Marie Pedersen // Long-term outcomes after ACL reconstruction or rehabilitation alone

DISSERTATION FROM THE NORWEGIAN SCHOOL OF SPORT SCIENCES
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Long-term clinical, functional, physical activity, and radiographic outcomes after anterior cruciate ligament reconstruction or rehabilitation alone

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Marie Pedersen

Oslo, February 2022

List of papers

This dissertation is based on the following original research papers, which are referred to in the text by their Roman numerals:

I. Pedersen M, Grindem H, Johnson JL, Engebretsen L, Axe MJ, Snyder-Mackler L, Risberg MA. Clinical, Functional, and Physical Activity Outcomes 5 Years Following the Treatment Algorithm of the Delaware-Oslo ACL Cohort Study. J Bone Joint Surg Am. 2021 May 17. doi: 10.2106/JBJS.20.01731. Epub ahead of print. PMID: 33999877

II. Pedersen M, Grindem H, Berg B, Gunderson R, Engebretsen L, Axe MJ, Snyder-Mackler L, Risberg MA. Low Rates of Radiographic Knee Osteoarthritis 5 Years After ACL Reconstruction or Rehabilitation Alone: The Delaware-Oslo ACL Cohort Study. Orthop J Sports Med. 2021 Aug 17;9(8):23259671211027530. doi: 10.1177/23259671211027530. PMID: 34423060; PMCID: PMC8375355

III. Pedersen M, Johnson JL, Grindem H, Magnusson K, Snyder-Mackler L, Risberg MA. Meniscus or Cartilage Injury at the Time of Anterior Cruciate Ligament Tear Is Associated With Worse Prognosis for Patient-Reported Outcome 2 to 10 Years After Anterior Cruciate Ligament Injury: A Systematic Review. J Orthop Sports Phys Ther. 2020 Sep;50(9):490-502. doi: 10.2519/jospt.2020.9451. Epub 2020 Aug 1. PMID: 32741324; PMCID: PMC7498413

IV. Pedersen M, Grindem H, Berg B, Engebretsen L, Axe MJ, Snyder-Mackler L, Risberg MA. Four distinct five-year trajectories of knee function emerge in patients who followed the Delaware-Oslo ACL Cohort treatment algorithm. Submitted to Am J Sports Med, 2021 Dec 2

Abbreviations

ACL – Anterior cruciate ligament

ACLR - Anterior cruciate ligament reconstruction

ADL - Activities of daily living

ANOVA – Analysis of variance

BMI – Body mass index

CI – Confidence interval

COMPARE trial – Conservative versus Operative Methods for Patients with ACL Rupture Evaluation trial

GRADE - Grading of Recommendations Assessment, Development, and Evaluation approach

HSS ACL Registry - Hospital of Special Surgery HSS ACL Registry

mJSW - minimum joint space width

IKDC-SKF – International Knee Documentation Committee Subjective Knee Score

K&L – Kellgren and Lawrence

KANON trial - Knee Anterior Cruciate Ligament, Nonsurgical versus Surgical Treatment trial

KOOS – Knee Osteoarthritis Outcome Score

LSI – Limb symmetry index (performance of the involved limb in percent of the contralateral)

MIC – Minimal important change

MOON - Multicenter Orthopaedic Outcomes Network

MRI – Magnetic resonance imaging

NKLR - Norwegian National Knee Ligament Registry

OA – Osteoarthritis

OARSI - Osteoarthritis Research International

PASS – Patient acceptable symptom state

PROM – Patient-reported outcome measure

QoL - Quality of life

QUIPS - Quality in Prognosis Study risk of bias tool

Sport/Rec - Sport and recreation

Summary

Introduction: Current literature does not demonstrate superior outcomes after anterior cruciate ligament (ACL) reconstruction (ACLR) compared with progressive rehabilitation alone. ACL injured patients are, however, a heterogeneous population and treatment do not fit into a one-size-fits-all paradigm. Also, the choice between ACLR and rehabilitation alone is only one part of ACL treatment: pre-and postoperative rehabilitation, surgical indications, and patient education are also important. We, therefore, need studies that evaluate treatment algorithms applicable in clinical practice to further inform treatment choices. Further, factors other than treatment choice may explain the heterogeneity in outcomes after ACL injury. We need to improve the knowledge of *how* patients' developmental trajectories differ, and factors associated with successful outcomes after both ACLR and rehabilitation alone to optimize individualized treatment.

The overall aims of this dissertation were to (I) evaluate the five-year outcomes of the treatment algorithm used in the Delaware-Oslo ACL cohort study and (II) explore subgroups of ACL injured patients and identify factors associated with outcomes.

Methods: The four papers included in this dissertation are based on two separate research projects. Papers I, II, and IV origin from the Delaware-Oslo ACL cohort study - a prospective cohort study including 276 patients with a first-time ACL injury. All patients followed a specific treatment algorithm: Patients participated in an informed shared decision-making process about treatment, including education, and they concurrently underwent five weeks of progressive neuromuscular and strength training exercises followed by clinical testing. In papers I and II, we described treatment choices and five-year clinical (patient-reported outcome measures, PROMs; knee pain; new knee injuries), functional (muscle strength; single-legged hop tests), physical activity (sports participation; Marx activity rating scale), and radiographic outcomes (tibiofemoral osteoarthritis, OA; radiographic features). Further, we used one-way analysis of variance, chi-square tests, and Fisher exact tests to compare outcomes among patients who chose (1) early ACLR (≤ six months) with pre- and postoperative rehabilitation, (2) delayed ACLR (> six months) with pre- and postoperative rehabilitation, or (3) progressive rehabilitation alone. Paper III was a systematic review on prognostic factors for PROMs and physical activity two to ten years after ACL reconstruction or injury. We selected only studies with appropriate study designs and statistical analyses, performed a rigorous risk of bias assessment using the Quality in Prognosis Study (QUIPS) risk of bias tool, and judged the quality of evidence for each prognostic factor according to the Grading of Recommendations Assessment, Development, and Evaluation

(GRADE) approach. In paper IV, we used group-based trajectory modeling to identify subgroups who share common trajectories of five-year PROMs, and multinomial logistic regression to assess associations with trajectory affiliation.

Main results: Within five years (80% follow-up rate), 64% of the patients had undergone early ACLR, 11% delayed ACLR, and 25% progressive rehabilitation alone (papers I and II). The rehabilitation alone group were older, had less concomitant medial meniscus injuries, and participated in less level-I versus level-II sports preinjury compared to the early and delayed ACLR groups. We found good clinical, functional, physical activity, and radiographic outcomes following our treatment algorithm: Among the whole cohort, 79% to 85% scored above a threshold for a patient acceptable symptom state for different PROMs (83%-87% after early ACLR, 65%-78% after delayed ACLR, and 77%-88% after rehabilitation alone), and >95% were still active in some kind of sports (paper I). Only 6% and 4% had tibiofemoral OA in the index and contralateral knee, respectively, and only 6% had knee pain in the index knee (paper II). No outcomes statistically significantly differed among the three treatment groups (papers I and II). The systematic review (paper III) found moderate certainty evidence for concomitant meniscus and cartilage injuries as prognostic factors for worse PROMs two to ten years after ACLR. Other prognostic factors had very low certainty. There was a lack of studies on patients treated with rehabilitation alone and 60% of the included studies were at high risk of bias. We identified four distinct five-year trajectories of PROMs – *Low* (8.9%), *Moderate* (50.2%), *High* (37.5%), and *High before declining* (3.4%) - indicating four subgroups of ACL injured patients. Concomitant meniscus injuries and new knee injuries were important characteristics of the unfavorable *Low* and *High before declining* trajectories, respectively. Factors associated with belonging to the *High* trajectory were mainly related to having better functional outcomes early after injury (paper IV).

Conclusions: We found good five-year clinical, functional, physical activity, and radiographic outcomes following the treatment algorithm used in the Delaware-Oslo ACL cohort study. There were no statistically significant differences in outcomes among patients who underwent early ACLR, delayed ACLR, and progressive rehabilitation alone (papers I and II). The systematic review (paper III) identified concomitant meniscus and cartilage injuries as prognostic factors for worse PROMs long-term after ACLR. We identified four distinct trajectories of five-year patient-reported knee function, whereof 9 of 10 patients belonged to the favorable *Moderate* and *High* trajectories. In accordance with paper III, concomitant meniscus injuries were associated with affiliation to the unfavorable *Low* trajectory (paper IV).

Sammendrag (summary in Norwegian)

Introduksjon: Nåværende litteratur viser like utfall etter kirurgisk rekonstruksjon og kun rehabilitering av fremre korsbåndskader. Korsbåndpasienter er imidlertid en heterogen pasientgruppe og én behandling passer ikke nødvendigvis alle. Valget mellom korsbånds-rekonstruksjon og kun rehabilitering er også bare én del av et behandlingsforløp: pre- og postoperativ rehabilitering, operasjonsindikasjoner og pasientinformasjon er også viktig. Vi trenger derfor studier som evaluerer behandlingsalgoritmer som kan brukes i klinisk praksis for å optimalisere behandlingsvalg. Videre kan andre faktorer enn behandlingsvalg (korsbåndrekonstruksjon versus kun rehabilitering) forklare heterogeniteten i utfall. For å optimalisere individualisert behandling bør vi øke kunnskapen om hvordan pasientenes forløp varierer etter skade/operasjon, og om hvilke faktorer som er assosiert med utfall.

De overordnede målene for denne doktorgradsavhandlingen var å (I) evaluere fem års utfall etter behandlingsalgoritmen som ble brukt i Delaware-Oslo ACL kohortstudien og (II) utforske subgrupper blant korsbåndpasienter og identifisere faktorer som er assosiert med utfall..

Metode: Denne avhandlingen inkluderer fire artikler fra to separate forskningsprosjekter. Artikkel I, II og IV er basert på Delaware-Oslo ACL kohortstudien - en prospektiv kohortstudie som inkluderer 276 pasienter med en førstegangs korsbåndskade. Alle pasientene fulgte en spesifikk behandlingsalgoritme: De deltok i en informert delt beslutningsprosess om behandlingsvalg, inkludert pasientinformasjon, samtidig som de gjennomgikk fem uker med progressive nevromuskulære- og styrketreningsøvelser etterfulgt av klinisk testing. I artikkel I og II beskrev vi pasientenes behandlingsvalg og en rekke fem års utfall: kliniske (pasient-rapportert knefunksjon; knesmerter; nye kneskader), funksjonelle (muskelstyrke tester; hinketester) fysisk aktivitet (idrettsdeltakelse; Marx activity rating scale) og radiologiske (tibiofemoral artrose; radiologiske trekk). Vi sammenlignet pasienter som valgte (1) tidlig korsbåndrekonstruksjon (≤ seks måneder) med pre- og postoperativ rehabilitering, (2) sen korsbåndrekonstruksjon (> seks måneder) med pre- og postoperativ rehabilitering, eller (3) kun progressiv rehabilitering, med enveis variansanalyser (ANOVA), kjikvadrattester og Fisher eksakte tester. Artikkel III var en systematisk oversiktsartikkel over prognostiske faktorer for pasient-rapportert knefunksjon og fysisk aktivitet to til ti år etter korsbåndsrekonstruksjon eller -skade. Vi utførte en streng seleksjon av studier basert på studiedesign, statistiske analyser og «risk of bias» samt vurderte sikkerheten for hver prognostisk faktor (Grading of Recommendations Assessment, Development, and Evaluation, GRADE, approach). I artikkel IV identifiserte vi subgrupper som fulgte distinkte forløp for endring av pasient-rapportert knefunksjon over tid og brukte logistisk regresjon til å identifisere assosiasjoner med de ulike forløpene.

Hovedresultater: Innen fem år (80% oppfølgingsprosent) hadde 64% av pasientene gjennomgått tidlig korsbåndrekonstruksjon, 11% sen korsbåndrekonstruksjon og 25% kun progressiv rehabilitering. Pasientene som valgte kun rehabilitering var eldre, hadde færre tilleggsskader på mediale menisk og deltok i mindre grad i nivå-I idretter før skaden enn de som valgte tidlig eller sen korsbåndrekonstruksjon (artikkel I og II). Både kliniske, funksjonelle, fysisk aktivitet og radiologiske utfall var gode etter vår behandlingsalgoritme: 79% til 85% av hele kohorten scoret over en terskel for pasienttilfredshet for pasient-rapportert knefunksjon (83%-87% etter tidlig korsbåndrekonstruksjon, 65%-78% etter sen korsbåndrekonstruksjon og 77%-88% etter kun rehabilitering), og >95% var fortsatt aktive i en form for idrett (artikkel I). Kun 6% hadde tibiofemoral artrose og 6% hadde smerter i det skadede kneet, mens 4% hadde tibiofemoral artrose i motsatt kne (artikkel II). Det var ingen statistisk signifikante forskjeller i utfall mellom de tre behandlingsgruppene (artikkel I og II). Den systematiske oversiktsartikkelen identifiserte moderat sikkerhet for tilleggsskader på menisk og brusk som prognostiske faktorer for dårligere pasient-rapportert knefunksjon to til ti år etter korsbåndrekonstruksjon. Andre faktorer hadde svært lav evidens. Det manglet studier etter kun rehabilitering og 60% av de inkluderte studiene hadde høy «risk of bias» (artikkel III). Vi identifiserte fire distinkte forløp for endring av pasient-rapportert knefunksjon over tid – *lav* (8,9%), *moderat* (50,2%), *høy* (37,5%) og *høy før avtakende* (3,4%) – noe som indikerer at det finnes fire subgrupper blant korsbåndpasienter. Tilleggsskader på menisk og nye kneskader var, henholdsvis, viktige karakteristika hos de som fulgte de dårligste forløpene (*lav* og *høy før avtakende*) mens gode resultater på funksjonstester tidlig etter skaden var assosiert med det beste forløpet (*høy*) (artikkel IV).

Konklusjoner: Vi fant gode fem års utfall med behandlingsalgoritmen som ble brukt i Delaware-Oslo ACL kohortstudien. Det var ingen statistisk signifikante forskjeller mellom pasienter som valgte tidlig korsbåndrekonstruksjon, sen korsbåndrekonstruksjon og kun progressiv rehabilitering (artikkel I og II). Den systematiske oversiktsartikkelen identifiserte tilleggsskader på menisk og brusk som prognostiske faktorer for dårligere pasient-rapportert knefunksjon etter korsbåndrekonstruksjon (artikkel III). Vi identifiserte fire distinkte forløp for endring av pasient-rapportert knefunksjon over tid, hvorav 9 av 10 pasienter fulgte de gunstigste forløpene (*moderat* og *høy*) (artikkel IV). Å ha tilleggsskader på menisk var assosiert med å følge et ugunstig forløp (*lav*) (artikkel IV)- i overenstemmelse med resultatene i artikkel III.

Preface

Two of my supervisors started a research collaboration in 2002: Professor Lynn Snyder-Mackler at the University of Delaware and Professor May Arna Risberg at the Norwegian Research Center for Active Rehabilitation (a collaboration between the Norwegian School of Sport Sciences, the Oslo University Hospital, and the Norwegian Sports Medicine Clinic). The background for this international collaboration was the differences in clinical practice between sites: the US practice patterns hindered long-term analyses of active, ACL-deficient patients, while Norwegian guidelines enabled such studies. With overall aims to assess outcomes and prognostic factors after both ACL reconstruction and rehabilitation alone, the Delaware-Oslo ACL Cohort Study included patients from Delaware and Oslo between 2006 and 2012. The National Institutes of Health initially funded the study through grant R01HD37985. In 2012, the study group led by Lynn Snyder-Mackler received an NIH MERIT (Method to Extend Research In Time) award (grant R37HD37985) to perform five-year and ten-year follow-ups.

Previous publications on subgroups of the cohort, using data collected from inclusion through the two-year follow-up, have reported that (I) A five-week rehabilitation program with progressive neuromuscular and strength training exercises result in large improvement in knee function (54). (II) Single-legged hop tests can predict a successful outcome after ACL injury and reconstruction (87, 139). (III) Patient-reported knee function can identify athletes who fail return-to-sport criteria up to one year after ACLR (138). (IV) More patients became potential copers after rehabilitation and potential copers were more likely to have successful two-year outcomes regardless of treatment choice (198). (V) Two-year outcomes after progressive rehabilitation alone are equivalent to those after ACLR (83). (VI) Two-year outcomes after ACLR among our cohort were superior to those after usual care in Norway and the US (61, 86). (VII) Simple decision rules for return to sports substantially reduce the reinjury rate after ACLR (88). (VIII) Activity and functional readiness, not age, are the critical factors for second ACL injury (85). (IX) Patients who are female, older in age, and have good knee function early after injury can be more confident in nonsurgical treatment choices (89).

Papers I, II, and IV of this dissertation are the first to report outcomes for the whole Delaware-Oslo ACL cohort – patients from both sites undergoing both ACLR and rehabilitation alone - and are mainly based on the five-year follow-up. Currently, we are finalizing a ten-year follow-up which will further contribute to the understanding of long-term outcomes after ACL injuries.

Introduction

Current literature does not demonstrate superior outcomes after anterior cruciate ligament (ACL) reconstruction (ACLR) compared with progressive rehabilitation alone (30, 73, 74, 136, 165, 177). ACL injured patients are, however, a heterogeneous population (3, 83, 155, 191, 198), and treatment does therefore not fit into a one-size-fits-all paradigm. Also, the choice between ACLR and rehabilitation alone is only one part of a treatment plan: pre- and postoperative rehabilitation, surgical indications, and patient education are also essential components (66). We, therefore, need studies that evaluate treatment algorithms applicable in clinical practice to further inform treatment choices.

It is important to focus on optimization of long-term outcomes already early after injury (178). Prognostic factors for long-term outcomes may help identify at-risk patients and possible targets of intervention. Current systematic reviews reporting prognostic factors for long-term patient-reported outcomes (PROMs) and level of physical activity generally have methodological limitations (145, 146, 195). Also, patients treated with rehabilitation alone have not been included in previous systematic reviews with higher quality (7, 48, 59). We, therefore, need a high-quality systematic review of the literature on prognostic factors for long-term PROMs and level of physical activity after both ACL reconstruction and rehabilitation alone, with an appropriate and thorough risk of bias assessment. To further inform treatment choices, there is also of great clinical interest to systematically review the literature on differences in prognostic factors between patients treated with ACLR versus rehabilitation alone.

Further, researchers usually report outcomes averaged over all patients – despite the large variation in short- and long-term impairments after ACL injuries (3, 83, 155, 191, 198). By identifying subgroups with different developmental trajectories, this diversity in response to injury and treatment can be better understood. Such studies have been more widely used in other research areas such as other musculoskeletal and psychological disorders (34, 105, 161). Such knowledge can improve both clinicians' and patients' understanding of prognosis after ACL injuries.

Theoretical background

ACL: Anatomy, function, and injury

The ACL arises from the area intercondylaris anterior on the tibia, has a dorsal, cranial, and lateral course, and attaches to the medial side of the lateral femur condyle. The ACL consists of two distinct bundles: one anteromedial and one posterolateral (47, 184, 221, 224). The main function of the ACL is to stabilize the knee in the sagittal plane and to control rotation of the tibia relative to the femur (26, 184, 221, 224). The ACL also plays an important role in the neuromuscular control of the knee (112, 127). Complete ACL injuries, which is the topic of this dissertation, are far more common than partial tears (223). Due to its intraarticular location, the ACL has limited healing capacity and often causes chronic passive anteroposterior and rotational knee laxity (18, 221, 222). Some degree of restored fiber continuity on magnetic resonance imaging (MRI) can occur, particularly for proximal ruptures, but the study quality in this area is too low to conclude (172).

ACL injuries typically occur in the young and active population (120, 164), most commonly in jumping, cutting, and pivoting sports such as soccer, American football, basketball, team handball, and alpine skiing (78, 81, 120, 122). The annual incidence is high: around 78 to 81 injuries per 100 000 persons (72, 164). In Norwegian elite handball, the incidence over the last decades has been between 0.2 and 0.3 injuries per team per season (159). The mean age at ACLR in Norway and the US is in the mid/late 20s, and playing soccer is the most common injury situation at both sites (147). In most sports (except some collision sports), women are 2-3 times at greater risk of sustaining ACL injures and also sustain them at a younger age than men (120, 147, 157, 211). However, slightly more men (58-65%) than women undergo ACLR (120, 147, 164, 211).

The most common injury mechanism in team sports such as soccer, handball, and basketball is an internal or external rotation of the tibia combined with valgus (167, 212). In soccer, most injuries are non-contact or indirect contact injuries, most often during pressing/tackling, being tackled, regaining balance after kicking, and landing from a jump (50, 212). In alpine skiing, ACL injuries most often occur in slip-catch situations where the outer ski catches the inside edge, forcing the outer knee into internal rotation and valgus (19).

ACL injuries rarely occur in isolation: Concomitant injuries to the menisci and cartilage, other ligament sprains, and bone marrow lesions are frequent. Data from the Norwegian National Knee Ligament Registry (NKLR) found a prevalence of concomitant meniscus and cartilage injuries of 47% and 26% in patients who undergo ACLR (80). The large forces resulting in ACL rupture also create a great impact between tibial and femoral joint surfaces, resulting in a high prevalence (5%-98%) of bone bruises (64).

Current treatment strategies for ACL injuries

Treatment of ACL injuries aims to restore knee function, regain or improve activity level, prevent new injuries, reduce the risk of knee osteoarthritis (OA), and optimize long-term quality of life (66).

Open primary repair was the most common surgical treatment of ACL injuries in the 1970s and 1980s but has been replaced with ACL reconstruction (ACLR) during the last decades due to better and more predictable outcomes, especially in mid-substance tears (196, 204).

Three main treatment strategies for ACL injuries are described in current clinical guidelines: (1) ACLR as the first-line treatment, followed by postoperative rehabilitation, (2) ACLR with pre- and postoperative rehabilitation, and (3) rehabilitation as the first-line treatment, with the option of delayed ACLR if the patients develop instability symptoms (66).

ACLRs aim to replace the torn ACL and regain its biomechanical properties (221). Today, ACLRs are performed arthroscopically using either the patient's own tendon tissue (autograft) or a cadaver tendon (allograft) as an ACL graft (225). Autografts are usually harvested from either the hamstrings, patellar, or quadriceps tendons (4, 75). The NKLR reports that bone-patellar-tendon-bone autografts (BPTB) were the most popular in 2016-2019 (approximately 60%), while the use of hamstrings autografts has decreased from >80% in 2010 to approximately 30% in 2016-2019 (56, 75). A similar distribution between BPTB and hamstrings autografts has been observed in the US (91). The decreased popularity of hamstrings grafts is probably related to higher revision rates compared to BPTB grafts (56, 91). Autografts are usually preferred over allografts for the same reason, and the use of allografts in young, active patients has decreased to <20% in the US and are rarely used in Norway (75, 123). The ACLR procedure is generally safe, but not free of complications: <1% of patients get infections (16), between 2 and 11% cyclops lesions (163), and between 4% and 38% arthrofibrosis (57).

A comprehensive recovery phase is required after ACLR, including activity restrictions and rehabilitation. Postoperative rehabilitation should continue for 9–12 months and aims to restore range of motion, symptoms, muscle strength, neuromuscular function, and motor skills (10, 66, 209). Rehabilitation usually consists of three phases: (I) impairment-based, (II) sport-specific training, and (III) return to play. A cluster of strength and hop tests, quality of movement, and psychological readiness should be emphasized to guide progression in rehab (209). Individual considerations should be made regarding concomitant injuries/surgeries, graft donor site morbidity, and degrees of impairments such as atrophy or inhibition. Passing return to sport criteria prior to return to level-I sports substantially decrease the reinjury risk after ACLR (88, 129). These involve both functional tests (>90% limb symmetry on functional tests of quadriceps strength, single-legged hop performance, and agility) and time criteria (a 50% risk reduction for each month return to pivoting sports is delayed until nine months postoperatively) (88, 129).

While ACLR is an extensive procedure with a long recovery and rehabilitation, non-surgical treatment usually consists of a shorter rehabilitation following the same principles, phases, and milestones as described above - absent the acute postoperative phase and activity restrictions related to graft harvesting and ligament healing (66, 70, 73). Some of the first studies on return to pivoting sports with an ACL deficient knee described potential criteria for choosing appropriate candidates and rehabilitation components and milestones – primarily to enable completion of a season or a scholarship before a delayed ACLR (69, 70).

In the last decade, between 26% and 77% of ACL injured patients undergo rehabilitation as their only treatment while the rest undergo ACLR at some point (35, 80, 164, 181).

Choosing a treatment strategy

Guidelines

We generally lack national guidelines regarding surgical indications, reflecting the complexity of this field. The Dutch Orthopaedic Association published national guidelines in 2012 recommending ACLR in patients with symptomatic knee instability after rehabilitation and in patients with high activity levels (151). An international consensus group of experts published best practice guidelines in the British Journal of Sports Medicine in 2021 with the following summary: "In highly active patients engaged in jumping, cutting, and pivoting sports, early anatomical ACL reconstruction is recommended due to the high risk of secondary meniscus and cartilage injuries with delayed surgery, although a period of progressive rehabilitation to resolve impairments and improve neuromuscular function is recommended. For patients who seek to return to straight plane activities, non-operative treatment with structured, progressive rehabilitation is an acceptable treatment option. However, with persistent functional instability, or when episodes of giving way occur, anatomical ACL reconstruction is indicated"(51).

Comparative studies on ACL reconstruction versus rehabilitation alone

Two high-quality randomized controlled trials (RCTs), the gold standard study design for assessing treatment effect (130), have compared the effect of early ACLR with postoperative rehabilitation versus rehabilitation alone with the option of delayed ACLR; the "Knee Anterior Cruciate Ligament, Nonsurgical versus Surgical Treatment" (KANON) trial (73, 74) and the "Conservative versus Operative Methods for Patients with ACL Rupture Evaluation" (COMPARE) trial (177). The KANON trial found no statistically significant differences in PROMs, clinical and functional outcomes, return to sport, or radiographic knee OA at two and five years after treatment (73, 74). The COMPARE trial found statistically significantly better PROMs after early ACLR but concluded that the difference was too small to be perceived as clinically relevant (177). Importantly, these studies included young, active patients without substantial concomitant injuries.

Several systematic reviews have also concluded with no differences in outcomes after ACLR and rehabilitation alone (30, 94, 136, 141, 143, 156, 188). The high-quality systematic review of Lien-Iversen et al. (136), which compared radiographic knee OA rates >10 years after ACLR versus rehabilitation alone, concluded that the original research on this area had too poor quality to provide robust conclusions. Their results also indicated that there are higher OA rates after ACLR (range 24%-80%) than after rehabilitation alone (range 11% to 68%) (136).

Important implications from both the KANON and the COMPARE trial were that around 50% of ACL injured patients manage to avoid an ACLR if a strategy with rehabilitation alone plus the opportunity of delayed ACLR is chosen – without compromising patient outcomes (73, 74, 177).

Based on two-year data from the Norwegian arm of the Delaware-Oslo ACL cohort, Grindem et al. (83) has previously reported similar knee function, sports participation, and knee reinjury after ACLR and rehabilitation alone - adjusted for differences between treatment groups at inclusion (age and preinjury sports participation level).

Other surgical considerations

In the presence of repairable meniscal lesions or multiple ligament injuries, there is consensus for the indication of early ACLR with concomitant treatment of the other injured structures (51). However, though concomitant meniscus repair instead of meniscus resection seems promising (171), systematic reviews report conflicting results (182). This is a hot topic but not the focus of this dissertation.

When ACLR is chosen, there is a broad consensus to await surgery until normalization of swelling, pain, range of motion, muscle strength, and neuromuscular function (151, 206). Preoperative rehabilitation is recommended because it is associated with better PROMs up to two years postoperatively (61, 86, 185): Possibly because preoperative rehabilitation targets quadriceps strength deficits: Preoperative quadriceps deficits smaller than 20% positively affects PROMs two years postoperatively (53, 209). Hence, when possible, ACLR with pre- and postoperative rehabilitation should be chosen over ACLR as the first-line treatment. However, we lack consensus on the optimal program content, frequency, and length (28).

Previously published treatment algorithms for ACL injuries

Before the Delaware-Oslo ACL cohort study was initiated, two published algorithms for surgical selection criteria existed: The surgical risk factor (SURF) algorithm (68) and the Delaware screening examination (69).

The SURF algorithm defined patients with frequent participation in pivoting sports and/or high passive anteroposterior knee laxity (moderate- and high-risk patients) as candidates for ACLR. Applying the SURF algorithm in a prospective cohort study showed that low-risk patients had a lower risk of requiring a late ACLR or a meniscus surgery than high- and moderate-risk patients (68). Based on these findings, the authors suggested that rehabilitation alone is appropriate for patients with less frequent participation in pivoting sports and less passive knee laxity (68). However, the accuracy of the SURF algorithm can be questioned as nearly half of their high-risk patients defied recommendations to undergo ACLR, whereof less than one-third required delayed surgery (68). Hence, many patients may undergo unnecessary ACLR following the SURF algorithm, possibly because of the poor association between passive knee laxity and functional outcomes (189).

The Delaware screening examination classified patients as either candidates (potential copers) or non-candidates (noncopers) for nonoperative treatment based on four single-legged hop tests, the incidence of give-way episodes, a patient-reported outcome measure, and a self-report global knee function rating (69). Patients who were classified as potential copers and opted to return to preinjury activities without surgery were encouraged to undergo structured rehabilitation. Fitzgerald et al. (69) initially reported great success with this decision-making as 79% of the potential copers returned to sports short-term without ACLR – without further episodes of instability or a reduction in functional status. Though later studies have reported a predictive value of coper classification for long-term success, both in patients undergoing rehabilitation alone and ACLR, they have also reported a substantial potential to change coper classification after a rehabilitation intervention (155, 198). Also, potential copers and noncopers have comparable return to sport rates (155). Hence, the classification system may have limited value in surgical decision-making.

Outcomes after ACL injury

ACL injuries can have serious negative long-term consequences such as lower extremity dysfunction, low levels of physical activity, poor quality of life, and early development of knee osteoarthritis (OA) (5, 14, 43, 65, 154, 165). Most research assessing outcomes after ACL injury include patients treated with ACLR, partly due to the excellent effort in establishing large national ACL registries including pre- and postsurgical data (80, 81, 169, 217).

To create a clear structure further in this dissertation, outcomes were categorized as clinical (PROMs, symptoms, and new knee injuries), functional (functional tests, for example, tests of muscle strength and hop performance), physical activity (measures of physical activity and sports participation), and radiographic (posttraumatic knee osteoarthritis and radiographic features). Indeed, there is difficult to make a clean cut between these categories of outcomes as they influence each other.

Clinical outcomes

Patient-reported outcome measures

There is a broad consensus to use PROMs to evaluate outcomes after ACL injuries (142, 193). The Knee injury and Osteoarthritis Outcome Score (KOOS) and the International Knee

Documentation Committee Subjective Knee Evaluation Form (IKDC-SKF) have good measurement properties and are frequently used as stand-alone PROMs for assessment of long-term outcomes after ACL injuries (8, 36, 114, 115, 180, 208). The KOOS consists of five subscales: pain, other symptoms, function in daily living, function in sport and recreation (Sport/Rec), and knee-related quality of life (QoL) (180). The IKDC-SKF measures symptoms, function, and sports activity in patients with different knee problems (114).

Between 55% to 89% report a patient acceptable symptom state (PASS) six months to five years after ACLR (110, 158). PASS thresholds for different PROMs have been identified by asking the following yes/no questions: "Taking into account all the activity you have during your daily life, your level of pain, and also your activity limitations and participation restrictions, do you consider the current state of your knee satisfactory?"(158) or "Considering your knee function, do you feel that your current state is satisfactory? With *knee function*, you should take into account all activities during your daily life, sport and recreational activities, your level of pain and other symptoms, and also your knee-related quality of life"(110). Similarly, Ardern et al. (12) reported that three years after ACLR, 44% of patients would feel satisfied, 28% mostly satisfied, and 28% dissatisfied if "you were to spend the rest of your life with your knee just the way it has been in the last week". When the PASS thresholds identified by Ingelsrud et al. (110) were applied to the two-year KOOS scores of the patients in the KANON trial, only 50% reported a PASS (179).

New knee injuries

The high risk of new knee injuries is a large concern after ACL injury and reconstruction. Between 5% and 52% sustain subsequent meniscus injuries (55). At least 3% to 8% sustain a graft rupture or a contralateral ACL injury, and the risk is highest among the youngest population (<25 years) who also return to sport, where the corresponding rate is around 20% (186, 219). Further, return to level-I sports leads to four-fold increased risk of new knee injuries compared to lower demand activities (88, 129). Among young (aged between 16 and 20 years at injury) female soccer players who returned to soccer after ACLR, as many as two-thirds sustained a new knee injury within a mean follow-up time of 6.5 years (76). However, passing return to sport criteria dramatically reduces the risk (88, 129).

Functional outcomes

ACL injured patients frequently present with muscle strength deficits (2, 40, 118), altered neuromuscular control and proprioception (9), and altered movement patterns such as gait dynamics (77, 97, 216) and landing techniques (106, 168). These alterations also persist over time: For example, even after two to five years, approximately two-thirds recover normal muscle function (>90% limb symmetry) measured with single tests of one-leg hop performance and muscle strength, and only half recover normal muscle function measured with batteries of functional tests (2).

Physical activity outcomes

Sports participation

Return to sports is an important outcome after ACL injury (142): It is strongly correlated to satisfaction with knee function (12, 190) and can contribute to increase physical activity and thereby general health (27). There is large variability in definitions of return to sports in the orthopaedic literature, and definitions can for example vary from "return to participation" to "return to performance" (11). Return to sports are often patient-reported based on the type of sport and level, expressed as return to preinjury activity or return to competitive sports (13, 14, 84, 92). Tegner Activity Scale is also used to grade activity level on a scale from 0 to 10 based on occupation and sports participation (0= sick leave due to knee problems, 10= elite sports) (21, 197). We should be aware of these differences in definitions when we compare return to sport rates.

According to a large meta-analysis, only 65% return to preinjury level of sports the first years after ACLR, and only 55% return to competitive sports (14). Among elite athletes, return to sport rates are markedly higher, up to 83% (14, 131), but they often return with reduced performance (153). Fewer studies have investigated long-term sports participation: At the five-year follow-up of the KANON trial, only 20% to 23% were active at their preinjury Tegner activity scale level (74).

General physical activity

Physical activity is highly important form a general health perspective (27). The well-documented cessation of sports activity at an early age after ACL injury may negatively affect long-term physical activity. Between 6 and 67 months postoperatively, ACL reconstructed patients have shown to spend less time in moderate to vigorous physical activity and have lower daily step counts than matched individuals with no history of knee injuries (17). No other identified studies have reported general physical activity measures in ACL injured patients using acknowledged tools such as accelerometers (42, 101, 149) or the International Physical Activity Questionnaire (39).

Radiographic outcomes

Knee OA is a frequently assessed outcome after ACL injury (134, 207). The American College of Rheumatology defines knee OA as "a heterogeneous group of conditions that lead to joint symptoms and signs which are associated with defective integrity of articular cartilage, in addition to related changes in the underlying bone and at the joint margins" (6). Current pathophysiological models describe OA as a disease of the whole joint; articular cartilage, subchondral bone, bone marrow, synovium, neural tissue, joint capsule, ligaments, and specific to the knee, also the menisci (137, 140). The global prevalence of radiographically confirmed symptomatic knee OA was estimated to be 3.8% in 2010 (41). Posttraumatic OA is defined as OA after a known medical condition (i.e. ACL injury) and accounts for approximately 10% of all knee OA cases (6, 25).

Most studies assess radiographic, not symptomatic, knee OA after ACL injury (134). Many different classification systems exist for radiographic knee OA: A systematic review summarized that among 31 included studies, seven different classification systems were used (165). All of them included evaluation of osteophyte formation and/or joint space width, but procedures of measuring the latter were not described in the included studies. There was also a discrepancy in cutoffs for defining radiographic knee OA (165).

ACL injured knees have a four-fold higher risk of developing radiographic knee OA compared to uninjured knees (5). The prevalence of radiographic tibiofemoral knee OA ≥10 years after ACL injury or reconstruction varies between 0% and 100% (134) - depending greatly on classification system and cut-offs used for assessing OA - but is probably between 20 and 28% (5, 32). The prevalence of patellofemoral OA is approximately as prevalent as tibiofemoral OA (44). Despite high-quality evidence that exercise improves pain, function, and quality of life (22-24, 71), individuals with knee OA still demonstrate reduced activity levels and general health - which represents a major public health problem and a burden for the health care system (31, 90). As ACL injuries usually occur at a young age, the consequences of posttraumatic knee OA may be even more detrimental than of primary OA.

The exact mechanisms involved in the development of posttraumatic knee OA is not fully understood, but both mechanical and inflammatory mechanisms have been relatively consistently identified (93, 135). Inflammation, which occurs early after joint injury, persists over time and contributes to altered tissue turnover in the joint which influence articular cartilage metabolism (93, 135). Biomarkers such as proteins and enzymes indicate an increased collagen turnover and degradation, degradation of proteoglycans, and cartilage breakdown (93). In addition to cartilage breakdown, subchondral bone and synovial tissue are also involved (93, 135). Chondral injury and bone-marrow edema sustained at the initial trauma may also be important contributors to the development and pathogenesis of posttraumatic knee OA (173). Kinematic and kinetic alterations in the lower limb joints during activities such as walking has been proposed as contributing factors to posttraumatic knee OA development after ACL injury, but the evidence is conflicting (117, 124, 216).

Early diagnosis is crucial to further develop the understanding of posttraumatic knee OA development and to enable detection of at-risk-patients. Knee OA diagnosed using MRI is evident already one to two years after injury, way earlier than established radiographic knee OA (43, 205). Measures of minimum joint space width (mJSW) based on radiographs can also contribute with other aspects of joint degeneration than traditional classification systems, reflecting articular cartilage thickness and meniscal pathology (109, 137, 175). Changes in mJSW are associated with worse clinical outcomes and are also common early after ACL injury (200, 201).

Prognostic factors

So, if outcomes after ACL injury do not differ significantly by treatment choice - what factors can cause or predict patients' outcomes?

A prognostic factor can either have a causal effect, expressed as an average effect adjusted for relevant confounders, or be part of a prediction model (103, 187). Both approaches provide important information on prognosis which can be used to create realistic expectations to future knee function or to make decisions about early interventions that can improve long-term outcomes. Current prognostic research in ACL injured patients is extensive and of varying quality: Systematic reviews on this topic are therefore necessary (7, 207).

Most prognostic systematic reviews on long-term outcomes in ACL injured patients have assessed knee OA as their outcome (134, 144, 145, 165, 205, 207). Concomitant meniscus injury/resection and cartilage injury, especially in the medial compartment, are the only consistent risk factors for cartilage degeneration and radiographic knee OA development after ACL injury (134, 144, 145, 165, 205, 207): The prevalence of radiographic knee OA increases from 0%-13% in patients with isolated ACL injuries to 21%-48% in patients with concomitant meniscus injuries (165). Most of this evidence is based on studies on patients treated with ACLR: For example, only 6% of the included studies in the systematic review of van Meer et al. (207) included non-surgically treated patients only.

Besides knee OA, prognostic factors for long-term clinical, functional, and physical activity outcomes after ACL injury and reconstruction are also of great clinical interest.

Some systematic reviews have reported prognostic factors for long-term PROMs after ACLR (7, 48, 59, 145, 146, 195), but a considerable portion of them are of poor quality due to lack of risk of bias assessments (145, 146, 195). Previously suggested prognostic factors for better PROMs or functional performance after ACLR include lower body mass index (BMI), not smoking, not having concomitant high-grade meniscus or full-thickness cartilage injuries, not undergoing other knee surgeries, better baseline PROMs, better preoperative functional outcomes, and positive psychological factors (7, 48).

Previous systematic reviews have reported prognostic factors for return to sports, but not measures of physical activity. Suggested prognostic factors for return to sports after ACLR include positive psychological factors, a normal BMI, younger age, and male sex (48, 59).

Previous systematic reviews on prognostic factors for long-term PROMs and return to sports have included patients treated with ACLR, but not patients treated with rehabilitation alone.

Heterogeneity in outcomes and potential subgroups of ACL injured patients

Even though impairments and dysfunction vary considerably among ACL injured patients - both in levels they reach and the time it takes (3, 15, 83, 155, 191, 198) - studies usually report outcomes averaged over all patients. Hence, current research may oversimplify complex variability in outcomes.

The previously mentioned coper classification was an attempt to group patients according to PROMs, functional performance, and instability symptoms (69). Whether patients in the same classifications followed distinct trajectories of outcomes over time is, however, not known. In other musculoskeletal research and psychology, sophisticated methods have been developed to identify different phenotypes and subgroups following distinct developmental courses over time. They have improved our understanding of different responses to disorders such as depression, hyperactivity, post-traumatic stress disorder, substance abuse, degenerative meniscus injuries, and OA (20, 34, 105, 161, 162). No such studies have been identified after ACL injury or in a comparable patient group (young, active individuals with acute knee injuries) – here lies a considerable potential for future research.

Aims of the dissertation

The overall aims of this dissertation were to (I) evaluate the five-year outcomes of the treatment algorithm used in the Delaware-Oslo ACL cohort study - which included patient education and a five-week progressive neuromuscular and strength training program prior to shared decision-making about treatment - and (II) explore subgroups of ACL injured patients and identify factors associated with outcomes. The first overall aim was addressed in papers I and II, and the second overall aim was addressed in papers III and IV.

The following specific aims were addressed in the four papers included in this dissertation:

1) To describe the five-year clinical, functional, physical activity, and radiographic outcomes for patients who followed our treatment algorithm (papers I and II)

2) To compare the five-year clinical, functional, physical activity, and radiographic outcomes among patients who chose (1) early ACLR with pre- and postoperative rehabilitation, (2) delayed ACLR with pre- and postoperative rehabilitation, or (3) progressive rehabilitation alone (papers I and II)

3) To systematically review the literature on prognostic factors for patient-reported outcome measures and physical activity two to ten years after ACL reconstruction or rehabilitation alone (paper III)

4) To identify subgroups of ACL injured patients who share common five-year trajectories of patient-reported knee function following our treatment algorithm (paper IV)

5) To assess associations with trajectory affiliation (paper IV)

Methods and material paper I, II, and IV

Ethical considerations

The study received approvals from the Regional Committee for Medical and Health Research Ethics of Norway, The Norwegian Data Protection Authority, and the University of Delaware Institutional Review Board (appendix I and III).

Participation in the study was voluntary. Written informed consents (or assent with parental consent for patients under 18 years of age) were acquired from all patients before inclusion and follow-ups (appendix II). The rights of the participants were protected by the principles outlined in the Declaration of Helsinki. During the first contact, the participants received information about the criteria for participation, the purpose of the study, the participant's right to withdraw at any time without any penalties, potential benefits and risks of participation, assurance of confidentiality and terms of remuneration. All patients were informed that participation in the study would not influence their treatment choice and other clinical decisions.

There is a slight risk that participants may experience "give way" in the knee or knee joint tenderness during/after the single-legged hop tests or muscle strength tests. The testing procedures are identical to the clinical procedures currently being used/have been used in our clinics. Therefore, this risk is not present in patients included in research exclusively.

There are minimal risks involved in the radiographic evaluation due to radiation. However, all participants were over 18 years old at the five-year follow-up and pregnant participants were not tested.

Study design

The Delaware-Oslo ACL Cohort Study is a prospective study on ACL injured athletes in pivoting sports. The study follows cohorts both in Delaware (n=150) and Oslo (n=150). Professor Lynn Snyder-Mackler is the principal investigator (PI) and in charge of the American arm of the project located at the University of Delaware. Professor May Arna Risberg is the co-PI and in charge of the Norwegian arm of the project which is formally anchored at Oslo University Hospital. The study is funded by the National Institutes of Health through grants R01HD37985 and R37HD37985.

Subjects

Three hundred patients were consecutively enrolled from the University of Delaware, Newark, Delaware, United States, or the Norwegian Sports Medicine Clinic, Oslo, Norway, between 2006 and 2012. Complete unilateral ACL injury and concomitant injuries were verified with MRI and increased anterior knee joint laxity measured with a KT1000 arthrometer (MEDmetric Corporation). The inclusion criteria were age between 13 and 60 years and preinjury participation in level-I or II sports as defined by Hefti et al. (99) ≥2 times/week (defined in table 1). We excluded patients with current or previous ipsilateral or contralateral knee injuries, concomitant grade-III ligament injuries, full-thickness articular cartilage damage or fracture, and patients who were unable to attend preoperative rehabilitation. Before inclusion in the study (within 3 months after injury in Oslo or within 7 months after injury in Delaware), all patients had to normalize acute impairments (have no or minimal pain or effusion during or after plyometric activities). Otherwise, they were excluded (for example, patients with symptomatic meniscal injuries). Patients who were diagnosed with obviously repairable menisci on MRI, such as bucket-handle tears with locked knees, were also excluded and referred to an orthopaedic surgeon.

Among the original cohort of 300 patients, 24 had had a previous ACLR and came to our clinics with a graft rupture; those patients were incorrectly included and therefore excluded from the present studies because we aimed to assess patients with primary ACL injuries. Hence, study I, II, and IV included 276 patients (142 from Oslo and 134 from Delaware).

Table 1. Sports Activity Classification as defined by Hefti et al. (99).

Level	Sports Activity	Example of Sports
I	Jumping, cutting, pivoting	Soccer, football, handball, basketball, floorball
II	Lateral movements, less pivoting than level-I	Tennis, squash, alpine skiing, snowboarding, gymnastics, baseball, softball
III	Straight-ahead activities, no jumping or pivoting	Running, cross-country skiing, weightlifting
IV	Sedentary	

The treatment algorithm used the Delaware-Oslo ACL cohort study

Figure 1 describes the treatment algorithm used in the Delaware-Oslo cohort, follow-up timepoints, patient flow, and publications from the cohort. All patients underwent acute rehabilitation to normalize effusion and range of motion before inclusion in the study (mean 58 days after injury). Immediately after impairment resolution, all patients underwent testing before a five-week (mean 10 sessions) rehabilitation program with progressive neuromuscular and strength training exercises as previously described by Eitzen et al. (54). Patient education, including information about ACLR versus rehabilitation alone, occurred during this rehabilitation phase. Patients were then tested again and made their treatment choices in a shared decision-making process with their orthopaedic surgeons and physiotherapists. Patients experiencing dynamic knee instability (220) after the five-week rehabilitation program and those who intended to return to level-I sports were more likely to be recommended ACLR. Grindem et al. (83) previously reported that 77% of those who chose early ACLR reported intention to return to level-I sports as their reason to choose surgery. Despite our recommendations, 34% of those who chose progressive rehabilitation alone reported that they intended to return to level-I sports (83). Achieving good knee function after rehabilitation was the main reported reason for choosing progressive rehabilitation alone as their management (83). Delayed ACLR was performed if patients changed their minds or experienced dynamic knee instability.

Early versus delayed ACLR was defined as reconstruction performed ≤six versus >six months after completion of the five-week rehabilitation program (timepoint of post training test).

Several experienced orthopaedic surgeons performed the ACLRs using bone-patellar tendon-bone autografts (21.5%), single-bundle or double-bundle hamstring autografts (51.5%), or allografts (27%). At the time of early or delayed ACLR, 81 of 197 (41%) patients had concomitant meniscal surgeries, whereof either repairs (56%), excisions (26%), or trephination/rasping (18%). Postoperative rehabilitation was individually adjusted to concomitant injuries, graft type, and knee function and consisted of three phases. (1) The acute postoperative phase addressed swelling, range of motion, and atrophy. (2) The milestones of the rehabilitation phase were to regain neuromuscular control and to achieve ≥80% muscle strength and hop performance limb symmetry index (LSI). (3) In the return to sport phase, the patients gradually increased participation in sports-specific training and the milestones were to achieve ≥90% muscle strength and hop performance LSI. Those who did not undergo ACLR typically continued progressive rehabilitation with the same phases for 3-4 months and underwent the same testing as those who underwent ACLR.

All patients were advised to regain ≥90% LSI on quadriceps and hamstring strength tests and single-legged hop tests before returning to level-I and level-II sports. After ACLR, patients were recommended to avoid level-II sports for the first six postoperative months and level-I sports for the first nine postoperative months.

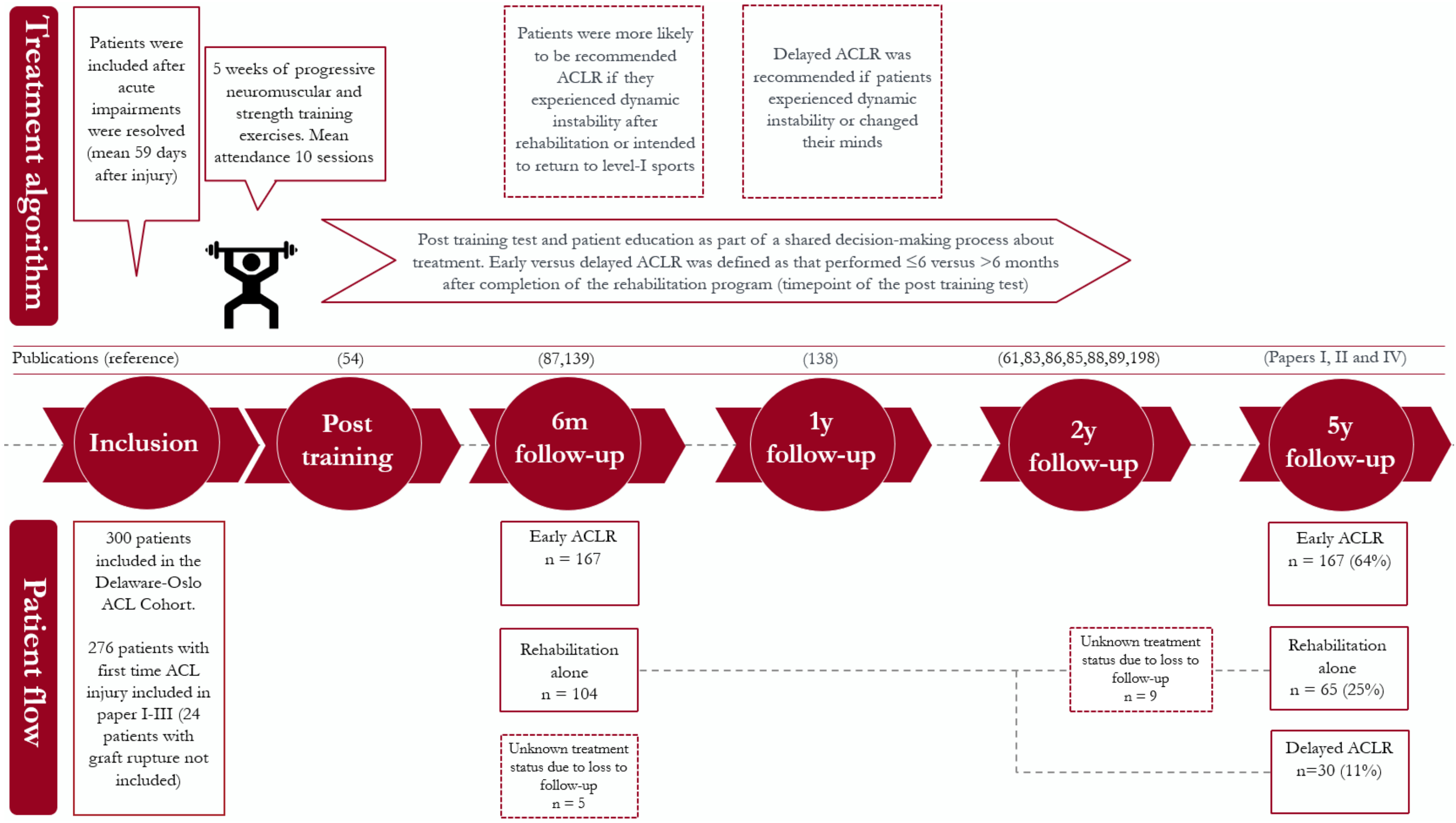

Figure 1. Treatment algorithm, follow-ups, patient flow, and publications from the cohort.

Outcomes

Paper I: Clinical, functional, and physical activity outcomes

Clinical outcomes

Patient-reported knee function was measured using the International Knee Documentation Committee Subjective Knee Form (IKDC-SKF)(8, 114, 115, 208) and Knee Osteoarthritis Outcome Score (KOOS)(37, 180). KOOS consists of five subscales: pain, other symptoms, activities of daily living (ADL), function in sport and recreation (Sport/Rec), and knee-related quality of life (QoL) (180). The minimal important change (MIC) is 11.5 points for the IKDC-SKF (115), 12.1 points for KOOS Sport/Rec, and 18.3 points for KOOS QoL (111).

In addition to calculating the mean and standard deviation, we classified patients as above or below the top 15th normative percentile for age and sex-matched subjects with healthy knees for the IKDC-SKF (8) and above or below the PASS threshold for the IKDC-SKF, KOOS Sport/Rec, and KOOS QoL (158).

Patients reported new ipsi- and contralateral knee injuries on a project-specific form. The diagnosis was verified with clinical examination, including arthrometer measurements, MRI reports and/or during surgery if indicated.

Functional outcomes

Quadriceps strength testing was performed with maximal voluntary isometric contraction in Delaware and with concentric isokinetic testing in Oslo (138). For both methods, the peak torque was recorded, and the uninjured leg was tested first. The isometric strength test (three repetitions) was performed with hips and knees in 90° of flexion using an electromechanical dynamometer (Kin-Com; DJO Global). The isokinetic strength test (four trial repetitions and five test repetitions) was performed at 60˚/seconds between 90˚ flexion and full extension (Biodex6000; Biodex Medical Systems).

Four single-legged hop tests were carried out in the following order: the single hop for distance, the crossover hop for distance, the triple hop for distance, and the six-meter timed hop (87, 139, 176). We tested the uninjured leg first. One practice trial was performed before we recorded two trials, whereof the mean score was calculated. During the three first hop tests, we considered trials valid if the final landing was stable: Trials were ruled invalid and repeated if the patients touched the floor or walls with their other foot or hands or performed an additional hop. Due to clinic guidelines, patients in Delaware completed the tests with a functional knee brace, while patients in Oslo did not wear a brace.

Physical activity outcomes

Sports participation was recorded using the question "What sports or exercise are you participating in now?". The most knee-demanding sport was graded from I to IV according to the classification of Hefti et al. (99) (table 1). The Marx Activity Rating Scale was used to assess frequency of participation in sports involving running, pivoting, cutting, and deceleration (148).

Paper II: Radiographic outcomes and knee pain

Radiographic outcomes, tibiofemoral joint

Standardized, weight-bearing radiographs of the tibiofemoral joint were taken bilaterally from a posteroanterior view. In Oslo, a fixed flexion protocol with 10° caudal beam angulation and a SynaFlexer Positioning Frame (Synarc, Inc, Denmark) to ensure reproducible knee alignment and angulation was used (108, 126). In Delaware, the Lyon-Schuss protocol was used: The x-ray beam was adjusted for each image to align with the medial tibial plateau (132), and the patients were positioned with a 30º knee flexion with the pelvis, thighs, and patella flush against the film cassette and coplanar with the tips of the great toes.

An experienced radiologist, previously demonstrated to have a high intrarater reliability (kappa = 0.77)(166), graded all the radiographs according to the Kellgren and Lawrence (K&L) classification (125). The K&L classification assesses radiographic knee OA based on osteophyte and joint space narrowing severity (grade 0, normal to 4, severe) and is well recognized (5, 125, 133). We used the modified K&L classification of Felson et al. (62) which distinguishes between both definite osteophyte and possible joint space narrowing (K&L grade 2) and definite osteophyte without joint space narrowing (K&L grade 2/osteophyte). K&L grade ≥2 was defined as radiographic OA, while K&L grade ≥2/osteophyte was included as an alternative cut-off for early radiographic changes in the tibiofemoral joint (62, 170). We included K&L grade ≥1 as another alternative cut-off for early radiographic changes: K&L grade 1 (doubtful joint space narrowing and possible osteophytic lipping) has been associated with progression of radiographic features (95), might be treated as early phase joint disease (183, 199).

Since the K&L classification is highly osteophyte-centric, another aspect of joint degeneration can be captured with measures of tibiofemoral minimum joint space width (mJSW). mJSW is a quantitative measure and reflects the thickness of articular cartilage and meniscal pathology (109, 137). Substantial tibiofemoral mJSW changes are associated with pain and worse quality of life and are common early after ACLR (200, 201). The radiologist used the most apparent cortical strip (interpreted as the anterior rim) of the femur and the tibia to perform manual measures of mJSW at the narrowest point in each compartment. Manual mJSW measurements have previously shown high reproducibility (175). One or more mJSW measures were impossible to perform due to poor projection or overexposure for 26 patients. Since variation in protocols and radiograph quality affect mJSW measures (132, 150, 210), we expressed medial and lateral mJSW as the difference between the index and the contralateral knee ($mJSW_{diff}$) for statistical analysis.

At the Oslo site, additional radiographs of the patellofemoral joint were taken using a skyline view and a lateral view. Due to the high prevalence of symptomatic patellofemoral OA after ACL injury (43, 44, 46), it would have been highly relevant to assess this variable for the whole cohort.

Knee pain

Patients were classified as having knee pain if they had KOOS pain scores ≤72 points (two standard deviations below the reported normal mean value in an athletic population). This cutoff has previously been used to identify patients with a painful knee or early symptomatic knee OA in ACL patients (213, 214).

Paper IV: Patient-reported outcome measures

We explored trajectories of patient-reported knee function using the IKDC-SKF. Patients completed the questionnaire at inclusion, after the five-week rehabilitation program with progressive neuromuscular and strength training exercises, and at follow-ups six months, one year, two years, and five years after either ACLR (surgically treated patients) or completion of the five-week rehabilitation program (patients treated with rehabilitation alone). For patients who underwent delayed ACLR before the two-year follow-up, their timelines were reset, and they underwent new six-month and one-year follow-ups as surgically treated. We included only the postoperative six-month and one-year data for this delayed ACLR group to allow for more equal comparisons of individual trajectories (avoid postoperative periods at different timepoints and include the same number of follow-ups across treatment groups).

Data management and statistics

Paper I

As previously described, early versus delayed ACLR was defined as reconstruction performed ≤six versus >six months after completion of the five-week rehabilitation program (timepoint of post training test).

The rates of new ipsilateral or contralateral knee injuries were calculated among those who attended either the two-year or the five-year follow-up. We reported muscle strength and single-legged hop performance with the LSI (i.e., the performance of the involved limb as a percentage of the performance of the contralateral limb).

Sample-size estimation showed that we needed 25 patients in each treatment group to detect a between-group difference in IKDC-SKF scores larger than the MIC of 11.5 points (115) with an estimated standard deviation of 12 (83) with an alpha level of 0.017 and 80% power.

We assessed differences in outcomes between patients who chose early ACLR, delayed ACLR, and rehabilitation alone with one-way analysis of variance (ANOVA) tests for continuous variables and chi-square tests or Fisher exact tests for categorical variables. According to the Kolmogorov-Smirnov test, most continuous variables were skewed. We still decided that they were close enough to a normal distribution to use parametric tests based on the high number of participants, and inspection of histograms and skewness (60).

Paper II

We reported descriptive statistics for all outcomes for each of the three treatment groups, including separate statistics for those with and without new/concomitant injuries to the index or contralateral knee. We assessed group differences in nominal outcome variables with chi-square tests, and group differences in continuous variables with ANOVA testes.

Paper IV

We used group-based trajectory modeling (GBTM) to identify subgroups of patients who followed distinct five-year trajectories of IKDC-SKF (160, 161). We used the *traj* software plugin for Stata (121). The censored normal model was chosen because the IKDC-SKF is measured on a continuous scale with a prespecified range (121). GBTM imputes missing values based on available data points (160).

We used a two-stage model selection process (160). First, we identified the optimal number of trajectories. The procedures changed the number of trajectories and repeated the analyses until the trajectory number with the highest (least negative) Bayesian information criterion (BIC) value was found. A higher BIC value indicates a better model fit through balancing improvements in model likelihood with the number of estimated parameters (160). Second, we identified the optimal trajectory shapes by changing the order of the polynomial for each trajectory (zero-order, linear, quadratic, or cubic). The optimal model with the highest BIC value was finally chosen. We also evaluated trajectory sizes (>5% of the cohort should belong to the smallest trajectory) (160).

To assess the model adequacy of the chosen model, we calculated posterior group-membership probabilities and odds of correct classification. The posterior group-membership probability is the probability that an individual with a specific IKDC-SKF profile belongs to each possible trajectory (the sum of probabilities for each patient is 1). All patients are then assigned to the trajectory with the highest posterior group-membership probability. The mean posterior probability for each trajectory should be ≥0.7 (scale from 0-1, where 1 indicates the lowest probability that the individuals could belong to a different trajectory than they were assigned to) (160). The odds of correct classification for each trajectory should be >5 and estimated group probabilities and percentages actually assigned should correspond well (160).

Two sensitivity analyses were performed to assess the robustness of the chosen model: (1) Excluding patients with only one data point for IKDC-SKF (n=5). (2) Using months since inclusion as the time variable for all patients: Including all follow-up time points for the patients who underwent delayed ACLR (six-month and one-year data both as non-surgically and surgically treated). This model contained the most valid timeline but caused challenges with different numbers of follow-ups between treatment groups. This model was also problematic because it allowed for postoperative periods at different time points which complicated the comparison of individual trajectories.

Multinomial logistic regression was used to assess associations with trajectory affiliation. Due to sample size, we chose univariable analyses. Post GBTM analysis, we chose the *Moderate* trajectory as the reference of the analysis based on clinical relevance and power. The different types of new ipsilateral and contralateral knee injuries were merged to increase statistical power.

Methods and material paper III

Paper III was a systematic review conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (152). The study protocol was published in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42018095602) on June 7th, 2018.

Eligibility criteria

Studies were included according to the inclusion and exclusion criteria described in table 2. Prognostic factors were defined as either patient characteristics (e.g. age, sex, psychological factors), factors related to the injury (e.g. concomitant injury), or knee symptoms and function (e.g. functional performance, PROMs) that were assessed within one year after injury or ACLR.

The following PROMs were selected based on their frequent use as stand-alone PROMs for long-term outcomes during the last decade and because they have good measurement properties (8, 36, 114-116, 180, 208); the KOOS, the IKDC-SKF, and the Knee Outcome Survey Activities of Daily Living Scale (KOS-ADLS). The KOOS and the IKDC-SKF have previously been described. The KOOS can be reported as individual subscales or as $KOOS_4$ which is an average score of four subscales (KOOS ADL excluded). The KOS-ADLS assesses the impact of symptoms on patients' ability to perform daily activities (116). All three questionnaires are scored from 0 (worst) to 100 (best).

Table 2. Inclusion and exclusion criteria paper III.

Inclusion criteria	**Exclusion criteria**
Study design: Prospective cohorts and randomised clinical trials Subjects: Adults and adolescents (mean age > 13 years) undergoing either ACLR or rehabilitation alone after complete ACL injury Reporting of prognostic factors for PROMs or level of physical activity, at a mean of ≥ two and <ten years after ACL injury or reconstruction Statistical analysis: Using regression analyses for assessment of association between exposure and outcome. Language: English	Studies *only* on revision ACLR, knee dislocations, partial tears, or bilateral injury. We included studies where a subset of patients had these conditions

We included all outcomes reflecting type and level of physical activity, including the three components defining physical activity: frequency, intensity, and duration (29) (e.g. objective measures such as accelerometers, patient-reported physical activity questionnaires, and return to sports). An example of a PROM that measures physical activity in ACL injured individuals is the Marx Activity Rating Scale - a brief survey on the frequency of participation in sports involving running, pivoting, cutting, and deceleration (148).

Data sources and searches

We systematically searched PubMed, Web of Science, and SPORTDiscus for articles published from database inception to 20th September 2018. Librarians at the Norwegian School of Sport Sciences and the University of Oslo both assisted in and reviewed the database searches. See the search strategy for PubMed in table 3. Filters on "Humans" and "English language" were used and all free text words/terms were searched on "Title/abstract". Relevant systematic reviews were identified with the same search terms in PubMed and reference lists from systematic reviews and included studies were hand-searched for relevant material. To identify additional literature, the following simplified search was performed in Google Scholar: "Anterior cruciate ligament"|ACL Prognosis|"Prognostic factors"|Predict|Associations "Return to sports"|Participation|"Activity level"|"Physical activity"|Tegner|Marx|KOOS |IKDC|KOS "Prospective study"|"Observational study"|"Cohort study"|RCT". The 100 first (and most relevant) results from Google Scholar were screened.

Study selection and data extraction

Screening for eligibility and data extraction was performed by two independent researchers (M.P. and J.L.J.). Customized data extraction forms and Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia, available at www.covidence.org) was used to assist this process. Calibration exercises were performed to ensure consistency between reviewers, but the agreement was not tested. We resolved discrepancies by discussion or a third reviewer (H.G. or M.A.R.). We screened titles and abstracts to identify potentially relevant studies for full-text eligibility assessment, and the reasons for exclusion were recorded. When several exclusion criteria were fulfilled, the first reason on a predefined list was chosen. We contacted study authors to resolve uncertainties when necessary.

Table 3. PubMed search paper III.

Search strategy and terms	
1)	Anterior cruciate ligament[mesh terms] OR Anterior cruciate ligament injury[mesh terms] OR Anterior cruciate ligament reconstruction[mesh terms]
2)	Anterior cruciate ligament OR ACL
3)	Prognosis[mesh terms]
4)	Prognosis OR Prognostic factors OR Prognostic factor OR Predictor OR Predictors OR Predict OR Prediction OR Predictive OR Effect modifiers OR Effect modifier OR Risk factors OR Risk factor OR Factor OR Factors OR Associated OR Association OR Associations
5)	Return to sport[mesh terms]
6)	Return to sport OR Return to sports OR Participation OR Activity level OR Physical activity OR "Tegner activity scale" OR "Marx activity rating scale" OR Return to play OR KOOS OR "Knee injury and Osteoarthritis Outcome score" OR "International Knee Documentation Committee subjective knee form" OR "IKDC-SKF 2000" OR IKDC-SKF2000 OR "International Knee Documentation Committee Subjective Knee Evaluation Form" OR "IKDC-SKF" OR "Knee Outcome Survey" OR KOS
7)	Prospective studies[mesh terms]
8)	Prospective studies OR Prospective study OR Observational study OR Cohort study OR Randomized controlled trial OR Randomized clinical trial OR Randomised controlled trial OR Randomised clinical trial OR RCT OR Randomised trial OR Randomized trial
9)	1 OR 2
10)	3 OR 4
11)	5 OR 6
12)	7 OR 8
13)	9 AND 10 AND 11 AND 12

Risk of bias assessment

Three independent reviewers (M.P., J.L.J., and K.M.) assessed risk of bias using the Quality in Prognosis Study (QUIPS) risk of bias tool (98). This tool was chosen because it was developed specifically for the methodological assessment of prognostic studies: QUIPS is a reliable tool for systematically assessing risk of bias in the following six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting (98). The confounding domain was classified as irrelevant for studies where the objective was prediction and not etiology (103, 187).

The overall risk of bias for each study was classified as (1) low, if there was a low risk of bias in all domains, (2) moderate, if there was a moderate risk of bias for ≥one domain and (3) high, if there was high risk of bias for ≥one domain (104). High risk of bias was defined as a level where the results of the study should not be trusted, and/or it was impossible to interpret due to research methodology and/or inadequate description of methodology. Classifying a high risk of bias was an overall decision - no study was classified as high risk of bias in any domain based on only one question.

Data synthesis and analysis

We included only studies with low or moderate risk of bias in the data synthesis to ensure robust conclusions and recommendations and to make the results easier to interpret and translate into practice. Results from all included studies (n = 20) were presented in supplemental material. We included only the most recent publication if data from the same patients were used in publications on the same prognostic factors and outcomes at different time points. We presented results separately for patients treated with ACLR and rehabilitation alone, and for the outcomes PROMs and level of physical activity and for. Results from adjusted analyses were preferred.

It was impossible to perform a meta-analysis due to methodological diversity in outcome measures and follow-up time.

We used the "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) approach to judge the certainty of evidence for each prognostic factor as high, moderate, low, or very low (107, 113). We used GRADEpro (Evidence Prime Inc, Hamilton, Canada) to help generate evidence summaries (79).

Results and discussion

Five-year outcomes following the treatment algorithm used in the Delaware-Oslo ACL cohort study (papers I and II)

Results papers I and II

At five years, 222 patients (80%; 74% in Delaware and 87% in Oslo) returned the IKDC-SKF, and 187 patients (68%; 55% in Delaware and 80% in Oslo) attended radiographic examination. Between 59% and 70% attended the different muscle strength and hop performance tests. Among the patients lost to five-year follow-up, 14 patients (5% of the cohort) had been managed with rehabilitation alone at their latest attended follow-up, but we were unable to ascertain whether they had had a subsequent operation. Important descriptive characteristics of the whole cohort (n=276) are given in table 4.

Table 4. Descriptive characteristics of the whole cohort at inclusion.

	Whole cohort (n=276)
Inclusion site (Delaware/Oslo)	134/142
Age, years*	26.5 ± 9.8
Sex, n females (%)	128 (46%)
BMI, kg/m²*	24.6 ± 4.0
Preinjury sports participation, n (%)	
Level-I	191 (69%)
Level-II	85 (31%)
Concomitant injuries, n (%)†	
Medial meniscus	64 (23%)
Lateral meniscus	48 (17%)
Cartilage	22 (8%)
MCL grade I or II	60 (22%)
LCL grade I or II	8 (3%)

*Values are given as the mean ± standard deviation. †Number of patients diagnosed with the injury using MRI at inclusion.

Among the patients with confirmed treatment status at five years, 167 (64%) had undergone early ACLR (defined as reconstruction performed ≤ six months after the five-week rehabilitation program), 30 (11%) delayed ACLR (defined as reconstruction performed > six months after the five-week rehabilitation program), and 65 (25%) progressive rehabilitation alone (figure 1). The patients who chose rehabilitation alone were older ($p<0.001$), had less concomitant medial meniscus injuries ($p=0.027$), and participated in less level-I versus level-II sports preinjury ($p<0.001$) compared to those who underwent early or delayed ACLR.

We found good clinical, functional, physical activity, and radiographic outcomes following our treatment algorithm: Among the whole cohort, 85%, 85%, and 79% scored above a PASS threshold for the IKDC-SKF, KOOS Sport/Rec, and KOOS QoL, respectively (83%-87% in the early ACLR group, 65%-78% in the delayed ACLR group, and 77%-88% in the rehabilitation alone group). Seventy-one percent of the cohort scored above the top 15th normative percentile for age and sex matched subjects with healthy knees for the IKDC-SKF (72% in the early ACLR group, 61% in the delayed ACLR group, and 73% in the rehabilitation alone group). The mean LSI for all muscle strength and single-legged hop tests were close to 100%. More than 95% were still active in some kind of sports. Among the two ACLR groups, 12% sustained a graft rupture. New ipsilateral meniscus injuries occurred in 8% of the cohort (paper I). Only 6% of the cohort had radiographic tibiofemoral OA (K&L grade ≥2) in the index knee, and 4% in the contralateral knee. Only 6% of the cohort had knee pain (paper II).

To contribute with different constructs of joint disease in paper II, we reported a range of tibiofemoral radiographic outcomes and knee pain in addition to the established OA cutoff at K&L grade ≥2. Using alternative OA cutoffs at K&L grade ≥2/osteophyte and K&L grade ≥1, 20% and 33% had knee OA in the index knee and 18% and 29% in the contralateral knee, respectively.

There were no statistically significant differences in any five-year clinical, functional, physical activity, or radiographic outcome among the three treatment groups.

Comparison of results to previous studies

How are the five-year outcomes of the Delaware-Oslo cohort compared to previous comparable studies?

Grindem et al. (86) and Failla et al. (61) have previously reported superior two-year KOOS outcomes among the surgically treated patients in the Delaware-Oslo ACL cohort compared to patients receiving "usual care" represented by matched patients from the NKLR and the Multicenter Orthopaedic Outcomes Network (MOON) cohort. These findings were attributed to the extended preoperative and high-quality postoperative rehabilitation (61, 86). No such statistical comparisons were performed in papers I and II, but simple comparisons of five-year outcomes of the Delaware-Oslo ACL cohort with other comparable studies are provided in table 5: The surgically treated patients in our cohort had superior five-year IKDC-SKF scores (difference in medians > the MIC for the instrument) compared to the six-year scores of the MOON cohort (191). They also had superior KOOS Sport/Rec scores (difference in means > the MIC for the instrument) compared to patients with primary ACLR in the Swedish National Anterior Cruciate Ligament Register (128). The outcomes of our cohort were, however, similar to the Hospital of Special Surgery (HSS) ACL Registry for the IKDC-SKF and to the MOON cohort for the KOOS Sport/Rec and QoL subscales.

The rate who scored above the PASS threshold for the IKDC-SKF, KOOS Sport/Rec, and KOOS QoL also seemed high across treatment groups in our cohort: 85% for the IKDC-SKF, 85% for the KOOS Sport/Rec, and 79% for the KOOS QoL - defined using the PASS thresholds identified by Muller et al. (158) at mean 3.4 ± 1.3 years after ACLR (figure 2). The rate who reported a PASS in the study of Muller et al. (158) was 89% - slightly higher than among our cohort. In contrast, only 65% reported a PASS two years after ACLR in the study of Ingelsrud et al. (110) from the NKLR (figure 2). When the PASS thresholds identified by Ingelsrud et al. (110) was applied to the two-year KOOS scores of the patients in the KANON trial, only 56% to 57% scored above the PASS threshold for the KOOS Sport/Rec and 42% to 48% for the KOOS QoL (179) (figure 2). It is, however, difficult to compare the rates who scored above the PASS threshold between our cohort and the KANON trial because Muller et al. (158) and Ingelsrud et al. (110) used different methods to establish the PASS thresholds.

The percentage who reported sports participation at their preinjury level at five years was quite high among the patients in our cohort who underwent rehabilitation alone and early ACLR (47% in both groups) compared to the corresponding treatment groups in the KANON trial (22% and 21%, respectively). The corresponding numbers were similar for the patients who underwent delayed ACLR in our cohort and in the KANON trial (26% versus 21%, respectively). Again, different definitions complicated comparisons: In our cohort, we defined sports participation at preinjury level as any reported participation in an activity at the same level (level-I or -II sports) at the time of follow-up. In the KANON trial, however, they defined sports participation at preinjury level as the same or higher Tegner activity scale which also considers the level of participation such as competition versus recreational sports. From the HSS ACL Registry, Randsborg et al. (174) reported that 69% of the patients had returned to sport after 8.1 years. However, they asked whether "they had returned to the sport they did before the injury", which does not implicate whether they still participated at the follow-up time point or not.

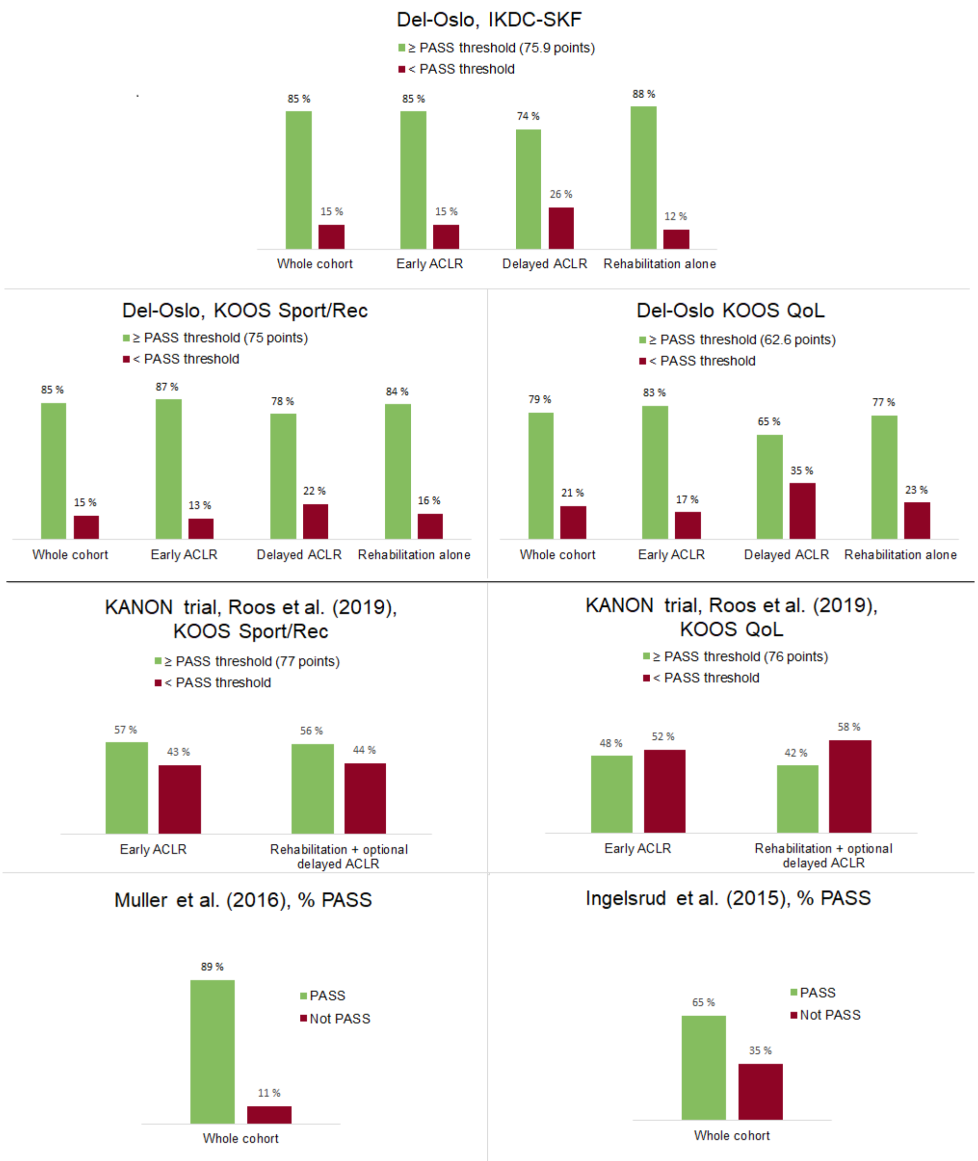

Figure 2. Comparisons of rates who reported a patient acceptable symptom state (PASS) or scored above a threshold for a PASS among the Delaware-Oslo cohort and comparable other studies.

Table 5. Outcomes following the Delaware-Oslo cohort and other comparable studies.

Study	Delaware-Oslo ACL cohort				MOON cohort	Swedish national ligament registry	KANON trial			HSS ACL registry	SURF cohort		
Follow-up timepoint (reference)	**5 years (papers I and II)**				**6 years (191)**	**5 years (128)**	**5 years (74)**			**7-9 years (174)**	**6.6 years (68)**		
Patient populations	**All with ACLR**	**Early ACLR**	**Delayed ACLR**	**Rehab-ilitation alone**	**All with ACLR**	**All with ACLR**	**Early ACLR**	**Delayed ACLR**	**Rehab-ilitation alone**	**All with ACLR**	**Early ACLR**	**Delayed ACLR**	**Rehab-ilitation alone**
IKDC-SKF	88[a]/93[b]	89[a]/94[b]	85[a]/92[b]	87[a]/91[b]	77[b]					84[a]			
KOOS Sport/Rec	88[a]/95[b]	89[a]/95[b]	81[a]/90[b]	87[a]/95[b]	90[b]	69[a]	76[a]	78[a]	81[a]				
KOOS QoL	78[a]/81[b]	80[a]/81[b]	70[a]/69[b]	78[a]/81[b]	81[b]	66[a]	71[a]	72[a]	66[a]				
Participation at preinjury activity level (%)	44%	47%	26%	47%			22%	20%	21%	69%	52%	37%	52%
Marx Activity scale	8[a]/8[b]	8[a]/8[b]	8[a]/8[b]	7[a]/7[b]	7[b]					8[a]			
Graft rupture (%)	12%	12%	19%				5%	3%					
Revision ACLR (%)						3%	3%	0%		7%			
New ipsilateral meniscus injuries (%)	8%	7%	11%	8%			5%	3%					
New ipsilateral meniscus surgeries (%)										7%			
Tibiofemoral OA (%)	8%	7%	15%	2%			16%	3%	12%				

[a] Values reported as means. [b] Values reported as medians. IKDC-SKF = International Knee Documentation Committee Subjective Knee Form, KOOS = Knee injury and Osteoarthritis Outcome Score, Sport/Rec= sports and recreation subscale, QoL= knee related quality of life, ACLR= Anterior Cruciate Ligament Reconstruction, OA= osteoarthritis

Direct comparison of radiographic tibiofemoral knee OA rates between studies can also be complicated: Different studies often use different classification systems and cut-offs, which highly affects OA rates. For example, the Osteoarthritis Research International (OARSI) atlas was used to assess five-year knee OA in the KANON trial and seems to produce twice as high OA rates compared to a K&L grade ≥2 which was used in our cohort (45). Hence, the five-year knee OA rates in the KANON trial and paper II correspond quite well (12% versus 6% for all patients in each study, respectively). Interestingly, the patients who underwent delayed ACLR had the lowest knee OA rate in the KANON trial but the highest rate in our cohort - even though there were no statistically significant differences between the treatment groups in any of our studies.

Outcomes after ACL reconstruction versus rehabilitation alone

Papers I and II showed, like the highest quality comparative studies on early ACLR versus rehabilitation alone with optional delayed ACLR, no statistically significant (73, 74) or clinically relevant (177) differences among treatment groups - for any clinical, functional, physical activity, or radiographic outcomes. The patient populations were also similar in our studies: Active patients in jumping, cutting and pivoting sports without substantial concomitant knee injuries. The "as-treated" analysis of the KANON trial also reported on the same treatment groups as papers I and II: early ACLR, delayed ACLR, and rehabilitation alone (73). Our studies consistently concluded that rehabilitation alone is a good solution for some patients. However, papers I and II are unique as they evaluate the outcomes of a specific treatment algorithm which included shared decision-making about treatment and an initial five-week rehabilitation program with progressive neuromuscular and strength training exercises for all included patients.

Unlike RCTs, the aims of papers I and II were to evaluate our treatment algorithm through describing and comparing outcomes in the three treatment groups. We, therefore, performed unadjusted analyses where differences in characteristics between treatment groups potentially influenced the results: Patients who chose rehabilitation alone were older, more likely to have participated in level-II sports preinjury, and less likely to have concomitant medial meniscal injuries compared with the two ACLR groups. Still, we found no statistically significant differences by treatment group, indicating similar outcomes even though different patients chose different treatments. Since our treatment algorithm is in line with current clinical practice in several countries and with current evidence-based recommendations (66), the external validity of our cohort study is high. Papers I and II also confirm the results of randomized trials (73, 74, 177) in a setting closer to the real world.

Systematic reviews including lower quality studies have also reported similar PROMs after ACLR and rehabilitation alone, while they found conflicting results whether patients treated with ACLR have fewer subsequent meniscus surgeries and higher activity levels (30, 188).

In contrast to our study - and longer term after ACL injury or reconstruction (>10 years versus five years after injury/surgery) – two recent systematic reviews found a higher risk of radiographic knee OA after ACLR compared to rehabilitation alone (94, 136). But due to low quality of included studies, we should interpret their results with caution (94, 136). Lien-Iversen et al. (136) reported that tibiofemoral knee OA rates ranged from 24% to 80% after ACLR and 11% to 68% after rehabilitation alone. These numbers were naturally much higher than our rates as our five-year radiographic outcomes represent early degenerative changes. In paper II, we concluded that our study reinforces the conclusions of previous studies with longer-term follow-ups (30, 136, 165) and animal studies (49) that ACL reconstruction does not protect the ACL injured knee from OA.

A five-year follow-up is quite early to assess knee OA. We, therefore, reported a range of tibiofemoral radiographic outcomes and knee pain in addition to the established OA cutoff at K&L grade ≥2 to contribute with different constructs of early joint disease in paper II. In paper II, we reported 3 to 7 times higher OA rates when alternative OA cutoffs at K&L grades ≥2/osteophyte and ≥1 were used. Still, we found no statistically significant differences by treatment group. We also found no differences in mJSW (expressed as the difference between the index and contralateral knee) between treatment groups. In contrast, studies using MRI to assess early cartilage degeneration show more pronounced changes after ACLR than after non-surgical treatment (205).

Even though not statistically significant, the results in paper I indicated a tendency towards worse clinical, functional, and physical activity outcomes in the delayed ACLR group - except for new meniscus injuries. We cannot rule out clinically relevant differences based on our study for two reasons. (I) The delayed ACLR group was small: It contained only 11% of the cohort, whereof 23 of 30 returned for five-year follow-up. (II) The 95% confidence interval (CI) for the mean differences between the delayed ACLR group and the two others included the MIC for the IKDC-SKF, KOOS Sport/Rec, and KOOS QoL (11.5 points for IKDC-SKF, 12.1 points for KOOS Sport/Rec, and 18.3 points for KOOS QoL) (111, 115) (Table 6). Also in paper II, we saw a tendency towards wide 95% CIs for knee OA (K&L ≥2), especially in the delayed ACLR group: 15% (95% CI, 3 to 38). The group who underwent early ACLR also had a tendency towards a more positive medial mJSWdiff than the delayed ACLR group: The mean difference between the two treatment groups at 0.4 mm (95% CI, –0.1 to 0.9) was larger than the previously reported smallest detectable difference between two measurements for mJSW of 0.26 to 0.28 mm (38, 52). It is important to bear in mind that the reasons for choosing delayed ACLR versus early ACLR were different, which may affect the outcomes: The main indication for delayed ACLR was dynamic instability, while the main reason for choosing early ACLR was to enable return to level-I sports. The KANON trial also performed subgroup analyses on the delayed ACLR group versus early ACLR and rehabilitation alone at two and five years with no statistically significant differences in KOOS scores or radiographic outcomes (73, 74). Hence, their results corresponded with ours. However, the KANON trial was not originally designed to assess the delayed ACLR subgroup specifically: Their power calculations were based on comparing outcomes after rehabilitation alone with optional delayed ACLR versus early ACLR and rehabilitation (73), not the delayed ACLR group versus the others. Hence, we need more studies to evaluate outcomes in this treatment group.

Table 6. Pairwise group comparisons for IKDC-SKF and KOOS outcomes, paper I.

	Progressive rehabilitation vs early ACLR mean difference (95% CI)	**Progressive rehabilitation vs delayed ACLR** mean difference (95% CI)	**Early ACLR vs Delayed ACLR** mean difference (95% CI)
IKDC-SKF	-1.6 (-6.4 to 3.1)	2.6 (-5.0 to 10.1)	4.2 (-2.8 to 11.2)
KOOS			
Pain	-0.1 (-3.6 to 3.3)	3.6 (-2.0 to 9.1)	3.7 (-1.4 to 8.9)
Symptoms	2.8 (-1.9 to 7.6)	5.7 (-2.0 to 13.3)	2.8 (-4.3 to 9.9)
ADL	-0.3 (-2.7 to 2.1)	0.5 (-3.4 to 4.4)	0.8 (-2.8 to 4.4)
Sports and recreation	-1.6 (-8.5 to 5.3)	5.9 (-5.1 to 16.9)	7.5 (-2.7 to 17.7)
Knee related quality of life	-2.0 (-9.5 to 5.5)	8.3 (-3.6 to 20.2)	10.3 (-0.8 to 21.3)

Abbreviations: IKDC-SKF, International Knee Documentation Committee Subjective Knee Form; KOOS, Knee Osteoarthritis Outcome Score

Even though long-term outcomes do not differ significantly statistically after early ACLR, delayed ACLR, and rehabilitation alone, these three treatment courses differ in nature. The length and timing of rehabilitation or a postoperative period may also matter to patients. When ACLR is chosen, we know that return to pivoting sports should be awaited until 9 to 12 months postoperatively (88, 209). In the first studies on rehabilitation alone, the primary aim was to enable completion of a sporting or labor season or a scholarship (69, 70) – which can be highly important for a patient. Choosing rehabilitation alone, however, can be more of a lottery: if successful, return to sports can be possible after a few months (215), but in the approximately

50% who opt for delayed ACLR, mostly due to instability symptoms (74, 177), their end of rehabilitation is postponed. This development of knee function, assessed using the $KOOS_4$, was very well described in the study of Frobell et al. (73), figure 3: At two years, all three "as-treated" groups in the KANON trial - early ACLR, delayed ACLR, and rehabilitation alone – had ended up at the same score. Their journeys of getting there were, however, different: The patients who underwent rehabilitation alone had the fastest improvement and at 6 and 12 months post-randomization, the patients who underwent delayed ACLR performed significantly worse - probably due to undergoing ACLR in this period or due to instability symptoms.

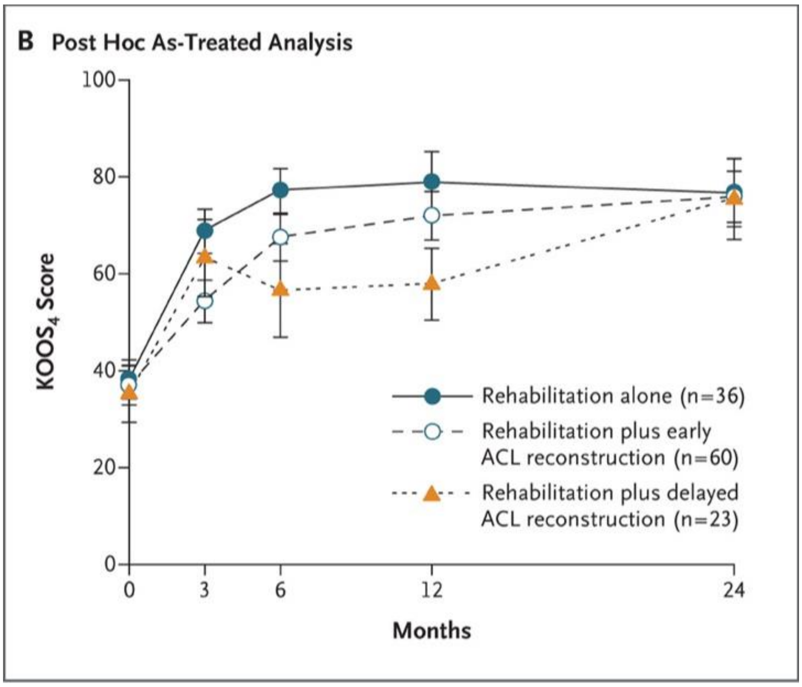

Figure 3. $KOOS_4$ scores for the three "as treated" groups, from Frobell et al. (74): rehabilitation alone, early ACLR, and delayed ACLR (Reprinted with permission. N Engl J Med 2010;363:331-42 Copyright 2010 Massachusetts Medical Society).

Both the KANON trial (73, 74) and the COMPARE trial (177) concluded that 50% of ACLRs can be avoided if a strategy with rehabilitation alone with optional delayed ACLR is chosen as the first-line treatment of ACL injuries in active athletes– without compromising patients' outcomes. Still, recommendations regarding ACLR versus rehabilitation alone are conflicting, especially for those who participate in level-I sports: An international consensus group of experts published "consensus regarding best available evidence on operative versus non-operative treatment for

ACL injury" in the British Journal of Sports Medicine (BJSM) in 2019 with a contradicting statement with 100% consensus: "In active patients wishing to return to jumping, cutting and pivoting sports (e.g., soccer, football, handball, basketball): Operative treatment is the preferred option to maintain athletic participation in the medium to long term (1 to 5+ years after injury)"(51). The big concern behind this statement was the risk of secondary meniscus and cartilage injuries in patients who return to sport with an ACL deficient knee (51).

Like the consensus paper of Diermeier et al. (51), patients in the Delaware-Oslo cohort were also recommended to undergo ACLR if they intended to return to level-I sports. Probably due to this advice, as many as 75% of our patients ended up with either early or delayed ACLR within five years: Based on the Norwegian patients in our cohort, Grindem et al. (83) previously reported that 77% of the patients who chose early ACLR reported intention to return to level-I sports as their reason to undergo surgery. Among those who initially chose rehabilitation alone, adherence to this recommendation was low: 34% of those who chose progressive rehabilitation alone reported that they intended to return to level-I sports (83). In paper I, we reported similar five-year rates of new meniscus and cartilage injuries after early ACLR, delayed ACLR, and rehabilitation alone: 7%, 11%, and 8% for meniscus injuries and 1%, 4%, and 0% for cartilage injuries, respectively. We also had almost identical rates of concomitant meniscus surgeries during early and delayed ACLR (41% and 40%) with no differences in concomitant meniscus injuries at inclusion (47% and 50%). Hence, our study did not confirm the reasoning for the consensus statement above (51) and the treatment advice given in our own study. Contrary, it indicates that rehabilitation alone does not increase the risk of new injuries compared to ACLR - supporting the conclusions of the other high-quality comparative studies in this area (73, 74, 177). On the other hand, neither paper I nor the referenced studies performed subgroup analyses on patients who returned to level-I sports, and future studies on this population are needed.

The real problem, however, seems to be that the prevalence of new knee injuries after ACL injury is high regardless of treatment: Among our cohort, a total of 20% (56 of 228) sustained one or more new injuries (meniscus, cartilage, ACL, or other ligaments) to either the same or contralateral knee within five years (paper IV). The risk is especially high in those who return to level-I sports (76, 88, 129). Fältström et al. (76) clearly captured this problem among young (aged 16-20 at injury) female soccer players: Within a mean follow-up at 6.5 years after ACLR, two-thirds of those who had returned to soccer had at some point sustained a new knee injury, whereof 42% were new ACL injuries to the same or contralateral knee.

Comparison of five-year outcomes in previous treatment algorithms

Compared to the SURF algorithm (68), the treatment algorithm used in the Delaware-Oslo cohort allocated more patients to ACLR: At a five-year follow-up, Fithian et al. (68) reported that 30%, 16%, and 54% had undergone early ACLR, delayed ACLR, and rehabilitation alone, respectively. Hence, with our corresponding rates of 64%, 11%, and 25%, almost twice as many underwent early ACLR, and less than half underwent rehabilitation alone in our cohort. The surgical advices in our two treatment algorithms were partly similar: Fithian et al. (68) recommended early ACLR if patients participated in level-I or -II sports >200 hours per year, while in the Delaware-Oslo cohort patients were more likely to be recommended ACLR if they intended to return to level-I sports. The recommendations in our two treatment algorithms differed in terms of knee stability: Fithian et al. (68) emphasized millimeters of passive anteroposterior knee laxity measured with an arthrometer, while in the Delaware-Oslo cohort, dynamic instability was a surgical indication.

Though both our cohorts included active patients in level-I and -II sports, comparisons between our cohorts are complicated by differences in study participants and outcomes: The SURF cohort was markedly older than the Delaware-Oslo cohort (mean age at inclusion 34 versus 26.5 years). Also, different PROMs were chosen as outcomes in the two cohorts: the Lysholm Knee Scoring Scale was assessed in the SURF cohort while IKDC-SKF and KOOS subscales were assessed in the Delaware-Oslo cohort. The rate who returned to preinjury activity levels were, however, similar among patients treated with early ACLR, delayed ACLR, and rehabilitation alone: 52%, 37%, and 52% returned among the SURF cohort, while 47%, 26%, and 47% returned among the Delaware-Oslo cohort, respectively.

Subgroups of ACL injured patients and factors associated with outcomes (papers III and IV)

Results papers III and IV

In paper III, the systematic review, we identified 974 references through database searches (PubMed, Web of Science, and SPORTDiscus) and 23 additional references through bibliographies, Google Scholar, and reference lists. Twenty studies met our inclusion criteria. Sixty percent of the included studies had a high risk of bias (judged using the QUIPS tool), and consequently, seven studies with low or moderate risk of bias remained for data synthesis. We found moderate certainty evidence (judged using the GRADE approach) for concomitant meniscus and cartilage injuries as prognostic factors for worse PROMs 2 to 10 years after ACLR. There was very low certainty evidence that higher BMI, smoking, and worse baseline PROMs were prognostic factors for worse PROMs, and that female sex and worse baseline Marx Activity Rating Scale score were prognostic factors for worse Marx Activity Rating Scale score 2 to 10 years after ACL reconstruction. There were too few studies on patients treated with rehabilitation alone to answer whether there were differences in prognostic factors between patients treated with ACLR versus rehabilitation alone.

In paper IV, we assessed the same 276 individuals as in papers I and II. We identified four distinct five-year trajectories of patient-reported knee function (measured with the IKDC-SKF) with good model-fit parameters: *Low* (8.9%), *Moderate* (50.2%), *High* (37.5%), and *High before declining* (3.4%) - indicating four subgroups of ACL injured patients. The trajectory with the largest number of patients (*Moderate*) follows typical clinical expectations; start low, end high. A slightly smaller but also considerable trajectory have relatively high scores at baseline and also progresses over time (*High*). A small percentage of patients (12%), however, either start low and stay low (*Low*) or start high and suffer a large deterioration between the two-year and five-year follow-up (*High before declining)*. Importantly, nearly 9 of 10 patients who followed our treatment algorithm belonged to the favorable *Moderate* and *High* trajectories, often not requiring surgery.

Early/preoperative quadriceps strength and hop symmetry, absence of give-way episodes between injury and inclusion, and undergoing rehabilitation alone versus early ACLR were predictors of a *High (*versus a *Moderate)* trajectory: For every 1% increase in quadriceps strength LSI and single-hop for distance LSI, there were 5% and 2% higher odds of affiliation to the *High* trajectory, respectively. Concomitant meniscus injuries and new ipsi- and contralateral knee injuries were the main characteristics of the patients who belonged to the unfavorable *Low* and *High before declining* trajectories. Concomitant meniscus injuries were associated with 3-fold higher odds of belonging to the *Low* versus the *Moderate* trajectory, which means increased odds of starting low and staying low instead of progressing to a good level of knee function. These associations were exploratory but supported the trajectories' validity (paper IV).

The association between concomitant meniscus injuries and worse PROMs was agreed in papers III and IV - in one systematic review and one experimental study. New ipsi- and contralateral knee injuries were also a prominent factor in the unfavorable *High before declining* trajectory in paper IV but was perhaps not assessed in paper III as an early prognostic factor was defined as measured within one year after injury/surgery. However, there is no logical reason to believe that a new knee injury would influence long-term outcomes any less than a concomitant one. The other identified associations in paper III were not supported as prognostic factors by the systematic review and should be assessed in future high-quality studies.

Comparison of results to previous studies

Like paper III, the systematic review of An et al. (7) also concluded that methodological shortcomings of included studies hindered solid conclusions on prognostic factors after ACLR. The only consistent prognostic factors for long-term PROMs identified in our systematic review (paper III) were concomitant meniscus and cartilage injuries. Previous systematic reviews confirm these associations with inferior outcomes (7, 48). Contrary, a recent high-quality cohort study found no effect of concomitant meniscus injuries or surgeries on five-year KOOS scores (203).

Prognostic factors with very low certainty in our systematic review (paper III) included higher BMI, smoking, and worse baseline PROMs (for worse PROM outcomes), and female sex and worse baseline Marx Activity Rating Scale (for Marx Activity Rating Scale outcome). Smoking and BMI were also identified as possible prognostic factors for long-term PROMs in the systematic review of de Valk et al. (48). As both of these factors are modifiable, smoking is associated with so many other negative health outcomes, and BMI is associated with increased risk of developing knee OA (96, 119, 226, 227), these factors should still be emphasized by clinicians.

The four distinct five-year trajectories of patient-reported knee function identified in paper IV were highly informative about expected outcomes and time to recovery for patients who undergo a similar treatment algorithm: They have a great potential for use in patient education about prognosis. However, no comparable studies – neither in ACL injured patients nor after other acute knee injuries – exist to support our findings. We, therefore, need future studies to validate our trajectory model.

Methodological considerations and limitations paper I,II, and IV

External validity

Compared with RCTs, the external validity of our study is high because our treatment algorithm is in line with current practice clinical recommendations (66, 209). Also, our cohort's mean age at inclusion was similar to large register studies in Norway and US (147). However, the external validity is limited to patients who are active in jumping, pivoting, or cutting sports preinjury; do not have substantial concomitant injuries; and have resolution of acute impairments within 3 to 7 months after injury. As most ACL injuries occur in pivoting sports (78, 81, 120, 122, 164), the first criterion did probably not exclude important ACL injured populations. In contrast, the exclusion of patients with substantial concomitant injuries such as bucket-handle meniscus tears, fractures, full-thickness cartilage, and other meniscus injuries leading to continued acute impairments such as pain and swelling, may lead to better clinical, functional, physical activity, and radiographic outcomes in our cohort compared to for example register studies.

Study design

In papers I and II, we did not measure the effect of ACLR versus rehabilitation alone. To assess treatment effect, the RCT is the gold standard study design. In our cohort study, different patients chose different treatments which introduce important confounding, especially confounding by indication (82). Based on two-year data from the Norwegian arm of the Delaware-Oslo cohort, Grindem et al. (83) have previously reported similar outcomes after ACLR and rehabilitation alone, adjusted for differences between treatment groups at inclusion (age and preinjury sports participation level). At five years, we aimed to describe and compare outcomes following our treatment algorithm for the whole cohort (papers I and II).

Follow-up rate

Our high five-year follow-up rate for PROMs (80%) is an important strength of a long-term follow-up (papers I and IV). Fewer patients, 59% to 70%, attended the functional tests (paper I). Also, fewer patients, only 68%, attended the radiographic examination (paper II). We found small but statistically significant differences between those who attended and those who did not attend the radiographic examination: The attendees (n=187) were significantly older (mean difference, 3.8 years) and had lower BMI at inclusion (mean difference, 1.3 kg/m^2) than those who did not attend (n= 89). These two factors may have affected our results: Among the attendees (versus non-attendees), older age may influence OA development in a negative direction (90), while lower BMI may influence in a positive direction (96, 119, 226, 227).

Power (paper I and II)

As previously discussed, there were tendencies towards worse clinical, functional, physical activity, and radiographic outcomes for the patients who underwent delayed ACLR compared to early ACLR and rehabilitation alone in paper I and II. This tendency could have been statistically significant if the delayed ACLR group was larger: Sample-size estimation showed that we needed 25 patients in each group to detect a between-group difference in IKDC-SKF scores larger than the MIC of 11.5 points (115) with an estimated standard deviation of 12 (83) with an alpha level of 0.017 and 80% power. Only 23 of 30 patients in the delayed ACLR group returned for follow-up. Further, the 95% CIs for the mean differences in five-year IKDC-SKF, KOOS Sport/Rec, KOOS QoL, and mJSWdiff between the delayed ACLR group and the other two treatment groups were wide and included the MIC or smallest detectable difference for these instruments.

Quality of radiographs and differences in protocols (paper II)

The difference in protocols for radiographic assessment between the two sites was a potential challenge in our study: The fixed flexion protocol using a SynaFlexer Positioning Frame (Synarc, Inc) (108, 126) was used in Norway, and the Lyon Schuss protocol (132) was used in Delaware. Though the two protocols offer similar reproducibility in JSW measurements (ICC 0.99 for both protocols), the Lyon-Schuss seems to be more sensitive to joint space narrowing, probably because it aligns the tibial plateau better (132). To further explore the consequence of using the two different protocols, we investigated the intermargin distance (IMD) of the radiographs.

The IMD is measured between the anterior and posterior margins of the medial tibial plateau and is affected by knee flexion and beam angle and indicates the alignment of the tibial plateau with the x-ray beam (150, 210). Importantly, IMD is correlated with JSW (132, 150, 210). The fixed flexion protocol may result in approximately twice as large IMDs as the Lyon-Schuss protocol, and a 1mm difference in IMD may result in a 0.10mm change in JSW (132). We measured the IMD of all radiographs to ensure that comparisons of mJSW between management groups and study sites were not affected by differences in IMD. IMD measures were performed manually approximately at the midpoint of the medial compartment in both knees.(194) Median (min-max) IMD in the index knee was 2.7 (0.5-11.5) mm, 3.2 (0.2-10.0) mm, and 1.5 (0.6-9.5) mm in the rehabilitation alone, early ACLR, and delayed ACLR groups, respectively. There were no statistically significant differences in IMD in the index (p=0.056) and contralateral knee (p=0.180) between the management groups. Also, there were no statistically significant differences in IMD in the index and contralateral knee between the two study sites (p=0.675 and 0.278).

Due to this crosscheck of IMD and no identified studies reporting variation in K&L scoring according to protocols for radiographic assessment, the K&L scorings in paper II were considered robust. To increase the reliability and validity of the mJSW measures, we chose to express medial and lateral mJSW as the difference between the index and contralateral knees (mJSWdiff).

Last, radiograph quality was also a challenge in some cases: For 26 patients, ≥1 mJSW measures were impossible to perform because of poor projection or overexposure.

Differences in protocols for muscle strength and single-legged hop tests (paper I)

In our statistical analyses, we had to account for differences in protocols between study sites for muscle strength and single-legged hop tests. In Delaware, patients wore a functional knee brace during single-legged hop tests, while patients in Oslo did not. Also, isometric quadriceps strength testing was performed in Delaware while isokinetic concentric strength testing was performed in Oslo. Therefore, we expressed results as LSI (limb symmetry index: the performance of the involved limb in percent of the contralateral) to overcome this issue.

Statistical analyses (paper IV)

Trajectory model selection process

The decision-making about statistical analysis in paper IV led to some comprehensive discussions that should be highlighted. (I) Choosing group-based trajectory modeling (GBTM), (II) defining the timeline, and (III) choosing a four-group over a three-group model.

(I) A trajectory describes the evolution of a repeated measure over time, for example, a quantity, behavior, or biomarker (162). There are several different approaches to assess trajectories: Both Growth mixture modeling (GMM) and group-based trajectory modeling (GBTM) are suitable for assessing parametric longitudinal data (162). According to the systematic review of Nguena Nguefack et al. (162), GBTM is often a practical choice because it is less complex and easier to interpret, while it has the same advantages i.e. regarding handling missing data and allowing for correlated residuals. Also, GBTM supposes that all individuals within a trajectory have the same behavior, whereas GMM allows for within-class variation. Hence, when GBTM is used, researchers can discuss differences between subgroups, but not differences within subgroups. The choice of GBTM was therefore most in line with the aim of study IV.

(II) It was also challenging to choose the best time variable: The most correct time variable (using time since inclusion or injury) versus the most practical and comparable time variable (using fixed intervals corresponding with the follow-up time points of the cohort study). We chose the latter to allow for more equal comparisons of individual trajectories. We also included only the postoperative six-month and one-year follow-ups for the delayed ACLR group to avoid postoperative periods at different time points within the trajectories and differences in the number of follow-ups across treatment groups. Hence, these time points should not be interpreted as a continuous timeline.

(III) It has previously been recommended that the smallest trajectory should contain >5% of the cohort (160). This recommendation was violated when we chose a four-group model over a three-group model. In the four-group model, the smallest *High before declining* trajectory contained only 3.4% of the cohort but had a higher (less negative) BIC value than the three-group model (BIC for the total number of participants at -5167 and BIC for the total number of observations at -5180 for the four-group model and corresponding -5182 and -5192 for the three-group model) - indicating a better model fit. Also, the *High before declining* trajectory was highly clinically relevant: these patients' trajectories deviated significantly from the three others. Hence, clinical relevance may have been prioritized over the model's robustness.

Univariable analyses of associations

Optimally, prognostic factors for trajectory affiliation would have been assessed - adjusted for relevant confounders. Sample size limited this option. For the smallest trajectory, the *High before declining,* comprising only 7 patients, it did not make sense to perform any statistical analyses at all – only descriptive statistics. The *Low* trajectory was also small (22 patients), and we were therefore not powered to include more than one factor in the regression analyses.

Methodological considerations and limitations paper III

It is important to highlight that overlap of patients between studies from the MOON cohort and the Swedish and Norwegian Knee Ligament Registries may have amplified the impact of the prognostic factors identified in paper III. To minimize this problem, we only included the most recent publication of data from the same patients and on the same prognostic factors.

Further, 12 of 20 included studies (60%) included in our systematic review were rated as having high risk of bias and were subsequently not included in the data synthesis. Bias was suspected especially in the domains "Study confounding" and "Statistical analysis and reporting". But grading risk of bias using the QUIPS tool was often challenging: Lack of clarity in aims and methods were often the reason for downgrading. Hence, these 12 studies might have had good quality but did not report accurately enough. For example, epidemiological research methodology has developed over time, and the distinction between explanatory and predictive aims was less clear at the time when some of the included studies were performed than when we performed our systematic review in 2020 (33, 103, 192, 218). We, therefore, included an appendix with a

GRADE evaluation of possible prognostic factors from all included studies (n=20) - and made the same conclusions.

Last, we might have missed high-quality research using other PROMs than the IKDC-SKF, KOOS, and KOS-ADLS, such as psychological, overall health, or overall QoL outcomes. For example, the Lysholm Knee Scoring Scale, Anterior Cruciate Ligament-Return to Sport after Injury scale, and SF-36.

Clinical implications

How should we guide surgical versus non-surgical decision-making based on the current knowledge?

The previous sections contain essential information that should be thoroughly communicated to ACL injured patients to guide their decision-making: (I) Approximately half (73, 74, 177) or potentially even more (papers I and II) of ACLRs can be avoided if a strategy with rehabilitation alone with optional delayed ACLR is chosen – without compromising long-term outcomes. (II) On a group level, there are no clinically important differences in any outcomes after early ACLR, delayed ACLR, and rehabilitation alone. (III) Yet, these treatment strategies differ in nature and timeframe. (IV) There is a broad agreement to recommend ACLR if patients experience dynamic instability after rehabilitation (51, 73, 74, 151, 177).

Since preoperative rehabilitation (61, 86, 185) and good preoperative muscle strength symmetry (53) can improve outcomes after ACLR, we have good evidence to recommend all patients to start a treatment course with rehabilitation alone and consider further decision-making about treatment as a process over their initial rehabilitation.

Shared decision-making is supported by evidence due to increased patient knowledge, more confidence in decisions, more active patient involvement - which is very important when compliance to rehabilitation is essential - and informed patients often choose more conservative treatment options (58). Proper patient education is fundamental for a shared decision-making process (58) and is also urgent as patients have way too high expectations to ACLR: A study on expectations to primary ACLR reported that all patients expected to regain normal or almost normal knee function and 94% expected to return to sports at the same level (63). Early patient education should also aim to facilitate focus on long-term outcomes such as prevention of secondary injuries and knee OA (178).

A few high-quality studies have started the important work of assessing predictors of success with rehabilitation alone: Based on two-year data from the Delaware-Oslo cohort, Grindem et al. (89) reported that patients with good early knee function, who were older or females, were more likely to succeed with rehabilitation alone - defined as having an IKDC-SKF score ≥15 normative percentile and not undergoing delayed ACLR. Notably, papers I and II showed that the factors distinguishing the patients who stayed with rehabilitation alone (n=65 of 95) from those who chose delayed ACLR (n=30 of 95) within five years were older age (age at inclusion 31.9 versus 24.4 years), preinjury participation in level-II instead of level-I sports (54% versus 17%), and less concomitant medial meniscus injuries (11% versus 27%). Based on a secondary analysis of the KANON trial, Filbay et al. (67) reported that patients with concomitant meniscus or cartilage injuries and lower KOOS scores early after injury may benefit most from an initial nonsurgical treatment choice. Further research on the topic is needed to draw conclusions and can make a great contribution to individualized treatment of ACL injuries.

Translating the identified prognostic factors and predictors into clinical practice

When clinicians implement prognostic studies in their clinical practice, it is important to distinguish between predictors versus causal effects and modifiable versus non-modifiable factors.

Single predictors or prediction models can help to anticipate whether a patient is likely to have favorable outcomes in the future or not (103, 187). The associations with trajectory affiliation identified in paper IV can be considered as single predictors as they were assessed using univariable analyses. These predictors can help us identify at-risk patients or patients with a good prognosis, but we don't know whether patients' outcomes improve if we change these factors. Hence, they should primarily be used to inform patients about prognosis. Since early/preoperative quadriceps strength and single-legged hop performance LSI are modifiable factors and possible targets of intervention, they can also form a foundation for future studies on causal effects.

In contrast, a causal factor can directly affect outcomes, given adjustment for relevant confounders: Targeting causal factors can directly improve patients' outcomes (103, 187). Such studies require high methodological standards (1). The conclusion of paper III - that concomitant meniscus and cartilage injuries were prognostic factors for worse PROMs at two to ten years after ACLR - was based on both studies of prediction and causal effect. As these factors are non-modifiable, they can still primarily be used to inform patients about prognosis and create realistic expectations. Additionally, they underpin the importance of preventing new knee injuries.

The size of the impact of concomitant meniscus and cartilage injuries on outcomes is, however, uncertain: The original studies included in our systematic review reported mean differences between those with and without concomitant cartilage injuries that were below the MIC for the outcome measures (67, 111, 202). Further, one of the included studies found a difference between patients with and without concomitant meniscus injuries that exceeded the MIC for the KOOS Sport/Rec subscale (67), while the difference was smaller for other outcome measures.

Conclusions

The following conclusions were made for the four specific aims of this dissertation:

1) Patients with ACL injuries who followed our treatment algorithm had good five-year outcomes across treatment groups; 85%, 85%, and 79% scored above a threshold for a patient acceptable symptom state for the IKDC-SKF, KOOS Sport/Rec, and KOOS QoL, respectively, and >95% were still active in some kind of sports (paper I). Only 6% and 4% had radiographic tibiofemoral OA in the index and contralateral knee, respectively, and only 6% had knee pain in the index knee (paper II).

2) Within five years, 64% of the patients had undergone early ACLR with preoperative and postoperative rehabilitation, 11% delayed ACLR with preoperative and postoperative rehabilitation, and 25% progressive rehabilitation alone. There were no statistically significant differences among the treatment groups for any clinical, functional, physical activity, or radiographic outcome (papers I and II).

3) Through a systematic review of the literature, we identified concomitant meniscus and cartilage injuries as prognostic factors for worse PROMs two to ten years after ACLR. We found very low certainty evidence for higher BMI, smoking, and worse baseline PROMs as prognostic factors for worse PROMs, and for female sex and worse baseline Marx Activity Rating Scale as prognostic factors for worse Marx Activity Rating Scale two to ten years after ACLR. There was a lack of studies on prognostic factors in patients treated with rehabilitation alone (paper III).

4) We identified four distinct five-year trajectories of patient-reported knee function following our treatment algorithm – *Low* (8.9% of the cohort), *Moderate* (50.2%), *High* (37.5%), and *High before declining* (3.4%) - indicating four subgroups of ACL injured patients. Almost 9 out of 10 patients who followed our treatment algorithm belonged to the favorable *Moderate* or *High* trajectories (paper IV).

5) The factors associated with belonging to the *High* trajectory were mainly related to having better functional outcomes early after injury. Concomitant meniscus injuries were associated with a *Low* trajectory, while a *High before declining* trajectory was characterized by new ipsi- and contralateral knee injuries (paper IV).

Future perspectives

We still need more high-quality comparative studies on outcomes after ACL reconstruction versus rehabilitation alone - following current clinical recommendations. Such randomized trials and prospective cohort studies can validate the findings of papers I and II. As discussed, future studies should assess level-I athletes specifically as decision-making about treatment is especially challenging for this patient group.

A few high-quality studies have started the important work of assessing predictors of successful outcomes with rehabilitation alone (67, 89, 198). Such studies can make great contributions to individualized treatment of ACL injuries and thereby optimizing outcomes for our patients.

In paper II, we emphasized that five-year radiographic outcomes represent early degenerative changes. End-stage joint disease must be assessed at later follow-ups of the cohort. A ten-year follow-up of the Delaware-Oslo cohort is finalized as this dissertation is written and will contribute to the understanding of long-term outcomes following our treatment algorithm. This ten-year follow-up can also contribute to explore whether K&L grades 1 and 2/osteophyte at five years predict progression of joint disease, and whether these radiographic findings should be considered early-phase knee OA. Long-term (>10 years) follow-ups of the high-quality KANON and COMPARE trials (73, 74, 177) will probably provide the best current evidence on the effect of early ACLR versus rehabilitation alone with optional delayed ACLR on knee OA outcomes.

Future prognostic factor research can contribute to improving patient education about prognosis and identify important targets of early intervention (modifiable prognostic factors such as muscle strength or activation, kinetics, kinematics, range of motion) to improve patients' outcomes. Paper III revealed a need to improve the quality of prognostic factor research: 60% of the included studies had a high risk of bias, especially in the QUIPS domains "study confounding" and "statistical analysis and reporting". Future research on prognostic factors should be prospective and observational in design and be clear about whether their goals and methods are aimed at prediction or etiology. If the aim is etiological, authors should carefully state their hypothesis and background and run an informed causal analysis ensuring that rules for adjustment for different types of covariates are followed (100, 102, 130). Further, more future prognostic factor research should include patients treated with rehabilitation alone. This patient group is important as it represents between 26% and 77% of the ACL injured population (35, 164, 181). Last, prognostic factors can be compared in patients treated with rehabilitation alone versus ACLR to help clinicians identify who is likely to have the best prognosis with ACLR versus who is likely to succeed with rehabilitation alone.

Paper IV was the first study to assess subgroups of ACL injured patients who follow distinct trajectories of patient-reported knee function. We need future studies to validate the identified trajectories. Instead of only reporting means and medians, such studies can improve our understanding of the diversity in response to ACL injury.

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Paper I

CLINICAL, FUNCTIONAL, AND PHYSICAL ACTIVITY OUTCOMES 5 YEARS FOLLOWING THE TREATMENT ALGORITHM OF THE DELAWARE-OSLO ACL COHORT STUDY

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ABSTRACT

Background: Anterior cruciate ligament (ACL) injuries can be treated with or without ACL reconstruction (ACLR), and more high-quality studies evaluating outcomes after the different treatment courses are needed. The purpose of the present study was to describe and compare 5-year clinical, functional, and physical activity outcomes for patients who followed our decision-making and treatment algorithm and chose (1) early ACLR with preoperative and postoperative rehabilitation, (2) delayed ACLR with preoperative and postoperative rehabilitation, or (3) progressive rehabilitation alone. Early ACLR was defined as that performed ≤6 months after the preoperative rehabilitation program, and late ACLR was defined as that performed >6 months after the preoperative rehabilitation program.

Methods: We included 276 patients from a prospective cohort study. The patients had been active in jumping, pivoting, and cutting sports before the injury and sustained a unilateral ACL injury without substantial concomitant knee injuries. The patients chose their treatment through a shared decision-making process. At 5 years, we assessed the International Knee Documentation Committee Subjective Knee Form (IKDC-SKF), Knee Osteoarthritis Outcome Score (KOOS), Marx Activity Rating Scale, sports participation, quadriceps muscle strength, single-legged hop performance, and new ipsilateral and contralateral knee injuries.

Results: The 5-year follow-up rate was 80%. At 5 years, 64% of the patients had undergone early ACLR, 11% had undergone delayed ACLR, and 25% had had progressive rehabilitation alone. Understandably, the choices that participants made differed by age, concomitant injuries, symptoms, and predominantly level-I versus level-II preinjury activity level. There were no significant differences in any clinical, functional, or physical activity outcomes among the treatment groups. Across treatment groups, 95% to 100% of patients were still active in some kind of sports and 65% to 88% had IKDC-SKF and KOOS scores above the threshold for a patient acceptable symptom state.

Conclusions: Patients with ACL injury who were active in jumping, pivoting, and cutting sports prior to injury; who had no substantial concomitant knee injuries; and who followed our decision-making and treatment algorithm had good 5-year knee function and high sport participation rates. Three of 4 patients had undergone ACLR within 5 years. There were no significant differences in any outcomes among patients treated with early ACLR, delayed ACLR, or progressive rehabilitation alone.

INTRODUCTION

Anterior cruciate ligament (ACL) injuries can be managed with or without ACL reconstruction (ACLR)[1-3]. The existing literature is sparse but generally has not demonstrated superior outcomes of ACLR compared with progressive rehabilitation alone[4-10].

Comparing outcomes after ACLR and progressive rehabilitation alone involves important challenges. First, the population of patients with ACL injuries is highly heterogeneous, and some patients do better with rehabilitation alone than others[11]. Consequently, treatment does not fit into a one-size-fits-all paradigm. Second, surgery is only one part of a treatment course; patient education, high-quality rehabilitation, surgical indications, and timing of treatment are also important[12]. Therefore, we need to move beyond relying only on randomized controlled trials (RCTs) evaluating the effect of single treatment components to inform clinical practice. An evaluation of a clinical treatment algorithm including shared decision-making based on patients' needs, expectations, and function is also needed.

The Delaware-Oslo ACL Cohort Study is a longitudinal cohort study of patients who had been active in jumping, pivoting, and cutting sports before injury and who had no substantial concomitant knee injuries. Before participating in an informed shared decision-making process with their physical therapists and orthopaedic surgeons, all patients underwent a 5-week preoperative rehabilitation program with progressive neuromuscular and strength training followed by clinical testing[13]. Patients were advised on treatment choice on the basis of dynamic instability, knee function, and intention to return to level-I sports. Achievement of good knee function after the preoperative rehabilitation was the main patient-reported reason for choosing progressive rehabilitation alone[14]. Regardless of treatment choice, all patients underwent progressive rehabilitation guided by functional testing[11,14].

Based on subgroups of the present cohort, we previously reported (1) large improvement in knee function after preoperative rehabilitation[13] and argued that knee function should be emphasized in treatment choices[15], (2) that a number of factors are prognostic for successful outcome[16,17], (3) that coper classification may change after preoperative rehabilitation and affect 2-year outcomes[18,19], (4) that 2-year outcomes after progressive rehabilitation alone are equivalent to those after ACLR[14], and (5) that 2-year outcomes in our surgically treated patients are superior to those after usual care in the United States[20] and Norway[21]˜We have yet to report the long-term clinical, functional, physical activity, and radiographic[22] outcomes for the whole cohort.

The purpose of the present study was to describe and compare the 5-year clinical, functional, and physical activity outcomes for patients who had gone through our decision-making and treatment algorithm and had chosen either (1) early ACLR with preoperative and postoperative rehabilitation, (2) delayed ACLR with preoperative and postoperative rehabilitation, or (3) progressive rehabilitation alone. Early ACLR was defined as that performed ≤6 months after the preoperative rehabilitation program, and late ACLR was defined as that performed >6 months after the preoperative rehabilitation program.

MATERIALS AND METHODS

Patients

Three hundred athletes were consecutively enrolled into this prospective cohort study from the University of Delaware, Newark, Delaware, United States, or the Norwegian Sports Medicine Clinic, Oslo, Norway, between 2006 and 2012. Complete unilateral ACL injury and concomitant injuries were verified with magnetic resonance imaging (MRI), and increased anterior knee joint laxity was measured with a KT1000 arthrometer (MEDmetric Corporation). The inclusion criteria were an age between 13 and 60 years and preinjury participation in level-I or II sports ≥2 times/week (Table I)[11,23]. We excluded patients with current or previous ipsilateral or contralateral knee injuries, those with concomitant grade-III ligament injury, those with full-thickness articular cartilage damage or fracture, and those who were unable to attend preoperative rehabilitation. All patients had to resolve acute impairments (have no or minimal pain or effusion during or after plyometric activities) before inclusion in the study (within 3 months after injury [Oslo] or within 7 months after injury [Delaware]. If not, they were excluded for example, patients with symptomatic meniscal injuries. Patients with obviously repairable menisci on MRI such as bucket-handle tears with locked knees were also excluded and were referred to an orthopaedic surgeon. Among the original 300 patients, 24 had had a previous ACLR and came to our clinics with a graft rupture; those patients were excluded from the present study. Hence, the present study included 276 patients (142 from Oslo and 134 from Delaware) with a first-time ACL injury.

We obtained written informed consent or assent with parental consent and approvals from the Regional Committee for Medical and Health Research Ethics of Norway and the University of Delaware institutional review board.

TABLE I Sports Activity Classification[14,44]

Level	Sports Activity	Example of Sports
I	Jumping, cutting, pivoting	Soccer, football, handball, basketball, floorball
II	Lateral movements, less pivoting than level-I	Tennis, squash, alpine skiing, snowboarding, gymnastics, baseball, softball
III	Straight-ahead activities, no jumping or pivoting	Running, cross-country skiing, weightlifting
IV	Sedentary	

Treatment Algorithm

After impairment resolution (mean, 59 days after injury) and inclusion in the study, all patients participated in a 5-week (10-session) preoperative rehabilitation program consisting of progressive neuromuscular and strength training exercises as described by Eitzen et al.[13]. The patients received education, including information about treatment alternatives, before they underwent functional testing and made their treatment choice in consultation with their orthopaedic surgeons and physical therapists. We were more likely to recommend ACLR to patients experiencing dynamic knee instability[24] after preoperative rehabilitation and those who intended to return to level-I sports. Achieving good knee function after rehabilitation was the main patient-reported reason for choosing progressive rehabilitation alone[14]. Despite recommendations, 34% of the patients who chose progressive rehabilitation alone intended to return to level-I sports[14]. Delayed ACLR was indicated for patients with dynamic knee instability[24] or if they changed their minds about the treatment choice that they had made.

Several experienced (and, in the United States, subspecialty-certified) sports orthopaedic surgeons performed the ACLRs, and graft choices were shared decisions. Bone-patellar tendon-bone autografts (21.5%), single-bundle or double-bundle hamstring autografts (51.5%), or allografts (27%) were used. Postoperative rehabilitation consisted of 3 phases and was individually adjusted for concomitant injuries, graft type, and knee function. The acute postoperative phase (phase 1) addressed swelling, range of motion, and atrophy. The milestones of the rehabilitation phase (phase 2) were to achieve a muscle strength and hop performance limb symmetry index (LSI) of ≥80%. In the return-to-sport phase (phase 3), participation in sports-specific training gradually increased and the milestones were a strength and hop LSI of ≥90%. Patients who did not undergo ACLR typically continued progressive rehabilitation for 3 to 4 months with the same phases.

Data Collection

At 5 years after completion of preoperative rehabilitation or after ACLR, patients completed the International Knee Documentation Committee Subjective Knee Form (IKDC-SKF)[25-28] and Knee Osteoarthritis Outcome Score (KOOS)[29,30]. The KOOS consists of 5 subscales: pain, other symptoms, function in daily living, function in sport and recreation (Sport/Rec), and knee-related quality of life (QoL)[30]. The minimum clinically important change (MCIC) is 11.5 points for the IKDC-SKF[27], 12.1 points for KOOS Sport/Rec, and 18.3 points for KOOS QoL[31].

We assessed quadriceps strength with use of the peak torque from maximum isometric contraction (3 repetitions) or from concentric isokinetic testing (4 trial repetitions and 5 test repetitions) with use of electromechanical dynamometers[32]. We tested the uninjured leg first. The isometric test (Delaware) was performed with hips and knees in 90° of flexion (Kin-Com; DJO Global). The isokinetic test (Oslo) was performed at 60°/second between 90° of flexion and full extension (Biodex6000, Biodex Medical Systems)

Four single-legged hop tests were performed in the following order: (1) the single hop for distance, (2) the crossover hop for distance, (3) the triple hop for distance, and (4) the 6-m timed hop[16,17,33]. We tested the uninjured leg first. One practice trial was performed before we recorded 2 trials, from which the mean score was calculated. During the 3 first hop tests, we considered trials valid if the final landing was stable (without touching the floor or walls with the other foot or hands or performing additional hops).

We assessed new ipsilateral and contralateral knee injuries with clinical examination, including arthrometer measurements. The diagnosis was verified with MRI and/or during surgery if indicated.

We recorded sports participation with use of the question, “What sports or exercise are you participating in now?” and graded the most-knee-demanding sport from I to IV (Table I). Frequency of participation in sports involving running, pivoting, cutting, and deceleration was assessed with use of the Marx Activity Rating Scale[34].

Data Management and Statistical Analysis

As previously noted, we classified ACLRs performed ≤6 months after the preoperative rehabilitation program as early and those performed >6 months as delayed.

We reported muscle strength and single-legged hop performance with LSI (i.e., the performance of the involved limb as a percentage of the performance of the contralateral limb). The rate of new ipsilateral or contralateral knee injuries was calculated among those who attended either the 2-year or 5-year follow-up. In addition to calculating the mean and standard deviation, we classified patients as above or below the top 15th normative percentile[25] for age and sex-matched subjects with healthy knees for the IKDC-SKF and above or below the patient acceptable symptom state (PASS) threshold for the IKDC-SKF, KOOS Sports/Rec, and KOOS QoL[35].

Sample-size estimation showed that we needed 25 patients in each group to detect a between-group difference in IKDC-SKF scores larger than the MCIC of 11.5 points[27] with an estimated standard deviation of 12[14] with an alpha level of 0.017 and 80% power.

Most continuous outcome measures were skewed according to the Kolmogorov-Smirnov test, but, because of the high number of participants, and after inspection of histograms and skewness, we concluded that they were close enough to a normal distribution to use parametric tests[36]. We assessed group differences with 1-way analysis of variance (ANOVA) tests (continuous variables) and with chi-square tests or Fisher exact tests (categorical variables)[37]. Because we aimed to evaluate outcomes in the 3 treatment groups following our treatment algorithm, and because this is not an effect study, we performed unadjusted analyses.

RESULTS

Of the 276 patients included in this study, 54 (20%, including 19 [13%] from the Oslo group and 35 [26%] from the Delaware group) were lost to 5-year follow-up. Of those, 14 patients (5% of the cohort) had been managed nonoperatively at the time of the latest follow-up but we were unable to ascertain whether they had had a subsequent operation (Fig. 1). More patients completed the patient-reported outcome measures (PROMs) (72% to 80%) than the clinical/functional tests (59% to 70%). Patients who were lost to follow-up (n = 54) were younger (mean difference, 3.8 years [95% confidence interval (CI), 0.9 to 6.7 years]; p = 0.010) and had a higher body mass index at inclusion (mean difference, 2.2 kg/m^2 [95% CI, 0.7 to 2.2 kg/m^2]; p = 0.004) than those who attended follow-up.

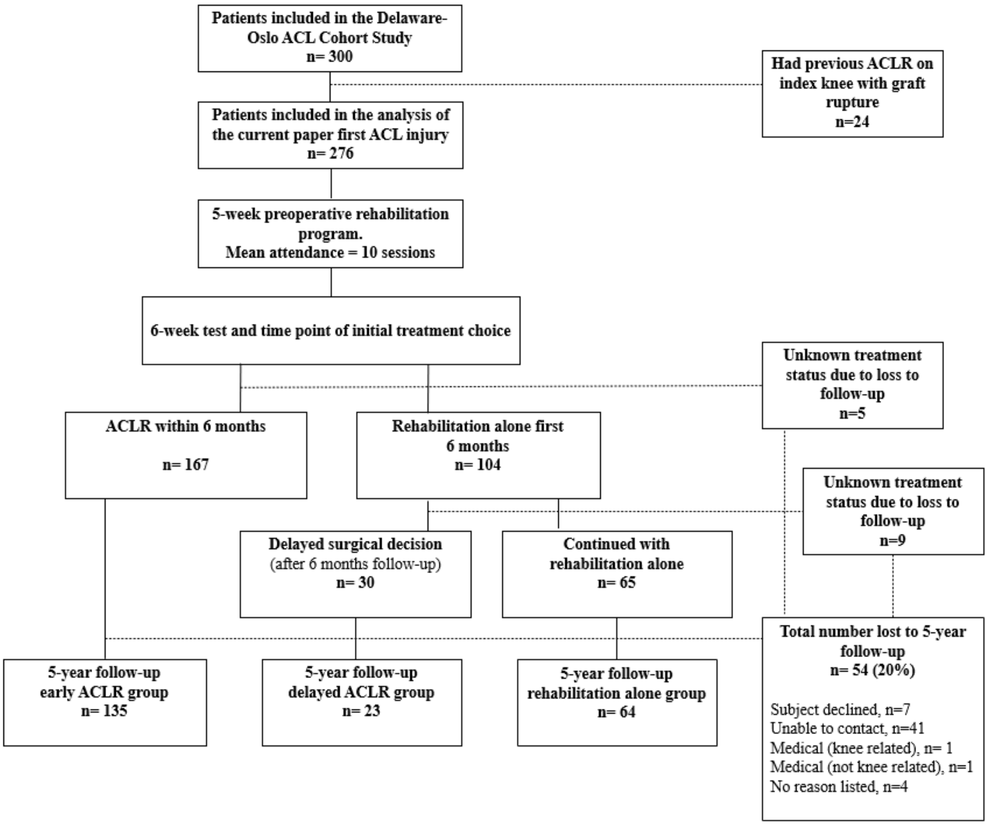

Fig.1. Patient flowchart.

Among the patients with ascertained treatment status at 5 years (95% of the cohort), 167 (64%) had undergone early ACLR, 30 (11%) had had delayed ACLR, and 65 (25%) had had progressive rehabilitation alone. Accordingly, 30 of the 95 (32%) who initially chose rehabilitation alone ended up with delayed ACLR (19 patients had surgery between 6 and 12 months after inclusion, 7 patients between 12 and 24 months, and 4 patients at >24 months). The patients who chose progressive rehabilitation alone were significantly older, less likely to participate in level-I sports preinjury, and less likely to have concomitant injuries to the medial meniscus compared with those who underwent early or delayed ACLR (Table II). The meniscal procedures that were performed during ACLR were either excisions (26%), repairs (56%), or trephination/rasping (18%).

TABLE II Descriptive Characteristics at Inclusion

	Early ACLR (N = 167)	**Delayed ACLR (N = 30)**	**Progressive Rehabilitation Alone (N = 65)**	**P Value**
Inclusion site (Oslo/Delaware)	48%/52%	70%/30%	54%/46%	0.078
Age* *(yr)*	24.7 ± 8.7	24.4 ± 9.4	31.9 ± 10.9	**<0.001**
Female sex *(no. of patients)*	76 (46%)	9 (30%)	36 (55%)	0.067
Body mass index* *(kg/m²)*	24.6 ± 4.0	24.4 ± 4.6	24.3 ± 3.2	0.838
Preinjury sports participation *(no. of patients)*				**<0.001**
Level-I	129 (77%)	25 (83%)	30 (46%)	
Level-II	38 (23%)	5 (17%)	35 (54%)	
Concomitant injuries† *(no. of patients)*				
Medial meniscus	45 (27%)	8 (27%)	7 (11%)	**0.027**
Lateral meniscus	34 (20%)	7 (23%)	6 (9%)	0.100
Cartilage	12 (7%)	5 (17%)	5 (8%)	0.220
Medial collateral ligament (grade I or II)	39 (23%)	6 (20%)	11 (17%)	0.552
Lateral collateral ligament (grade I or II)	3 (2%)	1 (3%)	4 (6%)	0.194
Meniscal surgery at time of ACLR *(no. of patients)*	69 (41%)	12 (40%)	NA‡	0.893

*The values are given as the mean and the standard deviation. †Number of patients diagnosed with the injury with use of MRI at the time of inclusion. ‡NA = Not applicable.

Five-Year Clinical, Functional, and Physical Activity Outcomes

There were no significant differences in any clinical, functional, or physical activity outcomes between the 3 treatment groups (Table III) (see also Appendix).

TABLE III Five-Year Outcomes

	Early ACLR	**Delayed ACLR**	**Progressive Rehabilitation Alone**	**P Value**
Time from injury to 5-year follow-up† (n = 222) *(yr)*	5.5 ± 0.5	6.1 ± 0.6	5.4 ± 0.5	**<0.001**
IKDC-SKF† (n = 222) *(points)*	89 ± 12	85 ± 15	87 ± 13	0.308
KOOS† *(points)*				
Pain (n = 220)	94 ± 9	90 ± 12	94 ± 9	0.213
Symptoms (n = 220)	89 ± 13	86 ± 15	92 ± 13	0.156
Activities of daily living (n = 220)	98 ± 7	97 ± 6	97 ± 5	0.860
Sports/Rec (n = 219)	89 ± 17	81 ± 22	87 ± 21	0.209
QoL (n = 219)	80 ± 21	70 ± 19	78 ± 19	0.083
Quadriceps muscle strength: limb symmetry index† (n = 193)	97% ± 12%	93% ± 16%	101% ± 21%	0.111
Single-legged hop tests: limb symmetry index†				
Single hop for distance (n = 166)	99% ± 10%	97% ± 8%	101% ± 9%	0.203
Crossover hop for distance (n = 162)	99% ± 9%	95% ± 8%	99% ± 9%	0.329
Triple hop for distance (n = 162)	99% ± 8%	97% ± 6%	100% ± 7%	0.471
6-meter timed hop (n = 163)	99% ± 7%	97% ± 6%	99% ± 7%	0.408
New knee injuries, ipsilateral *(no. of patients)*				
Graft rupture	19 (12%) of 153	5 (19%) of 27	NA	0.368
Meniscus	11 (7%) of 153	3 (11%) of 27	5 (8%) of 65	0.721
Cartilage	2 (1%) of 153	1 (4%) of 27	0 (0%) of 65	0.315
MCL/LCL	4 (3%) of 153	0 (0%) of 27	0 (0%) of 65	0.575
PCL	1 (1%) of 153	0 (0%) of 27	0 (0%) of 65	1.000
New knee injuries, contralateral *(no. of patients)*				
ACL rupture	12 (8%) of 153	0 (0%) of 27	4 (6%) of 65	0.399
Meniscus	2 (1%) of 153	0 (0%) of 27	3 (5%) of 65	0.211
Cartilage	0 (0%) of 153	0 (0%) of 27	1 (2%) of 65	0.376
MCL/LCL	0 (0%) of 153	0 (0%) of 27	0 (0%) of 65	
PCL	0 (0%) of 153	0 (0%) of 27	0 (0%) of 65	
Sports participation *(no. of patients)*				0.140
Level-I	47 (35%) of 135	4 (17.5%) of 23	16 (25%) of 64	
Level-II	36 (27%) of 135	4 (17.5%) of 23	20 (31%) of 64	
Level-III	45 (33%) of 135	15 (65%) of 23	26 (41%) of 64	
Level-IV	7 (5%) of 135	0 (0%) of 23	2 (3%) of 64	
Returned to preinjury sports participation *(no. of patients)*	64 (47%) of 135	6 (26%) of 23	30 (47%) of 64	0.159
Marx activity rating scale* (n = 199)	8 ± 4	8 ± 4	7 ± 4	0.314

*IKDC-SKF = International Knee Documentation Committee Subjective Knee Form, KOOS = Knee Osteoarthritis Outcome Score, MCL = medial collateral ligament, LCL = lateral collateral ligament, PCL = posterior cruciate ligament, ACL = anterior cruciate ligament, and NA = not applicable. †The values are given as the mean and the standard deviation.

Figure 2 shows the percentages with IKDC-SKF scores above/below the top 15th percentile[25] and IKDC-SKF, KOOS Sports/Rec, and KOOS QoL scores above/below the PASS threshold[35]. The percentages were similar across treatment groups (p = 0.144 to 0.520).

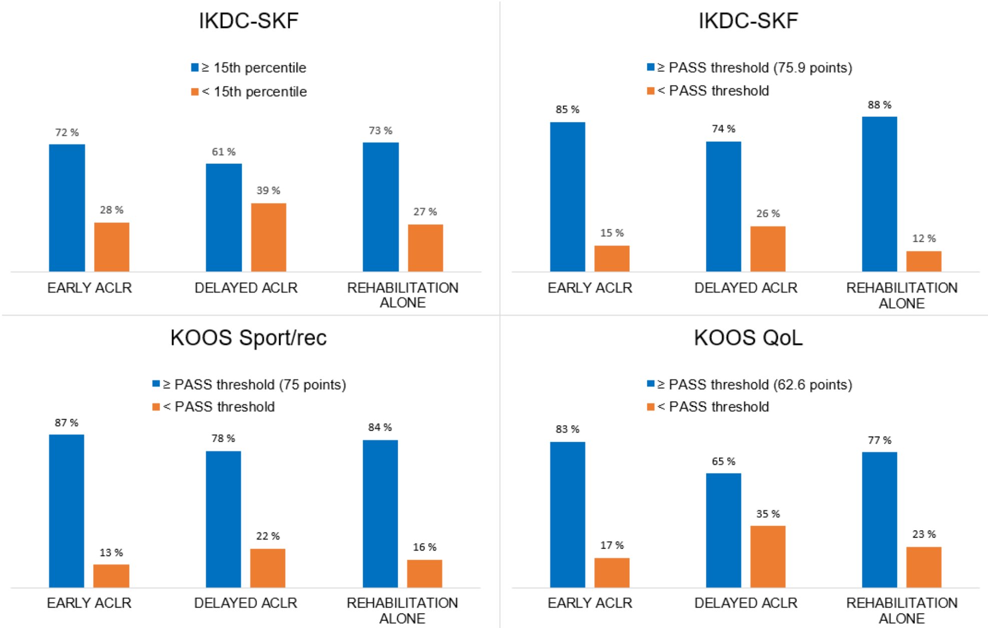

Fig. 2. Bar graphs showing the percentage of patients in each treatment group with IKDC-SKF scores above the 15th percentile and IKDC-SKF, KOOS Sports/Rec, and KOOS QoL scores above the patient acceptable symptom state (PASS) threshold.

DISCUSSION

Among patients in this prospective cohort study who followed our decision-making and treatment algorithm, 64% chose early ACLR, 11% chose delayed ACLR, and 25% chose progressive rehabilitation alone. Regardless of treatment, most patients in our cohort achieved good 5-year outcomes: between 65% and 88% had IKDC-SKF, KOOS Sports/Rec, and KOOS QoL scores above the PASS threshold[35], and nearly all patients still participated in some kind of sports. There were no significant differences in any outcomes among the 3 treatment groups. Except for new meniscal injuries, there was a tendency toward worse outcomes for the patients who underwent delayed ACLR. It is important to bear in mind that the reasoning for surgery were different for delayed ACLR compared to early ACLR - which may affect their outcomes.

Because the present study is not an effect study, and because we aimed to describe and compare outcomes in the 3 treatment groups following our treatment algorithm, we performed unadjusted analyses. Differences in characteristics between treatment groups likely played a role in who chose which treatments. Specifically, those who chose rehabilitation alone were older, more likely to have participated in level-II sports before the injury, and less likely to have concomitant meniscal injuries compared with the 2 ACLR groups. Those patients reported good function after preoperative rehabilitation as the reason for their treatment choice, whereas delayed ACLR was indicated for those with dynamic instability[14].

Comparisons with Other Studies

Others have also found similar outcomes between patients managed with ACLR and those managed with progressive rehabilitation alone[4,5,7,9,38]. However, the present cohort study is unique as it evaluated the outcomes of a specific shared decision-making and treatment algorithm wherein all patients participated in a preoperative rehabilitation program.

The surgically treated patients in our cohort had better 2-year outcomes than those who receive usual care (matched patients in the Norwegian National Knee Ligament Registry and the Multicenter Orthopaedic Outcomes Network [MOON] cohort)[20,21]. These findings were attributed to the extended preoperative and high-quality postoperative rehabilitation in our cohort[20,21]. The 5-year IKDC-SKF score for all patients managed with ACLR in our cohort (the early and delayed ACLR groups combined) was still superior to the 6-year score for the MOON cohort (median, 93 versus 77)[39], whereas the KOOS Sports/Rec and QoL scores were superior to the 5-year outcomes of primary ACLR in the Swedish National Anterior Cruciate Ligament Register (mean, 88 versus 69 points for KOOS Sports/Rec and 78 versus 66 for KOOS QoL)[40]. The differences between the cohorts exceed the MCIC for both the IKDC-SKF and KOOS Sports/Rec scores[27,31].

The rates of secondary ipsilateral and contralateral ACL injuries have been reported to be at least 3% to 8% in previous studies[38,41,42]. Our rates of contralateral ACL injuries in all groups (0% to 8%) and graft ruptures in the early ACLR group (12%) correspond with those rates. The graft rupture rate was higher among patients with delayed ACLR (19%), although it did not significantly differ from that among patients with early ACLR. Our rate of new ipsilateral meniscal injuries (7% to 11%) was low compared with those in previous studies (5% to 52%)[43], and, importantly, we found no differences among treatment groups.

Strengths and Limitations

Compared with RCTs, the external validity of our study is high because our treatment algorithm is in line with current practice clinical recommendations[12]. However, the external validity is limited to patients who are active in jumping, pivoting, or cutting sports preinjury without substantial concomitant injuries and who have resolution of acute impairments within 3 to 7 months after injury. Our high follow-up rate for PROMs (80%) is an important strength of a 5-year follow-up study.

Because the delayed ACLR group was small, the 95% CIs for the mean differences in IKDC-SKF, KOOS Sports/Rec, and KOOS QoL scores between this treatment group and the 2 other groups were wide. As 95% CIs included the MCIC for these instruments (see Appendix), we cannot exclude the existence of clinically meaningful differences.

Clinical Implications

Our results have important implications for clinical practice. First, progressive rehabilitation alone is a viable solution for some patients, and clinicians should communicate the possibility of living an active life with good knee function without surgery. Second, as the 5-year outcomes of our cohort exceeded those commonly reported in the literature[39,40], we advocate the use of our decision-making and treatment algorithm in clinical practice.

Implications for Future Research

An exceedingly small number of our cohort had IKDC-SKF and KOOS scores below the PASS threshold that represents poor knee function and patient satisfaction. Further research is needed to understand how these patients differ from other patients and to predict who will benefit the most from each treatment strategy. Recent studies have started this important work[11,19,44].

CONCLUSIONS

Patients with ACL injuries who had been active in jumping, pivoting, and cutting sports prior to injury; who had no substantial concomitant knee injuries; and who followed our decision-making and treatment algorithm had good 5-year knee function and high sport participation rates. Within 5 years, 64% had chosen early ACLR, 11% had chosen delayed ACLR, and 25% had chosen progressive rehabilitation alone. There were no significant differences in any outcomes among the 3 treatment groups. Understandably, the choices that participants made differed by age, concomitant injuries, symptoms, and predominantly level-I versus level-II preinjury activity level. We believe that progressive neuromuscular and strength training rehabilitation as a preoperative rehabilitation program, and patient education and clinical testing as part of an informed shared decision-making process, should be the gold standard for treating patients with ACL injury.

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APPENDIX

Appendix Pairwise group comparisons for continuous outcome measures

	Progressive rehabilitation vs early ACLR mean difference (95% CI)	**Progressive rehabilitation vs delayed ACLR** mean difference (95% CI)	**Early ACLR vs Delayed ACLR** mean difference (95% CI)
IKDC-SKF	-1.6 (-6.4 to 3.1)	2.6 (-5.0 to 10.1)	4.2 (-2.8 to 11.2)
KOOS			
Pain	-0.1 (-3.6 to 3.3)	3.6 (-2.0 to 9.1)	3.7 (-1.4 to 8.9)
Symptoms	2.8 (-1.9 to 7.6)	5.7 (-2.0 to 13.3)	2.8 (-4.3 to 9.9)
ADL	-0.3 (-2.7 to 2.1)	0.5 (-3.4 to 4.4)	0.8 (-2.8 to 4.4)
Sport/Rec	-1.6 (-8.5 to 5.3)	5.9 (-5.1 to 16.9)	7.5 (-2.7 to 17.7)
QoL	-2.0 (-9.5 to 5.5)	8.3 (-3.6 to 20.2)	10.3 (-0.8 to 21.3)
Quadriceps muscle strength (LSI)	3.9 (-2.2 to 10.0)	7.8 (-1.7 to 17.4)	3.9 (-4.9 to 12.7)
Single-legged hop tests			
Single hop for distance (LSI)	2.1 (-2.0 to 6.2)	4.5 (-1.8 to 10.9)	2.4 (-3.4 to 8.2)
Crossover hop for distance (LSI)	0.4 (-3.6 to 4.4)	3.6 (-2.5 to 9.8)	3.2 (-2.4 to 8.8)
Triple hop for distance (LSI)	0.4 (-2.9 to 3.7)	2.5 (-2.5 to 7.5)	2.1 (-2.5 to 6.7)
Six-meter timed hop (LSI)	0.3 (-2.6 to 3.2)	2.4 (-2.1 to 6.9)	2.1 (-2.0 to 6.2)
Marx Activity Rating Scale	-1.0 (-2.7 to 0.7)	-0.3 (-2.9 to 2.3)	0.8 (-1.6 to 3.1)

Abbreviations: IKDC-SKF, International Knee Documentation Committee Subjective Knee Form; KOOS, Knee Osteoarthritis Outcome Score; LSI, Limb Symmetry Index

Paper II

Original Research

Low Rates of Radiographic Knee Osteoarthritis 5 Years After ACL Reconstruction or Rehabilitation Alone

The Delaware-Oslo ACL Cohort Study

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Background: Patients and clinicians often struggle to choose the optimal management strategy for posttraumatic knee osteoarthritis (OA) after an anterior cruciate ligament (ACL) injury. An evaluation of radiographic outcomes after a decision-making and treatment algorithm applicable in clinical practice can help to inform future recommendations and treatment choices.

Purpose: To describe and compare 5-year radiographic outcomes and knee pain in individuals who had gone through our decision-making and treatment algorithm and chosen (1) early (<6 months) ACL reconstruction (ACLR) with pre- and postoperative rehabilitation, (2) delayed (>6 months) ACLR with pre- and postoperative rehabilitation, or (3) progressive rehabilitation alone.

Study Design: Cohort study; Level of evidence, 2.

Methods: We included 276 patients with unilateral ACL injury from a prospective cohort study. Patients chose management using a shared decision-making process and treatment algorithm, and 5-year postoperative radiographs of the index and contralateral knees were assessed using the Kellgren and Lawrence (K&L) classification and minimum joint space width measurements. We defined radiographic tibiofemoral OA as K&L grade ≥2 and knee pain as a Knee injury and Osteoarthritis Outcome Score for Pain ≤72. To further explore early radiographic changes, we included alternative cutoffs for radiographic knee OA using K&L grade ≥2/osteophyte (definite osteophyte without joint space narrowing) and K&L grade ≥1.

Results: At 5 years, 64% had undergone early ACLR; 11%, delayed ACLR; and 25%, progressive rehabilitation alone. Radiographic examination was attended by 187 patients (68%). Six percent of the cohort had radiographic tibiofemoral OA (K&L grade ≥2) in the index knee; 4%, in the contralateral knee. Using the alternative cutoffs at K&L grade ≥2/osteophyte and K&L grade ≥1, the corresponding numbers were 20% and 33% in the index knee and 18% and 29% in the contralateral knee. Six percent had a painful index knee. There were no statistically significant differences in any radiographic outcomes or knee pain among the 3 management groups.

Conclusion: There were no statistically significant differences in any 5-year radiographic outcomes or knee pain among the 3 management groups. Very few of the patients who participated in our decision-making and treatment algorithm had knee OA or knee pain at 5 years.

Keywords: knee; articular cartilage; ACL; physical therapy/rehabilitation; aging athlete

Many patients experience the devastating consequences of posttraumatic knee osteoarthritis (OA) after an anterior cruciate ligament (ACL) injury.[1,3,30,45] Patients and clinicians often struggle to choose the optimal management strategy. A randomized controlled trial (the KANON trial) found no difference in 5-year radiographic tibiofemoral OA or cartilage thickness between patients who underwent early ACL reconstruction (ACLR) plus rehabilitation versus rehabilitation alone (plus the option of delayed ACLR).[16,58] In clinical practice, however, shared decision-making tends to result in different patients choosing different management strategies.[4,39,47] Recent research

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has also discovered that certain patients do better with certain mangements.[15,19] We therefore need to evaluate both clinical and radiographic outcomes after decision-making and treatment algorithms applicable in clinical practice. Such studies hold high external validity and can help to inform future recommendations and management choices.

The Delaware-Oslo ACL Cohort Study is a longitudinal cohort study of patients with acute ACL injury. The patients underwent a 5-week preoperative rehabilitation program before they chose rehabilitation only or ACLR as part of an informed shared decision-making process with their treating clinicians. Several elements of our decision-making and treatment algorithm are included in evidence-based recommendations for the management of ACL injuries,[14] and our results are therefore highly relevant for patients and clinicians outside our cohort. We have previously reported no statistically significant differences in the 5-year clinical, functional, and physical activity outcomes between patients treated with early ACLR, delayed ACLR, or progressive rehabilitation alone.[43]

As the processes leading to knee OA start long before radiographic changes are evident,[12,38] measures of established OA do not sufficiently detect early OA development. Different criteria for defining early knee OA with and without radiological findings have been proposed without reaching a consensus, but knee pain is frequently included in previous definition proposals[33-35,49] and is often the first sign of knee OA.[12,50] Different radiographic outcomes also contribute with different constructs of joint disease.[25,26,32] It is therefore of great interest to report a range of radiographic features and knee pain in addition to the more established radiographic knee OA cutoff of Kellgren and Lawrence (K&L) grade $\geq$2.

This study aimed to describe and compare 5-year radiographic outcomes and knee pain in individuals who had gone through our decision-making and treatment algorithm and chosen (1) early (within 6 months) ACLR with pre- and postoperative rehabilitation, (2) delayed (later than 6 months) ACLR with pre- and postoperative rehabilitation, or (3) progressive rehabilitation alone.

METHODS

Patients

Between 2006 and 2012, we consecutively included 300 athletes at the Norwegian Sports Medicine Clinic in Oslo, Norway, or at the University of Delaware in Newark, Delaware. At inclusion, complete ACL injury and concomitant injuries were verified using magnetic resonance imaging (MRI) and increased anterior knee joint laxity (measured via a KT-1000 arthrometer; MED Metric). Of these 300, 24 had a graft rupture after a previous ACLR; hence, 276 patients with a first-time ACL injury (142 from Oslo and 134 from Delaware) were included in the analysis for this paper. Patients had to participate in level 1 (jumping, cutting, and pivoting sports such as soccer, football, handball, basketball, and floorball) or level 2 (lateral movements with less pivoting such as racket sports, alpine skiing, snowboarding, gymnastics, baseball, and softball) sports[22] $\geq$2 times per week preinjury and be between 13 and 60 years of age. They had to have resolved acute impairments (have no or minimal pain or effusion during or after plyometric activities) before inclusion (within 3 months after ACL injury in Norway and within 7 months in Delaware). We excluded patients with previous knee injuries or surgeries to either knee, bilateral injuries, other grade 3 ligament injuries, full-thickness articular cartilage damage, or fracture and patients who were unable to attend preoperative rehabilitation or had obviously repairable menisci on MRI.

We obtained written informed consent or assent with parental consent from all patients and approvals from the Regional Committee for Medical and Health Research Ethics of Norway and the University of Delaware Institutional Review Board before inclusion.

Treatment Algorithm

After inclusion (mean, 59 days after injury), all patients were educated on different management strategies and participated in a 5-week (10-session) preoperative rehabilitation program using progressive neuromuscular and strength training exercises.[9] Thereafter, they underwent functional testing and chose their management in dialogue with their physical therapists and orthopaedic surgeons.

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Ethical approval for this study was obtained from the Regional Committee for Medical and Health Research Ethics of Norway.

We were more likely to recommend ACLR to patients who wished to return to level 1 sports and to those who experienced dynamic knee instability. The most frequent patient-reported reason for choosing progressive rehabilitation alone was the achievement of good knee function after rehabilitation.[17] Delayed ACLR was indicated if patients subsequently experienced dynamic knee instability or changed their minds.

Graft choice was a shared decision with the orthopaedic surgeon. Bone–patellar tendon–bone autografts (21.5%), single-bundle or double-bundle hamstring autografts (51.5%), and allografts (27%) were used. Several experienced sports orthopaedic surgeons (in the United States, subspecialty certified) performed the ACLRs. Postoperative rehabilitation was individually adjusted depending on concomitant injuries, graft type, and knee function and consisted of 3 phases. The goal of the acute postoperative phase (phase 1) was to reduce swelling and atrophy and restore range of motion. The goal of the rehabilitation phase (phase 2) was to attain muscle strength and hop performance limb symmetry index ≥80% and to regain neuromuscular control. In the return-to-sports phase (phase 3), patients aimed to attain strength and hop performance limb symmetry index ≥90% and gradually increased participation in sports-specific training. The progressive rehabilitation alone group typically continued progressive rehabilitation for 3 to 4 months after the completion of the formal rehabilitation program and underwent the same testing as the ACLR groups.

Data Collection and Outcome Measurements

Information regarding patient characteristics, the injury, and surgical procedures was collected at inclusion or at the time of ACLR. New injuries to the index and contralateral knee were reported at follow-up. Follow-up was 5 years after completion of preoperative rehabilitation or ACLR. Clinical, functional, and physical activity outcomes at 2 years[11,17,18] and 5 years[43] have been reported previously.

Radiographic Outcomes. We used standardized weight-bearing radiographs taken bilaterally from a posteroanterior view. In Norway, a fixed flexion protocol using a SynaFlexer Positioning Frame (Synarc, Inc) and 10° caudal beam angulation was used to ensure consistent and reproducible knee angulation and alignment.[23,27] In Delaware, the Lyon Schuss protocol was used.[28] The patients were positioned with 30° of knee flexion with the pelvis, thighs, and patella flush against the film cassette and coplanar with the tips of the great toes. The radiographic beam was adjusted for each image to align with the medial tibial plateau.

An experienced radiologist (R.G.) with high intrarater reliability (kappa = 0.77)[41] graded all the radiographs from both study sites according to the K&L classification for the tibiofemoral joint.[26] The K&L classification is well recognized for assessing radiographic knee OA based on osteophyte and joint space narrowing severity (grade 0, normal, to grade 4, severe).[1,26,29] We used the modified K&L definition proposed by Felson et al,[13] which distinguishes between knees with both definite osteophyte and possible joint space narrowing (K&L grade 2) and knees with definite osteophyte without joint space narrowing (K&L grade 2/osteophyte). We defined K&L grade ≥2 as radiographic OA and included K&L grade ≥2/osteophyte as an alternative cutoff for early radiographic changes in the tibiofemoral joint.[13,42] K&L grade 1 (doubtful joint space narrowing and possible osteophytic lipping) has been associated with progression of radiographic features,[21] and some have argued that K&L grade 1 should be treated as early-phase joint disease.[48,51] We therefore included K&L grade ≥1 as another alternative cutoff for early radiographic changes.

Since the K&L classification is highly osteophyte-centric, measurements of tibiofemoral minimum joint space width (mJSW) can contribute another aspect of joint degeneration. mJSW is a quantitative measure reflecting thickness of articular cartilage and meniscal pathology.[25,32] Substantial tibiofemoral mJSW changes are common early after ACLR and are associated with pain and worse quality of life.[52,53] The radiologist measured the mJSW manually at the narrowest point in each compartment using the most apparent cortical strip (interpreted as the anterior rim) of the femur and the tibia. Manual mJSW measurements have previously shown high reproducibility.[44] For 26 patients, ≥1 mJSW measures were impossible to perform because of poor projection or overexposure. Because variation in radiograph quality and protocols affects mJSW measures,[28,36,55] we expressed medial and lateral mJSW as the difference between the index and contralateral knees ($mJSW_{diff}$) in our statistical analysis.

Knee Pain. Pain was evaluated using the Knee injury and Osteoarthritis Outcome Score (KOOS) Pain subscale, which ranges from 0 to 100 points (100 indicates no impairment).[46] Patients with scores ≤72 were classified as having knee pain. This cutoff (2 standard deviations below the reported normal mean value in an athletic population) has previously been used to identify patients with a painful knee and patients with early symptomatic knee OA after ACLR.[56,57]

Data Management and Statistical Analysis

A negative $mJSW_{diff}$ indicates a narrower joint space in the index knee than the contralateral knee, while a positive $mJSW_{diff}$ indicates a wider joint space in the index knee. The $mJSW_{diff}$ variables were skewed according to the Kolmogorov-Smirnov test, but by inspecting histograms and skewness, we considered them close enough to a normal distribution to use parametric tests.[10]

We report descriptive statistics for all outcomes for each treatment group, including separate statistics for those with and without new/concomitant injuries to the index or contralateral knee. We assessed group differences in nominal outcome variables using the chi-square test and group differences in $mJSW_{diff}$ using 1-way analysis of variance.

RESULTS

At 5 years, 187 patients (68%; 80% in Oslo and 55% in Delaware) attended radiographic examination, with

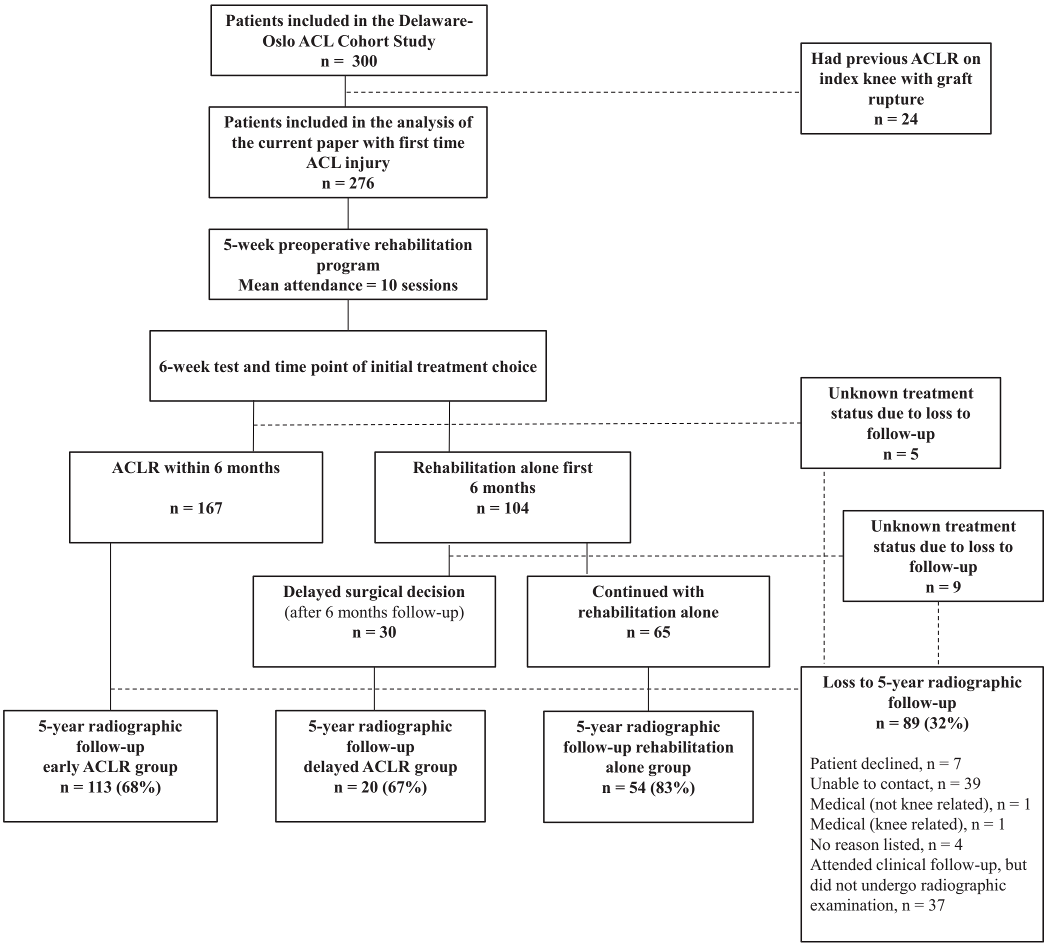

Figure 1. Study flowchart. ACL, anterior cruciate ligament; ACLR, ACL reconstruction.

similar attendance in the management groups (P = .055) (Figure 1). Loss to follow-up caused an inability to ascertain the treatment status for 14 patients who had been nonsurgically managed at the last follow-up (5% of the cohort). Patients who attended the follow-up were significantly older (mean difference, 3.8 years) and had lower body mass index (BMI) at inclusion (mean difference, 1.3) than did those who did not (n = 89). KOOS Pain scores were available for 220 patients (80%).

Of the 262 patients with ascertained treatment status, 167 (64%) had undergone early ACLR, 30 (11%) delayed ACLR, and 65 (25%) progressive rehabilitation alone. Most patients who crossed over from the rehabilitation alone group to delayed ACLR did so early: 19 patients crossed over between 6 and 12 months after inclusion; 7 patients, between 12 and 24 months; and only 4 patients, at >24 months. The 2 ACLR groups were significantly younger, were more likely to participate in level 1 sports preinjury, and had more concomitant injuries to the medial meniscus at inclusion compared with the progressive rehabilitation alone group (Table 1). During ACLR, 41% and 40% in the early and delayed ACLR groups, respectively, had meniscal surgeries, of which 26% were excisions, 56% were repairs, and 18% were trephination/rasping.

Five-year tibiofemoral K&L grades in the index and contralateral knees are presented in Figure 2. Using the cutoff at K&L grade ≥2, 6% (95% confidence interval [CI], 3-11) of the cohort had radiographic tibiofemoral OA in the index knee; 4% (95% CI, 2-8), in the contralateral knee (Table 2). Using the alternative cutoffs at K&L grade ≥2/osteophyte and K&L grade ≥1, the corresponding numbers were 20% (95% CI, 15-27) and 33% (95% CI, 27-40) in the index knee and 18% (95% CI, 13-25) and 29% (95% CI, 22-36) in the contralateral knee. Regardless of K&L cutoff used, there

TABLE 1
Characteristics at Inclusion: Group Comparisons[a]

	Early ACLR (n = 167)	Delayed ACLR (n = 30)	Progressive Rehabilitation Alone (n = 65)	P Value
Inclusion site, Oslo/Delaware, %	48/52	70/30	54/46	.078
Age, y	24.7 ± 8.7	24.4 ± 9.4	31.9 ± 10.9	**<.001**
Female sex	76 (46)	9 (30)	36 (55)	.067
BMI	24.6 ± 4.0	24.4 ± 4.6	24.3 ± 3.2	.838
Preinjury sports participation				**<.001**
Level 1	129 (77)	25 (83)	30 (46)	
Level 2	38 (23)	5 (17)	35 (54)	
Concomitant injuries assessed via MRI at baseline				
Medial meniscus	45 (27)	8 (27)	7 (11)	**.027**
Lateral meniscus	34 (20)	7 (23)	6 (9)	.100
Cartilage	12 (7)	5 (17)	5 (8)	.220
MCL (grade 1 or 2)	39 (23)	6 (20)	11 (17)	.552
LCL (grade 1 or 2)	3 (2)	1 (3)	4 (6)	.194
Meniscal treatment at ACLR	69 (41)	12 (40)	NA	.893

[a]Data are reported as n (%) or mean ± SD unless otherwise indicated. Boldface *P* values indicate statistically significant differences among the 3 management groups ($P < .05$). ACLR, anterior cruciate ligament reconstruction; BMI, body mass index; LCL, lateral collateral ligament; MCL, medial collateral ligament; MRI, magnetic resonance imaging; NA, not applicable.

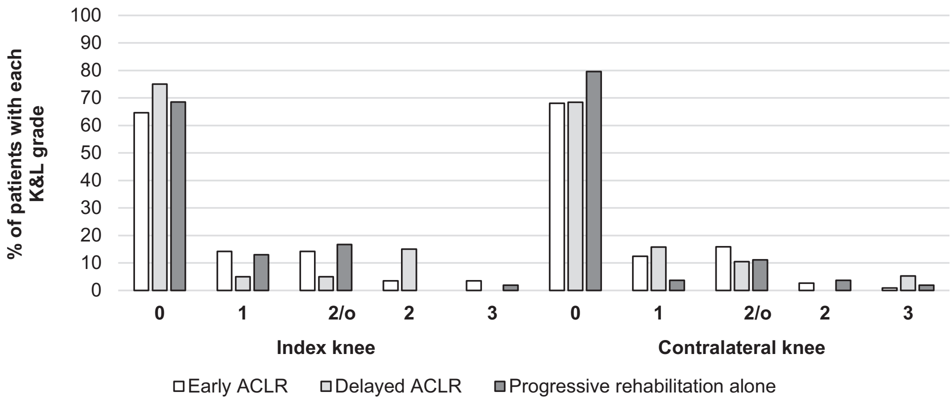

Figure 2. Kellgren & Lawrence (K&L) grades for all index and contralateral knees in percentage for each management group (n = 187). 2/o, 2/osteophyte. ACLR, anterior cruciate ligament reconstruction.

were no statistically significant differences in the prevalence of radiographic tibiofemoral OA in either the index ($P = .110$-.919) or contralateral ($P = .291$-.869) knee among the 3 management groups (Table 2). Six percent (95% CI, 2.8-9.3) of the cohort had a painful index knee, and there were no statistically significant differences among the 3 management groups ($P = .184$).

Five-year mJSW measurements in both compartments of the index and contralateral knees are described in Figure 3, while $mJSW_{diff}$ is expressed in Table 2. The $mJSW_{diff}$ was similar across the 3 management groups in both the medial ($P = .053$) and lateral ($P = .305$) compartments.

We did not assess prognostic factors for knee OA or knee pain, as it was beyond the aim of this paper and because we had few observed cases.

DISCUSSION

We found no statistically significant differences in any radiographic outcomes or knee pain among the 3 management groups. More importantly, few patients who participated in our decision-making and treatment algorithm had radiographic tibiofemoral OA (K&L grade ≥2): 7% of the index and 4% of the contralateral knees in the early ACLR group, 15% and 5% in the delayed ACLR group, and 2% and 6% in the progressive rehabilitation alone group. K&L grades ≥2/osteophyte and ≥1, which may represent early-phase joint disease, were found in 19% to 21% and 25% to 35% of the index knees, respectively, and 16% to 20% and 20% to 32% of the contralateral knees, respectively. Only 6% of the cohort had a painful index knee.

TABLE 2
Five-Year Outcomes: Group Comparisons[a]

Population (n)	Early ACLR	Delayed ACLR	Progressive Rehabilitation Alone	*P* Value
Index Knee				
Radiographic OA (K&L ≥2)				
All (187)	8/113 (7) (95% CI, 3-14)	3/20 (15) (95% CI, 3-38)	1/54 (2) (95% CI, 0-10)	.110
No additional injuries (101)	3/55 (6)	0/7 (0)	1/39 (3)	
Additional injuries[b] (86)	5/58 (9)	3/13 (23)	0/15 (0)	
K&L ≥2/osteophyte				
All (187)	24/113 (21) (95% CI, 14-30)	4/20 (20) (95% CI, 6-44)	10/54 (19) (95% CI, 9-31)	.919
No additional injuries (101)	10/55 (18)	0/7 (0)	7/39 (18)	
Additional injuries[b] (86)	14/58 (24)	4/13 (31)	3/15 (20)	
K&L ≥1				
All (n = 187)	40/113 (35) (95% CI, 27-45)	5/20 (25) (95% CI, 9-49)	17/54 (32) (95% CI, 20-46)	.630
No additional injuries (n = 101)	17/55 (31)	0/7 (0)	12/39 (31)	
Additional injuries[b] (n = 86)	23/58 (40)	5/13 (39)	5/15 (33)	
Knee pain[c]				
All (n = 220)	5/133 (4) (95% CI, 1-9)	3/23 (13) (95% CI, 3-34)	4/64 (6) (95% CI, 2-15)	.184
No additional injuries (n = 121)	0/64 (0)	2/10 (20)	2/47 (4)	
Additional injuries[b] (n = 99)	5/69 (7)	1/13 (8)	2/17 (12)	
Contralateral Knee				
Radiographic OA (K&L ≥2)				
All (n = 186)	4/113 (4) (95% CI, 1-9)	1/19 (5) (95% CI, 0-26)	3/54 (6) (95% CI, 1-15)	.815
Healthy contralateral knee (n = 170)	4/102 (4)	1/19 (5)	3/49 (6)	
Injured contralateral knee[d] (n = 14)	0/9 (0)	0/0 (0)	0/5 (0)	
K&L ≥2/osteophyte				
All (n = 186)	22/113 (20) (95% CI, 13-28)	3/19 (16) (95% CI, 3-40)	9/54 (17) (95% CI, 8-29)	.869
Healthy contralateral knee (n = 170)	16/102 (16)	3/19 (16)	9/49 (18)	
Injured contralateral knee[d] (n = 14)	5/9 (56)	0/0 (0)	0/5 (0)	
K&L ≥1				
All (n = 186)	36/113 (32) (95% CI, 23-41)	6/19 (32) (95% CI, 13-57)	11/54 (20) (95% CI, 11-34)	.291
Healthy contralateral knee (n = 170)	30/102 (29)	6/19 (32)	11/49 (22)	
Injured contralateral knee[d] (n = 14)	5/9 (56)	0/0 (0)	0/5 (0)	
Difference in mJSW[e]				
Medial compartment, mm				
All (n = 172)	0.3 ± 0.9	–0.2 ± 0.9	0.0 ± 0.7	.053
Healthy contralateral knee (n = 157)	0.2 ± 0.8	–0.2 ± 0.9	0.0 ± 0.7	
Injured contralateral knee[d] (n = 14)	0.7 ± 1.0	—	0.1 ± 0.8	
Lateral compartment, mm				
All (n = 162)	–0.3 ± 1.0	–0.2 ± 1.1	–0.0 ± 0.9	.305
Healthy contralateral knee (n = 147)	–0.3 ± 0.9	–0.2 ± 1.1	–0.1 ± 1.0	
Injured contralateral knee[d] (n = 14)	–0.1 ± 1.4	—	0.0 ± 0.8	

[a]Data are reported as n/N (%) or mean ± SD unless otherwise indicated. Dashes illustrate that there were no patients in these subgroups to perform calculations on. ACLR, anterior cruciate ligament reconstruction; K&L, Kellgren and Lawrence; mJSW, minimum joint space width; OA, osteoarthritis.

[b]Graft ruptures or concomitant/new injuries to meniscus or cartilage of the index knee.

[c]Knee injury and Osteoarthritis Outcome Score Pain of 72.

[d]Contralateral injuries to the anterior cruciate ligament, meniscus, or cartilage.

[e]A negative joint space difference indicates a narrower joint space in the index knee compared with the contralateral knee, while a positive joint space difference indicates a wider joint space in the index knee.

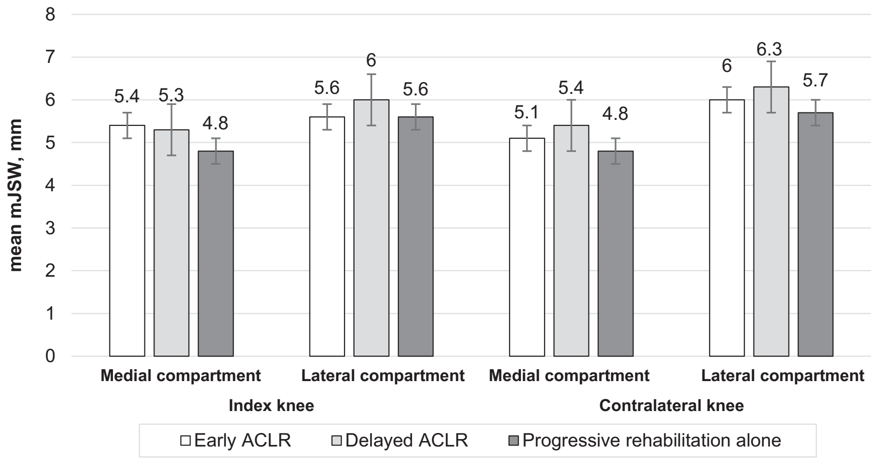

Figure 3. Mean medial and lateral minimum joint space width (mJSW) measurements for all index and contralateral knees (n = 164-176) in millimeters and 95% CI for each management group. ACLR, anterior cruciate ligament reconstruction.

Following our decision-making and treatment algorithm, we have previously reported excellent 5-year clinical, functional, and physical activity outcomes with no statistically significant differences among the management groups.[43] To our knowledge, this is the first study to compare 5-year radiographic outcomes following a specific treatment algorithm where management was chosen based on shared decision-making. As in clinical practice, different patients choose and are recommended different managements, which increases the external validity of our study. Because this study was not an effect study and because we aimed to describe and compare outcomes in the 3 management groups following our decision-making and treatment algorithm, we performed unadjusted analyses. Differences among management groups at inclusion (age, preinjury activity level, and concomitant meniscal injuries) may therefore have affected outcomes: for example, older age may have increased the risk of OA[20] in the rehabilitation alone group, while fewer concomitant meniscal injuries may have acted in the opposite direction.[1,41] There were also small but statistically significant differences in age and BMI between those who did and those who did not attend the 5-year radiographic follow-up, which may have affected our results.

The previously mentioned KANON trial also reported on the incidence of 5-year radiographic knee OA after early ACLR (plus rehabilitation) and after rehabilitation alone (plus the option of delayed ACLR).[16] Similar to our results, they found no statistically significant differences among the treatment groups.[16] According to the Osteoarthritis Research International (OARSI) atlas, 12% of the patients in the KANON trial had radiographic tibiofemoral OA in the index knee at 5 years. As the OA rates are reported to be almost twice as high when using the OARSI atlas compared with using K&L grade ≥2,[6] their rate corresponds well with ours. In contrast to our study—and longer term after ACL injury or reconstruction—a recent systematic review found a higher risk of radiographic knee OA >10 years after ACLR (range, 24%-80%) than after rehabilitation alone (range, 11%-68%), but because of low quality of included studies, the results should be interpreted with caution.[31] Early cartilage degeneration assessed using MRI has also been shown to be more pronounced after ACLR than after rehabilitation alone in some studies,[54] while no differences have been found in others.[58] Our study, along with studies with longer-term follow-ups[2,31,40] and animal studies,[7] reinforces the conclusion that reconstruction does not protect the ACL-injured knee from OA. Hence, rehabilitation alone does not provide inferior long-term outcomes compared with ACLR and is a viable solution for some patients.

The KOOS Pain cutoff at ≤72 points applied in this study has previously been used to define significant knee pain and OA after primary unilateral ACLR.[56,57] The prevalence rates in these previous studies were 9% at 6 years postoperatively[57] and 10% at 7 years postoperatively.[56] These numbers correspond well with those of our cohort, where the 5-year prevalence rates of knee pain were 13% in the early ACLR group, 6% in the delayed ACLR group, and 4% in the progressive rehabilitation alone group. Importantly, different definitions of knee pain result in different prevalence rates. In the study of Wasserstein et al,[57] the KOOS Pain cutoff at ≤72 points was 1 of 3 models used to explore prevalence of knee pain using the KOOS subscales. The prevalence rates were 39% and 12% when the other 2 models were used.[57] The reported threshold for a Patient Acceptable Symptom State (PASS) for the KOOS Pain subscale of 88.9 points[37] is also considerably higher than the cutoff used in our study, and hence we might have diagnosed more patients with knee pain if we had used a cutoff similar to the the PASS threshold. The recent work of Luyten et al[33] suggested more comprehensive classification criteria for early knee OA, which included clinical examination of joint line tenderness or crepitus in addition to KOOS subscales. Such a clinical examination was unfortunately not performed in our study.

Future research could apply more comprehensive definitions of symptomatic knee OA and early joint disease. In our study, using the alternative OA cutoffs at K&L grades $\geq$2/osteophyte and $\geq$1, we diagnosed 3 to 7 times more patients with knee OA than using the acknowledged cutoff at K&L grade $\geq$2. As very few patients in our cohort had knee pain and the OA rates were similar in the contralateral knees, we do not know how clinically relevant these radiographic findings are. Longer follow-ups of our cohort can explore whether K&L grades 1/- and 2/osteophyte at 5 years predict development or progression of the disease and contribute to the discussion of whether these radiographic findings should be considered early-phase joint disease. Other imaging techniques such as MRI are also valuable in the assessment of early knee OA.[23,24] We also need more studies with high quality and power to compare rates of radiographic and symptomatic knee OA after different management processes and decision-making algorithms. Such studies can provide more robust estimates and conclusions to guide clinical practice and thereby improve outcomes for patients with ACL-injured knees.

Limitations

Even though it was similar across management groups, the loss to follow-up for radiographic outcomes of 32% was a limitation of our study. Furthermore, the radiograph quality was in some cases ($n = 26$) unsuitable for the assessment of mJSW. Although the study design and treatment algorithm increase the external validity of our study, we can only generalize our results to patients who are active in jumping, pivoting, or cutting sports preinjury; do not have significant concomitant injuries; manage to resolve acute impairments within 3 to 7 months after injury; and are able and willing to attend rehabilitation and follow-ups. We also emphasize that 5-year radiographic outcomes represent early degenerative changes and differences in end-stage joint disease must be assessed at later follow-ups of the cohort.

Power may be another limitation of this study: the 95% CIs for our estimates of OA rates were quite wide, especially in the small delayed ACLR group. Therefore, we might have been unable to detect clinically relevant group differences for all outcomes. Even though not statistically significant ($P = .053$), the early ACLR group had a more positive medial $mJSW_{diff}$ than did the delayed ACLR group (mean difference, 0.4 mm; 95% CI, –0.1 to 0.9), and this group difference exceeded the previously reported smallest detectable difference between 2 measurements for mJSW of 0.26 to 0.28 mm.[5,8]

CONCLUSION

Following our decision-making and treatment algorithm, there were no statistically significant differences in any 5-year tibiofemoral radiographic outcomes or knee pain among the 3 management groups: early ACLR, delayed ACLR, and progressive rehabilitation alone. Few patients in our cohort had radiographic tibiofemoral OA (K&L grade $\geq$2) in the index (6%) or contralateral (4%) knee. Only 6% of the cohort had knee pain.

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Paper III

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Meniscus or Cartilage Injury at the Time of Anterior Cruciate Ligament Tear Is Associated With Worse Prognosis for Patient-Reported Outcome 2 to 10 Years After Anterior Cruciate Ligament Injury: A Systematic Review

OBJECTIVES: (1) To assess prognostic factors for patient-reported outcome measures (PROMs) and physical activity 2 to 10 years after anterior cruciate ligament reconstruction (ACLR) or anterior cruciate ligament (ACL) injury, and (2) to assess differences in prognostic factors between patients treated with ACLR and with rehabilitation alone.

DESIGN: Prognosis systematic review.

LITERATURE SEARCH: Systematic searches were performed in PubMed, Web of Science, and SPORTDiscus.

STUDY SELECTION CRITERIA: We selected prospective cohort studies and randomized clinical trials that included adults or adolescents undergoing either ACLR or rehabilitation alone after ACL rupture. Studies had to assess the statistical association between potential prognostic factors (factors related to patient characteristics, injury, or knee symptoms/function measured at baseline or within 1 year) and outcomes (PROMs and physical activity).

DATA SYNTHESIS: Our search yielded 997 references. Twenty studies met the inclusion criteria. Seven studies with low or moderate risk of bias remained for data synthesis.

RESULTS: Moderate-certainty evidence indicated that concomitant meniscus and cartilage injuries were prognostic factors for worse PROMs 2 to 10 years after ACLR. Very low–certainty evidence suggested that body mass index, smoking, and baseline PROMs were prognostic factors for worse outcome. Very low–certainty evidence suggested that female sex and a worse baseline Marx Activity Rating Scale score were prognostic factors for a worse Marx Activity Rating Scale score 2 to 10 years after ACLR. There was a lack of studies on prognostic factors after rehabilitation alone.

CONCLUSION: Concomitant meniscus and cartilage injuries were prognostic factors for worse long-term PROMs after ACLR. The certainty was very low for other prognostic factors. *J Orthop Sports Phys Ther 2020;50(9):490-502. Epub 1 Aug 2020. doi:10.2519/jospt.2020.9451*

KEY WORDS: *knee surgery, ligament, prognosis, sporting injuries*

Anterior cruciate ligament (ACL) injuries have serious negative long-term consequences, such as lower extremity dysfunction, low levels of physical activity, poor quality of life, and early development of knee osteoarthritis (OA).[3,7,15,21,25,50,53] Resolving impairments and returning to sport are often the main short-term goals for patients.[6,7] Clinicians must consider the long-term consequences of ACL injury when providing patient education and making decisions about interventions early after injury or reconstruction.[55] There is a need for high-quality studies on prognostic factors for important long-term outcomes, such as patient-reported outcome measures (PROMs), levels of physical activity, and OA.

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A prognosis study can aim to predict the total individual risk, given all available information in a prediction model, or to estimate the average causal effect of an exposure or treatment on an outcome in a population, given adjustment for relevant confounders. Both approaches may provide important information on prognostic factors, as a prognostic factor can be either causally or noncausally related to an outcome variable.[32,62,73] Many systematic reviews have evaluated prognostic factors for developing knee OA after ACL injury.[42,45,53,67,69,70] A few systematic reviews have reported prognostic factors for long-term PROMs and level of physical activity,[4,16,19,45,46,67] but half of them were of poor quality due to lack of risk of bias assessments.[45,46,67] Also, patients treated with rehabilitation alone have not been included in previous systematic reviews.

Consequently, a high-quality systematic review on prognostic factors for PROMs and level of physical activity 2 to 10 years after ACL reconstruction or injury, with an appropriate and thorough risk of bias assessment, is needed. Such a study could provide information about prognostic factors that can be targeted with early treatment, and thereby help to improve outcomes for patients with ACL injury.

Current evidence suggests similar clinical courses following rehabilitation alone and ACL reconstruction,[2,23-26,48] but we do not know whether prognostic factors differ in the 2 treatment groups. There is great clinical interest to identify early prognostic factors associated with better outcome after both ACL reconstruction and rehabilitation alone. This knowledge can help inform treatment choices. No systematic review has previously addressed this topic.

Therefore, the aims of our systematic review were (1) to assess prognostic factors for PROMs and physical activity 2 to 10 years after ACL injury or ACL reconstruction, and (2) to assess differences in prognostic factors between patients treated with ACL reconstruction and those treated with rehabilitation alone.

METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[49] Our study protocol was published in PROSPERO (CRD42018095602) on June 7, 2018.

Eligibility Criteria

Eligible studies met the following inclusion criteria: prospective cohort studies and randomized clinical trials that reported prognostic factors for PROMs or level of physical activity at a mean of 2 or more and less than 10 years in adults and adolescents (mean age, older than 13 years) undergoing either ACL reconstruction or rehabilitation alone after complete ACL rupture. Studies had to assess the association between exposure and outcome with regression analyses. Studies that exclusively reported on revision ACL reconstruction, knee dislocation, partial tear, or bilateral injury were excluded; those that reported on a subset of patients with these conditions were included. Prognostic factors were defined as patient characteristics (eg, age, sex, psychological factors), factors related to the injury (eg, concomitant injury), or knee symptoms and function (eg, functional performance, PROMs) that were assessed within 1 year after injury or ACL reconstruction.

The following PROMs were selected: the Knee injury and Osteoarthritis Outcome Score (KOOS), International Knee Documentation Committee Subjective Knee Evaluation Form (IKDC-SKF), and Knee Outcome Survey-Activities of Daily Living Scale (KOS-ADLS). These PROMs were chosen based on their frequent use as stand-alone PROMs for long-term outcomes during the last decade, and because they have good measurement properties.[5,13,37-39,58,71] The KOOS consists of 5 subscales: pain, other symptoms, function in daily living, function in sport and recreation (S/R), and knee-related quality of life (QoL).[58] The KOOS can be reported as individual subscale scores or as the "KOOS-4," which is an average score of 4 subscales (function in daily living excluded). The IKDC-SKF measures symptoms, function, and sports activity in patients with different types of knee problems.[37] The KOS-ADLS assesses the impact of symptoms on the ability of the patient to perform daily activities.[39] All 3 questionnaires are scored from 0 (worst) to 100 (best).

We included all outcomes that reflect type and level of physical activity, including the 3 components that define physical activity: frequency, intensity, and duration (eg, objective measures such as accelerometers, patient-reported physical activity questionnaires, and return to sport).[10] An example of a PROM of physical activity for ACL-injured individuals is the Marx Activity Rating Scale. The Marx Activity Rating Scale is a brief survey on the frequency of participation in sports involving running, pivoting, cutting, and deceleration.[47]

Data Sources and Searches

We systematically searched PubMed, Web of Science, and SPORTDiscus for articles published from database inception to September 20, 2018. The search strategy for PubMed is displayed in **TABLE 1**. Filters on "Humans" and "English language" were used, and all free-text words/terms were searched on "Title/abstract." Relevant systematic reviews were identified with the same search terms in PubMed. Reference lists from systematic reviews and included studies were hand searched for relevant material to supplement electronic database searches. To identify additional literature, the following simplified search was performed in Google Scholar: "Anterior cruciate ligament"|ACL Prognosis|"Prognostic factors"|Predict|Associations "Return to sports"|Participation|"Activity level"|"Physical activity"|Tegner|Marx|KOOS|IKDC|KOS "Prospective study"|"Observational study"|"Cohort study"|RCT. The 100 first (and most relevant) results from Google Scholar were screened.

The searches were performed with assistance from and reviewed by librarians at the Norwegian School of Sport Sciences and the University of Oslo.

Study Selection and Data Extraction

Two independent researchers (M.P. and J.L.J.) screened for eligibility and extracted data with customized data-extraction forms. Covidence systematic review software (Veritas Health Innovation Ltd, Melbourne, Australia) was used to assist this process. Calibration exercises were performed to ensure consistency between reviewers, but without testing agreement. Discrepancies were resolved by discussion or a third reviewer (H.G. or M.A.R.). We contacted study authors to resolve uncertainties when necessary. Titles and abstracts were screened to identify potentially relevant studies for full-text eligibility assessment. The reasons for exclusion were recorded. When several exclusion criteria were fulfilled, the first reason on a predefined list was chosen.

Risk of Bias Assessment

Risk of bias was assessed with the Quality In Prognosis Studies (QUIPS) tool.[29] We chose this tool because it was developed specifically for the methodological assessment of prognostic studies. The QUIPS tool is reliable for systematically assessing risk of bias in the following 6 domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting.[29] Three independent reviewers (M.P., J.L.J., and K.M.) performed the scoring of the different domains. Our operationalization of the QUIPS items is described in supplemental material (available at www.jospt.org). For studies where the objective was prediction and not etiology, the confounding domain was classified as irrelevant (because the goal of a prediction model is to predict the total individual risk given all information, for example, independent of the covariates' influence on each other).[32,62]

The overall risk of bias for each study was classified as follows: low when there was low risk of bias in all domains, moderate when there was moderate risk of bias in 1 or more domains, and high when there was high risk of bias in 1 or more domains.[33] For all domains, high risk of bias was defined as a level where the results of the study should not be trusted, and/or they were impossible to interpret due to research methodology and/or inadequate description of methodology. This was an overall assessment and decision, hence no study was classified as high risk of bias in any domain based on only 1 question.

Data Synthesis and Analysis

Results from all included studies (n = 20) are presented in supplemental material (available at www.jospt.org). We included only studies with low or moderate risk of bias in the data synthesis. The purpose was to ensure that conclusions and recommendations to clinicians and patients were robust, and to make the results easier to interpret and to translate into practice. When data from the same patients were used in publications on the same prognostic factors and outcomes at different time points, we included the most recent publication. Results were presented separately for PROMs, level of physical activity, and patients undergoing ACL reconstruction versus rehabilitation alone. When possible, results from studies on each treatment group were extracted separately. Results from adjusted analyses were preferred. It was not possible to perform a meta-analysis due to methodological diversity in outcome measures and follow-up times.

Certainty of evidence for each prognostic factor was judged as high, moderate, low, or very low according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[34,36] We used GRADEpro GDT (Evidence Prime Inc, Hamilton, Canada) to help generate evidence summaries.

TABLE 1 PubMed Search

	Search Term
1	Anterior cruciate ligament[MeSH terms] OR Anterior cruciate ligament injury[MeSH terms] OR Anterior cruciate ligament reconstruction[MeSH terms]
2	Anterior cruciate ligament OR ACL
3	Prognosis[MeSH terms]
4	Prognosis OR Prognostic factors OR Prognostic factor OR Predictor OR Predictors OR Predict OR Prediction OR Predictive OR Effect modifiers OR Effect modifier OR Risk factors OR Risk factor OR Factor OR Factors OR Associated OR Association OR Associations
5	Return to sport[MeSH terms]
6	Return to sport OR Return to sports OR Participation OR Activity level OR Physical activity OR "Tegner activity scale" OR "Marx activity rating scale" OR Return to play OR KOOS OR "Knee injury and Osteoarthritis Outcome score" OR "International Knee Documentation Committee subjective knee form" OR "IKDC-SKF 2000" OR IKDC-SKF2000 OR "International Knee Documentation Committee Subjective Knee Evaluation Form" OR "IKDC-SKF" OR "Knee Outcome Survey" OR KOS
7	Prospective studies[MeSH terms]
8	Prospective studies OR Prospective study OR Observational study OR Cohort study OR Randomized controlled trial OR Randomized clinical trial OR Randomised controlled trial OR Randomised clinical trial OR RCT OR Randomised trial OR Randomized trial
9	1 OR 2
10	3 OR 4
11	5 OR 6
12	7 OR 8
13	9 AND 10 AND 11 AND 12

RESULTS

Search Results

Database searches identified 974 references, and 23 additional references were identified through bibliographies (n = 2), Google Scholar (n = 3), and reference lists (n = 18). After removing duplicates, 561 references remained. All were screened for eligibility, and 431 were ineligible due to objectives, outcome, or follow-up time. The remaining 130 articles were read in full text, and 20 met all eligibility criteria (**FIGURE**). Seventeen of the included studies were identified through the systematic search, while 3 were identified through other sources. Due to more recent publications on the same prognostic factors and outcomes, we excluded the results on concomitant cartilage lesions, but not meniscus lesions, from Røtterud et al,[59] and all results from Magnussen et al[43] from 2016. Seven studies with low or moderate risk of bias remained for data synthesis.[1,22,27,44,59,64,68]

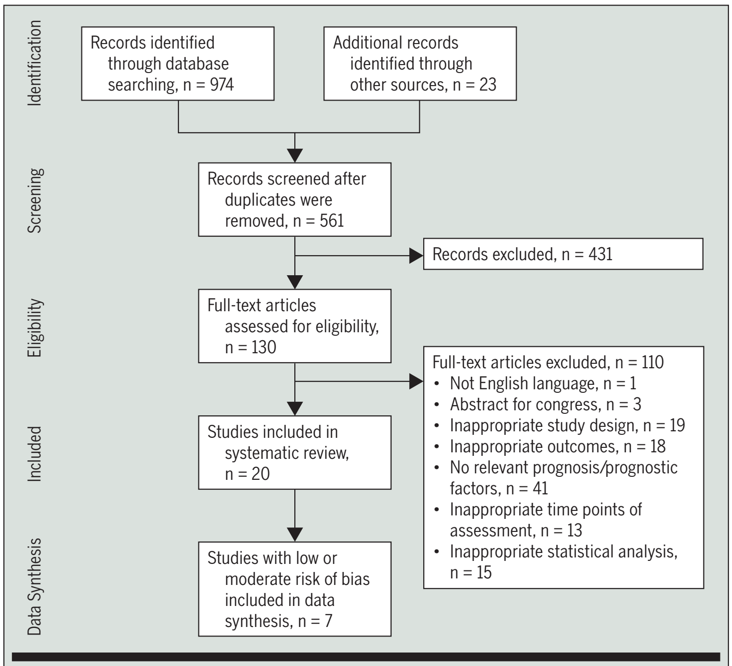

FIGURE. Flow chart.

Study Characteristics

Characteristics of the included studies (n = 20) are presented in **TABLE 2**. Most of the cohort studies were based on data from the Multicenter Orthopaedic Outcomes Network (MOON) cohort (n = 8)[9,14,17,43,44,64,65,72] and the Swedish and/or Norwegian Knee Ligament Registers (n = 5).[1,8,27,59,68] In the included randomized clinical trials (RCTs), both treatment groups were treated as one cohort for the assessment of prognostic factors.[18,22,56,61] Three of the RCT publications were based on the Knee Anterior Cruciate Ligament, Nonsurgical versus Surgical Treatment (KANON) trial.[18,22,56] The studies included a median of 495 (Q1-Q3 range, 121-2333) patients. Because several publications involving the large registries reported on the same patients, it was challenging to estimate the total number of unique patients included in this systematic review. Most studies included patients undergoing primary ACL reconstruction only, and no study included only patients treated with rehabilitation alone. Patients with substantial concomitant injuries[8,14,18,22,27,40,43,44,51,56,61,63,65] and/or contralateral ACL injury[14,17,27,59,61,64,65,68,72] were frequently excluded from the included studies. The median age at inclusion was 26 years (range, 18-27 years). The median percentage of women was 44% (range, 26%-77%). Preinjury activity level was reported in 7 studies, of which 4 studies[17,40,51,63] included patients active in pivoting sports preinjury and 3 studies[18,22,56] included patients with a Tegner activity scale score between 6 and 9 (6, recreational pivoting sports; 9, competitive sports).

Sixteen studies were etiological[1,9,14,17,18,22,27,40,43,44,56,59,61,63,65,68] and 4 were predictive.[8,51,64,72] Among the studies included in our data synthesis, only Spindler et al[64] was a predictive study.

Risk of Bias

Risk of bias for the 6 QUIPS domains and an overall rating is shown in **TABLE 3**. Studies generally performed poorly on the domains "study confounding" and "statistical analysis and reporting," because they did not explicitly state which covariates were adjusted for and why; did not separate between confounders, mediators, and colliders (and subsequently did not treat these covariates in accordance with existing rules for adjustment); or had mixed predictive and etiological statistical approaches, which led to uninterpretable results.[31,62,73]

Data Synthesis of Studies With Low or Moderate Risk of Bias (n = 7)

Prognostic Factors for PROMs in Patients Treated With ACL Reconstruction Prognostic factors for PROMs in patients treated with ACL reconstruction were assessed in 7 studies from 4 cohorts. The IKDC-SKF was an outcome in 2 studies[44,64] and the KOOS was an outcome in 7 studies.[1,22,27,44,59,64,68] The following 13 factors were assessed by 1 or more studies with low or moderate risk of bias: sex, age, body mass index (BMI), smoking, ethnicity, type of sport, concomitant injury to the medial or lateral collateral

TABLE 2 — Characteristics of Included Studies (n = 20)

	Study Characteristics						Patient Characteristics	
Study/Type	n	Treatment	Follow-up, y	Prognostic Factors Assessed	Outcome	Included in Data Synthesis	Sex (female), %	Age, y[a]
Ageberg et al[1] SKLR	10164	Primary ACLR	2	Age	KOOS	Yes	42	27
Barenius et al[8] SKLR	8584	Primary ACLR	2	Sex, age, baseline PROM, concomitant meniscus/cartilage injury, knee laxity, previous knee surgery	KOOS	No	49	NR
Brophy et al[9] MOON	2198	Primary or revision ACLR	2	Diabetes	IKDC-SKF KOOS Level of physical activity	No	44	24
Cox et al[14] MOON	1512	Primary or revision ACLR	6	Sex, age, BMI, smoking, education, ethnicity, type of sport, competition level, baseline PROMs, concomitant meniscus/cartilage injury	IKDC-SKF KOOS Level of physical activity	No	44	23
Dunn et al[17] MOON	446	Primary or revision ACLR	2	Sex, age, BMI, smoking, education, marital status, ethnicity, type of sport, competition level, baseline PROM, concomitant meniscus/cartilage injury, hearing a pop at injury	Level of physical activity	No	44	23
Ericsson et al[18] KANON	121	ACLR or nonsurgical	2 and 5	Early physical performance	KOOS	No	26	26
Filbay et al[22] KANON	121	ACLR or nonsurgical	5	Baseline PROM, concomitant meniscus/cartilage injury, knee extension deficit	KOOS	Yes	26	26
Hamrin Senorski et al[27] SKLR	15204	Primary ACLR	2	Concomitant MCL/LCL or meniscus/cartilage injury	KOOS	Yes	50	NR
Ithurburn et al[40] Cohort	48	Primary ACLR	2	Early physical performance	KOOS	No	77	18
Magnussen et al[43] MOON	2333	Primary ACLR	2	Knee laxity	IKDC-SKF KOOS	No	44	27

Table continues on page 495.

ligament (MCL/LCL), meniscus, or cartilage, an audible pop at injury, knee laxity, extension range-of-motion deficit, and baseline PROMs. These factors were measured at baseline, preoperatively, or during ACL reconstruction.

Patient Characteristics One predictive study reported higher baseline BMI as a prognostic factor for worse 6-year IKDC-SKF and KOOS S/R outcomes, and smoking as a prognostic factor for worse IKDC-SKF score.[64] The same study found no association between higher BMI and KOOS QoL score, or between smoking and KOOS QoL and KOOS S/R scores.

There were no statistically significant associations between the factors of sex, age, ethnicity, and type of sport and the outcomes of 2- and 6-year IKDC-SKF and KOOS scores.[1,64]

Factors Related to the Injury Concomitant meniscus injury was reported as a prognostic factor in some studies, but not in others. Three studies (2 etiological and 1 predictive) of 3 different cohorts found a statistically significant negative association between concomitant meniscus injury and 2-year patient-reported success (KOOS-4 score in the 80th percentile or greater)[27] and 5- and 6-year KOOS S/R and QoL outcomes.[22,64] The mean difference between those with and without concomitant meniscus injury was 10 to 14.4 points for the KOOS S/R[22,64] and 8.9 points for the KOOS QoL.[64] The same studies found, however, no statistically significant associations between meniscus injury and the other KOOS subscales and the IKDC-SKF.[22,64] In 1 etiological study, concomitant meniscus injury was not a prognostic factor for any 2-year KOOS subscale.[59]

Concomitant cartilage injury was assessed in 4 studies from 4 different cohorts.[22,27,64,68] In 2 etiological studies, there was a statistically significant association between concomitant cartilage lesions and 5-year KOOS scores (all subscales), particularly for the full-thickness lesions.[22,68] The mean difference between those with and without concomitant cartilage injury was 8.1 points for the KOOS S/R[68] and 8.0 to 12.3 points for the KOOS QoL.[22,68] The results of Filbay et al[22] applied only to the 5-year KOOS QoL score in patients with early (not delayed) ACL reconstruction.

TABLE 2 CHARACTERISTICS OF INCLUDED STUDIES (N = 20) (CONTINUED)

	Study Characteristics						Patient Characteristics	
Study/Type	n	Treatment	Follow-up, y	Prognostic Factors Assessed	Outcome	Included in Data Synthesis	Sex (female), %	Age, y[a]
Magnussen et al[44] MOON	2333	Primary ACLR	6	Knee laxity	IKDC-SKF KOOS Level of physical activity	Yes	44	27
Nawasreh et al[51] Cohort	107	Primary ACLR	2	Sex, age, baseline PROM, early physical performance	Level of physical activity	No	34	27
Roessler et al[56] KANON	121	ACLR or nonsurgical	2	Psychological factors	KOOS	No	26	26
Røtterud et al[59] SKLR, NKLR	15783	Primary ACLR	2	Concomitant meniscus/cartilage injury	KOOS	Yes	42	26
Sasaki et al[61] RCT	150	Primary ACLR	2	Sex, age, BMI, baseline PROM, concomitant meniscus injury	KOOS	No	58	26
Sonnery-Cottet et al[63] Cohort	541	Primary ACLR	3	Sex, age, type of sport, concomitant meniscus injury	Level of physical activity	No	27	22
Spindler et al[65] MOON	314	Primary ACLR	5	Sex, age, type of sport, concomitant meniscus/cartilage injury, hearing a pop at injury, onset of swelling after injury	IKDC-SKF KOOS	No	45	27
Spindler et al[64] MOON	448	Primary or revision ACLR	6	Sex, age, BMI, smoking, ethnicity, marital status, type of sport, baseline PROMs, concomitant MCL/LCL or meniscus/cartilage injury, hearing a pop at injury	IKDC-SKF KOOS Level of physical activity	Yes	43	23
Ulstein et al[68] SKLR, NKLR	15783	Primary ACLR	5	Concomitant cartilage injury	KOOS	Yes	42	27
Wasserstein et al[72] MOON	1761	Primary ACLR	2 and 6	Sex, age, BMI, smoking, education, baseline PROM, concomitant meniscus/cartilage injury, previous knee pathology	KOOS	No	44	23

Abbreviations: ACLR, anterior cruciate ligament reconstruction; BMI, body mass index; IKDC-SKF, International Knee Documentation Committee Subjective Knee Evaluation Form; KANON, Knee Anterior Cruciate Ligament, Nonsurgical versus Surgical Treatment; KOOS, Knee injury and Osteoarthritis Outcome Score; LCL, lateral collateral ligament; MCL, medial collateral ligament; MOON, Multicenter Orthopaedic Outcomes Network; NKLR, Norwegian Knee Ligament Register; NR, not reported; PROM, patient-reported outcome measure; RCT, randomized clinical trial; SKLR, Swedish Knee Ligament Register.
[a]*Values are either median or mean.*

In a third etiological study, the absence of concomitant cartilage injury predicted 2-year patient-reported success (as previously defined), while having a concomitant cartilage injury predicted failure (KOOS-4 score in the 20th percentile or less).[27] One predictive study found no association between concomitant cartilage injury and 6-year KOOS S/R and QoL and IKDC-SKF scores.[64]

There were no statistically significant associations between concomitant MCL/LCL injury or an audible pop at injury and the outcomes of 2-year patient-reported success or failure[27] and 6-year IKDC-SKF, KOOS QoL, and KOOS S/R scores.[64]

Knee Symptoms/Function In 1 etiological study, baseline KOOS-4 score predicted 5-year scores on the KOOS other symptoms, S/R, and QoL subscales, but not on the pain subscale, in patients with early ACL reconstruction.[22] In those with delayed ACL reconstruction, baseline KOOS-4 score did not predict any of the 5-year KOOS subscale scores.[22] A predictive study found conflicting results for the association between baseline and 5-year KOOS scores.[64]

Preoperative knee laxity, defined as severely abnormal Lachman, anterior drawer, or pivot-shift test score, was assessed in 1 etiological study.[44] There was a small, statistically significant association between preoperative knee laxity and 6-year IKDC-SKF and KOOS QoL scores (mean differences between those with and without preoperative laxity of 2.3 and 2.7 points, respectively) that was not considered clinically relevant.[44]

There were no statistically significant associations between baseline Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) score and knee extension deficit greater than 10° and 5-year KOOS outcomes.[22]

GRADE Evaluation for Prognostic Factors for PROMs in Patients Treated With ACL Reconstruction The evidence for concomitant meniscus and cartilage injuries was moderate certainty, while for the other factors it was low or very low certainty (**TABLE 4**). Our conclusions did not differ when all 20 eligible studies were included in the GRADE evaluation (supplemental material, available at www.jospt.org).

Prognostic Factors for Physical Activity in Patients Treated With ACL Reconstruction Prognostic factors for level of physical activity in patients treated with ACL reconstruction were assessed in 2 studies from the same cohort, both using the Marx Activity Rating Scale questionnaire as the outcome.[44,64] The following 13 factors were assessed by 1 or more studies with moderate risk of bias: sex, age, BMI, smoking, marital status, ethnicity, type of preinjury sport, baseline PROMs, concomitant injury to the LCL/MCL, meniscus, or cartilage, knee laxity, and hearing a pop at injury (**TABLE 2**).

Patient Characteristics One predictive study assessed several demographic factors as possible prognostic factors for 6-year Marx Activity Rating Scale score.[64] Female sex and worse baseline Marx Activity Rating Scale score were prognostic factors for worse 6-year Marx Activity Rating Scale score, while age, BMI, smoking, marital status, ethnicity, and type of preinjury sport were not.[64]

Factors Related to the Injury None of the following factors were prognostic factors for 6-year Marx Activity Rating Scale score: concomitant MCL/LCL, meniscus, or cartilage injury and an audible pop at injury.[64] One etiological study found a statistically significant association between preoperative laxity (as previously defined) and 6-year Marx Activity Rating Scale score.[44] The mean difference between those with and without preoperative laxity was small (0.5 points) and not clinically relevant.[44]

GRADE Evaluation for Prognostic Factors for Level of Physical Activity in Patients Treated With ACL Reconstruction Certainty of evidence was very low for all the prognostic factors for level of physical activity in patients treated with ACL reconstruction. Serious limitations in several GRADE domains occurred because evidence for all factors was based on only 1 study with moderate risk of bias.

Prognostic Factors for PROMs and Physical Activity in Patients Treated With Rehabilitation Alone One etiological study separately assessed prognostic factors for 5-year KOOS-4 score in a group of patients treated with rehabilitation alone.[22] None of the following factors were prognostic factors: baseline cartilage defect, meniscus damage, osteochondral lesion, extension deficit, SF-36 score, and KOOS-4 score.[22] Certainty of evidence was very low due to few studies. No study assessed prognostic factors for physical activity in this patient group.

Differences in Prognostic Factors Between Treatment Groups One etiological study with low risk of bias assessed differences in prognostic factors between those treated with rehabilitation alone and with ACL reconstruction.[22] Based on dif-

TABLE 3 Risk of Bias Assessment (n = 20)

	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting	Overall
Ageberg et al[1]	Low	Moderate	Low	Low	Moderate	Low	Moderate
Barenius et al[8]	Low	Moderate	Low	Moderate	Irrelevant	High	High
Brophy et al[9]	Low	Low	Low	Low	High	High	High
Cox et al[14]	Low	Low	Low	Low	High	High	High
Dunn et al[17]	Low	Low	Low	Low	High	High	High
Ericsson et al[18]	Low	Moderate	Moderate	Low	High	High	High
Filbay et al[22]	Low	Low	Low	Low	Low	Low	Low
Hamrin Senorski et al[27]	Low	Moderate	Moderate	Low	Low	Low	Moderate
Ithurburn et al[40]	Moderate	High	Low	Low	High	High	High
Magnussen et al[43]	Low	Low	Low	Low	Moderate	Moderate	Moderate
Magnussen et al[44]	Low	Low	Low	Low	Moderate	Moderate	Moderate
Nawasreh et al[51]	Low	High	Low	Low	Irrelevant	Low	High
Roessler et al[56]	Low	Low	Low	Low	High	Moderate	High
Røtterud et al[59]	Low	Moderate	Low	Low	Low	Low	Moderate
Sasaki et al[61]	Low	Low	Low	Low	High	High	High
Sonnery-Cottet et al[63]	Low	Low	Low	Low	High	High	High
Spindler et al[65]	Low	High	Low	Low	High	High	High
Spindler et al[64]	Low	Low	Low	Low	Irrelevant	Moderate	Moderate
Ulstein et al[68]	Low	Moderate	Low	Low	Moderate	Low	Moderate
Wasserstein et al[72]	Low	Low	Low	Low	Irrelevant	High	High

ferences in prognostic factors for 5-year KOOS-4 score between the treatment groups, the authors suggested that patients with concomitant meniscus injury and those with worse KOOS other symptoms, S/R, and QoL subscale scores in the early phase may benefit most from exercise therapy before choosing treatment.[22]

DISCUSSION

Concomitant meniscus and cartilage injuries were, with moderate certainty, prognostic factors for worse PROMs 2 to 10 years after ACL reconstruction. Smoking, BMI, and baseline PROMs were prognostic factors for 2- to 10-year PROMs with very low certainty. For level of physical activity 2 to 10 years after ACL reconstruction, we concluded, with very low certainty, that female sex and worse baseline Marx Activity Rating Scale score were prognostic factors for worse long-term Marx Activity Rating Scale score. The other factors assessed in this systematic review were not associated with the outcomes. No studies included only patients treated with rehabilitation alone. One study assessed differences in prognostic factors between patients treated with rehabilitation alone and those treated with ACL reconstruction.[22] Patients with concomitant meniscus and cartilage injuries and lower KOOS scores in the acute phase may benefit most from an initial nonsurgical treatment choice, but further research on the topic is needed to draw conclusions. Hence, we could not answer the second aim of this systematic review.

The impact of the prognostic factors of BMI, smoking, baseline PROMs, sex,

TABLE 4 GRADE Evidence Profile: Potential Prognostic Factors for 2- to 10-Year PROMs in ACL-Reconstructed Patients for Studies With Low or Moderate Risk of Bias (n = 7)

			GRADE Factors[a]							
Potential Prognostic Factors	**Studies, n**	**Patients, n**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Certainty**
Sex[b]	1	448	×[c]	✓	✓	×	×[d]	×	×	Very low
Age[e]	2	10612	×[f]	✓	✓	×	×[d]	×	×	Low
Higher BMI[g]	1	448	×[c]	✓	✓	×[c]	×[d]	×	×	Very low
Smoking[g]	1	448	×[c]	×[h]	✓	×	×[d]	×	×	Very low
Ethnicity[b]	1	448	×[c]	✓	✓	×	×[d]	×	×	Very low
Type of sport[b]	1	448	×[c]	✓	✓	×	×[d]	×	×	Very low
Concomitant MCL or LCL injury[i]	2	15652	×[f]	✓	✓	×	×[d]	×	×	Low
Concomitant meniscus injury[j]	4	31556	✓	×[h]	✓	✓	×[d]	✓	×	Moderate
Concomitant cartilage injury[k]	4	31556	✓	×[h]	✓	✓	×[d]	✓	✓	Moderate
Hearing pop at injury[b]	1	448	×[c]	✓	✓	×	×[d]	×	×	Very low
Preoperative knee laxity[b]	1	2333	×[c]	✓	✓	×	×[d]	×	×	Very low
Preoperative extension deficit[b]	1	121	×[l]	✓	✓	×	×[d]	×	×	Very low
Higher baseline PROMs[m]	2	569	×[f]	×[h]	✓	×	×[d]	×	×	Very low

Abbreviations: ✓, no serious limitations; ×, serious limitations (or not present for moderate/large effect size, dose effect); ACL, anterior cruciate ligament; BMI, body mass index; GRADE, Grading of Recommendations Assessment, Development and Evaluation; LCL, lateral collateral ligament; MCL, medial collateral ligament; PROM, patient-reported outcome measure.

[a]*Items: 1, Study limitations; 2, Inconsistency; 3, Indirectness; 4, Imprecision; 5, Publication bias; 6, Moderate/large effect size; 7, Dose effect.*

[b]*Nonsignificant effect on multivariable analysis (1 study). The multivariable analysis represents a summary of the authors' conclusions when several outcomes for each factor were assessed.*

[c]*Evidence is based on only 1 study with moderate risk of bias.*

[d]*Due to a small number of included studies, we could not assess small-study biases with a funnel plot. We therefore cannot rule out publication bias.*

[e]*Nonsignificant effect on univariable analysis (1 study) and nonsignificant effect on multivariable analysis (1 study). The multivariable analysis represents a summary of the authors' conclusions when several outcomes for each factor were assessed.*

[f]*Evidence is based on only 2 studies with moderate risk of bias.*

[g]*Negative significant effect on multivariable analysis (1 study). The multivariable analysis represents a summary of the authors' conclusions when several outcomes for each factor were assessed.*

[h]*Inconsistency within/between study/studies.*

[i]*Nonsignificant effect on multivariable analysis (2 studies). The multivariable analysis represents a summary of the authors' conclusions when several outcomes for each factor were assessed.*

[j]*Negative significant effect on multivariable analysis (3 studies) and nonsignificant effect on multivariable analysis (1 study). The multivariable analysis represents a summary of the authors' conclusions when several outcomes for each factor were assessed.*

[k]*Negative significant effect on multivariable analysis (4 studies) and nonsignificant effect on multivariable analysis (1 study). The multivariable analysis represents a summary of the authors' conclusions when several outcomes for each factor were assessed.*

[l]*Evidence is based on only 1 study with low risk of bias.*

[m]*Positive significant effect on multivariable analysis (2 studies). The multivariable analysis represents a summary of the authors' conclusions when several outcomes for each factor were assessed.*

and baseline Marx Activity Rating Scale score on outcomes was small (see supplemental material, available at www.jospt.org) and probably not clinically relevant. The impact of concomitant meniscus injury as a prognostic factor was larger, as the mean difference between those with and without meniscus injury was 10.0 to 14.4 points for the KOOS S/R[22,64] and 8.9 points for the KOOS QoL.[64] The impact of concomitant meniscus injury on KOOS S/R outcomes, but not on KOOS QoL outcomes, was clinically relevant, with minimal important changes of 12.1 (95% confidence interval: 9.3, 14.8) points on the KOOS S/R and 18.3 (95% confidence interval: 16.0, 20.6) points on the KOOS QoL.[35] The impact of having a concomitant cartilage injury on the KOOS S/R (8.1 points) and QoL (8-12.3 points) outcomes also seemed important, but the mean differences between those with and without concomitant cartilage injury were below the minimal important changes for the instruments.[22,68]

Comparison With Other Studies

The high methodological quality of this systematic review makes an important contribution to this field. Our high-quality search strategy, rigorous risk of bias assessment, and data synthesis ensured robust conclusions and recommendations for clinicians and patients. Due to these methodological factors, we could not replicate the findings of previous systematic reviews that male sex, younger age, and psychological factors were positive prognostic factors and that quadriceps weakness and range-of-motion deficits were negative factors.[16,19]

To our knowledge, ours is the first systematic review to assess prognostic factors for PROMs and level of physical activity after ACL injury, both in patients treated with ACL reconstruction and rehabilitation alone. However, the paucity of studies on patients treated with rehabilitation alone made it impossible to answer questions regarding prognostic factors for PROMs and level of physical activity for this treatment group, or to assess differences in prognostic factors between treatment groups.

Our results highlighted the importance of risk of bias assessments in systematic reviews, as 12 (60%) of the 20 included studies had high risk of bias. Bias was most often in the domains of "study confounding" and "statistical analysis and reporting." Lack of clarity in aims and methods about whether studies were predictive or etiological was a recurring limitation. Effect estimates calculated from one model, often a prediction model, and presented in one table may mislead, because the underlying associations between covariates are not accounted for.[73] In many papers with an etiological aim but a statistically driven rather than a theoretically driven approach, it was unclear whether estimates were adjusted for all of the relevant confounders and should have been interpreted as total effect or direct effect.[32] Epidemiological research methodology has developed over time, and the distinction between explanatory and predictive aims was less clear at the time when the included studies were performed.

Limitations

An important limitation in the literature in this field was the overlap of patients within the different publications from the MOON cohort and the Swedish and/or Norwegian Knee Ligament Registers. This overlap might have led to a correlation between study results that we could not account for. To minimize this problem, we included only the most recent publication of data from the same patients and on the same prognostic factors. Further, our strict inclusion criteria might have led us to miss high-quality research in which other PROMs than the IKDC-SKF, KOOS, and KOS-ADLS were used, such as the Lysholm Knee Scoring Scale, Anterior Cruciate Ligament-Return to Sport after Injury scale, and SF-36. The included studies did not differentiate between types of meniscus injuries, and we therefore could not assess prognosis after different injury types (eg, dislocated bucket-handle tears versus stable, horizontal tears).

Our results apply to individuals with first-time, complete unilateral ACL injury, not including knee dislocations. The prognostic factors are also only applicable to the PROMs used in this study and to level of physical activity 2 or more and fewer than 10 years after ACL reconstruction. We did not consider psychological, overall health, or overall QoL outcomes.

Implications for Clinical Practice

When planning future physical activities and discussing patient expectations, it is useful for patients, physical therapists, orthopaedic surgeons, and athletic trainers to be aware that concomitant meniscus or cartilage injuries may lead to worse knee function 2 to 10 years after ACL reconstruction. As concomitant meniscus injuries are also the most frequently reported prognostic factor for knee OA after ACL injury,[53,70] patients should be informed about preventive interventions for knee OA, such as knee extensor muscle strength training and maintaining a healthy body weight.[20,28,41,54,57,74,75] Although with very low certainty, higher BMI was a prognostic factor for worse PROMs after ACL reconstruction. Due to the relationship of BMI to both knee function and development of knee OA, BMI should be incorporated as a prognostic factor in early patient education. We also found that smoking was a negative prognostic factor for PROMs. As this factor is modifiable, patients should be informed that avoiding smoking might contribute to better long-term outcomes.

Implications for Future Research on Prognostic Factors After ACL Injury and ACL Reconstruction

Future studies should be clear about whether their goals and methods are aimed at prediction or etiology. If the aim is etiological, authors should carefully state their hypothesis and background and run an informed causal analysis, ensuring that rules for adjustment for different types of covariates (confounders, mediators, and colliders) are followed.[30,32] If the aim is predictive, authors should systematically build a prediction model based on all available predictors, study the model's discriminative ability and calibration, and, subsequently, internally and externally validate findings.[11,66] Preregistration of study protocols for observational studies on prognostic factors might enable researchers to assess whether selective reporting and publication biases occur within this field.

Future high-quality prognosis studies should include patients treated with rehabilitation alone. This patient group is important, as it represents between 26% and 77% of the ACL-injured population.[12,52,60] New studies should also compare prognostic factors between patients treated with rehabilitation alone and with ACL reconstruction in order to help clinicians identify those who have the best prognosis with ACL reconstruction and those who may succeed with rehabilitation alone. Future studies should also assess modifiable prognostic factors that can be targeted in early rehabilitation, such as muscle strength, range of motion, and hop performance.

Our systematic review also uncovered a lack of studies on level of physical activity in the long term after ACL injury. Most studies were at high risk of bias, and the study outcomes only included an activity rating scale (Marx Activity Rating Scale) and the prevalence of return to sport, neither of which aligns with the most common definition of level of physical activity,[10] as they only measure participation in specific types of sports. Future studies should therefore include more general outcomes of level of physical activity (eg, accelerometry, International Physical Activity Questionnaire).

CONCLUSION

Concomitant meniscus and cartilage injuries were prognostic factors for worse PROMs 2 to 10 years after ACL reconstruction. There was very low–certainty evidence that higher BMI, smoking, and worse baseline PROMs were prognostic factors for worse PROMs, and that female sex and worse baseline Marx Activity Rating Scale score were prognostic factors for worse Marx Activity Rating Scale score 2 to 10 years after ACL reconstruction. ◉

KEY POINTS

FINDINGS: We have moderate confidence that concomitant meniscus and cartilage injuries are prognostic factors for worse long-term patient-reported outcome measures after anterior cruciate ligament (ACL) reconstruction. The certainty is low or very low for other prognostic factors.

IMPLICATIONS: When planning future activities and discussing patient expectations, it is useful for patients, physical therapists, orthopaedic surgeons, and athletic trainers to consider that concomitant meniscus or cartilage injuries may lead to worse knee function 2 to 10 years after ACL reconstruction.

CAUTION: A large proportion (60%) of included studies in this systematic review were at high risk of bias, and there is a lack of studies on prognostic factors in patients treated with rehabilitation alone.

STUDY DETAILS

AUTHOR CONTRIBUTIONS: All authors made a substantial contribution to the (1) conception/design of the study (Marie Pedersen and Drs Johnson, Grindem, Risberg, and Snyder-Mackler) or to the analysis or interpretation of the data (Marie Pedersen and Drs Johnson and Magnusson), and to the (2) drafting (Marie Pedersen and Dr Johnson) or critical revision (Drs Grindem, Magnusson, Risberg, and Snyder-Mackler) of the article. All authors gave final approval of the manuscript and agreed to be accountable for all aspects of the work.

DATA SHARING: All data relevant to the study are included in the article or are available as supplemental material (available at www.jospt.org).

PATIENT AND PUBLIC INVOLVEMENT: There was no patient or public involvement in this research.

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Appendix 1 – QUIPS: Comments and clarifications

Biases	Descriptions in QUIPS tool	Our comments and clarifications
1. Study Participation		
Source of target population	The source population or population of interest is adequately described for key characteristics (LIST).	What group they want to target. In this case ACL-injured patients.
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health care)	For example recruitment at hospitals, singe surgeon practice or register data + sample size calculations
Recruitment period	Period of recruitment is adequately described	-
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described	-
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).	-
Adequate study participation	There is adequate participation in the study by eligible individuals	Cut-off for low risk of bias related to adequate participation in the study by eligible individuals was set at ≥80% (1)
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for key characteristics (LIST).	-
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.**	-
2. Study Attrition		
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.	Cut-off for low risk of bias for adequate response rate (domain 2: Study Attrition) was set at 80% (1, 2). Studies with <80% follow-up rate with no important differences between key characteristics in participants who completed the study and those who did not, were scored with moderate risk of bias. Studies with <80% follow-up rate that did not provide this information were scored with high risk of bias.
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.	If they actually did collect this information, not just attempts to do so.
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.	-
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).	-

	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.	-
Study Attrition Summary	**Loss to follow-up (from baseline sample to study population analysed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome.**	
3. Prognostic Factor Measurement		
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).	-
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	-
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.	-
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.	-
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.	Adequate proportion: 80-90%
Method used for missing data	Appropriate methods of imputation are used for missing 'PF' data.	Were there any attempts at describing and explaining the pattern of missing data and were appropriate methods for imputation assessed accordingly?
PF Measurement Summary	***PF* is adequately measured in study participants to sufficiently limit potential bias.**	
4. Outcome Measurement		
Definition of the Outcome	A clear definition of outcome is provided, including duration of follow-up and level and extent of the outcome construct.	-
Valid and Reliable Measurement of Outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and confirmation of outcome with valid and reliable test).	-
Method and Setting of Outcome Measurement	The method and setting of outcome measurement is the same for all study participants.	-
Outcome Measurement Summary	***Outcome of interest* is adequately measured in study participants to sufficiently limit potential bias.**	
5. Study Confounding		

Important Confounders Measured	All important confounders, including treatments (key variables in conceptual model: LIST), are measured.	Was there any theoretical justification for including certain confounders and did the authors separate between assumed confounders, mediators and colliders.
Definition of the confounding factor	Clear definitions of the important confounders measured are provided (e.g., including dose, level, and duration of exposures).	-
Valid and Reliable Measurement of Confounders	Measurement of all important confounders is adequately valid and reliable (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).	-
Method and Setting of Confounding Measurement	The method and setting of confounding measurement are the same for all study participants.	-
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data.	Were there any attempts at describing and explaining the pattern of missing data and were appropriate methods for imputation assessed accordingly?
Appropriate Accounting for Confounding	Important potential confounders are accounted for in the study design (e.g., matching for key variables, stratification, or initial assembly of comparable groups).	-
	Important potential confounders are accounted for in the analysis (i.e., appropriate adjustment).	Were the covariates described for point "Important confounders measured" treated according to rules for adjustment in the analyses?
Study Confounding Summary	**Important potential confounders are appropriately accounted for, limiting potential bias with respect to the relationship between *PF* and *outcome*.**	

6. Statistical Analysis and Reporting

Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.	-
Model development strategy	The strategy for model building (i.e., inclusion of variables in the statistical model) is appropriate and is based on a conceptual framework or model.	Was a conceptual framework or model described as a basis for the statistical analyses and the clarity of this description.
	The selected statistical model is adequate for the design of the study.	-
Reporting of results	There is no selective reporting of results.	-
Statistical Analysis and Presentation Summary	**The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid or spurious results.**	

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Appendix 2 – Results on prognostic factors for PROMs from all included studies (n=20)

Several studies have both significant and non-significant results. Therefore, authors conclusions on the different possible prognostic factors are given (+ =significant results. - =non-significant results).

	Study	Study's overall risk of bias	Non-significant results	Female gender significant negative predictor	Male gender significant negative predictor	Magnitude of association OR/β (95% CI)	Authors conclusions
Sex	**Barenius et al. (2013)**	High	2y treatment failure[e]	2y functional recovery[d]		OR=0.73(0.62-0.86)	+
	Cox et al. (2014)	High	6y KOOS	6y IKDC-SKF		OR=0.72(0.58-0.88)	+
	Sasaki et al. (2016)	Higha	2y KOOS pain 2y KOOS symptoms 2y KOOS S/R 2y KOOS QoL	2y KOOS ADL		β=-0.34(-3.62 to -1.0)	+
	Spindler et al. (2005)	High	5y KOOS 5y IKDC-SKF				-
	Spindler et al. (2011)	Moderate	6y IKDC-SKF 6y KOOS QoL 6y KOOS S/R				-
	Wasserstein et al. (2015)	High	2 and 6y symptomatic knee model 1[a] 2 and 6y symptomatic knee model 2[b]		Symptomatic knee model 3[c]	OR= 0.67 (0.47-0.96)	-
Age	**Author**		**Non-significant results**	**Higher age significant negative predictor**		**Magnitude of association** OR/β (95% CI)	**Authors conclusions**
	Ageberg et al. (2010)	Moderate	2y KOOS (all subscales)				-
	Barenius et al. (2013)	High		2y functional recovery 2y treatment failure		OR age <18 vs >55= 2.43(1.12-5.25) OR age 35-54 vs <18= not given. but p=0.001	+
	Cox et al. (2014)	High	6y IKDC-SKF 6y KOOS				-
	Sasaki et al. (2016)	High	2y KOOS pain 2y KOOS symptoms 2y KOOS S/R	2y KOOS ADL 2y KOOS QoL		β=-0.27(-0.13 to -0.02) β=-0.3(-0.67 to -0.13)	+
	Spindler et al. (2005)	High	5y KOOS 5y IKDC-SKF				-
	Spindler et al. 2011)	Moderate	6y KOOS QOL 6y KOOS S/R 6y IKDC-SKF				-

	Wasserstein et al. (2015)	High	2 and 6y symptomatic knee all models				-
	Author		**Non-significant results**	**Higher BMI significant negative predictor**		**Magnitude of association** OR/β/IQROR (95% CI)	**Authors conclusions**
	Cox et al. (2014)	High		6y IKDC-SKF 6y KOOS sym 6y KOOS pain 6y KOOS ADL 6y KOOS S/R 6y KOOS QOL		OR BMI 28 vs 23= 0.79(0.69-0.91) OR BMI 28 vs 23= 0.88(0.78-1.00) OR BMI 28 vs 23= 0.84(0.73-0.95) OR BMI 28 vs 23= 0.79(0.69-0.91) OR BMI 28vs 23= 0.82(0.72-0.93) OR BMI 28 vs 23= 0.86(0.75-0.98)	+
	Sasaki et al. (2016)	High	2y KOOS sym 2y KOOS pain 2y KOOS QoL	2y KOOS ADL 2y KOOS S/R		β=-0.31 (-0.51 to -0.13) β=-0.23 (-1.48 to -0.1)	+
BMI	**Spindler et al. 2011)**	Moderate	6y KOOS QoL	6y IKDC-SKF 6y KOOS S/R		β= -0.54 (-0.95 to -0.12) β= -0.66 (-1.23 to -0.09)	+
	Wasserstein et al. (2015)	High	Symptomatic knee model 3[c] 6y symptomatic knee model 1[a] 6y symptomatic knee model 2[b]	2y symptomatic knee model 1[a] 2y symptomatic knee model 2[b]		OR=1.24 (1.01 to 1.53) OR=1.52 (1.04 to 2.2)	+
	Author		**Non-significant results**	**Current smoking at ACLR significant negative predictor[f]**	**Previous smoking significant negative predictor[f]**	**Magnitude of association** OR (95% CI)	**Authors conclusions**
	Cox et al. (2014)	High	6y KOOS S/R (previous)	6y IKDC-SKF 6y KOOS symptoms 6y KOOS pain 6y KOOS ADL 6y KOOS S/R 6y KOOS QOL	6y IKDC-SKF 6y KOOS sym 6y KOOS pain 6y KOOS ADL 6y KOOS QOL	OR=0.61 (0.44-0.83) OR=0.65 (0.47-0.91) OR=0.58 (0.42-0.80) OR=0.57(0.42-0.77) OR=0.69 (0.50-0.93) OR=0.49 (0.36-0.67) OR=0.58 (0.42-0.79) OR=0.58 (0.41-0.83) OR=0.51 (0.37-0.70) OR=0.58 (0.41-0.81) OR=0.63(0.45-0.87)	+
Smoking	**Spindler et al. (2011)**	Moderate	6y KOOS QOL 6y KOOS S/R		6y IKDC-SKF	β=-7.75 (-13.04 to -2.46)	+
	Wasserstein et al. (2015)	High	2 and 6y symptomatic knee model 1[a] + 2y model 2[b] + model 3[c] (current) 6y symptomatic knee model 1[a] + 2y model 2[b] + model 3[c] (previous)	6y symptomatic knee model 2[b]	2y symptomatic knee model 1[a] 6y symptomatic knee model 2[b]	OR=1.66 (1.12-2.45) OR=1.96(1.02-3.75) OR=2.83(1.46-5.49)	+
	Author		**Non-significant results**	**Diabetes significant negative predictor**		**Magnitude of association** OR (95% CI)	**Authors conclusions**

Diabetes	**Brophy et al . (2016)**	High	2y KOOS sym 2y KOOS QoL	2y IKDC-SKF 2y KOOS pain 2y KOOS ADL 2y KOOS S/R	OR=0.47(0.23-0.98) OR=0.44(0.21-0.90) OR=0.42(0.19-0.93) OR=0.44(0.22-0.88)	+
Education	**Authors**		**Non-significant results**	**Higher education significant positive predictor**	**Magnitude of association** OR/β (95% CI)	**Authors conclusions**
	Cox et al. (2014)	High		6y IKDC-SKF 6y KOOS sym. 6y KOOS pain 6y KOOS ADL 6y KOOS S/R 6y KOOS QOL	OR 16y vs 12y= 1.35 (1.11-1.64) 1.48-(1.21-1.81) 1.39(1.14-1.70) 1.57(1.27-1.93) 1.42(1.16-1.74) 1.30(1.06-1.59)	+
	Wasserstein et al. (2015)	High	2 and 6y symptomatic knee model 1[a] + 2y model 2[b] + model 3[c]	6y symptomatic knee model 2[b]	OR=2.33 (1.27-4.35)	+
Ethnicity	**Authors**		**Non-significant results**	**Ethnicity significant positive predictor**	**Magnitude of association** OR/β (95% CI)	**Authors conclusions**
	Cox et al. (2014)	High	6y IKDC-SKF 6y KOOS all subscales			-
	Spindler et al. (2011)	Moderate	6y KOOS S/R 6y KOOS QoL 6y IKDC-SKF			-
Type of sport	**Authors**		**Non-significant results**	**Type of sport significant positive predictor**	**Magnitude of association** OR/β (95% CI)	**Authors conclusions**
	Cox et al. (2014)	High		6y KOOS pain (basketball) 6y KOOS sym (basketball)	Baseball compared to basketball: OR=1.49 (1.06-2.11) OR=1.52(1.06-2.19)	+
	Spindler et al. (2005)	High	5y IKDC-SKF 5y KOOS (both type and contact/non-contact and jumping/non-jumping)			-
	Spindler et al. 2011	Moderate	6y KOOS 6y IKDC-SKF			-
Competition level	**Authors**		**Non-significant results**	**Competition level significant positive predictor**	**Magnitude of association** OR/β (95% CI)	**Authors conclusions**
	Cox et al. (2014)	High	6y IKDC-SKF 6y KOOS			-
Psychological factors Reason for participation in sports	**Authors**		**Non-significant results**	**Psychological factors significant positive/negative predictor**	**Magnitude of association** OR/β (95% CI)	**Authors conclusions**
	Roessler et al. (2015)	High		2y KOOS pain (fun and well-being)	β= -0.258	+

measured and categorized (achievement. health. social integration or fun and well-being)				2y KOOS S/R (achievement) 2y KOOS S/R (fun and well-being)		β= -0.234 β= 0.253	
	Author		**Non-significant results**	**Higher baseline score positive predictor**	**Higher score negative predictor**	**Magnitude of association OR/β (95% CI)**	**Authors conclusions**
Baseline Tegner, MARX, WOMAC, KOOS, IKDC-SKF, SF 36	**Barenius et al. (2013)**	High	2y treatment failure (Tegner at surgery+6m)	2y functional recovery (Tegner at surgery) 2y functional recovery (Tegner at 6m)	2y treatment failure (preinjury Tegner)	OR=1.19(1.07-1.32) OR=1.11(1.01-1.23) OR=1.25 (1.09-1.43)	-
	Cox et al. (2014)	High		6y IKDC-SKF (IKDC-SKF) 6y KOOS (KOOS)	6y IKDC-SKF (baseline MARX)	In text significant. numbers not found OR=1.32(1.00-1.75).	+
	Filbay et al. (2017)	Low	5y KOOS pain, sym, S/R and QoL (SF 36 in Non-op + early/delayed ACLR) 5y KOOS sympt, S/R and QoL (SF36 in all patients) 5y KOOS pain, sym, S/R and QoL ($KOOS_4$ in all, delayed ACLR and non-op) 5y KOOS pain ($KOOS_4$ in early ACLR)	5y KOOS pain (SF36 in all patients) 5y KOOS symptoms (KOOS4 in early ACLR) 5y KOOS S/R ($KOOS_4$ in early ACLR) 5y KOOS QoL (KOOS4 in early ACLR)		β=0.2 (0.0-0.3) β=0.5 (0.1-0.8) β=0.5(0.0-0.9) β=0.7 (0.3-1.1).	+
	Sasaki et al. (2016)	High	2y KOOS all subscales (Preop. Tegner)				-
	Spindler et al. (2011)	Moderate	6y KOOS (MARX) 6y IKDC-SKF (MARX) 6y KOOS pain (KOOS pain) 6y KOOS symptoms (KOOS sympt) 6y KOOS ADL (KOOS ADL)	6y KOOS S/R (KOOS S/R) 6y KOOS QoL(KOOS QoL) 6y IKDC-SKF (IKDC-SKF)		β=0.18 (0.11-0.26)	-
	Wasserstein et al. (2015)	High	2 and 6y symtomatic knee model 1-3 (MARX)	2y symptomatic knee model 1[a] (KOOS ADL)		OR= 0.53(0.36-0.79) OR=1.63(1.13-2.34)	+

			2 and 6y symptomatic knee model 2-3 (WOMAC)		2y symptomatic knee model 2[b] (KOOS S/R)		
Concomitant MCL or LCL injury	**Authors**		**Non-significant results**	**Concomitant MCL or LCL injury significant positive/negative predictor**		**Magnitude of association** OR/β (95% CI)	**Authors conclusions**
	Hamrin Senorski et al. (2018)	Moderate	2y success [g] 2y failure [h]				-
	Spindler et al. (2011)	Moderate	6y IKDC-SKF 6y KOOS QoL 6y KOOS S/R				-
Concomitant meniscus injury	**Author**		**Non-significant results**	**Concomitant meniscus injury significant positive predictor**	**Concomitant injury on EITHER menisci significant negative predictor**	**Magnitude of association** OR/β (95% CI)	**Authors conclusions**
	Barenius et al. (2013)	High	2y functional recovery (medial and lateral)		2y treatment failure (medial)	OR from univariable analysis. OR not reported from multivariable 1.20 (1.02-1.42)	+
	Cox et al. (2014)	High	Specific results to extensive to present in this format. Summarized by authors: Meniscus tears were significant predictors of 6-year outcomes on the IKDC-SKF and KOOS. Lateral meniscus repairs did not correlate with inferior results, but medial meniscus repairs predicted worse IKDC-SKF and KOOS scores. Lateral meniscus tares left alone significantly improved prognosis. Small partial meniscectomies (<33%) on the medial meniscus fared worse; conversely, larger excisions (>50%) on either the medial or lateral menisci improved prognosis.				+
	Filbay et al. (2017)	Low	5y KOOS4 (All and non-op) 5y KOOS pain. symptoms & QoL (Early ACLR group) 5y KOOS sympt. S/R & QoL (Delayed ACLR group)	5y KOOS pain (Delayed ACLR group)	KOOS S/R (Early ACLR group)	β=-14.4(-27.6 t -1.3) β= 14.3 (0.7 to 27.9).	+
	Hamrin Senorski et al. (2017)	Moderate	2y failure [g]		2y success[h]	OR=0.81 (0.72-0.92)	+ (success only)
	Røtterud et al. (2013)	Moderate	2y KOOS. all subscales				-
	Sasaki et al. (2016)	High	2y KOOS pain 2y KOOS symp 2y KOOS ADL 2y KOOS S/R		2y KOOS QoL	β=-0.2 (-12.92 to -0.75)	+
	Spindler et al. (2005)	High	5y KOOS 5y IKDC-SKF				-
	Spindler et al. (2011)	Moderate	6y IKDC-SKF (medial)		6y KOOS S/R 6y KOOS QoL Sig. better results for untreated lateral tears compared to normal meniscus	β=9.96 (4.43-15.49) β=8.88 (3.00-14.76)	+

	Wasserstein et al. (2015)	High	2 and 6y symptomatic knee all 3 models (medial) 6y symptomatic knee model 1 + 2 and 6y model 2 + model 3 (lateral)	2y symptomatic knee model 1 (lateral)	OR normal lateral meniscus compared to untreated lateral tear: 0.59 (0.39-0.89)	-

	Author		**Non-significant results**	**Concomitant cartilage injury significant negative predictor**	**Magnitude of association** OR/β (95% CI)	**Authors conclusions**
Concomitant cartilage injury	**Barenius et al. (2013)**	High	2y functional recovery 2y treatment failure			
	Cox et al. (2014)	High	Specific results to extensive to present in this format. Summarized by authors: Articular cartilage lesions were significant predictor of 6-year outcomes on the IKDC-SKF and KOOS. Grade 3 and 4 cartilage lesions (excluding patella) significantly reduced IKDC-SKF and KOOS scores at 6 years. The IKDC-SKF demonstrated worse outcomes with the presence of a grade 3 or 4 chondral lesion on the MFC, MTP and LFC. Likewise, the KOOS score was negatively affected by cartilage injury.			+
	Filbay et al. (2017)	Low	5y KOOS 4 (in All. delayed ACLR and non-op) 5y KOOS pain. symptoms & S/R (Osteochondral lesions in group with Early ACLR)	5y KOOS QoL (Osteochondral lesions in group with Early ACLR)	β=-12.3(-24.2 to -0.4)	+
	Hamrin Senorski et al. (2017)	Moderate		2y Success 2y Failure	Cartilage injury vs none: OR=0.70 (0.61-0.81) OR=1.27 (1.11-1.44)	+
	Røtterud et al. (2013)	Moderate	2y KOOS all domains (Partial lesions)	2y KOOS pain (full-thickness) 2y KOOS symptoms (full-thickness) 2y KOOS ADL (full-thickness) 2y KOOS S/R (full-thickness) 2y KOOS QoL(full-thickness)	Full-thickness vs none: β=-3.3 (–4.8 to –1.8) β=-4.8 (-6.5 to -3.1) β=-2.6 (-3.9 to -1.3) β=-6.6 (-9.2 to -4.1) β=-6.3 (-8.6 to -4.1)	+
	Spindler et al. (2005)	High	5y KOOS 5y IKDC-SKF			-
	Spindler et al. (2011)	Moderate	6y KOOS S/R 6y KOOS QoL 6y IKDC-SKF			-
	Ulstein et al. (2018)	Moderate	5y KOOS pain. symptoms and ADL (partial lesions)	PARTIAL LESIONS: 5y KOOS S/R 5y KOOS QoL FULL THICKNESS LESIONS: 5y KOOS pain 5y KOOS symptoms 5y KOOS ADL 5y KOOS S/R 5y KOOS QOL	β=-1.8 (-3.2 to -0.3) β= -1.5 (-2.8 to -0.1). β=-6 (-7.5 to -0.45) β= -6.5 (-8.2 to -4.9) β=-4.6(-5.9 to -3.3) β=-8.1 (-10.5 to -5.7) β=-8.0 (-10.2 to -5.7).	+
	Wasserstein et al. (2015)	High	Specific results to extensive to present in this format. Summarized by authors: The grade of chondral damage at initial arthroscopy was an inconsistent predictor in the patellofemoral. medial and lateral compartments. In general. when chondral damage influenced			-

			the odds of reporting either a painful knee or significant activity-related pain. the tendency was for the effect to be driven by grade 3/4 change.			
Knee laxity	**Authors**		**Non-significant results**	**Knee laxity significant negative predictor**	**Magnitude of association** OR/β (95% CI)	**Authors conclusions**
	Barenius et al. (2013)	High	2y Treatment failure 2y Functional recovery (KT-1000 measures at 6 months postoperatively)			-
	Magnussen et al. (2016)	Moderate	2y IKDC-SKF 2y KOOS QoL (Preoperative laxity[i])			-
	Magnussen et al. (2018)	Moderate		6y IKDC-SKF 6y KOOS QoL (Preoperative laxity[i])	β=-2.26(-3.77 to -0.75) β=-2.67(-4.81 to -0.53)	Not clinically relevant
Previous meniscal or cartilage pathology	**Authors**		**Non-significant results**	**Previous meniscal or cartilage pathology significant negative predictor**	**Magnitude of association** OR/β (95% CI)	**Authors conclusions**
	Wasserstein et al. (2015)	High	Meniscus: 2 and 6y symptomatic knee model 1 and 2 Cartilage: All models.	Meniscus: 6y symptomatic knee (model 3)	Previous meniscal pathology vs. without OR=0.43(0.19. 0.97)	-
Previous surgery to index knee	**Authors**		**Non-significant results**	**Previous surgery to index knee significant negative predictor**	**Magnitude of association** OR/β (95% CI)	**Authors conclusions**
	Barenius et al. (2013)	High	2y functional recovery (cartilage) 2y treatment failure (cartilage)	2y functional recovery (medial meniscus) 2y functional recovery (lateral meniscus) 2y treatment failure (medial meniscus) – POSITIVE PREDICTOR 2y treatment failure (lateral meniscus)	Only p-values in multivariable analysis	+
Hearing a pop at injury	**Authors**		**Non-significant results**	**Hearing a pop at injury significant negative predictor**	**Magnitude of association** OR/β (95% CI)	**Authors conclusions**
	Spindler et al. (2005)	High		5y KOOS 5y IKDC-SKF	Only p-values presented	
	Spindler et al. (2011)	Moderate	6y KOOS S/R 6y KOOS QoL 6y IKDC-SKF			-
Onset of swelling after injury	**Authors**		**Non-significant results**	**Hearing a pop at injury significant negative predictor**	**Magnitude of association** OR/β (95% CI)	**Authors conclusions**
	Spindler et al. (2005)	High	5y KOOS 5y IKDC-SKF			-

Knee extension deficit	**Authors**		**Non-significant results**	**Preoperative knee extension deficit significant negative predictor**	**Magnitude of association** OR/β (95% CI)	
	Filbay et al. (2017)	Low	5y KOOS4			-
	Author		**Non-significant results**	**Better strength or hop performance positive predictor**	**Magnitude of association OR/β/IQROR (95% CI)**	**Authors conclusions**
	Ericsson et al. (2013)	High	2 and 5y $KOOS_4$ (Biodex/1RM. hop tests and balance after rehab)	2y $KOOS_4$ (One-leg rise test after rehab) 5y $KOOS_4$ (One leg rise test after rehab)	β=1.12 (0.46-1.79) β=0.88 (0.34-1.42). 2y: R2=0.25 5y: R2=0.24 Treatment (op/non-op) not mediator.	+
Early physical performance	**Ithurburn et al. (2017)**	High	2y knee functional recovery on all KOOS subscales (Peak trunk flexion LSI and peak internal knee extension moment LSI during a single single-leg landing at time of RTS)	2y knee functional recovery on KOOS pain (symmetric knee flexion excursion during a single single-leg landing at time of RTS) 2y knee functional recovery on KOOS QoL (symmetric knee flexion excursion during a single single-leg landing at time of RTS)	OR=2.16(1.06-4.81) OR=4.05(1.43-12.76)	+

KOOS, Knee injury and Osteoarthritis Outcome Score; S/R, sport and recreation; QoL, knee-related quality of life; ADL, function in daily living; IKDC-SKF, International Knee Documentation Committee Subjective Knee Form; OR, odds ratio; LSI, limb symmetry index; RTS, return to sport; 1RM, one repetition maximum; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index: SF 36

[a] KOOS QoL <87.5 & ≥2 of: KOOS pain <86.1, KOOS symptoms <85.7, KOOSADL <86.8 or KOOS sports/rec <85.0
[b] KOOS pain≤ 72
[c] 10-points KOOS pain drop from 2 to 6 years postoperatively
[d] KOOS pain >90, KOOS symptoms >8, KOOSADL >91, KOOS Sport/Rec >80, KOOS QoL>81
[e] KOOS QoL<44
[f] All compared to never smokers
[g] ≥80th percentile using $KOOS_4$
[h] ≤20th percentile using $KOOS_4$
[i] Preoperative laxity defined as IKDC-SKF grade D on either Lachman, anterior drawer or pivot-shift test

Appendix 3 – Results on prognostic factors for physical activity level from all included studies (n=20)

Several studies have both significant and non-significant results. Therefore, authors conclusions on the different possible prognostic factors are given (+=significant results. - =non-significant results).

	Study	Study's overall risk of bias	Non-significant results	Female gender significant negative predictor	Magnitude of association OR/β (95% CI)	Authors conclusions
Sex	**Cox et al. (2014)**	High		6y MARS	OR=0.51 (0.42-0.62)	+
	Dunn & Spindler (2010)	High		2y MARS	OR=0.60 (0.39–0.91)	+
	Nawasreh et al. (2018)	High	2y RTS			-
	Sonnery-Cottet et al. (2017)	High		3y RTS	OR=0.59 (0.37-0.94)	+
	Spindler et al. (2011)	Moderate		6y MARS	β=-2.09 (-3.04 to -1.15)	+
	Author		**Non-significant results**	**Older age significant negative predictor**	**Magnitude of association** OR/β (95% CI)	**Authors conclusions**
Age	**Cox et al. (2014)**	High		6y MARS	OR age 35 compared to 15= 0.38 (0.24-0.62)	-
	Dunn & Spindler (2010)	High	2y MARS			-
	Nawasreh et al. (2018)	High	2y Return to preinjury activity level			-
	Sonnery-Cottet et al. (2017)	High	3y RTS			-
	Spindler et al. (2011)	Moderate	6y MARS			-
	Authors		**Non-significant results**	**Higher BMI significant negative predictor**	**Magnitude of association** OR/β/IQROR (95% CI)	**Authors conclusions**
BMI	**Cox et al. (2014)**	High		6y MARS	OR BMI 28 compared to 23= 0.83 (0.73-0.95)	+
	Dunn & Spindler (2010)	High		2y MARS	IQROR= 0.73 (0.55–0.96)	+
	Spindler et al. (2011)	Moderate	6y MARS			-
	Authors		**Non-significant results**	**Smoking significant negative predictor**	**Magnitude of association** OR (95% CI)	**Authors conclusions**
Smoking	**Cox et al. (2014)**	High	6y MARS (previous smoking)	6y MARS (current smoking at ACLR)	OR= 0.66 (0.50-0.89)	-
	Dunn & Spindler (2010)	High		2y MARS (current smoking at ACLR)	OR= 0.55 (0.33-0.92)	-
	Spindler et al. (2011)	Moderate	6y MARS (both current and previous)			-
	Authors		**Non-significant results**	**Diabetes significant positive predictor**	**Magnitude of association** OR (95% CI)	**Authors conclusions**
	Brophy et al. (2016)	High		2y MARS	OR= 2.96 (1.30-6.77)	+

Education	**Authors**		**Non-significant results**	**Education significant predictor**	**Magnitude of association** OR (95% CI)	**Authors conclusions**
	Cox et al. (2014)	High		6y MARS	OR 16y vs 12y= 1.22 (1.02-1.45)	**+**
	Dunn & Spindler (2010)	High	2y MARS			**-**
Marital status	**Authors**		**Non-significant results**	**Marital status significant predictor**	**Magnitude of association** OR (95% CI)	**Authors conclusions**
	Dunn & Spindler (2010)	High	2y MARS			**-**
	Spindler et al. (2011)	Moderate	6y MARS			**-**
Ethnicity	**Authors**		**Non-significant results**	**Marital status significant predictor**	**Magnitude of association** OR (95% CI)	**Authors conclusions**
	Cox et al. (2014)	High	6y MARS			**-**
	Dunn & Spindler (2010)	High	2y MARS			**-**
	Spindler et al. 2011)	Moderate	6y MARS			**-**
Type of sport	**Authors**		**Non-significant results**	**Type of sport significant positive predictor**	**Magnitude of association** OR/β (95% CI)	**Authors conclusions**
	Cox (2014)	High		6y MARS (baseball) 6y MARS (basket) 6y MARS(basket)	Compared to no sports: OR=2.3 (1.52-3.57) Compared to volleyball: OR=1.89 (1.3-2.7) Compared to other sports: OR=1.28 (1.01-1.61)	+
	Dunn & Spindler (2010)	High		2y MARS (soccer)	Soccer compared to no sports: OR=2.8 (1.3-5.7)	**-**
	Sonnery-Cottet et al. (2017)	High	3y RTS			**-**
	Spindler et al. (2011)	Moderate	6y MARS			**-**
Competition level	**Authors**		**Non-significant results**	**Higher competition level significant positive predictor**	**Magnitude of association** OR/β (95% CI)	**Authors conclusions**
	Cox et al. (2014)	High		6y MARS (amateur) 6y MARS (college level)	Compared to none/recreational sports: OR=1.61 (1.26-2.05) Compared to none/recreational sports: OR= 2.1 (1.51-2.93)	**+**
	Dunn & Spindler (2010)	High		2y MARS (high school level) 2y MARS (college level)	Compared to recreational sports: OR=2.52 (1.27-5.01) Compared to recreational sports: OR=4.23 (1.85-9.66)	**-**
	Author		**Non-significant results**	**Higher baseline score positive predictor**	**Magnitude of association** **OR/β/IQROR (95% CI)**	**Authors conclusions**
	Cox et al. (2014)	High		6y MARS (MARS)	OR= 1.32 (1.00-1.75)	**+**

Baseline MARS, KOS-ADLS, GRS	**Dunn et al. (2010)**	High		2y MARS (MARS)	IQROR=3.84 (1.98-7.43)	+
	Nawasreh et al. (2017)	High	2y RTS (KOS-ADLS) 2y RTS (GRS)			-
	Spindler et al. (2011)	Moderate		6y MARS (MARS)		+
Concomitant MCL or LCL injuries	**Authors**		**Non-significant results**	**Concomitant MCL or LCL injuries significant predictor**	**Magnitude of association** OR/β (95% CI)	**Authors conclusions**
	Spindler et al. (2011)	Moderate	6y MARS			-
Concomitant meniscus injury	**Author**		**Non-significant results**	**Concomitant MED meniscus injury significant negative predictor**	**Magnitude of association** OR/β (95% CI)	**Authors conclusions**
	Cox et al. (2014)	High	6y MARS			-
	Dunn & Spindler (2010)	High	2y MARS			-
	Sonnery-Cottet et al. (2017)	High	3y RTS (None vs lateral. None vs both. Medial vs both. lateral vs both)	3y RTS	Medial vs none: OR= 0.46 (0.27-0.78). Medial vs lateral tear: OR= 0.3 (0.097-0.99)	+
	Spindler et al. (2011)	Moderate	6y MARS (both lateral and medial)			-
Concomitant cartilage injuries	**Author**		**Non-significant results**	**Concomitant cartilage injury significant negative predictor**	**Magnitude of association** **OR/β (95% CI)**	**Authors conclusions**
	Cox et al. (2014)	High	6y MARS (LFC, MTP, LTP and patella)	6y MARS (MFC)	Lower scores in grade 4 vs. normal/grade 1: OR= 0.47(0.24-0.92)	+
	Dunn & Spindler (2010)	High	2y MARS			-
	Spindler et al. (2011)	Moderate	6y MARS			-
Knee laxity	**Authors**		**Non-significant results**	**Preoperative knee laxity significant negative predictor**	**Magnitude of association** OR/β (95% CI)	**Authors conclusions**
	Magnussen et al. (2018)	Moderate		6y MARS	β= -0.54 (-1.0 to -0.09)	NOT CLINICALL Y RELEVANT
Hearing a pop at injury	**Author**		**Non-significant results**	**Hearing a pop at injury significant predictor**	**Magnitude of association** **OR/β (95% CI)**	**Authors conclusions**
	Dunn & Spindler (2010)	High	2y MARS			-
	Spindler et al. (2011)	Moderate	6y MARS			-
	Author		**Non-significant results**	**Better strength/hops positive predictor**	**Magnitude of association** **OR/β/IQROR (95% CI)**	**Authors conclusions**

Early physical performance	**Nawasreh et al. (2017)**	High		2y RTS (single hop LSIs) 2y RTS (Classifying PASS vs FAIL at 6m)	Six-meter timed hop and single hop LSIs explained 43.6% of the outcome's variance. R2=0.21 OR=0.21 (0.06-0.72).	+

OR, odds ratio; LSI, limb symmetry index; RTS, return to sport; MARS, Marx Activity Rating Scale; KOS-ADLS, Knee Outcome Survey Activities of Daily Living Scale; GRS, Global Rating Score; LFC, lateral femoral condyle; MFC, medial femoral condyle; MTP, medial tibial plateau; LTP, lateral tibial plateau

Appendix 4: GRADE[a] evidence profile: potential prognostic factors for 2- to 10-year self-reported knee function in ACL[b] reconstructed participants. All included studies (n=20).

Potential prognostic factors (№ of studies)	**№ of participants**	**GRADE factors**							**Summary of findings**						**Certainty**
		Study limitations	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Moderate/large effect size**	**Dose effect**	**Univariable analysis**			**Multivariable Analysis[c]**			
									+	**0**	**-**	**+**	**0**	**-**	
Female sex (6)	12769	×	×	✓	×	×[d]	×	×		1			2	3	⊕◯◯◯ VERY LOW
Higher age (7)	22933	×	✓	✓	×	×[d]	×	×		2			3	2	⊕⊕◯◯ LOW
Higher BMI (4)	3871	×	×[e]	✓	×	×[d]	×	×						4	⊕◯◯◯ VERY LOW
Smoking (3)	3721	×	×[e]	✓	×	×[d]	×	×						3	⊕◯◯◯ VERY LOW
Diabetes (1)	2198	×	×[e]	✓	×	×[d]	×	×						1	⊕◯◯◯ VERY LOW
Higher education (2)	3273	×	✓	✓	×	×[d]	×	×				2			⊕◯◯◯ VERY LOW
Ethnicity (2)	1960	×	✓	✓	×	×[d]	×	×					2		⊕◯◯◯ VERY LOW
Type of sport (3)	2274	×	✓	✓	×	×[d]	×	×		1		1	1		⊕◯◯◯ VERY LOW
Competition level (1)	1512	×	✓	✓	×	×[d]	×	×					1		⊕◯◯◯ VERY LOW
Psychological factors (1)	121	×	✓	✓	×	×[d]	×	×				1			⊕◯◯◯ VERY LOW
Concomitant MCL or LCL injuries (2)	15652	×	✓	✓	×	×[d]	×	×					2		⊕⊕◯◯ LOW
Concomitant meniscus injuries (9)	43877	✓	✓	✓	×	×[d]	×	×		1			2	6	⊕⊕⊕◯ MODERATE
Concomitant cartilage injuries (8)	43727	✓	×	✓	×	×[d]	✓	✓		1			3	4	⊕⊕⊕◯ MODERATE
Hearing pop at injury (2)	762	×	×	✓	×	×[d]	×	×					1	1	⊕◯◯◯ VERY LOW
Onset of swelling after injury (1)	314	×	✓	✓	×	×[d]	×	×		1					⊕◯◯◯ VERY LOW
Pre- or postoperative knee laxity (3)	10917	×	✓	✓	×	×[d]	×	×		1			1		⊕◯◯◯ VERY LOW
Previous meniscal or cartilage pathology (1)	1761	×	×[e]	✓	×	×[d]	×	×					1		⊕◯◯◯ VERY LOW
Previous surgery to index knee (1)	8584	×	×[e]	✓	×	×[d]	×	×						1	⊕◯◯◯ VERY LOW
Preoperative extension deficit (1)	121	×	✓	✓	×	×[d]	×	×					1		⊕◯◯◯ VERY LOW
Higher baseline PROMs (6)	12576	✓	×	✓	×	×[d]	×	×		1		3	2		⊕◯◯◯ VERY LOW

Early physical performance	169	✕	✕[e]	✓	✕	✕[d]	✕	✕	2	⊕◯◯◯ VERY LOW

For uni- and multivariable analyses: +, number of significant effects with a positive value; 0, number of non-significant effects; -, number of significant effects with a negative value.
For GRADE factors: ✓, no serious limitations; ✕, serious limitations (or not present for moderate/large effect size, dose effect)

a) Grading of Recommendations Assessment, Development and Evaluation
b) Anterior Cruciate Ligament
c) Summary of authors conclusions when several outcomes for each factor were assessed
d) Due to a small number of included studies, we could not assess small study biases with a funnel plot. We therefore cannot rule out publication bias
e) Inconsistency within study/studies

Paper IV

FOUR DISTINCT FIVE-YEAR TRAJECTORIES OF KNEE FUNCTION EMERGE IN PATIENTS WHO FOLLOWED THE DELAWARE-OSLO ACL COHORT TREATMENT ALGORITHM

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ABSTRACT

Background: Impairments and dysfunction vary considerably after anterior cruciate ligament (ACL) injury, and distinct subgroups may exist.

Purpose: (1) To identify subgroups of ACL injured patients who share common trajectories of patient-reported knee function from initial presentation to 5 years after a treatment algorithm where they chose either ACL reconstruction (ACLR) plus rehabilitation or rehabilitation alone. (2) To assess associations with trajectory affiliation.

Study design: Prospective cohort study.

Methods: We included 276 patients with first-time complete unilateral ACL injury early after injury; before a 5-week neuromuscular and strength training program and shared decision-making about treatment. Patients completed the International Knee Documentation Committee Subjective Knee Form (IKDC-SKF) at inclusion, after the 5-week program, and 6 months, 1 year, 2 years, and 5 years after ACLR or completion of the 5-week program (patients treated with rehabilitation alone). We used group-based trajectory modeling to identify trajectories of IKDC-SKF and multinomial logistic regression to assess associations with trajectory affiliation**.**

Results: Four distinct trajectories of IKDC-SKF were identified: *Low* (8.9% of the cohort), *Moderate* (50.2%), *High* (37.5%), and *High before declining* (3.4%)**.** The *High* trajectory had higher scores at inclusion than the *Moderate*, but both improved considerably within 1 year and had thereafter stable high scores. The *High before declining* trajectory also started relatively high and improved considerably within 1 year but suffered a large deterioration between 2 and 5 years. The *Low* trajectory started low and had minimal improvement. New knee injuries were important characteristics of the *High before declining* trajectory, while concomitant meniscus injuries were significantly associated with following the *Low (*vs *Moderate*) trajectory.

Conclusion: We identified 4 distinct 5-year trajectories of patient-reported knee function, indicating 4 subgroups of ACL injured patients. Importantly, nearly 9 of 10 patients who followed our treatment algorithm followed the *Moderate* and *High* trajectories characterized by good improvement and high scores. Concomitant meniscus injuries and new knee injuries were important factors in the unfavorable *Low* and *High before declining* trajectories. These associations were exploratory but support the trajectories' validity. Our findings can contribute to patient education about prognosis and underpin the importance of continued secondary injury prevention.

Key terms: Knee, prognosis, rehabilitation

INTRODUCTION

Short- and long-term impairments and dysfunction after anterior cruciate ligament (ACL) injury vary considerably and patients progress at different paces,[1,12,27,38,39] indicating diversity in response to ACL injury and treatment. Researchers, however, too often report outcomes averaged over all patients.

In other research areas, such as osteoarthritis research, homogenous subgroups or phenotypes that share common trajectories of knee function have been identified.[4,17,31] Identifying such subgroups among ACL injured patients may further highlight differences in responses to injury or surgery and develop our knowledge about prognosis for our patients. This information can help clinicians to better educate patients about expected outcomes and time to recovery. Further, associations with trajectory affiliation may help to identify at-risk-patients and targets of intervention.

Our prospective cohort study, the Delaware-Oslo ACL Cohort, has assessed patient-reported knee function using the International Knee Documentation Committee Subjective Knee Form (IKDC-SKF) [2,18,19,41] at 6 timepoints from initial presentation to 5 years: a very good base for exploring different trajectories of knee function. We included patients early after injury, before a 5-week rehabilitation program and shared decision-making process about treatment. Following the same treatment algorithm, it has previously been reported equivalent 2-year and 5-year outcomes after progressive rehabilitation alone and ACL reconstruction (ACLR),[12,33,34] and prognostic factors for short term outcomes.[14,26,28,39]

We, therefore, aimed to identify subgroups of ACL injured patients who share common trajectories of patient-reported knee function from initial presentation to 5 years after a treatment algorithm where they chose either ACLR plus rehabilitation or rehabilitation alone. Further, we aimed to assess clinical associations with trajectory affiliation.

METHODS

Participants

We included 276 patients with first-time complete unilateral ACL injury from the Delaware-Oslo ACL cohort study: a prospective cohort study including 300 patients from the University of Delaware, Newark, Delaware, USA and the Norwegian Sports Medicine Clinic, Oslo, Norway between 2006 and 2012. ACL injury and concomitant injuries were verified with MRI and increased anterior knee joint laxity (measured with a KT-1000 arthrometer, MED Metric, San Diego, CA). The patients were between 13 and 60 years of age, participated in pivoting sports ≥2 times/week preinjury, and had resolved acute impairments (no/minimal pain or effusion during or after plyometric activities) before inclusion (within 3 months after ACL injury in Oslo and 7 months in Delaware). We excluded patients with current or previous ipsi- or contralateral knee injuries, concomitant grade III ligament injury, full-thickness articular cartilage damage, or fracture.

We obtained informed consent or assent with parental consent and approvals from the Regional Committee for Medical and Health Research Ethics of Norway and the University of Delaware Institutional Review Board before inclusion.

Treatment algorithm

After inclusion and resolution of acute impairments (mean 59 days after injury), all patients underwent a 5-week rehabilitation program with progressive neuromuscular and strength training exercises as previously described by Eitzen, et al. [8] All patients were educated about treatment alternatives before they underwent functional testing and made their treatment choice in consultation with their physical therapists and orthopedic surgeons. At 5 years, 64% (n=167) had undergone early ACLR (<six months after the 5-week rehabilitation program), 11% (n= 30) delayed ACLR (>six months after the 5-week rehabilitation program), and 25% (n=65) progressive rehabilitation alone.[34] Patients who chose progressive rehabilitation alone were older, less likely to participate in level-I sports preinjury, and had less concomitant medial meniscus injuries than those who underwent early or delayed ACLR.[34] The main patient-reported reason for choosing rehabilitation alone was the achievement of good knee function after rehabilitation, while intention to return to level-I sports was the main reason for choosing early ACLR.[12] Delayed ACLR was indicated if patients experienced dynamic knee instability[42] or if they changed their minds.

Several experienced sports orthopedic surgeons performed the ACLRs using bone-patellar tendon-bone autografts (21.5%), hamstring autografts (51.5%), or allografts (27%). Forty percent also had meniscus surgery at the time of early or delayed ACLR. Postoperative rehabilitation consisted of 3 phases: (1) acute postoperative phase, (2) rehabilitation phase, and (3) return to sport phase as previously described.[10,12,13] Patients who did not undergo ACLR, typically continued progressive rehabilitation for 3-4 months.

We have previously reported similar 5-year clinical, functional, physical activity, and radiographic outcomes- including the IKDC-SKF- after early ACLR, delayed ACLR, and progressive rehabilitation alone.[33,34]

Assessments, outcomes, and timepoints of follow-ups

We explored trajectories of patient-reported knee function using the IKDC-SKF, a patient-reported questionnaire for symptoms, function, and sports activity, which is scored from 0 (worst) to 100 (best).[18] The IKDC-SKF is reliable and valid at various timepoints after ACL injury and is frequently used as a stand-alone outcome measure.[2,5,18-20,41]

Patients completed the IKDC-SKF at inclusion, after the 5-week rehabilitation program (mean 6 weeks after inclusion), and at follow-ups 6 months, 1 year, 2 years, and 5 years after either ACLR (patients treated surgically) or completion of the 5-week rehabilitation program (patients treated with rehabilitation alone). If delayed ACLR was performed before the 2-year follow-up, patients' timelines were reset and they were scheduled for new 6-month and 1-year follow-ups as surgically treated. To allow for more equal comparisons of individual trajectories, we included only the postoperative 6-month and 1-year follow-ups for the delayed ACLR group to avoid postoperative periods at different timepoints and differences in number of follow-ups across treatment groups.

Associations with IKDC-SKF trajectory affiliation

We explored associations between trajectory affiliation and the following factors: Patient characteristics at inclusion (age, sex, BMI, preinjury activity level) injury severity (concomitant meniscus or cartilage injuries), new ipsilateral and contralateral knee injuries, knee function and symptoms at inclusion (give-way episodes, quadriceps muscle strength LSI, single hop for distance), and treatment status at last attended follow-up (rehabilitation alone, early ACLR, or delayed ACLR).

We assessed quadriceps strength using the peak torque from maximal isometric contraction testing or concentric isokinetic testing.[25] We chose the single-hop for distance[32] among a cluster of single-legged hop tests due to its superior measurement properties and previous association with outcomes.[14,16,24,26,36,37] One practice trial was performed before we recorded two trials of which the mean score was calculated. We considered trials valid if patients performed stable landings (without touching the floor/walls with the other foot or hands or performing additional hops). For strength and hop tests, we tested the uninjured leg first, and expressed the results as limb symmetry indexes, LSIs (ipsilateral limb's performance in % of the contralateral). We also reported total distance in cm for the single-hop for distance. New knee injuries were patient-reported and verified with clinical examination plus MRI and/or during surgery if indicated.

Statistical methods

We used group-based trajectory modeling (GBTM) to identify subgroups of patients who followed distinct trajectories of IKDC-SKF from initial presentation to 5 years.[30,31] We used the *traj* software plugin for Stata.[22] We used the censored normal model because our outcome was measured on a continuous scale with a prespecified range.[22] The timepoints of the model were fixed intervals corresponding with the follow-up timepoints. GBTM imputes missing values based on available data points.[30]

We used a two-stage model selection process (more details in the Appendix).[30] (1) First, we found the optimal number of trajectories. The procedures changed the number of trajectories and repeated the analyses until we found the trajectory number with the highest (least negative) Bayesian information criterion (BIC) value; a higher BIC value indicates better model fit as it balances improvements in model likelihood with the number of parameters estimated.[30] (2) Second, we found the optimal trajectory shapes by changing the order of the polynomial for each trajectory (zero-order, linear, quadratic, or cubic). Finally, we chose the optimal model with the highest BIC value, while we also evaluated trajectory sizes (optimally, >5% of the cohort should belong to the smallest trajectory).[30]

Thereafter, we calculated posterior group-membership probabilities and odds of correct classification to assess model adequacy. The posterior group-membership probability is the probability that an individual with a specific profile belongs to each possible trajectory: the sum of probabilities for each patient is 1 and all patients are assigned to the trajectory with the highest posterior group-membership probability. The mean posterior probability for each trajectory should be ≥0.7 (scale from 0-1, where 1 indicates the smallest probability that the individuals could belong to a different trajectory than they were assigned to).[30] The odds of correct classification for each trajectory should be >5, and estimated group probabilities and percentages actually assigned should correspond well.[30]

We performed two sensitivity analyses to assess the robustness of the chosen model: (1) Excluding patients with only 1 datapoint for IKDC-SKF (n=5). (2) Using months since inclusion as the time variable and including all follow-up timepoints (both as non-surgically and surgically treated) for the patients who underwent delayed ACLR. This model contained the most valid timeline but introduced challenges with different number of follow-ups between different treatment groups. It was also challenging to compare individual trajectories using this model because it allowed postoperative periods at different timepoints.

For our second aim, we used multinomial logistic regression to assess associations with trajectory affiliation. Due to sample size, we chose univariable analyses. We chose the reference trajectory of the analysis post GBTM analysis based on clinical relevance and power. To increase statistical power, we merged the different types of new ipsilateral and contralateral injuries.

RESULTS

Subjects

Data from all 276 patients were included and their characteristics are described in Table 1.

Table 1 *Descriptive characteristics at inclusion*

	Missing values, n (%)	Whole cohort (n=276)
Inclusion site (no Delaware/Oslo)	0	134/142
Age, years[a]	0	26.5 ± 9.8
Sex (no of females)	0	128 (46%)
Body mass index[a]	0	24.6 ± 4.0
Preinjury sports participation (no of patients)	0	
Level-I		191 (69%)
Level-II		85 (31%)
Concomitant injuries[b] (no of patients)		
Meniscus	0	91 (33%)
Cartilage	0	22 (8%)
≥1 give-way episode between injury and inclusion (no of patients)	2 (1%)	92 (34%)
Quadriceps strength LSI (%)[a]	0	90 ± 11
Single hop for distance	12 (4%)	
Centimeters index limb[a]		117 ± 32
LSI (%)[a]		89 ± 13

[a] The values are given as the mean ± standard deviation
[b] Number of patients diagnosed with the injury using MRI at inclusion
Abbreviations: LSI, Limb symmetry index

Trajectories of IKDC-SKF

The model selection process is described in the Appendix.

We identified 4 distinct trajectories of IKDC-SKF from inclusion to 5 years: *Low* (n=22, 8.9%), *Moderate* (n=142, 50.2%), *High* (n=105, 37.5%), and *High before declining* (n=7, 3.4%) (Figure 1). Nearly 9 of 10 patients belonged to the two largest trajectories - *Moderate* and *High.* The *High* trajectory had higher scores at inclusion than the *Moderate* trajectory (mean 80 ±9 vs. 65 ±10), but both improved considerably up to 1 year (mean 96 ±5 and 89 ±8) and had stable high scores over time. The *High before declining* trajectory also started out with relatively high scores (mean 77 ±12) and improved considerably up to 1 year (mean 92 ± 8), but suffered a large deterioration between 2 and 5 years (mean 49 ±10 at 5 years). The *Low* trajectory had low scores at inclusion (mean 60 ±12) and minimal improvement over time.

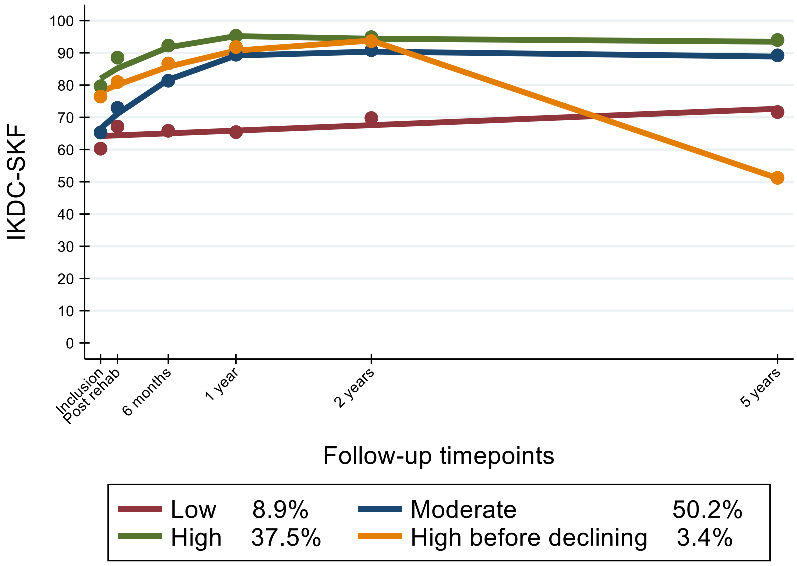

Figure 1: *Trajectories of International Knee Documentation Committee Subjective Knee Form (IKDC-SKF) from inclusion to 5 years. The red, blue, green, and orange colors represent the Low, Moderate, High, and High before declining trajectories, respectively. The points represent the mean IKDC-SKF scores at each timepoint. The solid lines represent the predicted trajectories.*

The model-fit parameters indicate good model fit for all 4 trajectories (Table 2): average posterior group-membership probabilities above the recommended threshold of 0.7 (0.86 to 0.98), odds of correct classification above the recommended threshold of 5.0 (6.4 to 2064.1), and good correspondence between estimated group probabilities and percentages actually assigned.[30]

Table 2. *Model-fit parameters of the selected model*

	Mean average posterior probability	Odds of correct classification	Estimated group probability	Percentage assigned
Low	0.95	222.0	8.0	8.9
Moderate	0.87	6.4	51.4	50.2
High	0.86	9.8	38.0	37.5
High before declining	0.98	2064.1	2.5	3.4

Sensitivity analyses

The first sensitivity analysis looked almost identical to the original model and led to minor changes in model-fit parameters. The second sensitivity analysis led to moderate changes: the polynomials of the optimal model were slightly different, the BIC values were slightly lower, the trajectory sizes changed moderately, and the model-fit parameters changed substantially, but were still within the recommended thresholds (Appendix).

Trajectory profiles

Profiles for the patients belonging to the 4 trajectories are described in Table 3. Compared to the *Moderate* and *High* trajectories, the *Low* trajectory had a high rate of graft ruptures and concomitant meniscus and cartilage injuries. The *High before declining* trajectory consisted predominantly of males (6 of 7) who were active in level-I sports preinjury (6 of 7), and suffered one or more new ipsi- or contralateral knee injuries (6 of 7 patients, all between 2 and 5 years) and/or underwent delayed ACLR ≤7 months before the 5-year follow up (2 of 7).

Associations with IKDC-SKF trajectory affiliation

We used the *Moderate* trajectory as reference in the analysis due to high *n* (statistical power), and because the comparison between the *Low* and *Moderate* trajectories was especially clinically interesting - both have low IKDC-SKF scores at inclusion, but only the *Moderate* trajectory progresses. Too few patients belonged to the *High before declining* trajectory in order to assess statistical associations, but all patients with this trajectory either had sustained a new ipsi- or contralateral knee injury or underwent delayed ACLR ≤7 months before final follow-up.

Concomitant meniscus injuries were significantly associated with belonging to the *Low* versus the *Moderate* trajectory (Table 4). The factors significantly associated with belonging to the *High* versus the *Moderate* trajectory were to undergo rehabilitation alone instead of early ACLR and having better quadriceps strength LSI, single hop for distance (LSI and distance) and no give-way episodes between injury and inclusion. Hence, early/preoperative quadriceps strength and hop symmetry were clear predictors of a *High* trajectory; For every 1% increase in quadriceps strength LSI and single-hop for distance LSI, there were 5% and 2% higher odds of affiliation to the *High* trajectory, respectively.

Table 3 *Trajectory profiles*

	Low trajectory (n=22)	**Moderate trajectory** (n=142)	**High trajectory** (n=105)	**High before declining trajectory** (n=7)
Factors measured at inclusion				
Age, years[a]	27.4 ± 10.7	27.4 ± 9.8	25.1 ± 9.4	24.3 ± 9.8
Sex (no of females)	12 (55%)	70 (49%)	45 (43%)	1 (14%)
Body mass index[a]	24.3 ± 4.3	25.0 ± 4.2	24.3 ± 3.7	22.3 ± 1.7
Preinjury sports participation (no of patients)				
Level-I	17 (77%)	94 (66%)	74 (70%)	6 (86%)
Level-II	5 (23%)	48 (34%)	31 (30%)	1 (14%)
Concomitant injuries[b] (no of patients)				
Meniscus	14 (64%)	49 (35%)	27 (26%)	1 (14%)
Cartilage	3 (14%)	10 (7%)	9 (9%)	0 (0%)
≥1 give-way episode between injury and inclusion (no of patients)	6 (27%)	58 (41%)	25 (24%)	3 (43%)
Quadriceps strength LSI[a] (%)	92 ± 11	87 ± 10	93 ± 12	86 ± 5
Single hop for distance				
Cm for index limb[a]	114 ± 32	112 ± 32	123 ± 33	144 ± 30
LSI (%)[a]	88 ± 18	88 ± 12	92 ± 12	90 ± 8
Factors measured within the 5-year follow-up				
Treatment status at last attended follow-up (no of patients)				
Early ACLR	16 (73%)	93 (67%)	55 (53%)	3 (43%)
Delayed ACLR	3 (14%)	13 (9%)	12 (12%)	2 (29%)
Rehabilitation alone	3 (14%)	32 (23%)	36 (35%)	2 (29%)
New ipsilateral knee injuries (no of patients)				
Graft rupture	5 (25%)	12 (10%)	6 (7%)	1 (14%)
PCL/MCL/LCL injury	2 (11%)	1 (1%)	1 (1%)	0 (0%)
Meniscus injury	0 (0%)	10 (9%)	4 (5%)	5 (71%)
Cartilage injury	1 (5%)	2 (2%)	0 (0%)	0 (0%)
New contralateral knee injuries (no of patients)				
ACL injury	1 (5%)	6 (5%)	7 (8%)	2 (29%)
PCL/MCL/LCL injury	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Meniscus injury	0 (0%)	1 (1%)	3 (4%)	1 (14%)
Cartilage injury	0 (0%)	0 (0%)	1 (1%)	0 (0%)

[a] The values are given as the mean and standard deviation
[b] Number of patients diagnosed using MRI at inclusion
Abbreviations: ACLR, Anterior cruciate ligament reconstruction; LSI, Limb Symmetry Index

Table 4 *Associations with IKDC-SKF trajectory affiliation. P-values <0.05 indicate statistically significant associations. Odds ratios >1 favor affiliation to the Low or High instead of the Moderate trajectory, while odds ratios <1 favor affiliation to the Moderate trajectory.*

	Low trajectory (vs. Moderate)		**High trajectory** (vs. Moderate)	
	Odds ratio (95% CI)	P-value*	Odds ratio (95% CI)	P-value*
Factors measured at inclusion				
Age, years	1.00 (0.96, 1.05)	0.998	0.98 (0.95, 1.00)	0.073
Sex, males (females ref.)	0.81 (0.33, 2.00)	0.647	1.30 (0.78, 2.15)	0.316
Body mass index	0.96 (0.85, 1.08)	0.457	0.96 (0.90, 1.02)	0.192
Preinjury sports participation (level I ref.)	0.58 (0.20, 1.66)	0.306	0.82 (0.48, 1.41)	0.476
Concomitant injuries (none ref.)				
Meniscus	3.32 (1.30, 8.46)	**0.012**	0.66 (0.38, 1.15)	0.140
Cartilage	2.08 (0.53, 8.26)	0.296	1.24 (0.48, 3.16)	0.656
≥1 give-way episodes between injury and inclusion (n [%]) (none ref.)	0.53 (0.20, 1.44)	0.212	0.44 (0.25, 0.77)	**0.004**
Quadriceps strength LSI (%)	1.04 (1.00, 1.09)	0.051	1.05 (1.03, 1.08)	**<0.001**
Single hop for distance				
Cm index limb	1.00 (0.99, 1.02)	0.858	1.01 (1.00, 1.02)	**0.015**
LSI (%)	1.00 (0.96, 1.03)	0.891	1.02 (1.00, 1.05)	**0.031**
Factors measured within the 5-year follow-up				
Treatment status at last attended follow-up				
Early ACLR vs. rehab alone	1.84 (0.50, 6.71)	0.359	0.53 (0.29, 0.94)	**0.030**
Delayed ACLR vs. rehab alone	2.46 (0.44, 13.82)	0.306	0.82 (0.33, 2.05)	0.673
New ipsilateral knee injury (none ref.)	2.44 (0.87, 6.85)	0.091	0.47 (0.20, 1.12)	0.088
New contralateral knee injury (none ref.)	0.85 (0.10, 7.32)	0.882	1.59 (0.55, 4.56)	0.391

*Bold p-values indicate statistical significance
Abbreviations: ACLR, Anterior cruciate ligament reconstruction; LSI, Limb Symmetry Index

DISCUSSION

We identified 4 distinct 5-year trajectories of patient-reported knee function after a treatment algorithm where all patients first went through a 5-week neuromuscular and strength training program before they chose either ACLR plus rehabilitation or rehabilitation alone – *Low* (8.9%), *Moderate* (50.2%), *High* (37.5%), and *High before declining* (3.4%) - indicating 4 subgroups of ACL injured patients. Indeed, the trajectory with the largest number of patients (*Moderate*) follows typical clinical expectations; start low, end high. A slightly smaller but also considerable number have relatively high scores at baseline and also progress over time (*High*). A small percentage of patients (12%), however, either start low and stay low (*Low*) or start high and suffer a large deterioration between the 2-year and 5-year follow-up (*High before declining)*. Importantly, nearly 9 of 10 patients who followed our treatment algorithm belonged to the favorable *Moderate* and *High* trajectories, often not requiring surgery. Early/preoperative quadriceps strength and hop symmetry were clear predictors of a *High* trajectory. Further, we found that concomitant meniscus injuries and new ipsi- and contralateral knee injuries were the main characteristics of the patients who belonged to the unfavorable *Low* and *High before declining* trajectories.

The trajectories identified in this study are visual and informative of expected outcomes and time to recovery for patients who undergo a similar treatment algorithm; They have great potential for use in patient education about prognosis. Additionally, the clinical associations with each trajectory support the trajectories' validity: they appear as clinically meaningful and several associations correspond with previous prognostic studies as described below.

Our trajectory profiles and associations with trajectory affiliation may help clinicians to identify at-risk-patients and targets of intervention. Concomitant meniscus injuries were associated with 3-fold higher odds of belonging to the *Low* vs. the *Moderate* trajectory, which means increased odds of starting low and staying low instead of progressing to a good level of knee function. Optimizing other aspects of follow-up and rehabilitation[11,40] may therefore be crucial for patients with concomitant meniscus injuries. Concomitant meniscus injuries as an important negative prognostic factor in ACL injured patients is also consistent with previous research.[6,35] New ipsi- and contralateral knee injuries with quite late timing (between 2 and 5 years) were frequent in the *High before declining* trajectory (6 of 7 patients) and had deteriorating consequences. This finding underpin the importance of long-term follow-up with aims of normalizing knee function, applying strict return to play criteria, and secondary prevention of new injuries[11,15,23] – and continuing these measures over time. The factors associated with belonging to the *High* versus the *Moderate* trajectory were mainly related to better early knee function and underscore the importance of high-quality early rehabilitation as suggested by current clinical guidelines.[11] For every 1% increase in early/preoperative quadriceps strength LSI and single-hop for distance LSI, there were 5% and 2% higher odds of affiliation to the *High* trajectory, respectively. Again, underscoring the value of preoperative rehabilitation beyond impairment resolution. This finding add to the body of evidence of associations between early functional performance and short- and long-term patient-reported outcomes.[7,9,21]

We used a data-driven statistical method, and the differences between the trajectories appeared clinically meaningful: The *Low* trajectory had mean IKDC-SKF scores well below the previously established "patient acceptable symptom state" (PASS) at 75.9 points[29] at all timepoints, while the *Moderate* and *High* trajectories had scores well above the PASS at all follow-ups ≥6 months. Also the improvement from inclusion to 1 year of the *Moderate* and *High* trajectories exceeded the minimally clinically important change (MIC) for the IKDC-SKF at 11.5 points[19] (mean 15 and 24 points, respectively). There was a clinically meaningful difference in mean IKDC-SKF score (larger than the MIC) between the *High* and the *Moderate* trajectories early on (from inclusion to 6 months), but not from 1 to 5 years – potentially important for patients with high knee demands who aim to return to sports or a physically demanding job as soon as possible.

To our knowledge, this study is the first to explore different trajectories after ACL injury or in a comparable patient group (young active patients with acute knee injuries). Similar trajectories to the *Low*, *Moderate,* and *High* trajectories have previously been found for middle-aged patients with degenerative meniscal tears and no/minimal concomitant knee osteoarthritis in the study of Berg, et al. [3].

Limitations

The identified trajectories resulted from a data-driven statistical method - it is an estimation. Though the model-fit parameters rule out poor model fit, and two sensitivity analyses were performed without substantially changing the model, our results should be validated or repeated in other data sets.

Since we assessed associations with trajectory affiliation using univariate analyses, the factors identified may not be causal: they are exploratory and spurious associations may exist. For example, we should interpret the association between choosing rehabilitation alone and affiliation to the *High* trajectory carefully because patients with poor knee function were likely to undergo delayed ACLR.

Due to eligibility criteria and procedures in our cohort, we can only generalize our model to athletes without major concomitant injuries who follow a similar treatment algorithm

CONCLUSION

We identified 4 distinct 5-year trajectories of patient-reported knee function after a treatment algorithm where all patients first went through a 5-week rehabilitation program before they chose either ACLR plus rehabilitation or rehabilitation alone – *Low* (8.9%), *Moderate* (50.2%), *High* (37.5%), and *High before declining* (3.4%) - indicating 4 subgroups of ACL injured patients. Importantly, almost 9 out of 10 patients who followed our treatment algorithm belonged to the favorable *Moderate* and *High* trajectories characterized by good progression and IKDC-SKF scores above the PASS threshold - often not requiring surgery. Concomitant meniscus injuries and new knee injuries were important factors in the unfavorable *Low* and *High before declining* trajectories, while factors associated with belonging to the *High* trajectory were mainly related to having better knee function early after injury. For every 1% increase in quadriceps strength LSI and single-hop for distance LSI, there were 5% and 2% higher odds of affiliation to the *High* trajectory, respectively. These clinical/functional outcomes are modifiable and may present a target for rehabilitation after ACL injury. These associations were exploratory but support the trajectories' validity. Our findings contribute to patient and clinician education about prognosis, and underpin the importance of continued secondary prevention of new knee injuries and high-quality early rehabilitation**.**

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APPENDIX: Model selection process and sensitivity analyses

Final decision: The optimal four-group model (1 3 3 2) was selected because (1) it had the highest (best) BIC values, (2) the fourth trajectory was considered clinically relevant, (3) it had good model-fit parameters, and (4) the two sensitivity analyses did not substantially change the model and it was therefore considered robust.

First model selection stage: We changed the number of trajectories and repeated the analyses until we found the trajectory number with the highest (least negative) Bayesian information criterion (BIC) value: a higher BIC value indicates better model fit as it balances improvements in model likelihood with the number of parameters estimated. All trajectories were quadratic at this stage. The BIC values increased with every increase in number of trajectories up to four (Table 1). **Decision: Proceed to identify the optimal four-group model.**

Table 1. BIC for IKDC-SKF group-based trajectory modeling according to number of trajectories.

Number of trajectories[3]	BIC[1] (n=276)	BIC[2] (n=1408)
1	-5284	-5288
2	-5210	-5216
3	-5182	-5192
4	-5167	-5180
5	-5167	-5183

[1]BIC = Bayesian information criterion (for the total number of participants)
[2]BIC = Bayesian information criterion (for the total number of observations)

Second model selection stage: We changed the shapes for one trajectory at a time: we used a linear before a zero-shape if the quadratic component of the model was not statistically significant, otherwise we changed to a cubic shape to assess whether the BIC value increased. To be considered, shape components had to be statistically significant. The size and shape of each trajectory should not change substantially in this process. Finally, we chose the model with the highest BIC value (Table 2.1), while we also evaluated group size (optimally, >5% of the cohort should belong to the smallest trajectory).

The smallest trajectory, *High before declining,* of the optimal four-group model (1 3 3 2) (Table 2.1 and Figure 1.1) contained only 3.4% (n=7) of the cohort. It was, however, considered to be clinically relevant. **Decision: Proceed to calculate model-fit parameters for the optimal four-group model (1 3 3 2).**

Table 2.1 BIC for IKDC-SKF group-based trajectory modelling according to trajectory shapes – a four-group model

Trajectory shapes[1]	BIC[2] (n=276)	BIC[3] (n=1411)
1 2 2 2	-5165	-5177
1 3 2 2	-5133	-5146
1 3 3 2	**-5123**	**-5137**

[1]Trajectory shapes; 0 = zero-order; 1 = linear; 2 = quadratic; 3= cubic
[2]BIC = Bayesian information criterion (for the total number of participants)
[3]BIC = Bayesian information criterion (for the total number of observation)

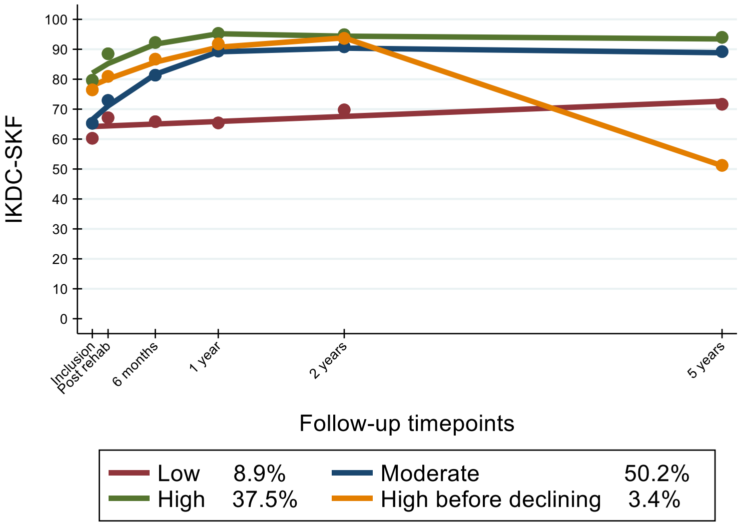

Figure 1.1 The optimal four-group model (1 3 3 2) identified in table 2.1

Model-fit parameters for the optimal four-group model (1 3 3 2) (Table 3.1). The mean posterior probability for each trajectory should be > 0.7 (scale from 0-1, where 1 indicates the smallest probability that the individuals could belong to a different trajectory than they were assigned to). The odds of correct classification should be >5 for each trajectory, and the estimated group probability and the percentage assigned should correspond. **Decision: The optimal four-group model (1 3 3 2) had good model-fit parameters. Proceed to perform two sensitivity analyses to assess the model's robustness.**

Table 3.1 Model-fit of the optimal four-group model (1 3 3 2)

Trajectory group	Mean posterior probability	Odds of correct classification	Estimated group probability	Percentage assigned	n
Low	0.95	222.0	8.0	8.9	22
Moderate	0.87	6.4	51.4	50.2	142
High	0.86	9.8	38.0	37.5	105
High before declining	0.98	2064.1	2.5	3.4	7

Sensitivity analysis 1 (excluding patients with only 1 datapoint for IKDC-SKF, n=5) identified the same model (1 3 3 2) and was almost identical to the original model. The BIC values were slightly higher (-5104/-5118 vs -5123/-5137), but the model-fit parameters did not significantly change.

Sensitivity analysis 2 (using months since inclusion as the time variable and including all follow-up timepoints - both as non-surgically and surgically treated - for the patients who underwent delayed ACLR) were moderately different from the original analysis: The polynomials of the optimal model were slightly different (1 3 3 3 instead of 1 3 3 2), the BIC values was slightly lower (-5254/-5269.71 vs-5123/-5137), and the trajectory sizes changed moderately (Figure 1.2). The model-fit parameters were above the recommended thresholds. **Decision: The two sensitivity analyses did not substantially change the model and the model was considered robust enough.**

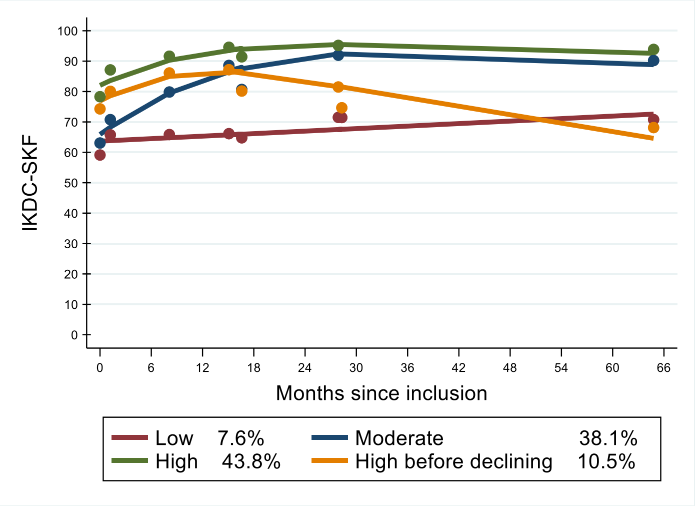

Figure 1.2 The optimal four-group model (1 3 3 3) identified in sensitivity analysis 2

Appendix I

Approvals from the Regional Committee for Medical and Health Research Ethics of Norway and the University of Delaware Institutional Review Board

REGIONAL KOMITE FOR MEDISINSK FORSKNINGSETIKK

Øst-Norge (REK I)

Mottatt
21 NOV 2006

Forskningsleder May Arna Risberg
NAR, Ortopedisk Senter
Ullevål universitetssykehus

Deres ref.: Vår ref.: 685-06289 1.2006.3281 Dato: 20. november 2006

Dynamisk stabilitet i et korsbåndsskadet kne – et forskningssamarbeid mellom Universitetet i Delaware, USA, Ortopedisk senter, Ullevål universitetssykehus

Regional komité for medisinsk forskningsetikk, Øst-Norge, vurderte det reviderte prosjektet på sitt møte 09.11.06.

Komiteen finner at prosjektlederen har tatt tilfredsstillende hensyn til de merknader komiteen tidligere har gitt, og har ingen innvendinger mot at prosjektet blir gjennomført.

Med vennlig hilsen

Knut Engedal
professor dr.med.
leder

Ida Nyquist
sekretær

Kopi: Forskningsdirektør Andreas Moan, Ullevål Universitetssykehus

Postboks 1130, Blindern, 0318 Oslo. Tlf.: 22 84 46 67. Fax: 22 84 46 61

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Olaug Twedt Myhre	+47 22845519	25.01.2012	2011/2131 C
			Deres dato:	**Deres referanse:**
			19.01.2012	

To whom it may concern:

Confirmation:

We hereby confirm that the project “Dynamic Stability in the ACL injured knee" is approved by the Regional Committee for Medical Research Ethics, South-East Norway (REK South-East).

The approval was first granted on 20.11.2006.

Yours Sincerely

Arvid Heiberg (p.p.)

Chair of the Regional Committee for Medical
Research Ethics of South-East Norway, Section C

Olaug Twedt Myhre

Higher Executive Officer

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Vi ber om at alle henvendelser sendes inn via vår saksportal eller på e-post. Vennligst oppgi vårt referansenummer i korrespondansen.

REK REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Tor Even Svanes	22845521	16.11.2011	2011/2131
			Deres dato:	**Deres referanse:**
			25.10.2011	

Vår referanse må oppgis ved alle henvendelser

May Arrna Risberg
Sognsvannsveien 220
0806 Oslo

Dynamisk stabilitet i et korsbåndsskadet kne - et forskningssamarbeid mellom Universitetet i Delaware, USA, Ortopedisk senter, Ullevål universitetssykehus

Vi viser til prosjektendringssøknad for overnevnte studie, mottatt 25.10.2011.

Endringen består i det følgende:
1. Datainnsamlingen utvides til å inkludere 5-7 års oppfølging for alle deltakerne med røntgenundersøkelse i tillegg til andre tester.
2. Tre nye selvrapporteringsskjemaer - KOOS, ACL-RSI og MARS - inkluderes i prosjektet.
3. I tillegg til aktivitetsregistrering som allerede er godkjent av REK, vil deltakerne bli forespurt om å fullføre den samme registreringen to dager etter, for å evaluere test-retest reliabilitet av metoden.

Komiteen har ingen innvendinger til prosjektendringene, men ber om at oversatte versjoner av ACL-RSI og MARS ettersendes når disse er klare. Ut fra dette setter komiteen følgende vilkår
for prosjektendringssøknaden:
1. Oversatte selvrapporteringsskjemaer skal ettersendes komiteen til orientering.

Vedtak:
Komiteen godkjenner prosjektendringssøknaden, jf. helseforskningslovens § 11.

I tillegg til vilkår som fremgår av dette vedtak, er tillatelsen gitt under forutsetning av at prosjektendringen gjennomføres slik det er beskrevet i prosjektendringsmeldingen og endringsprotokoll, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for *Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren.*

Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jf. Forvaltningslovens § 28 flg. Eventuell klage sendes til REK Sør-Øst. Klagefristen er tre uker fra mottak av dette brevet.

Med vennlig hilsen,

Arvid Heiberg
prof. dr.med
leder REK sør-øst C

Tor Even Svanes
Seniorrådgiver

Kopi til: Oslo Universitetssykehus: oushfdlgodkjenning@ous-hf.no

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Tor Even Svanes	22845521	06.07.2012	2011/2131
			Deres dato:	Deres referanse:
			26.06.2012	

Vår referanse må oppgis ved alle henvendelser

May Arna Risberg
Sognsvannsveien 220
Postboks 4014
0806 Oslo

2011/2131 S-06289 C Dynamisk stabilitet i et korsbåndsskadet kne - et forskningssamarbeid mellom Universitetet i Delaware USA og Ortopedisk senter Ullevål universitetssykehus

Forskningsansvarlig: Oslo Universitetssykehus
Prosjektleder: May Arna Risberg

Vi viser til søknad om prosjektendring datert 26.06.2012 for ovennevnte forskningsprosjekt. Søknaden er behandlet av leder for REK sør-øst på fullmakt, med hjemmel i helseforskningsloven § 11.

Endringen består i at selvrapportert knefunksjon hos en gruppe pasienter rehabilitert etter fremre korsbåndruptur ved Norsk forskningssenter for aktiv rehabilitering (NAR) vil bli sammenlignet med et referansemateriale i det nasjonale korsbåndsregisteret. Gruppen hentet fra det nasjonale korsbåndregisteret representerer standard behandling etter korsbåndsskader i Norge. Formålet vil være å finne ut om det er forskjell mellom en gruppe som er behandlet med NAR-rehabilitering og en gruppe hentet fra korsbåndregisteret.

Marie Vedelden Heitmann og Lars Petter Granan går inn som prosjektmedarbeidere i studien.

Vedtak
Prosjektendringssøknaden godkjennes.

Tillatelsen er gitt under forutsetning av at prosjektendringen gjennomføres slik det er beskrevet i prosjektendringsmeldingen og endringsprotokoll, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for *Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren.*

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningslovens § 28 flg. Klagen sendes til REK sør-øst. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK sør-øst, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

Arvid Heiberg
prof. dr.med
leder REK sør-øst C

Tor Even Svanes
seniorrådgiver

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Institutional Review Board
210H Hullihen Hall
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DATE:	May 20, 2021
TO:	Karin Gravare Silbernagel, PT, ATC, PhD
FROM:	University of Delaware IRB
STUDY TITLE:	[165436-20] Dynamic Stability of the ACL Injured Knee
SUBMISSION TYPE:	Continuing Review/Progress Report
ACTION:	APPROVED
APPROVAL DATE:	May 20, 2021
EXPIRATION DATE:	May 19, 2022
REVIEW TYPE:	Full Committee Review

Thank you for your Continuing Review/Progress Report submission to the University of Delaware Institutional Review Board (UD IRB). The UD IRB has reviewed and APPROVED the proposed research and submitted documents via Full Committee Review in compliance with the pertinent federal regulations.

As the Principal Investigator for this study, you are responsible for and agree that:

- All research must be conducted in accordance with the protocol and all other study forms as approved in this submission. Any revisions to the approved study procedures or documents must be reviewed and approved by the IRB prior to their implementation. Please use the UD amendment form to request the review of any changes to approved study procedures or documents.
- Informed consent is a process that must allow prospective participants sufficient opportunity to discuss and consider whether to participate. IRB-approved and stamped consent documents must be used when enrolling participants and a written copy shall be given to the person signing the informed consent form.
- Unanticipated problems, serious adverse events involving risk to participants, and all non-compliance issues must be reported to this office in a timely fashion according with the UD requirements for reportable events. All sponsor reporting requirements must also be followed.

Oversight of this study by the UD IRB REQUIRES the submission of a CONTINUING REVIEW seeking the renewal of this IRB approval, which will expire on May 19, 2022. A continuing review/progress report form and up-to-date copies of the protocol form and all other approved study materials must be submitted to the UD IRB at least 45 days prior to the expiration date to allow for the required IRB review of that report.

If you have any questions, please contact the UD IRB Office at (302) 831-2137 or via email at hsrb-research@udel.edu. Please include the study title and reference number in all correspondence with this office.

Appendix II

Patient informed consents

Oslo universitetssykehus

Hjelp24

Ortopedisk Avdeling
FOU-enheten, NAR

Informasjon til pasienter som har en isolert fremre korsbåndskade, omhandlende deltagelse i prosjektet

Dynamisk stabilitet i et korsbåndsskadet kne

I forbindelse med din deltagelse i prosjektet "Dynamisk stabilitet i et korsbåndsskadet kne", ønsker vi nå å utføre en oppfølgingstest 5-7 år etter skade/kirurgi. Formålet med prosjektet er som tidligere å identifisere de med fremre korsbåndsskade og med god evne til å stabilisere kneet fra de med dårligere evne til å stabilisere kneet under aktivitet. I tillegg ønsker vi nå å undersøke radiologiske tegn til artrose i kneet. Artrose (slitasje i brusken i kneet) er den vanligste og største belastningsskaden i kneet etter fremre korsbåndskade.

Du skal gjennomføre de samme funksjonstestene som du tidligere har gjennomført: Måling av instabiliteten i kneet, muskelstyrketest, 4 ulike hinketester og utfylling av spørreskjema om funksjon. Det vil også bli tatt vanlige røntgenbilder av kneet.

Funksjonsundersøkelsen med røntgen vil ta 1,5-2 timer.

Risiko

Det kan være at du kan oppleve noe ubehag i kneet ved gjennomføring av hinketestene, men det er svært liten risiko for at dette skal føre til forverring av din skade. Ved røntgen av kneet vil man utsettes for stråling. Imidlertid er dosen stråling sammenlignbar med den naturlige bakgrunnsstrålingen mennesker utsettes for over noen få dager. Risikoen ved å ta røntgen av kneet er derfor minimal. Gravide kvinner vil ikke gjennomføre røntgenundersøkelsen.

Kompensasjon

Du vil motta kroner 200,- for å dekke dine reiseutgifter/parkeringsutgifter og tiden som er involvert i testingen hvis du ikke har andre dokumenterte reiseutgifter.

Anonymitet og data

Dataene som innhentes vil lagres i manuelle arkiv med personidentifikasjon som låses inn, og du har til enhver tid full innsynsrett i dataene. Dataene avidentifiseres ved elektronisk lagring på Oslo universitetssykehus og Hjelp24 NIMIs sikre nettverk for statistiske analyser. Elektronisk lagres dataene kun med nummer. Ingen av dataene sammenholdes med elektroniske registre. Lagringen av data vil foregå i henhold til personsopplysningsloven. Prosjektet er vurdert av den Regionale Etiske Komité for medisinsk forskning.

Prosjektet planlegges avsluttet i 2020, og alle sensitive persondata vil bli slettet innen 2 år etter at studien er ferdig. Dersom nye studier basert på innsamlede opplysninger blir aktuelle, ber vi om tillatelse til å henvende oss til deg for nytt samtykke for slik bruk.

Har du spørsmål kan du kontakte prosjektleder Hege Grindem på telefon 95106154, eller e-post hege.grindem@hjelp24.no.

Med vennlig hilsen

Professor og fysioterapeut
May Arna Risberg
Norsk forskningssenter for Aktiv Rehabilitering,
Ortopedisk avdeling, Oslo Universitetssykehus Ullevål og
Seksjon for idrettsmedisin, Norges idrettshøgskole

Samtykkeerklæring

Jeg har lest og blitt forklart informasjonen på medfølgende informasjonsskriv om prosjektet, og sier meg villig i å delta i undersøkelsen.
Jeg har forstått at deltakelsen er frivillig.

_______________ _______________

Sted Dato

____

Underskrift

UNIVERSITY OF DELAWARE
DEPARTMENT OF PHYSICAL THERAPY
INFORMED CONSENT FORM

Study Title: Dynamic Stability in the ACL Injured Knee – Medium Term Follow-up
Principal Investigator: Karin Silbernagel, PT, ATC, PhD

PURPOSE AND BACKGROUND

You are being asked to participate in a follow-up study that will investigate functional abilities and joint changes of individuals who have injured their ACLs. You have been referred to this study because you were a participant in the short term follow-up aspect of this study, evaluating the effects of perturbation training on people with ACL injuries.

Your participation is important in the aims of this study. We have data from your course of care after injury and at standard time points between injury and 2 years. With the addition of two more time points (5 year and approximately 10 years) results, we can investigate relationships between your early injury performance and longer term outcomes. This will help us to better educate and treat athletes who tear their ACL in the future.

Participation in this research study is voluntary. This program will include testing protocols we currently use in our clinic to assess patients with ACL injury. Your surgeon and physical therapist have agreed that all of the testing procedures included in the study are acceptable.

The study includes clinical and radiographic assessment of your knee. If you have already completed the 5 year time point then you are only being asked to complete 1 additional testing session at approximately 10 years after surgery or completion of perturbation training if you did not have surgery. If you did not complete the 5 year time point then you are being asked to complete testing at both the 5 and 10 year time points. This research study will involve approximately one hundred fifty (150) subjects with ACL injury between the ages of 13-55 years at the time of injury. Persons of all sexes, races, and ethnic origins may serve as subjects for this study.

A description of each procedure and the approximate time it takes for each test and the study procedure are outlined below.

PROCEDURES

<u>ACL Functional Test</u>

Functional testing will take place in the Physical Therapy Clinic at the University of Delaware, 540 South College Avenue, Newark, DE 19713 and will last approximately 1 hour. Testing will be performed at approximately 5 and 10 years after surgery/injury. This test is commonly performed at the University of Delaware Physical Therapy Clinic as part of our ACL rehabilitation protocol.

 Subject's Initials_______

Strength Testing

The test will measure the strength of the quadriceps muscle on the front of your thigh. You will be seated in a dynamometer, a device that resists your kicking motion, and measures how much force your muscle can exert. Self adhesive electrodes will be attached to the front of your thigh, and you will be asked to kick as hard as you can against the arm of the dynamometer. An electrical stimulus will be activated while you are kicking, to fully contract your muscle. During the electrical stimulus you may feel a cramp in your muscles, like a "Charlie Horse", lasting less than a second. Each test will require a series of practice and recorded contractions. Trials will be repeated (up to a maximum of 4 trials) until a maximum contraction is achieved for both legs.

Hop Testing

A series of four (4) single leg hop tests (Diagram 1) will be performed assuming there is minimal swelling in your knee and you demonstrate good thigh muscle strength. The tests are performed in the order seen in Diagram 1. You can wear your own knee brace or a standard off-the-shelf knee brace on your injured knee during this portion of the testing, if you desire.

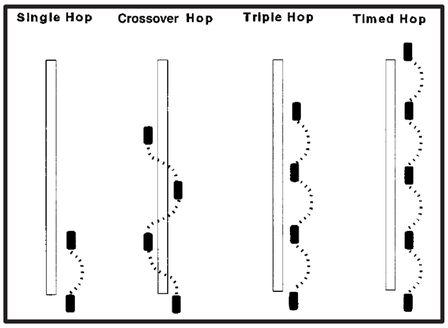

Diagram 1. Four (4) hop tests as part of the functional test protocol.

Two practice trials will precede each of the hop tests before the recorded testing begins. You can put your other leg down at any time to prevent yourself from losing your balance. However, only the two trials in which you are able to 'stick the landing' on one foot will be counted towards your scores. This series of hop tests will be performed on both legs.

Questionnaires

You will be asked to complete a test packet which includes questions about your injury, past and current functional status, and perceived functional capabilities.

X-Rays

X-rays will take place at Abby Medical Center, One Centurian Drive, Newark, DE 19713, at approximately 5 and 10 years after your ACL injury or ACL surgery. You will have two types of x-rays taken while you are standing. These x-rays will allow us to look at the joint space in your injured knee, and will help a radiologist (a medical doctor

 Subject's Initials_______

specializing in medical imaging) determine the presence, severity, and location of any knee osteoarthritis you may have. These x-rays will be locked in a cabinet for research purposes only.

Actigraph

You will be asked to wear a small accelerometer called an Actigraph. This device measures your daily amount of physical activity. This includes the number and speed of steps you take in a day. We ask that you wear the monitor from the time you wake up in the morning until you go to sleep. You may only remove it when it may get wet, such as bathing or swimming. You will wear the Actigraph around your waist at your right hip.

Risks/Discomfort

Subjects with ACL injury could experience a loss of balance during testing, however your other leg is free to touch down to provide support and prevent loss of balance. The strength testing can be associated with local muscle soreness and fatigue. Following the testing, your muscles may feel as if you have exercised vigorously. If you are injured during research procedures, you will be offered first aid at no cost. If you require additional medical treatment, you or your third-party payer (for example your health insurance) will be responsible for the cost. By signing this document you are not waiving any rights that you may have if injury was the result of negligence of the University or its investigators

The x-rays that will be taken are the same type that physicians use during regular clinical practice. This research study involves exposure to radiation from a standard radiograph. This radiation exposure is not necessary for your medical care and is for research purposes only. The total amount of radiation that you will receive in this study is about 0.12 mSv or 12 mrem, and is approximately equivalent to a uniform whole body exposure of 15 days of exposure to natural background radiation. This use involves minimal risk per National Institutes of Health guidelines, and is necessary to obtain the research information desired. To reduce exposure all subjects will wear a lead apron to cover the rest of your body while the x-rays of your leg are captured.

There are no known risks wearing an Actigraph monitor.

Benefits

The benefits include comprehensive testing sessions that will document your progress following surgery. The results of this study may help us improve the way we treat patients with ACL injury.

Compensation

You will be paid an honorarium of $100 for the functional testing and $50 for the radiographs to compensate you for travel expenses and the time involved. If only the questionnaire packet is completed, you will be paid an honorarium of $25. You will receive an additional $25 after you wear and return the Actigraph.

Confidentiality and records

Only the investigators, you and your physician will have access to the data. All of your data will be de-identified for the purposes of data management and processing.

Subject's Initials_______

Neither your name nor any identifying information will be used in publication or presentation resulting from this study. A statistical report, which may include slides or photographs which will not identify you, may be disclosed in a scientific paper. Data will be archived indefinitely and may be used for secondary analysis of scientific and clinical questions that arise from this research.

Study Title: Dynamic Stability in the ACL Injured Knee
Principal Investigator: Karin Silbernagel PT, ATC, PhD

Subject's Statement:

I have read this consent/assent form and have discussed the procedure described above with a principal investigator. I have been given the opportunity to ask questions regarding this study, and they have been answered to my satisfaction.

I have been fully informed of the above described procedures, with its possible risks and benefits, and I hereby consent/assent to the procedures set forth above.

______________________ ___________________________ ____________
Subject's Name Subject's Signature Date

_______________________________________ ____________
Investigator Date

If you have any questions concerning the rights of individuals who agree to participate in research, you may contact the Institutional Review Board (302-831-2137). The Institutional Review Board is created for the protection of human subjects involved in research conducted at the University of Delaware.

Further questions regarding this study may be addressed to:
Karin Silbernagel PT, ATC, PhD
Physical Therapy Department, (302) 831-3613

 Subject's Initials_______

Appendix III

Approval from the Norwegian Data Protection Authority

Godkjenning fra personvernombudet ved Oslo universitetssykehus

Linn Gjersing

From: Thorstensen Heidi [Heidi.Thorstensen@ulleval.no]
Sent: 29. januar 2007 20:58
To: Linn Gjersing
Cc: Thorstensen Heidi
Subject: Formalisering av personvern i studien - Dynamisk stabilitet i et korsbåndsskadet kne - et forskningssamarbeid mellom Universitetet i Delaware, USA og Ortopedisk senter, Ullevål Universitetssykehus og NIMI

[Ta vare på denne eposten]

Kjære forsker

Viser til melding om behandling av personopplysninger / helseopplysninger. Det følgende er et formelt svar på meldingen. Forutsetningene nedenfor må være oppfylt før rekruttering av pasienter til studien kan starte.

Mandat for tilrådning
Med hjemmel i Personopplysningsforskriftens § 7-12 og Helseregisterlovens § 36 har Datatilsynet ved oppnevning av Heidi Thorstensen som personvernombud ved UUS, fritatt sykehuset fra meldeplikten til Datatilsynet. Behandling og utlevering av person- /helseopplysninger til forskning meldes derfor til sykehusets personvernombud. Konsesjonsplikten gjelder fremdeles, men personvernombudet tar stilling til om melding er dekkende eller om det må søkes om konsesjon hos Datatilsynet, se for øvrig www.datatilsynet.no for oversikt over oppnevnte personvernombud.

Tilrådning med forutsetninger
Personvernombudet har vurdert den planlagte databehandlingen av personopp lysninger/helseopplysninger og vurderer denne til å tilfredsstille forutsetningene for melding gitt i personopplysningsforskriften § 7-27 og er derfor unntatt konsesjon, Personvern ombudet har ingen innvendninger og tilrår at studien gjennomføres med den planlagte behandlingen av person- / helseopplysninger under forutsetning av følgende:

1. Behandling av personopplysninger/helseopplysninger i studien skjer i samsvar med og innenfor det formål som er oppgitt i meldingen (se vedlagte meldeskjema)
2. Vedlagte samtykke benyttes.
3. Studien remeldes på eget skjema (se www.uus.no/personvern) hvert tredje år, første gang i 2010
4. Melding pr. epost om avsluttet studie sendes personvernombudet senest 2019

Øvrige forutsetninger:

a. Positiv uttalelse er innhentet fra Regional Komité for medisinsk forskningsetikk ("REK")
b. Studien er godkjent av avdelingsledelse og forskningsutvalget ved sykehuset og

registrert hos FUS v/Evi Faleide.

Endringer
Dersom det underveis i studien blir aktuelt å gjøre endringer i behandlingen av de avidentifiserte dataene, eller endringer i samtykket, skal dette forhåndsmeldes til personvernombudet.

Lykke til med studien!

<<Samtykkeerklæring endelig versjon.doc>> <<UUSmeldeskjemaforpersonvern Ingrid ACL161106.rtf>>

Mvh
Heidi
IKKE SENSITIVT INNHOLD

Heidi Thorstensen
IKT-sikkerhetssjef/personvernombud, Konsern IT
Ullevål universitetssykehus HF
Mobil: 48016349
Personvern i medisinsk forskning: www.uus.no/personvern

Appendix IV

Patient-reported outcome measures:

International Knee Documentation Committee Subjective Knee Form (IKDC-SKF)

Knee Injury and Osteoarthritis Outcome Score (KOOS)

Marx Activity Rating Scale

2000 IKDC Kne- evalueringsskjema

*NAVN:*_______________________________

Gradér symptomene på det høyeste aktivitetsnivå som du tror du kan fungere uten betydelige symptomer, selv om du ikke egentlig driver aktiviteter på dette nivået.

1. **Hva er det høyeste aktivitetsnivå du kan delta på uten betydelige knesmerter?**
   - ❑ Veldig harde aktiviteter som hopping og vendinger som ved basket eller fotball
   - ❑ Harde aktiviteter som tungt fysisk arbeid, ski eller tennis
   - ❑ Moderate aktiviteter som moderat fysisk arbeid, løping eller jogging
   - ❑ Lette aktiviteter som gange, husarbeid eller hagearbeid
   - ❑ Umulig å foreta noen av de overnevnte aktiviteter på grunn av knesmerter

2. **I løpet av de <u>siste 4 uker</u> (eller siden kneskaden); hvor ofte har du hatt smerter? (sett ring rundt)**

Aldri 0 1 2 3 4 5 6 7 8 9 10 Alltid

3. **Hvis du har hatt smerter; hvor alvorlig er det (ring rundt)?**

Ingen smerte 0 1 2 3 4 5 6 7 8 9 10 Verst tenkelige smerte

4. **I løpet av de <u>siste 4 uker</u> (eller siden kneskaden); hvor <u>stivt</u> eller <u>hovent</u> har kneet ditt vært?**
   - ❑ Ikke i det hele tatt
   - ❑ Lett
   - ❑ Moderat
   - ❑ Veldig
   - ❑ Ekstremt

5. **Hva er det høyeste aktivitetsnivå du tror du kan drive med uten betydelig <u>hevelse</u> i kneet?**
   - ❑ Veldig harde aktiviteter som hopping og vendinger som ved basket eller fotball
   - ❑ Harde aktiviteter som tungt fysisk arbeid, ski eller tennis
   - ❑ Moderate aktiviteter som moderat fysisk arbeid, løping eller jogging
   - ❑ Lette aktiviteter som gange, husarbeid eller hagearbeid
   - ❑ Umulig å foreta noen av de overnevnte aktiviteter på grunn av hevelse

6. **I løpet av de <u>siste 4 uker</u>, (eller siden kneskaden); har kneet låst seg? (sett ring rundt)**

JA **NEI**

7. **Hva er det høyeste aktivitetsnivå du tror du kan drive med uten betydelig <u>svikt</u> av kneet?**
   - ❑ Veldig harde aktiviteter som hopping og vendinger som ved basket eller fotball
   - ❑ Harde aktiviteter som tungt fysisk arbeid, ski eller tennis
   - ❑ Moderate aktiviteter som moderat fysisk arbeid, løping eller jogging
   - ❑ Lette aktiviteter som gange, husarbeid eller hagearbeid
   - ❑ Umulig å foreta noen av de overnevnte aktiviteter på grunn av svikt av kneet

<u>IDRETTSAKTIVITETER:</u>

8. **Hva er det høyeste aktivitetsnivå du kan delta på jevnlig basis?**

- ❑ Veldig harde aktiviteter som hopping og vendinger som ved basket eller fotball
- ❑ Harde aktiviteter som tungt fysisk arbeid, ski eller tennis
- ❑ Moderate aktiviteter som moderat fysisk arbeid, løping eller jogging
- ❑ Lette aktiviteter som gange, husarbeid eller hagearbeid
- ❑ Umulig å foreta noen av de overnevnte aktiviteter på grunn av kneet

9. Hvordan påvirker kneet din evne til å (sett kryss):

		Ikke vanskelig i det hele tatt	Litt vanskelig	Moderat vanskelig	Ekstremt vanskelig	Kan ikke i det hele tatt
a.	Gå opp trapper					
b.	Gå ned trapper					
c.	Knele/gå ned på kne					
d.	Gå ned på huk/gjøre knebøy					
e.	Sitte med bøyd kne					
f.	Reise deg opp fra stol					
g.	Løpe rett fram					
h.	Hinke på ditt skadede ben					
i.	Starte og stoppe raskt					

<u>FUNKSJON:</u>
Hvordan vil du gradere din knefunksjon på en skala fra 0 til 10 der 10 er normal, utmerket funksjon og 0 er at du ikke kan gjøre noen av dine daglige aktiviteter som også kan inkludere idrett?

10. FUNKSJON FØR KNESKADEN:

Kan ikke gjøre daglige aktiviteter	0	1	2	3	4	5	6	7	8	9	10	Ingen begrensninger i daglige aktiviteter

NÅVÆRENDE KNEFUNKSJON:

Kan ikke gjøre daglige aktiviteter	0	1	2	3	4	5	6	7	8	9	10	Ingen begrensninger i daglige aktiviteter

(Original artikkel: Irrgang et al. Development and Validation of the International Knee Documentation Committee Subjective Knee Form. The American Journal of Sports Medicine 2001. vol. 29 no.5 pp. 600-613)
Oversatt av NAR- Ortopedisk senter, UUS, Oslo; 2005, til og med trinn IV etter retningslinjer utarbeidet av: Guillemin F, Bombardier C, Beaton D. Cross-cultural adaptation of health-related quality-of-life measures: literature review and proposed guidelines. J Clin. Epidemiol 1993. vol. 46 pp. 1417-32.

KOOS – SPØRRESKJEMA FOR KNEPASIENTER

DATO: _____/_____/_____ FØDELSENR (11 siffer): ___________________

NAVN: ____

Veiledning: Dette spørreskjemaet inneholder spørsmål om hvordan du opplever kneet ditt. Informasjonen vil hjelpe oss til å følge med i hvordan du har det og fungerer i ditt daglige liv. Besvar spørsmålene ved å krysse av for det alternativ du synes passer best for deg (kun ett kryss ved hvert spørsmål). Hvis du er usikker, kryss likevel av for det alternativet som føles mest riktig.

Symptom

Tenk på de **symptomene** du har hatt fra kneet ditt den **siste uken** når du besvarer disse spørsmålene**.**

S1. Har kneet vært hovent?

Aldri	Sjelden	I blant	Ofte	Alltid
☐	☐	☐	☐	☐

S2. Har du følt knirking, hørt klikking eller andre lyder fra kneet?

Aldri	Sjelden	I blant	Ofte	Alltid
☐	☐	☐	☐	☐

S3. Har kneet haket seg opp eller låst seg?

Aldri	Sjelden	I blant	Ofte	Alltid
☐	☐	☐	☐	☐

S4. Har du kunnet rette kneet helt ut?

Alltid	Ofte	Iblant	Sjelden	Aldri
☐	☐	☐	☐	☐

S5. Har du kunnet bøye kneet helt?

Alltid	Ofte	I blant	Sjelden	Aldri
☐	☐	☐	☐	☐

Stivhet

De neste spørsmålene handler om **leddstivhet**. Leddstivhet innebærer vanskeligheter med å komme i gang eller økt motstand når du bøyer eller strekker kneet. Marker graden av leddstivhet du har opplevd i kneet ditt den **siste uken**.

S6. Hvor stivt er kneet ditt når du nettopp har våknet om morgenen?

Ikke noe	Litt	Moderat	Betydelig	Ekstremt
☐	☐	☐	☐	☐

S7. Hvor stivt er kneet ditt **senere på dagen** etter å ha sittet, ligget eller hvilt?

Ikke noe	Litt	Moderat	Betydelig	Ekstremt
☐	☐	☐	☐	☐

Smerte

P1. Hvor ofte har du vondt i kneet?

Aldri	Månedlig	Ukentlig	Daglig	Hele tiden
☐	☐	☐	☐	☐

Hvilken grad av smerte har du hatt i kneet ditt den **siste uken** ved følgende aktiviteter?

P2. Snu/vende på belastet kne

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

P3. Rette kneet helt ut

Ingen	Lett	Moderate	Betydelig	Svært stor
☐	☐	☐	☐	☐

P4. Bøye kneet helt

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

P5. Gå på flatt underlag

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

P6. Gå opp eller ned trapper

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

P7. Om natten i sengen (smerter som forstyrrer søvnen)

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

P8. Sittende eller liggende

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

P9. Stående

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

Funksjon I hverdagen

De neste spørsmål handler om din fysiske funksjon. **Angi graden av vanskeligheter du har opplevd den siste uken ved følgende aktiviteter på grunn av dine kneproblemer**.

A1. Gå ned trapper

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

A2. Gå opp trapper

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

Angi graden av **vanskeligheter** du har opplevd ved hver aktivitet den **siste uken**.

A3. Reise deg fra sittende stilling

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

A4. Stå stille

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

A5. Bøye deg, f.eks. for å plukke opp en gjenstand fra gulvet

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

A6. Gå på flatt underlag

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

A7. Gå inn/ut av bil

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

A8. Handle/gjøre innkjøp

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

A9. Ta på sokker/strømper

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

A10. Stå opp fra sengen

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

A11. Ta av sokker/strømper

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

A12. Ligge i sengen (snu deg, holde kneet i samme stilling i lengre tid)

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

A13. Gå inn og ut av badekar/dusj

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

A14. Sitte

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

A15. Sette deg og reise deg fra toalettet

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

Angi graden av **vanskeligheter** du har opplevd ved hver aktivitet den **siste uken.**

A16. Gjøre tungt husarbeid (måke snø, vaske gulv, støvsuge osv.)

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

A17. Gjøre lett husarbeid (lage mat, tørke støv osv.)

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

Funksjon, sport og fritid

De neste spørsmålene handler om din fysiske funksjon. Angi graden av vanskeligheter du har opplevd **den siste uken** ved følgende aktiviteter på grunn av dine kneproblemer.

SP1. Sitte på huk

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

SP2. Løpe

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

SP3. Hoppe

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

SP4. Snu/vende på belastet kne

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

SP5. Stå på kne

Ingen	Lett	Moderat	Betydelig	Svært stor
☐	☐	☐	☐	☐

Livskvalitet

Q1. Hvor ofte gjør ditt kneproblem seg bemerket?

Aldri	Månedlig	Ukentlig	Daglig	Alltid
☐	☐	☐	☐	☐

Q2. Har du forandret levesett for å unngå å overbelaste kneet?

Ingenting	Noe	Moderat	Betydelig	Fullstendig
☐	☐	☐	☐	☐

Q3. I hvor stor grad kan du stole på kneet ditt?

Fullstendigl	I stor grad	Moderat	Til en viss grad	Ikke i det hele tatt
☐	☐	☐	☐	☐

Q4. Generelt sett, hvor store problemer har du med kneet ditt?

Ingen	Lette	Moderate	Betydelige	Svært store
☐	☐	☐	☐	☐

Takk for at du tok deg tid og besvarte samtlige spørsmål!

MARX

I løpet av det siste året, hvor ofte utførte du hver av de følgende aktiviteter da du var på ditt beste helsemessige og mest aktive nivå:

	Mindre enn en gang i måneden	**En gang i måneden**	**En gang i uken**	**2 eller 3 ganger i uken**	**4 ganger i uken eller mer**
Løping: Løping, enten i forbindelse med idrett, eller ren jogging					
Brå retningsendring: Endre retning mens man løper					
Oppbremsing: Bråstoppe når man løper					
Vending: Snu kroppen mens en fot er plantet i bakken under utførelse av en idrett; for eksempel ski, skøyter, sparking, kasting, slå en ball (golf, tennis, squash) etc.					

2000 IKDC SUBJECTIVE KNEE EVALUATION FORM

SYMPTOMS*:

*Grade symptoms at the highest activity level at which you think you could function without significant symptoms, even if you are not actually performing activities at this level.

1. What is the highest level of activity that you can perform without significant knee pain?

   4❑Very strenuous activities like jumping or pivoting as in basketball or soccer
   3❑Strenuous activities like heavy physical work, skiing or tennis
   2❑Moderate activities like moderate physical work, running or jogging
   1❑Light activities like walking, housework or yard work
   0❑Unable to perform any of the above activities due to knee pain

2. During the past 4 weeks, or since your injury, how often have you had pain?

	10	9	8	7	6	5	4	3	2	1	0	
Never	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	Constant

3. If you have pain, how severe is it?

	10	9	8	7	6	5	4	3	2	1	0	
No pain	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	Worst pain imaginable

4. During the past 4 weeks, or since your injury, how stiff or swollen was your knee?

   4❑Not at all
   3❑Mildly
   2❑Moderately
   1❑Very
   0❑Extremely

5. What is the highest level of activity you can perform without significant swelling in your knee?

   4❑Very strenuous activities like jumping or pivoting as in basketball or soccer
   3❑Strenuous activities like heavy physical work, skiing or tennis
   2❑Moderate activities like moderate physical work, running or jogging
   1❑Light activities like walking, housework, or yard work
   0❑Unable to perform any of the above activities due to knee swelling

6. During the past 4 weeks, or since your injury, did your knee lock or catch?

   0❑Yes 1❑No

7. What is the highest level of activity you can perform without significant giving way in your knee?
   4❑Very strenuous activities like jumping or pivoting as in basketball or soccer
   3❑Strenuous activities like heavy physical work, skiing or tennis
   2❑Moderate activities like moderate physical work, running or jogging
   1❑Light activities like walking, housework or yard work
   0❑Unable to perform any of the above activities due to giving way of the knee

SPORTS ACTIVITIES:

8. What is the highest level of activity you can participate in on a regular basis?

- 4❑Very strenuous activities like jumping or pivoting as in basketball or soccer
- 3❑Strenuous activities like heavy physical work, skiing or tennis
- 2❑Moderate activities like moderate physical work, running or jogging
- 1❑Light activities like walking, housework or yard work
- 0❑Unable to perform any of the above activities due to knee

9. How does your knee affect your ability to:

		Not difficult at all	Minimally difficult	Moderately Difficult	Extremely difficult	Unable to do
a.	Go up stairs	4❑	3❑	2❑	1❑	0❑
b.	Go down stairs	4❑	3❑	2❑	1❑	0❑
c.	Kneel on the front of your knee	4❑	3❑	2❑	1❑	0❑
d.	Squat	4❑	3❑	2❑	1❑	0❑
e.	Sit with your knee bent	4❑	3❑	2❑	1❑	0❑
f.	Rise from a chair	4❑	3❑	2❑	1❑	0❑
g.	Run straight ahead	4❑	3❑	2❑	1❑	0❑
h.	Jump and land on your involved leg	4❑	3❑	2❑	1❑	0❑
i.	Stop and start quickly	4❑	3❑	2❑	1❑	0❑

FUNCTION:

10. How would you rate the function of your knee on a scale of 0 to 10 with 10 being normal, excellent function and 0 being the inability to perform any of your usual daily activities which may include sports?

FUNCTION PRIOR TO YOUR KNEE INJURY:

Couldn't perform daily activities	0	1	2	3	4	5	6	7	8	9	10	No limitation in daily activities
	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	

CURRENT FUNCTION OF YOUR KNEE:

Cannot perform daily activities	0	1	2	3	4	5	6	7	8	9	10	No limitation in daily activities
	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	

KOOS KNEE SURVEY

INSTRUCTIONS: This survey asks for your view about your knee. This information will help us keep track of how you feel about your knee and how well you are able to perform your usual activities.
Answer every question by ticking the appropriate box, only one box for each question. If you are unsure about how to answer a question, please give the best answer you can.

Symptoms
These questions should be answered thinking of your knee symptoms during the **last week**.

S1. Do you have swelling in your knee?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S2. Do you feel grinding, hear clicking or any other type of noise when your knee moves?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S3. Does your knee catch or hang up when moving?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S4. Can you straighten your knee fully?

Always	Often	Sometimes	Rarely	Never
☐	☐	☐	☐	☐

S5. Can you bend your knee fully?

Always	Often	Sometimes	Rarely	Never
☐	☐	☐	☐	☐

Stiffness
The following questions concern the amount of joint stiffness you have experienced during the **last week** in your knee. Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.

S6. How severe is your knee joint stiffness after first wakening in the morning?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

S7. How severe is your knee stiffness after sitting, lying or resting **later in the day**?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Pain

P1. How often do you experience knee pain?

Never	Monthly	Weekly	Daily	Always
☐	☐	☐	☐	☐

What amount of knee pain have you experienced the **last week** during the following activities?

P2. Twisting/pivoting on your knee

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P3. Straightening knee fully

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P4. Bending knee fully

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P5. Walking on flat surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P6. Going up or down stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P7. At night while in bed

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P8. Sitting or lying

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P9. Standing upright

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, daily living

The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A1. Descending stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A2. Ascending stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A3. Rising from sitting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A4. Standing

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A5. Bending to floor/pick up an object

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A6. Walking on flat surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A7. Getting in/out of car

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A8. Going shopping

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A9. Putting on socks/stockings

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A10. Rising from bed

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A11. Taking off socks/stockings

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A12. Lying in bed (turning over, maintaining knee position)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A13. Getting in/out of bath

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A14. Sitting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A15. Getting on/off toilet

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A16. Heavy domestic duties (moving heavy boxes, scrubbing floors, etc)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A17. Light domestic duties (cooking, dusting, etc)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, sports and recreational activities

The following questions concern your physical function when being active on a higher level. The questions should be answered thinking of what degree of difficulty you have experienced during the **last week** due to your knee.

SP1. Squatting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP2. Running

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP3. Jumping

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP4. Twisting/pivoting on your injured knee

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP5. Kneeling

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Quality of Life

Q1. How often are you aware of your knee problem?

Never	Monthly	Weekly	Daily	Constantly
☐	☐	☐	☐	☐

Q2. Have you modified your life style to avoid potentially damaging activities to your knee?

Not at all	Mildly	Moderately	Severely	Totally
☐	☐	☐	☐	☐

Q3. How much are you troubled with lack of confidence in your knee?

Not at all	Mildly	Moderately	Severely	Extremely
☐	☐	☐	☐	☐

Q4. In general, how much difficulty do you have with your knee?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Marx Activity Rating Scale

Marx Activity Rating Scale (Marx et al., 2001)

Please indicate how often you performed each activity in your healthiest and most active state, in the past year.

	Less than one time in a month	One time in a month	One time in a week	2 or 3 times in a week	4 or more times in a week
Running: running while playing a sport or jogging					
Cutting: changing directions while running					
Decelerating: coming to a quick stop while running					
Pivoting: turning your body with your foot planted while playing a sport (skiing, skating, kicking, throwing hitting a ball (golf, tennis, squash, etc.					

Marie Pedersen // Long-term outcomes after ACL reconstruction or rehabilitation alone