A Systematic Review of Factors Associated with Both Bilateral and Recurrent Anterior Cruciate Ligament Disruption

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ABSTRACT:

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Background: Numerous studies have reported factors associated with recurrent or subsequent contralateral anterior cruciate ligament disruption, but a comprehensive review of the literature has not been performed.

Purpose: This study attempts to systematically review the literature and provide an overview of the currently reported risk factors for recurrent and subsequent contralateral ACL reconstructions in order to allow for more efficient identification and intervention of high-risk patients.

Study Design: Systematic Review.

Methods: The Pubmed and Embase databases were searched using a combination of keywords such as "ACL reconstruction" and "bilateral or recurrent" and "risk factors" and medical subject headings. All studies were screened by two independent reviewers, and articles that met inclusion criteria (non-contact ACL injury, study analyzed risk factors for contralateral ACL injury or graft rupture) were downloaded and read.

Results: The initial search yielded 129 articles, of which 36 met inclusion criteria. After duplicates were removed, 23 articles remained. The reference lists of included articles were cross-referenced, and an additional 2 articles were included.

Conclusion: Graft harvest site, allograft usage, return to sport, younger age, a positive family history, increased posterior tibial slope, and the number of previous ACL reconstructions are well-reported risk factors for second ACL injury. Recent studies suggest a patients who have negative psychological states in the perioperative periods have worse long-term functional outcomes.

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Key Terms: knee, anterior cruciate ligament, ACL reinjury, knee injury

18 1. INTRODUCTION

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20 Tearing the anterior cruciate ligament (ACL) is a common injury among active populations, 21 with re-rupture presenting a devastating complication. Injury to the ACL results in severe 22 instability of the knee joint. Though non-operative management may be an appropriate first-23 line treatment in older and less active patients, surgical repair or reconstruction is preferred for younger patients or those with high-activity levels. Patients undergo 6-12 months of 24 25 rehabilitation after surgery to build strength, stability and range-of-motion before returning to activity ^{1, 2}. The outcomes of initial ACL reconstruction remain excellent; the 5-year survival 26 rate in all patients with autografts is over 95% ³⁻⁹. However, for the unfortunate 5%, re-27 28 reconstructed ACL can catastrophic. While rupture of the be primary ACL 29 reconstructions are associated with risk of residual knee pain, recurrent

* Telephone: 1-908-872-9776; fax: (215) 707-8330 E-mail address: tud10415@temple.edu instability, and premature osteoarthritis, revision ACL reconstructions are associated with
 worse clinical outcomes².

Some patients who successfully rehabilitate and return to cutting/pivoting activities tear their native contralateral ACL ^{3, 9}. The rate of contralateral ACL injury following primary ACL reconstruction has been reported between 3.0-20.5% ^{2, 5, 7-13}, increasing risk for bilateral knee pain, instability, and osteoarthritis.

36 Graft failure and/or contralateral injury is financially, psychologically, and physiologically 37 traumatic for the patient and his family. While prevention of primary ACL injury has been 38 heavily studied, it is of interest to study the factors associated with recurrent and subsequent contralateral ACL reconstructions. A review of the literature reveals numerous reports of associated modifiable and non-modifiable factors ^{2-3, 5-8, 12-19}, but no comprehensive 39 40 evaluation. Awareness of modifiable and non-modifiable factors allows for intervention 41 42 to decrease rates of recurring ACL rupture. We aim to provide a comprehensive report of 43 risk factors associated with recurrent and subsequent contralateral ACL reconstructions in 44 the adult population.

45 2. METHODS

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A systematic review of the literature was performed to identify studies which reported risk factors for recurrent or subsequent contralateral ACL reconstruction. The study was registered with the PROSPERO database. The PubMed and Embase databases were searched from January 1, 2010 until December 31, 2017. The search utilized a combination of keywords such as "ACL reconstruction" and "contralateral or recurrent" and "risk factors." Where appropriate, our initial search included medical subject headings (MeSH), to ensure the consideration of all relevant articles.

All study designs were considered, apart from systematic reviews. Two authors independently searched the listed electronic databases for any eligible articles. Abstracts from all search results were reviewed; articles that met inclusion criteria were reviewed. An overview of our search strategy is included (Table 1).

Criteria	Details
Searched databases	PubMed/MEDLINE, Embase
Search string	("anterior cruciate ligament" OR ACL) AND (lesion OR tear OR rupture OR injury OR reconstruction OR repair) AND (bilateral OR recurrent OR contralateral) AND risk factors
Inclusion criteria	non-contact ACL injury, study analyzed risk factors for contralateral ACL injury or graft rupture
Exclusion criteria	study is a systematic review, study has no data, population studied is skeletally immature or elderly, study is evaluating risk factors for primary ACL injury, study was not published in English, study was not related to the ACL, access to full article was not available
Time filter	2010-2017
Language filter	English
Age filter	19-44, 19+
Other filters	Human studies

58 Table 1. Search Strategy

59 **3. RESULTS**

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The initial search yielded one hundred twenty-nine articles, of which thirty-six were deemed relevant once inclusion and exclusion criteria were applied. Once duplicates were removed, twenty-three articles remained. An additional two articles were included, yielding a total of twenty-five articles included in this review.

The included articles had the following designs: five retrospective cohort studies ^{5,8, 20-22}, six prospective cohort studies ^{2, 23-27}, four case series studies ^{28,-31}, five controlled laboratory studies ³²⁻³⁶, three retrospective case control studies ^{13, 15, 37}, and two prospective case control studies ^{16, 38}. The risk factors catalogued in these studies are grouped into factors the patient can alter against factors the patient has no control over (Table 2).

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71 Table 2. Risk Factors Associated with Graft Rupture and/or Contralateral ACL 72 Rupture

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Patient-controlled Factors	74 Factors Patients Cannot Control ₅
Graft harvest site Allograft vs. autograft Return to activity	Age at index procedure76Sex77Significant history78Rotational asymmetry79Rotational asymmetry80Neuromuscular asymmetry81Strength asymmetry81Increased posterior tibial slope82Narrow femoral intercondylar notch84Technical errors during surgery8586

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89 4. DISCUSSION

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91 PATIENT-CONTROLLED FACTORS

92 GRAFT HARVEST SITE

While surgeons offer patients an opinion for the most appropriate intervention, patients do
 have significant input on graft harvest site. Furthermore, if a patient has experienced graft
 rupture, the patient and surgeon might have limited graft options.

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Thompson *et. al* reported a 90% survival rate of the bone-patellar tendon-bone (BPTB) graft at 20-years (average age at surgery 24.6 ± 9.8 years), which is notably higher than the 67% survival rate of the contralateral ACL ³¹. This suggests the BPTB graft may be more durable than the native ACL, though this could be secondary to a variety of other factors such as more dedicated rehabilitation on the operative side or patients favoring their non-operative leg upon return to activity, which could render the non-operative side more susceptible to injury. One obstacle for the BPTB graft is pain upon kneeling; 67% of patients reported kneeling pain at 20 years post-reconstruction ³¹.

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Another study concluded BPTB autografts were associated with an increased risk for contralateral ACL injury ²⁵, noting a trend towards an increased rupture rates with hamstring tendon (HT) autografts ²⁵. The BPTB autograft carries an increased risk for osteoarthritis,

109 knee extension deficits, and decreased single-legged hop performance at 15 years post-ACL reconstruction ²⁵. However, the surgeries were performed in 1993-1994, so these results 110 could be influenced by outdated surgical techniques. Bourke et. al reported no significant 111 difference in 15-year rates of graft rupture between BPTB and HT autografts²⁹. At 15 years 112 post-reconstruction (average age at surgery 29 years), the odds of contralateral ACL rupture 113 were more than doubled in patients with a BPTB autograft ²⁹, while those with HT autografts 114 experienced similar rates of contralateral ACL injury or primary graft rupture²⁹, but higher 115 rates of revision ¹⁷. 116

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Though HT and BPTB autograft have achieved good long-term results, neither are perfect options. BPTB grafts appear to be more durable and have lower graft rupture rates ^{17, 25}, but may increase the odds of contralateral ACL injury ^{17, 25, 29}, osteoarthritis, anterior knee pain, and kneeling pain ^{25, 31}. The process of harvesting the BPTB graft may interrupt the afferent signals from the injured knee more than harvesting the hamstring tendon graft, altering central nervous system (CNS) feedback loops and predisposing to contralateral ACL injury ²⁹.

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The quadriceps tendon (QT) autograft has become popular because it is easier to harvest, requires a smaller incision, and has comparable strength to the BPTB autograft³⁹. Several studies comparing the BPTB and QT autografts found no difference in functional outcomes between the two grafts^{40.41}. Similarly, studies comparing the QT and HT autografts have also reported equal outcomes^{39, 42.44}. While the outcomes of the QT autograft appear promising, this requires further study with longer follow ups to identify rates of graft rupture and contralateral ACL injury.

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134 AUTOGRAFT VS. ALLOGRAFT

Some studies found allografts carry an increased risk of future injury ^{2, 8-9, 17, 45}, while others have not ⁴⁶. Some surgeons believe allograft reconstructions have fewer postoperative complications, a faster rehabilitation, and are better for older patients ^{8, 55}. Others believe autografts provide fast bone-to-bone healing, encourage return to sport, and are less likely to rupture ²⁷.

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Kaeding *et. al* found allografts had 5.2 times greater odds of graft rupture than autografts², a finding which is supported by several other studies¹⁷. A study reported patients who received an autograft were 2.78 times less likely to experience subsequent graft rupture²⁷. This study standardized the source of allografts, using grafts with minimal irradiation exposure²⁷, suggesting graft processing may not cause the higher failure rate. An *in vivo* sheep model concluded allografts took longer to heal than autografts, which could impair graft strength and knee stability⁴⁵.

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While allografts might be an appropriate choice for older patients, patients who return to a high level of activity should be informed of the associated risks. Though allografts offer shorter rehabilitations, this is inconsequential if the patient requires repeat ACL reconstruction.

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154 **RETURN TO ACTIVITY**

Returning to high intensity activity is a well-reported risk factor for ensuing ACL injury ^{13, 21, 23, 26, 26}. Activity level at index surgery is also a risk factor for both graft rupture and contralateral ACL injury ². Patients who return to high intensity sports involving cutting, pivoting and jumping movements are especially predisposed to graft and contralateral rupture.

160 While returning to sports risks future ACL injury, avoiding all athletic activity after surgery is unrealistic. However, the timeline of a patient's return to activity can affect their risk for future 161 ACL injury ^{23-24, 36}. For each month a patient's return to sport was delayed, up to 9 months 162 postoperative, the reinjury rate was reduced by 51%²³. Athletes who regained 90% of 163 hamstring, quadriceps, and hopping performance before resuming athletic activities have significantly decreased risk of reinjury ²³⁻²⁴. *Myer* et. al reported deficits on vertical hop ability 164 165 on the reconstructed limb up to 11 months post-surgery ³⁶. Delaying return to sport until after 166 athletes have met specific clinical discharge criteria could decrease the risk of second ACL 167 168 injury.

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Lastly, certain sports such as soccer ^{2, 28}, lacrosse ³³, basketball ², and football ² carry a higher risk of second injury; identifying high-risk activities allows physicians, patients, and coaches to intervene and decrease the risk for future injury.

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174 FACTORS PATIENTS CAN'T CONTROL

175 AGE AT INDEX SURGERY

Age at index surgery is a risk factor for secondary ACL injuries ^{2, 8, 13, 17, 26, 28, 31,38}. Webster *et. al* found 29% of patients younger than 20 experienced a secondary ACL injury within 5 years of their index surgery, compared to 8% of patients older than 20 ¹³.

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Another study concluded patients younger than 18 at index surgery did not have significantly higher rates of graft ruptures, but did have higher rates of contralateral ACL rupture (56%) compared to patients older than 18 (25%)³¹. However, this study had a small sample size (n=90), which could account for the lack of association between age and graft rupture.

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185 It is unclear whether age is a confounding factor, or if there are specific age-related risk 186 factors. Younger persons are more likely to return to pre-injury activity level, risking graft and 187 contralateral injury ^{13, 23, 26, 29}. Younger patients also engage in more risk-taking behavior and 188 can be less compliant with rehabilitation protocols, which could predispose to future injury.

189 190 <u>SEX</u>

Maletis *et. al* reported males had a higher risk of revision ACL reconstruction because males return more often than females to high-level sports involving cutting, pivoting and jumping ¹⁷. Females had a higher risk of contralateral reconstruction ¹⁷, which is supported by other studies ^{29, 47}. This might be due to a larger-sized graft than the native female ACL having a protective effect on the operated leg ¹⁷.

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An analysis of the Swedish National ACL Register found 22% of female soccer players between ages 15-18 underwent secondary ACL reconstruction, compared to 9.8% of male soccer players ²⁸. Moreover, female athletes underwent nearly double the ACL reconstructions (11.8% vs. 5.4%) ²⁸, which suggests sex-specific characteristics may predispose female athletes to future ACL injuries. Females have larger quadriceps femoral angles (Q angle), hormonal fluctuations, more joint laxity, are more likely to have valgus knees, and are more prone to lower extremity neuromuscular imbalances than males ⁴⁸⁻⁵¹.

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205 Webster *et. al* and Sato *et. al* found no relationship between patient sex and the risk of graft 206 rupture 26,52 . It is worth noting that these studies report rates of rupture, not reconstruction, 207 which might affect the statistical analysis.

There is currently no definitive relationship between sex and rates of revision or contralateral ACL reconstruction. All studies were retrospective, and included patient populations from over a decade ago. As the number of female athletes increases yearly, these populations likely represent an outdated demographic.

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214 SIGNIFICANT HISTORY

Several studies reported the number of previous revision surgeries or a positive family history as risk factors for revision or contralateral ACL reconstruction ^{13, 27, 29}. Wright *et. al* found patients who underwent more than 3 revisions were 25.8 times more likely to sustain graft rupture within 2 years ⁹. Surgeons operating on patients after multiple ACL reconstructions are limited in graft selection, which might compromise the surgical outcome. Additionally, repeat operations induce joint trauma and complications such as bone tunnel widening or compromised secondary stabilizers. Moreover, re-injury is an overwhelming experience, which might offset the patient's ability to rehabilitate their injury.

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Webster *et. al* and Bourke *et. al* concluded ACL injury in a first-degree relative doubles the odds of graft rupture or a contralateral ACL ¹³, which is also a risk factor for index ACL injury ⁵²⁻⁵⁴. Certain collagen and proteoglycan polymorphisms (COL1A1, COL5A1, and COL12A1, chromosome 11 MMP gene cluster) have been proposed to be associated with these injuries ^{55-56, 58}, but it is possible body morphology, activity level, hobbies, etc. predispose patients to ACL injuries.

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231 ROTATIONAL, STRENGTH, AND NEUROMUSCULAR ASYMMETRIES

232 Two controlled laboratory studies demonstrated that athletes who underwent ACL 233 reconstruction had asymmetries in force generation and absorption on their injured leg 234 Another study compared the performance of ACL-reconstructed patients to healthy controls 235 and concluded ACL-reconstructed patients showed reduced range-of-motion (ROM), single-236 leg jumping distance, and hamstring strength on their operated leg 18-30 months postreconstruction ³⁵. Kyritsis et. al concluded reduced hamstring strength is a risk factor for 237 future injury ²⁴. The hamstring muscles impart strength on the knee joint, resist anterior tibial 238 239 translation, and protect the ACL; weak hamstring muscles are a reported risk factor for injury 58, 59, and reduced hamstring strength is associated with lower Lysholm knee function scores 240 60 241

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A study found limiting femoral internal rotation incites earlier ACL failure ³². Improving internal rotation on patients with limited hip mobility may decrease ACL load, reducing ligament failure ^{32, 61-62}.

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247 Dai *et. al* suggested restoring strength and ROM symmetry in a clinical setting does not 248 translate to kinetic knee symmetry, and found significant asymmetry between surgical and 249 non-surgical limbs in patients returning to activity ³⁴. Future research should focus on low-250 cost methods to identify kinetic knee asymmetries.

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Patients might overcompensate if the strength and ROM of one leg is reduced, and could predispose patients to injury. Additionally, because asymmetries were observed over one year post-ACL reconstruction, the injured leg may never recover to its pre-operative state.

256 **POSTERIOR TIBIAL SLOPE**

Posterior tibial slope (PTS) is most often measured on lateral radiograph with specialized software ³⁸. An increased PTS is a reported risk factor for index and recurrent ACL injury ²⁰, ^{30, 38}, resulting in an increased anterior tibial translation, which strains the ACL ^{30, 63-65}.

Hendrix *et. al* used lateral radiographs to compare the PTS of 50 patients who had either unilateral, bilateral, or no ACL injury ²⁰. The mean PTS of the healthy group was significantly lower than the mean PTS of both ACL-deficient groups ²⁰. Moreover, the study reported a 1^o increase in PTS was associated with 20% increase in the odds of unilateral ACL injury and a 34% increase in the odds of bilateral ACL injury ²⁰. Webb *et. al* reported patients with PTS over 12^o had 5 times higher odds of sustaining a subsequent ACL injury ³⁸. A finite element computer model found PTS was related to anterior tibial translation and ACL stress in both active and passive gait models ⁶⁶.

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269 Patients with increased PTS should be counseled regarding predisposition for future ACL 270 injury. Moreover, performing a tibial wedge osteotomy could restore knee stability Sonnery-Cottet et. al performed proximal tibial anterior closing wedge osteotomies during 271 272 ACL re-revision on 5 patients who had "pathological PTS" over 12° and reported no further injury on patients who returned to sport ³⁰. Arun et. al performed open wedge high-tibial 273 274 osteotomy during primary ACL reconstruction on 30 patients with osteoarthritis and reported improved functional outcomes 67. Another study performed anterior closing wedge tibial 275 osteotomies on 9 patients with increased PTS during ACL re-revision and reported no graft ruptures or recurrent instability at 2 years post-op ^{14, 67}. Using tibial osteotomies to decrease 276 277 278 pathologic PTS and reduce stress on ACL grafts requires further study with larger sample 279 sizes.

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281 NARROW FEMORAL INTERCONDYLAR NOTCH WIDTH

Femoral intercondylar notch width can be measured on radiograph or intra-operatively, and is often reported as the notch width index (NWI), the ratio of intercondylar notch width to femoral condylar width.

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A radiographic study reported significantly smaller NWIs in patients with bilateral ACL injury compared to patients with unilateral injury and healthy volunteers ¹⁵. Another compared several factors between an injured and uninjured group and reported a significantly more narrow intercondylar notch in injured patients ³⁷. Levins *et. al* reported a 28% decrease in graft rupture in females for every 1-millimeter increase in femoral intercondylar notch, but no significant association between graft rupture and intercondylar notch width in males ¹⁶.

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Wolf *et. al* intraoperatively measured the femoral intercondylar notch and concluded a smaller intercondylar notch was not a risk factor for graft rupture ²². The authors proposed the NWI is unreliable, and accredited discrepancies in the literature to different measurement tools ²². However, this study utilized arthroscopic measurements, which are more variable than radiographic measurements.

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The relationship between femoral intercondylar notch width and graft rupture or contralateral ACL injury requires further study utilizing standardized measurements.

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302 MISCELLANEOUS FACTORS

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Thompson *et. al* found patients with non-ideal tunnel position were more likely to rupture their graft ³¹. Ideal tunnel position was quantified as 80% along the Blumensaat line, a graft inclination angle of greater than 17° from vertical, and tibial tunnel 40-50% along the tibial plateau ³¹. Though the literature poorly defines ideal tunnel position, various surgical techniques can affect knee stability ⁶⁸⁻⁷⁰. Anterior tibial tunnel placement decreases anterior tibial translation ⁶⁸, while increasing sagittal and coronal obliquity decreases anterior tibial translation and rotary motion ^{68, 70}.

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312 A study found index surgeries performed in a teaching hospital were associated with higher 313 rates of revision ACL reconstructions (3.6%) compared to those performed in a non-314 academic institution (2.1%), with surgeon volume having no significant impact on reoperation rates ⁸. Residents and medical students are trained in academic institutions, which might 315 contribute to the observed trend. However, the author proposes higher revision rates in 316 academic settings reflects that academic hospital surgeons are more willing to perform 317 revision ACL reconstruction, instead of an increased failure rate ⁸. The study reported an 318 overall revision rate of 3%, indicating ACL reconstructions performed at both academic and 319 nonacademic centers are successful⁸, but patients and providers should be aware of all 320 321 contributing factors to graft failure to accurately assess risks of revision surgery.

323 PSYCHOLOGICAL IMPACT324

Almost all studies regarding rehabilitation and prevention of ACL injuries focus on tangible factors. Low confidence, fear of re-injury and low perioperative self-efficacy are associated with performance years after surgery ⁷¹⁻⁷², which could affect rehabilitation adherence. Athletes who suffered a second ACL rupture had a higher fear of re-injury in the 5 weeks before and after index ACL reconstruction ⁷³.

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It is important to counsel patients and attempt to improve self-efficacy and confidence. In a 331 randomized controlled trial, patients underwent nine guided imagery sessions to improve coping skills, simulate motor activities, and improve self-confidence ⁷⁴. When compared to 332 333 334 controls, the treatment group had less knee laxity, lower noradrenaline levels, and lower dopamine levels, which may improve healing ⁷⁴. The treatment group experienced a smaller 335 reduction in self-efficacy ⁷⁴. After a severe, painful injury, patients may be apprehensive to 336 337 fully utilize the leg with the injured ACL, encouraging injury-predisposing neuromuscular 338 imbalances. Guided imagery and relaxation sessions may alleviate patients' fears and allow 339 equal employment of their lower limbs. Another study found motor imagery increased muscle activation, enabling a more complete strength rehabilitation ⁷⁵. The relationship between 340 341 psychology and recovery requires further study; it is important to correct anatomic 342 imbalances, but it is also important to intervene if a patient is mentally predisposed to 343 suboptimal rehabilitation or poor functional outcomes.

345 **LIMITATIONS**

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This study was not without limitations. The reviewers were not blinded to authors,
institutions, or journals during the review process, which introduces the possibility for bias.
Moreover, the strength of evidence of systematic reviews is limited by the quality of
publications it contains, and there was a significant heterogeneity amongst included studies.
Nonetheless, an extensive search of published literature was conducted with strict inclusion
and exclusion criteria to minimize the potential for bias .

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355 5. CONCLUSION

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The literature demonstrates predisposition to second ACL injury is indeed multifactorial.
 Because many of these factors cannot be controlled, responsibility lies on the medical
 profession to assess risk factors and find appropriate interventions so patients can return to

360 an enjoyable lifestyle. Graft harvest site, allograft usage, return to sport, younger age, a 361 positive family history, increased posterior tibial slope (PTS) and the number of previous 362 ACL reconstructions were predictors for second ACL injury. It is crucial for healthcare 363 professionals to address any neuromuscular, rotational or strength asymmetries between the 364 injured and uninjured leg before the patient returns to sport because these are well-reported 365 risk factors for contralateral ACL rupture and graft rupture. There was some debate in the literature whether narrow femoral intercondylar notch predicts future ACL injury, which can 366 367 be attributed to a variety of measurement tools used in different studies. This area of 368 research requires further study with a unified method of measurement. The association between sex and future ACL injury was widely debated in the literature, and requires 369 370 prospective study to represent a current patient demographic. Lastly, it appears that a 371 patient's psychological state throughout rehabilitation is associated with long-term functional 372 outcomes, which requires future study to prove a definitive relationship and examine 373 possible interventions for improved outcomes.

- 374
- 375 Consent, ethics: NA
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- 377

378 COMPETING INTERESTS

379 Authors have declared that no competing interests exist.

381 AUTHORS' CONTRIBUTIONS

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Author A designed the study, performed the literature search, and wrote the first draft of the
manuscript. Author B performed an independent literature search and edited the first draft of
the manuscript. Author C designed the study protocol and oversaw the literature searches.
All authors read and approved the final manuscript.

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