussion of risk assessment, as much of the important knowns and directions for future research remain relevant today.

## Structural Factors

Greater anterior knee laxity<sup>42–51</sup> and greater body mass index (BMI)<sup>11,49,51–53</sup> are well-documented risk factors that are substantially more predictive of ACL injury risk when both are accounted for relative to a univariate modeling of risk.<sup>49,51</sup> Females develop greater anterior knee laxity<sup>54–56</sup> and BMI (representing more fat mass relative to total body mass)<sup>57–60</sup> as they mature, and these maturational changes coincide with their disproportional rise in ACL injury risk compared with males.<sup>9,11,61</sup> At the last retreat,<sup>7</sup> it was suggested that greater magnitudes of knee laxity may have both biological and biomechanical consequences. Research presented there indicated that clinical measures of anterior knee laxity may provide insights into the structural size and quality of the ACL (Wang et al abstract #1, Shultz et al abstract #2).<sup>23</sup> Greater absolute anterior knee laxity was related to the in vivo combination of *smaller* ligament size and intrinsic structural characteristics (larger T2\* relaxation times) of the ligament (Wang et al abstract #1). When examining the magnitude of change in knee laxity across the menstrual cycle and during exercise (which were strongly correlated), investigators found that smaller and less organized ACLs (larger T2\* relaxation times) were associated with a *smaller* magnitude of change in laxity and a smaller magnitude of change tended to be associated with a greater baseline value (Shultz et al abstract #2).

Quantitative magnetic resonance imaging (MRI) relaxation mapping has been primarily validated for articular cartilage tissue.<sup>62-64</sup> In addition to the research presented at ACL Research Retreat VIII, including the use of novel MRI ultrashort echo time T2\* to evaluate healing ACL grafts,<sup>21,65</sup> T2\* relaxation has been used to study animal ACL grafts<sup>66,67</sup> and has been negatively associated with the yield load of healing ACL grafts.<sup>66</sup> Additionally, these imaging sequences have been used to evaluate the structural characteristics of the Achilles<sup>68</sup> and patellar<sup>69</sup> tendons. The ability to noninvasively assess ligamentous structural characteristics via a clinical measure such as knee laxity may help us to better understand and identify the risk of injury in clinical settings.

Further insights into BMI as a primary risk factor were not discussed. However, BMI was addressed relative to secondary prevention and the development of PTOA (see later sections).

## Neurologic Factors

Central neurologic factors represent a rapidly emerging area of ACL injury risk assessment. Adding to published work,<sup>70-77</sup> data presented at the retreat further suggest neurophysiological contributions to ACL injury (Diekfuss et al abstract #5, Bonnette et al abstract #6) and recovery (Lepley et al abstract #14); however, our understanding of both areas remains limited. As discussed at ACL Research Retreat VII by Buz Swanik, PhD, ATC,<sup>77</sup> a noncontact ACL injury event can be conceptualized as a sequence of neural-activity errors that results in an inability to maintain joint stability. Neuroimaging studies presented at ACL Research Retreat VIII further indicate a potentially direct association between alterations in neural activity or connectivity and high-risk biomechanics and ACL injury risk (or a combination of these). Specifically, individuals classified as *high risk* ( $\geq 21.74$ -Nm knee-abduction moment [KAM]) versus *low risk* ( $\leq 10.6$ -Nm KAM) during 3-dimensional motion analysis of a double-legged landing displayed increased sensorimotor neural activity during neuroimaging of a simulated landing (similar hip and knee ranges of motion as in the laboratory-based landing but supine in the MRI scanner; Criss et al abstract #3). Additionally, high-risk individuals exhibited decreased neural activity in the cingulate gyrus (attention) and parietal cortex (sensory processing) during a single-legged knee-repositioning task and increased brain activity of the frontal cortex (cognition) during a single-legged knee force-attenuation task (Grooms et al abstract #4). These alterations in activity suggest a manifestation of maladapted spatial awareness and attention to knee motor control that may contribute to a decreased ability to control frontal-plane loading during landing. Decreased activity in the sensory and attentional regions and increased activity in the cognitive and motor regions to control knee-joint position and force during a simulated landing task in those at high risk for injury may indicate a rapid saturation of motor-coordination capacity. Specifically, dynamic maneuvers with high environmental-navigation or spatial-processing demands may lead to a deterioration in neuromuscular coordination that results in high KAMs.

Prospective neuroimaging risk factors were also presented at the retreat. Among female athletes compared with control participants, individuals who went on to experience an ACL injury exhibited less electroencephalography (EEG) power in the  $\theta$  and  $\alpha$ -2 frequency bands, findings that are thought to be

associated with decreased attentional and sensorimotor electrocortical functioning (Bonnette et al abstract #6). As the ACL injury typically occurs from rapid and high loading forces, any deficit or delay in sensory or attentional processing may contribute to an inability to correct potential sensorimotor-coordination errors, resulting in knee positions that increase the ACL injury risk.<sup>78</sup> Also, in male athletes, using baseline resting-state functional MRI (fMRI), individuals who went on to sustain an ACL injury displayed decreased connectivity between multiple sensorimotor regions compared with uninjured control participants (Diekfuss et al abstract #5). Together, these findings indicate that the underlying neural processes related to sensorimotor control may play a role in ACL injury risk and that the neural contributions to injury risk may be sex dependent.

Collectively, this emerging area of research implicates a cognitive-motor as opposed to a sensory-motor neural-activation strategy in those with an elevated injury risk. More research is needed to determine if these processes contribute to an inability to manage unanticipated events or visual-spatial challenges and subsequently generate sufficient muscle stiffening to avoid injury.

## Directions for Future Research

### Structural Factors.

- Because many of the structural risk factors associated with ACL injury develop or change during physical maturation, we need to better understand the maturational processes that contribute to ACL injury risk.
- Research using quantitative in vivo imaging, such as T2, T2\*, and ultrashort echo time-T2\*\* relaxation mapping, is warranted to further elucidate the potential compositional differences that contribute to greater joint and ligament laxity.
- Muscle size and quality may be an emerging area of structural risk assessment.

### Biomechanical Factors.

- Continue to investigate multifactorial models that determine how relevant combinations of risk factors contribute to movement biomechanics that may acutely (1 time) or chronically (repetitively<sup>79</sup>) overload the ACL and result in ligamentous failure.
- Many of the tools currently used for screening of biomechanical risk factors have involved bilateral tasks (eg, drop vertical jump, squatting, double-legged landing). A building consensus among attendees suggested that single-legged activities may offer additional insight into ACL injury risk.
- The risk of injury among athletes who specialize in 1 sport should be further examined. An analysis of more than 700 athletes (DiCesare et al abstract #20) identified larger longitudinal increases in KAM during a drop vertical jump in sport-specialized athletes compared with multisport athletes.

### Biological Factors.

- A better understanding of hormonal and genetic contributions to ACL injury risk continues to be an important direction in research.
- Future studies of hormone-associated injury risk need to comprehensively and directly assess hormone profiles to

determine cycle phase rather than rely on indirect calendar-based estimation methods.

- Research on twins and families or cohorts with or without a higher prevalence of injury may help us to differentiate genotypic traits that may be associated with ACL injury risk.
- The reader is referred to the 2015 ACL Retreat consensus statement<sup>7</sup> for a more thorough discussion of future directions in this area.
- Females are reported to have lower muscle quality than males (ie, more intermuscular fat per unit area).<sup>57,80</sup> Although lower muscle quality has been associated with less bone strength and density in 8- to 13-year-old girls,<sup>80,81</sup> associations between muscle quality and ligament quality have not been studied.

### Neurologic Factors.

- We need to understand the neural activity associated with more complex lower extremity sensorimotor-control tasks. Establishing the neural correlates of ACL injury risk will allow for the scientific examination of novel therapies overlaid on traditional therapeutic goals that can uniquely target hypothesized neural-activation strategies that contribute to injury risk.
- The quantification of neurophysiology related to ACL injury and therapy is becoming more accessible using new technological developments. Recent advances in dynamic EEG provide real-time complete cortical neural activation with low signal artifact for complex motor behaviors, such as gait and landing.<sup>82–84</sup> Further breakthroughs with functional magnetoencephalography may provide the spatial accuracy of fMRI along with the temporal dynamics of EEG without the head-motion restrictions of either.<sup>85</sup> These emerging technologies provide avenues for mobile in vivo brain imaging to increase the ecologic validity of neurophysiological evaluations of knee sensorimotor control and injury risk. As technological advances become more cost efficient, the potential to deliver direct neural-activity feedback may soon become available to clinicians.<sup>86–88</sup> Such approaches may enhance sensorimotor adaptations by allowing targeted sensory reweighting, motor learning, and progressive integration of cognitive, anticipatory, and visual challenges.

### Psychosocial Factors.

- Research on psychosocial measures surrounding primary ACL injury risk is limited. We must better understand the individual's perceptions of his or her confidence in safely participating in physical activity. Specifically, measures of kinesiophobia should be investigated to understand their utility in helping to identify those at risk of ACL injury.
- Incorporating these measures largely involves the concept of connecting brain-based measures to more clinically accessible tools. Additional patient-centered approaches may help us to better understand the risk of primary ACL injury.

## PRIMARY PREVENTION

Several high-quality meta-analyses<sup>89–94</sup> indicated that the ACL injury incidence was reduced with neuromuscular-training programs. In female athletes, these programs

resulted in a decrease of half of all ACL injuries and two-thirds of noncontact ACL injuries.<sup>90</sup> Successful programs incorporated progressive landing-stabilization exercises that focus on proper knee alignment and soft landings in addition to exercises targeting the hip and hamstrings musculature. Neuromuscular-training programs implemented before the sport season and continued through the season appeared to be more effective in reducing the risk of ACL injury. Additionally, these programs should be implemented early in middle school– and high school–aged athletes.<sup>89</sup>

The structured discussion at the ACL Research Retreat VIII highlighted the current state of knowledge about the success of neuromuscular-training programs and the use of promising new technologies (eg, virtual and augmented reality, real-time biofeedback, and wearable sensors).<sup>95,96</sup> The consensus was that externally focused biofeedback techniques, which engage implicit motor-learning mechanisms, are advantageous for sensorimotor adaptation.<sup>97–101</sup> MacPherson et al (abstract #19) presented preliminary data on the effects of delivering augmented biofeedback to female athletes. This intervention not only demonstrated increased sensorimotor-related brain activation for knee motor control (using fMRI) but the observed neural adaptations were also strongly correlated with safer landing biomechanics assessed using 3-dimensional motion analyses. Additionally, preliminary data on augmented biofeedback indicated that it may induce adaptive neuroplasticity, thereby increasing the retention and transfer of those movement patterns to sport.<sup>102</sup> These early data highlight the utility of real-time biofeedback systems for sensorimotor adaptation that could eventually be personalized to target individual movement deficiencies. The previous consensus statement<sup>7</sup> highlighted the need for future work in this area, and several National Institutes of Health–funded randomized controlled trials<sup>95,96</sup> currently being performed will likely inform future programs.

## Directions for Future Research

- Continue clinical trials to inform future evidence-based programming.
- Future primary-prevention research must seek to reduce barriers to program implementation. Barriers include, but are not limited to, a lack of (1) appropriately trained individuals to implement a program, (2) support or buy-in from involved groups and key stakeholders (ie, players, parents, coaches, teams, organizations), and (3) time.
- Peer-reviewed studies are needed on the effects of interventions aimed at reducing the risk of ACL injury in male athletes.<sup>103</sup>
- Neuromuscular-training programs may benefit from the addition of more game-like environments, as increased cognitive load may help transfer proper biomechanical movement patterns to the field<sup>104–106</sup> (See Myer et al keynote<sup>22</sup> and MacPherson et al abstract #19). Virtual- and mixed- or augmented-reality technologies are likely to advance this area.

## SECONDARY AND TERTIARY RISK AND PREVENTION

The majority of individuals who sustain an ACL injury and undergo ACLR and traditional rehabilitation return to

some level of physical activity.<sup>107</sup> However, as previously noted, 50% of those who tear their ACLs do not return to their prior competitive level of sport.<sup>14</sup> Of the young athletes (<25 years old) who do return to sport, 1 in 4 are likely to experience a second ACL injury,<sup>19</sup> and many of these injuries occur within 24 months of returning to sport.<sup>108–110</sup> The risk of secondary injury is of particular concern for adolescent girls, who are 2 to 4 times more likely than adolescent boys or older age groups to sustain a second ACL injury<sup>15–18</sup> and subsequently experience poorer health outcomes.<sup>111,112</sup> Thus, secondary prevention efforts are critically needed.

Even more debilitating than the ACL injury itself are the initiation and accelerated rate of progression of PTOA that are frequently observed after injury,<sup>20,113</sup> which further compound patient-reported disability and reduced performance in activities of daily living.<sup>114</sup> Among young and physically active populations, roughly 50% of ACL injuries progress to radiographic PTOA within 12 years; similar findings have been reported for meniscal tears.<sup>115,116</sup> Effective surgical interventions are available to repair these injuries and restore short-term function and mobility to preinjury performance levels, but surgical repair does not prevent the early development and rapid progression of PTOA in the knee joint.<sup>117</sup> Furthermore, significant deficits in patient-reported outcomes,<sup>118</sup> neuromuscular function,<sup>119</sup> biomechanical movement patterns,<sup>120</sup> and psychosocial factors<sup>121,122</sup> have been noted even after patients have undergone ACLR and completed a full course of therapy.

A new focus at ACL Research Retreat VIII was on how ACL injury affects short-term and long-term joint health, with the goal of mitigating the risk of secondary injury and PTOA. Traditionally, the management of ACL injuries has ended when athletes are deemed fit to return to participation. Treatment has focused on restoring anatomic structures and initial functional capabilities through surgical repair and rehabilitation; patients with uncomplicated courses are typically discharged from follow-up care 6 to 9 months after surgery. However, it is clear from previous evidence that these traditional approaches to ACLR surgery, rehabilitation, and return to play do not adequately reduce the risk of subsequent injury<sup>109,123</sup> or the development of PTOA.<sup>20</sup> Therefore, ACL injuries are the starting point for impaired joint function and a cascade of progressive degenerative joint changes in the knee that lead to altered function and chronic pain and result in physical limitations affecting both performance and activities of daily living.<sup>8,124</sup> The interplay among biomechanical, structural, neuromuscular, and biological changes after ACL injury and surgical reconstruction likely contributes to the development of PTOA.<sup>125</sup> Understanding the mechanisms responsible for the development of persistent symptoms, impaired joint function, and biochemical changes within the joint is paramount to identifying novel therapeutic targets to improve short-term and long-term patient outcomes after ACLR.

### **Impaired Neuromuscular and Biomechanical Function Postinjury**

The ACL Research Retreat VIII featured abstract presentations that highlighted a multifaceted range of factors that alter neuromuscular function, joint-loading

patterns, and movement biomechanics after ACLR, including ACL grafting techniques.

**Grafting Techniques.** The quadriceps tendon is an increasingly popular autograft type that showed similar interlimb symmetry in loading during jump landing as the bone-patellar tendon-bone autograft (Hunnicuttt et al abstract #8). It also displayed similar interlimb symmetry as the bone-patellar tendon-bone autograft in quadriceps strength, size, and activation, as well as hop distance and patient-reported outcomes.<sup>126</sup> However, biomechanical modeling work (Domire et al abstract #7) suggested that alterations in the semitendinosus attachment site after the tendon was used for an ACL graft may result in alterations to the moment arm of the semitendinosus. This raises the question of whether some of the differences observed in movement mechanics after ACLR result from the change in moment arm of the lower extremity muscles as a result of the surgical reconstruction.

**Muscle Dysfunction.** The inability to contract the quadriceps is hypothesized to be a primary mechanism linking ACL injury and ACLR to aberrant movement biomechanics after injury and surgery,<sup>119</sup> which may increase the risk of a second ACL injury or the development of PTOA. Quadriceps weakness in individuals who have undergone ACLR is associated with worse patient-reported function<sup>127,128</sup> as well as deleterious changes in joint structure and<sup>129</sup> cartilage composition.<sup>130</sup>

Extensive discussion at the retreat addressed the neural and morphologic mechanisms associated with muscular changes after ACL injury and ACLR. A neural-morphologic link between changes in spinal reflexive and cortical excitability and changes in muscle structure together influenced persistent muscle weakness after ACLR (Lepley et al abstract #14). In addition to reduced muscle volume, novel diffusion tensor MRI methods demonstrated an increased muscle-fiber angle in the vastus medialis after ACLR compared with the uninjured limb (Lepley et al abstract #13). Other, more clinically applicable imaging modalities, such as ultrasonography, were also used to assess altered muscle quality after ACLR (Johnston et al abstract #17). We still poorly understand the factors associated with optimal treatments to reverse the multifaceted neuromuscular sequelae of ACL injury and ACLR. Also, whether strengthening the quadriceps results in beneficial changes to movement biomechanics remains uncertain. Although quadriceps weakness may result in immediate changes in gait,<sup>131</sup> improving quadriceps strength does not necessarily alter gait biomechanics in patients after ACLR<sup>132</sup> or with knee osteoarthritis (OA).<sup>133,134</sup> This was further supported by Kryszak et al (abstract #18), who found that a plyometric intervention improved quadriceps strength limb symmetry without subsequent changes in hop movement among individuals after ACLR. In addition, these results showed that integrative motor-learning and muscle-strengthening approaches are warranted to restore holistic sensorimotor capabilities after injury.

**Aberrant Joint Loading.** Aberrant lower extremity joint loading is commonly observed after ACLR.<sup>135</sup> Evidence suggested that either excessive<sup>136</sup> or insufficient loading<sup>137,138</sup> of joint tissues may lead to joint injury or hasten the progression of PTOA. Greater loading of the ACLR limb has been demonstrated during gait compared with the

contralateral limb<sup>139</sup> and the limbs of uninjured control participants.<sup>140</sup> Conversely, others have observed less loading of the ACLR limb during gait, and this reduced loading was associated with greater biochemical markers of inflammation<sup>141</sup> and cartilage breakdown,<sup>142</sup> altered cartilage composition,<sup>143</sup> worse patient-reported outcomes,<sup>144</sup> thinner tibiofemoral cartilage,<sup>145</sup> and radiographic knee OA 5 years after ACLR.<sup>146</sup> The mechanisms leading to abnormal amounts of more or less loading during gait after ACLR are not clear, but data presented at the retreat helped to shed light on potential mechanisms and stimulate directions for future research.

Preliminary data provided at the retreat demonstrated an association between greater femoral articular cartilage T1ρ MRI relaxation times (ie, interpreted as worse proteoglycan density) and greater peak vertical ground reaction force as well as smaller quadriceps-related knee moments in individuals with ACLR during a jump landing (Pfeiffer et al abstract #30). These data support the hypothesis that excessive tibiofemoral loading may be minimized after ACLR in individuals who maximize quadriceps-related moments during dynamic movements. Other investigators found that poorer proprioception was associated with less loading during gait, suggesting that offloading of the ACLR limb may be correlated with altered somatosensory function in the lower extremity (Blackburn et al abstract #29). These seemingly conflicting findings may point to complex associations among muscle function, joint loading, and deleterious joint tissue changes after ACLR. Not understanding this interplay was considered a major gap in our knowledge of the mechanisms causing PTOA after ACLR. Unfortunately, this critical knowledge gap impairs the development of optimal evidence-based load-management guidelines for maximizing long-term joint health after ACLR.

**Alterations in Gait Biomechanics.** Aberrant walking-gait biomechanics are common in individuals with ACLR<sup>135,147,148</sup> and are likely to be highly influential in PTOA development.<sup>149</sup> A stiffened-knee strategy, characterized by a more extended knee and a smaller quadriceps-related moment through stance, is common after ACLR and may result in impaired energy attenuation in tissues about the knee.<sup>150,151</sup> Preliminary evidence from the retreat showed that individuals with weaker quadriceps (ie, <3.0 Nm/kg of body mass) displayed more extended knees throughout stance and smaller moments and greater vertical ground reaction force in the first 20% of stance than individuals who met strength cutoffs (ie, >3.0 Nm/kg of body mass; Pietrosimone et al abstract #11). Minimizing strength loss after ACL injury and ACLR was associated with gait strategies that may mitigate the risk of PTOA development.

Additionally, individuals with a greater BMI demonstrated differences in gait biomechanics compared with those who had a normal BMI.<sup>152</sup> Greater BMI (associated with greater fat mass relative to total body mass) and obesity have been strongly implicated in the risk of primary ACL injury<sup>11,49,51,52</sup> and the development of OA.<sup>153</sup> Individuals with ACLR who were overweight or obese had greater peak knee-adduction moments and vertical ground reaction force (normalized to total body mass) than uninjured individuals who were overweight or obese (Pamukoff et al abstract

#10). The influence of obesity on gait biomechanics may be further affected by sex (Davis-Wilson abstract #9).

### Return-to-Play Considerations After ACLR

Functional assessments were discussed as critical components for improving return-to-play decision making after ACLR. New data indicated that individuals who achieved 90% interlimb symmetry during a triple-hop-for-distance test exhibited asymmetric lower extremity joint work and power outcomes, suggesting that movement strategies to achieve symmetric hop distances may differ between limbs (White et al abstract #26). Further data are needed to determine if asymmetric movement strategies in the presence of symmetric hop distances influence the risk of reinjury on return to sport.

Current return-to-participation or return-to-sport criteria have focused on minimizing the risk of subsequent ACL injury,<sup>154</sup> yet previously published criteria did not specifically address the risk of PTOA development. We need to collect patient-reported outcomes after ACLR to identify individuals who may need additional psychological support. Specifically, individuals with ACLR who reported greater fear of reinjury also described greater physical and psychological barriers to returning to sport (Burland et al abstract #24). Additionally, a novel case study integrated the measurement of movement quality and monitoring of external load in an adolescent female soccer player (Taylor et al abstract #25). The authors highlighted the clinical feasibility of measuring both the quality and quantity of movement to make more informed clinical decisions regarding whether athletes are ready to meet the demands of sport. Fluid biochemical analyses (Trump et al abstract #32) and MRI markers of cartilage morphology and composition<sup>155</sup> may allow the early detection of deleterious changes to joint tissues. However, these techniques are expensive, technically demanding, generally investigational, and inaccessible to many clinicians. Measures such as habitual walking speed,<sup>156,157</sup> quadriceps strength (normalized to total body mass),<sup>128</sup> and patient-reported outcomes<sup>158</sup> show promise as clinically relevant measures associated with early changes in joint tissue health after ACLR.

### Development and Progression of PTOA

Mounting evidence suggests that the progression to PTOA is influenced by the interplay between aberrant joint biomechanics and altered joint tissue metabolism after injury.<sup>126,159–162</sup> Work reflecting more than a decade of longitudinal study<sup>21,163</sup> of ACL-injured patients at the University of Pittsburgh and Stanford University presented by keynote speaker Constance Chu, MD, showed that approximately half of patients had quantitative MRI ultrashort echo time-T2\*, mechanical, or biological markers indicating a higher OA risk just 2 years after ACLR. Several researchers sought to characterize the effects of early structural, biomechanical, and biological changes after ACL injury and their association with important outcomes related to joint health status over time (Blackburn abstract #29, Pfeiffer abstract #30, Wallace abstract #31, and Trump abstract #32). Characterizing how these changes are related to long-term joint health status and outcomes is of critical importance to the secondary and tertiary

prevention of PTOA after ACL injury and may facilitate emerging models of care that are focused on preserving joint health and mitigating the risk of PTOA.<sup>8,164,165</sup>

Historically, our understanding of neuromuscular function after ACLR has been limited to gross measures of quadriceps strength recovery, neglecting the intricate relationships between the neural and morphologic environments that interact to produce force and maintain muscle health. However, recent advances in technologies, such as fMRI for neural activity and improved MRI for quantifying muscle quality and cartilage health, have been successfully implemented and led to key observations about poor long-term neuromuscular recoveries that degrade joint health. From a neural perspective, we have seen that those with ACL injury displayed increased cognitive and visuospatial proprioception-related neural activity and altered cortical motor excitability throughout recovery.<sup>74–76</sup> This altered neurocognitive scheme directly impairs sensorimotor neural efficiency, which in turn degrades physical function and performance.<sup>77,102,166</sup> New data presented at the retreat focused on muscle health and neuromuscular control; these continue to be dysregulated long after the traditional ACLR rehabilitation period has ended. Notably, these studies provided evidence for markers of greater muscle fat accumulation after ACLR in concert with a fibrotic extracellular matrix (Johnston et al abstract #17), altered muscle phenotyping (Lepley et al abstract #14), changes in muscle-fiber angle (Lepley et al abstract #13), and dynamic muscle function (Davi et al abstract #16). From a biomechanical viewpoint, a hazardous link between neuromuscular-control strategies and long-term joint health was reported, whereby inadequate knee somatosensory recovery during gait (Blackburn et al abstract #29) and altered interlimb jump-landing strategies (Pfeiffer et al abstract #30) after ACLR were linked with factors associated with PTOA risk. To date, our observations of these disruptions in neural efficiency, protracted morphologic abnormalities, and biomechanical dysfunction are limited to cross-sectional studies and small-scale preoperative-to-postoperative ACLR cohorts. To better inform clinical practice, future prospective cohort studies are needed to identify the timing of these neuromuscular changes across the ACLR rehabilitation continuum and determine whether interventions can alter the deleterious outcomes that have long-term effects on neuromuscular function and joint health.

Early structural and biomechanical changes observed after ACL injury and surgical reconstruction may also be associated with changes in molecular biomarkers of cartilage collagen turnover and joint health status after injury.<sup>167–169</sup> New data presented at the retreat suggested that significant differences were present in the ratio of type II collagen degradation (C1, 2C, and C2C) to synthesis (CPII) within 15 days of injury (Trump et al abstract #32) between patients with ACL injuries and uninjured control participants. Furthermore, these ratios continued to decrease at the time of surgery and 6 months after surgery in patients with ACL injuries but did not change in uninjured control participants. These decreases were primarily driven by an increase in serum CPII concentration, which indicates that cartilage collagen turnover may be dysregulated early after ACL injury. This finding is consistent with the emerging literature in this area<sup>168</sup>; however, the implications for long-term joint health and the risk of PTOA remain unclear.

## Directions for Future Research

The following priorities for research in this area were discussed.

### Structural Factors.

- There is a need to continue implementing and improving imaging studies to quantify structural changes in joint health status over time and how they are influenced by movement biomechanics, neuromotor function and control, and biological changes after ACL injury. The Osteoarthritis Research Society International<sup>170</sup> recommended radiography or MRI to demonstrate structural modifications, and the choice of imaging technique should be predicated on the objectives of the research.
- To characterize early changes or pre-OA changes, primary outcomes such as joint-space narrowing (eg, Kellgren-Lawrence grade) and quantitative cartilage morphology (eg, mean thickness) should be considered. Secondary outcomes such as effusion and synovitis volume, bone marrow lesion volume, and compositional MRI as well as semiquantitative MRI scoring systems (eg, MRI Osteoarthritis Knee Score) should also be considered when appropriate. Emerging imaging measures from fractal signature analyses and ultrasound may also be useful in assessing structural changes related to joint health status after ACL injury in the near future.

### Biomechanical Factors.

- Whether differences in aberrant movement biomechanics result from changes in the moment arm of muscles in the lower extremity after ACLR should be investigated.
- Determining if improving quadriceps strength modulates walking-gait biomechanics is important.
- Integrative approaches that combine motor learning and muscle strengthening to recover sensorimotor capabilities after injury are needed.
- We must identify how knee-joint loading during dynamic rehabilitation activities may influence changes in joint tissue composition, structure, and PTOA onset. Future authors should also seek to improve muscle function in a way that promotes enhanced movement biomechanics.
- Biomechanical movement patterns at the time patients are returned to full activity and released from follow-up care after ACL injury and ACLR should be evaluated to identify risk factors for reinjury and deteriorating joint health status over time.
- Assessing muscle strength and function at the time patients are released from care will allow us to determine how factors related to muscle function are associated with the risk for reinjury and long-term joint health. The current return-to-activity or return-to-participation criteria and guidelines may be inadequate in mitigating the risk for reinjury and deteriorating joint health status over time.
- Understanding the additive and interactive effects of ACL injury, BMI, and sex on gait biomechanics, which may influence the risk of PTOA, is necessary.

### Biological Factors.

- We must characterize the time course of biochemical changes after ACL injury and ACLR in humans.

- Establishing biorepository capabilities to examine how biological changes over time in ACL injury are related to clinically important outcome measures, such as movement biomechanics, structural changes on imaging, and patient-reported outcome measures related to joint health status, is important. Repositories should consider banking serum, plasma, peripheral blood mononuclear cells, PAXgene RNA, synovial fluid, and urine. Procedures for biospecimen collection and storage for OA applications have been described elsewhere.<sup>171</sup>
- The use of a systems biology approach (panomics [ie, proteomics, metabolomics, genomics, transcriptomics, and lipidomics]) in conjunction with big-data technologies should be considered to characterize how early biological changes are associated with the initiation and progression of PTOA and deteriorating joint health over time.

### Secondary and Tertiary Risk Identification.

- A critical need is to increase our understanding of the relationships among movement biomechanics, neuromuscular function, biological processes, and structural changes that affect long-term joint health after ACL injury and ACLR.<sup>120,126,160</sup>
- Prospective cohort studies are required to identify the timing of neuromuscular deficiencies across the ACLR rehabilitation continuum and whether interventions can alter these deleterious outcomes.
- We must comprehend the effects of psychosocial factors (eg, fear of movement, fear of reinjury) on long-term joint health and their associations with comorbidities such as obesity and other chronic diseases.<sup>172,173</sup>
- Clinically accessible screening methods to evaluate early changes in joint health status associated with PTOA risk after ACL injury and ACLR should be developed.

### Return to Participation Versus End of Care.

- General agreement was that return to participation should not be viewed as the end of care, particularly given the high rate of reinjury and the increased risk for PTOA after ACL injury and ACLR. Interventions to educate patients about their increased risk of PTOA and self-management risk-reduction strategies should be implemented as part of the return-to-participation protocol.
- Clinicians and researchers should continue to regularly monitor indexes of joint health, perhaps annually, to identify early signs of deteriorating joint health. Wearable technologies and apps may be helpful in motivating patients to engage in self-management strategies to maintain and preserve joint health (eg, maintain quadriceps strength and function, maintain a healthy weight, engage in lower-risk physical activity when possible).
- The Chronic Osteoarthritis Management Initiative has recommended a chronic disease management approach for OA, which was recently advocated in a consensus statement on the role of athletic trainers in managing patients with OA.<sup>8</sup> Further research is needed on the efficacy and effectiveness of this model in optimizing long-term joint health after ACL injury.<sup>164</sup>

### Comorbidities and Chronic Health Concerns.

- Measures indicative of deteriorating joint health status and the risk for potential comorbidities and chronic

health conditions should be studied in patients after ACL injury and ACLR. These include monitoring changes in physical activity level (eg, decreases) and BMI or body composition over time after return to participation and release from care.

- We must develop effective interventions for maintaining healthy levels of physical activity and BMI in this population to mitigate the comorbidities and chronic health conditions that have been commonly associated with OA (eg, obesity, diabetes). As noted previously, emerging wearable technologies could be useful in addressing these research priorities.

## IS IT TIME FOR AN ACL INJURY RESEARCH NETWORK?

Participants also engaged in a discussion (led by Kenneth L. Cameron, PhD, MPH, ATC) about the potential for establishing a collaborative, multicenter ACL injury research network. With an added focus on early deficits after ACL injury and the long-term consequences of ACL injury at this year's meeting, attendees discussed opportunities for establishing a collaborative ACL injury research network that could span the time course of ACL injury from primary injury prevention to secondary and tertiary prevention of PTOA after injury. Many studies of ACL injury risk factors and outcomes have been cross-sectional or retrospective in design, involved small samples, applied disparate methods, and produced conflicting results. These factors make it challenging to answer important questions and limit the ability of researchers and clinicians to interpret the findings. The goal of a collaborative, multicenter research network would be to address some of these existing limitations. The ongoing interest in the ACL Research Retreat and other such meetings suggests that such a need and interest exist, and this was further reinforced by the postmeeting survey, which indicated that all respondents (N = 31) were in favor of such a network, and 84% of respondents had a strong interest in participating. A brief overview of that discussion follows, with the identified critical steps and barriers to forming a collaborative, multicenter research network in this area.

Initially, the discussion focused on existing multicenter research groups, how they are structured, lessons learned from these groups, and existing gaps that are not currently being addressed. Multicenter research networks include the National Collegiate Athletic Association-Department of Defense (NCAA-DoD) Grand Alliance Concussion Assessment, Research and Education (CARE) Consortium<sup>174</sup>; the Multicenter Orthopaedic Outcomes Network (MOON)<sup>175</sup>; the Multicenter ACL Revision Study (MARS)<sup>176</sup>; and the Military Orthopaedics Tracking Injuries and Outcomes Network (MOTION).<sup>177</sup> Most closely aligned with the goal of developing a collaborative multicenter ACL injury research network were the MOON and MARS groups, which are primarily focused on patient-reported and surgical outcomes after primary ACL reconstruction and revision surgery, respectively. However, primary injury-prevention efforts, physical function after rehabilitation, and return to participation and full activity have received little attention from these groups.<sup>175</sup> The simultaneous collections of patient-report-



**Table 2. Current Gaps Related to Anterior Cruciate Ligament (ACL) Injury Prevention and Outcomes After Treatment**

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Primary injury factor identification and prevention

- Characterize factors that prospectively identify those at risk for primary ACL injury (structural, hormonal, genetic, neurocognitive, psychosocial, neuromuscular, and biomechanical).
- Determine how identified risk factors develop and change over time (eg, before and during maturation when the ACL injury risk is rising).
- Establish the optimal risk screening and assessment protocols to identify risk before it occurs.
- Identify and evaluate the most effective evidence-based injury-prevention strategies.
- Ascertain and address barriers to intervention efficacy, adoption, and adherence (implementation science).

Secondary and tertiary prevention

- Determine deficits in neuromotor and biomechanical function after ACL injury.
- Establish the mechanisms for neuromuscular and biomechanical deficits and their association with ACL injury outcomes.
- Identify and test evidence-based interventions to intervene for neuromuscular and biomechanical deficits.
- Evaluate the role of psychosocial factors in return-to-play and postinjury outcomes (eg, reinjury, posttraumatic osteoarthritis, other health-related outcomes, physical activity, body mass index).
- Assess joint structural changes after ACL injury. Use imaging biomarkers to quantify changes over time and their association with intermediate and long-term joint health status.
- Evaluate biochemical changes in the joint postinjury. Use molecular biomarkers that may affect ACL injury outcomes (eg, healing, reinjury risk, posttraumatic osteoarthritis). Monitor changes over time relative to joint health.
- Develop evidence-based return-to-activity criteria that mitigate the reinjury risk and optimize long-term joint health.

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ed outcomes, quantitative MRI results, and mechanical and biochemical markers as performed for the Stanford University prospective ACLR cohort,<sup>178,179</sup> while challenging, were considered highly important to understanding PTOA development. The current knowledge gaps that could be addressed by a collaborative, multicenter ACL injury research network are described in Table 2.

Next, the group addressed the critical first steps to establishing a network, including practical considerations such as interest in participating, the feasibility of collaborative, multicenter research (including potential barriers and strategies to overcome), and the potential for funding support. Considerations for research network structure, organization, leadership, and function included the potential role of study cores (eg, biomechanics, imaging, neuromotor function, biospecimens), special interest groups (eg, return-to-participation criteria and outcomes), and implications for data sharing and dissemination.

Finally, the group discussed possible common data elements across primary, secondary, and tertiary risk and prevention that could be collected as part of this network (Table 3). Clinical measures that could be readily obtained by all network participants are followed in the list by biomarkers requiring specialized equipment or technical training (or both). This compilation is intended to provide a starting point for further discussion of the primary data elements to be collected. Although examples of specific measures are provided in some cases, the actual measures would ultimately be deter-

**Table 3. Anterior Cruciate Ligament (ACL) Injury Research Network: Proposed Biomarkers**

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Clinical biomarkers (measurable in any clinical setting)

- Patient-report questionnaires
  - Baseline injury history (include personal and family history of ACL injury)
  - Knee-specific function (eg, Knee Injury and Osteoarthritis Outcome Score [KOOS], Knee Outcome Survey [KOS], International Knee Documentation Committee [IKDC] form)
  - General health status (eg, Patient-Reported Outcomes Measurement Information System [PROMIS], Short Form-12, Short Form-36)
  - Menstrual history (females)
  - Physical activity status (eg, International Physical Activity Questionnaire [IPAQ], Marx Activity Rating)
  - Psychosocial (eg, anxiety, fear, sleep, depression, TAMPA Scale for Kinesiophobia)
- Body composition (eg, body mass index)
- Joint laxity (eg, generalized joint laxity, anterior-posterior knee laxity)
- Lower extremity strength (eg, single-legged hop test)
- Lower extremity function (eg, 5-0-5 Agility Test, Y-Balance Test, walking speed, Timed Up-and-Go Test)
- Neurocognitive tests (to assess neuromotor and neurocognitive deficits)

Biomechanical biomarkers

- Dynamic functional task (eg, asymmetry, knee-abduction moment, vertical ground reaction forces)
- Gait assessment (eg, knee-abduction moment)
- Contractile muscle function
- Accelerometry (eg, training load)

Biochemical biomarkers (see Kraus et al<sup>171</sup> for the collection, processing, and storage of biospecimen samples)

- Plasma
- Serum
- Peripheral blood mononuclear cells
- PAXgene RNA
- Urine

Imaging biomarkers

- Body composition (eg, dual-energy x-ray absorptiometry, BodPod [Cosmed, Concord, CA])
- Muscle morphology: size and quality (eg, ultrasound, MRI)
- Joint geometry: notch width, tibial slope (eg, MRI)
- ACL morphology: ACL size and quality (eg, MRI)
- Cartilage morphology: thickness and quality (eg, MRI, ultrasound)
- Brain function: structural, activity, and connectivity measures during rest and function (eg, functional MRI [fMRI], functional near-infrared spectroscopy, electroencephalography)
- Joint space width and alignment (standing radiographs)

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Abbreviation: MRI, magnetic resonance imaging.

mined by network members based on the best available evidence that continues to emerge, feasibility, and acceptable multicenter measurement consistency and precision. In some areas, further research may be required to determine specific measures. For example, it is increasingly apparent that psychosocial factors are extremely important, but few researchers have examined these factors in relation to ACL injury risk and outcomes after injury and surgery.

Ideally, network participants would begin to collect these measures before injury (preinjury baseline) to separate preexisting risk factors from those resulting from the injury. Postinjury visits should then include time of injury; time of surgery; 6-month, 12-month, and 24-month follow-ups; and

time of return to activity to determine how these variables changed over time after injury, how the patients responded to therapeutic interventions, how clinicians assessed safe return to play, and how the various factors were associated with initiation and progression of PTOA and changes in joint health over time. As much as possible, these postinjury visits should be aligned with medical visits to enhance feasibility and reduce the participant burden. For those measures that change over time (eg, hormones, laxity, BMI, strength), consideration should be given to assessing these relative to maturational status and, in menstruating females, relative to cycle phase.

## SUMMARY

Advances in research continue to shape what we know about the ACL injury continuum and the important directions for future research that are needed to move the field forward. Our expectation is that these proceedings will continue to stimulate strategic research initiatives to more effectively identify those at risk and promote high-quality clinical interventions to prevent the initial injury from occurring and to improve both the short-term and long-term patient outcomes when ACL injury does occur.

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