Allograft for anterior and posterior cruciate ligament reconstruction

Systematic Review

Ludwig Boltzmann Institut
Health Technology Assessment

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Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

CONTENT INFORMATION

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Content

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List of abbreviations

AAOS ..... American Academy of Orthopaedic Surgeons
AATB ..... American Association of Tissue Banks
ACL ..... Anterior Cruciate Ligament
ACLR ..... Anterior Cruciate Ligament Reconstruction
Allo ..... Allograft
Auto ..... Autograft
BPTB ..... Bone-Patellar Tendon Bone
CI ..... Confidence Interval
CPG ..... Clinical Practice Guideline
CRD ..... Centre for Reviews and Dissemination

DARE..... Database of Abstracts of Reviews of Effects
Diff. ..... Difference
DVT..... Deep Venous Thrombosis
EU ..... European Union
EUTCD..... EU Tissue and Cells Directive
FDA..... Food and Drug Administration
FU ..... Follow-Up
GRADE..... Grading Of Recommendations Assessment, Development and Evaluation
HIV..... Human Immune-Deficiency Virus
HRQoL ..... Health-Related Quality of Life
HTA ..... Health Technology Assessment
IKDC..... International Knee Documentation Committee
IQR..... Interquartile Range
KOOS..... Knee Injury and Osteoarthritis Outcome Score
LARS..... Ligament Augmentation and Reconstruction System
LBI-HTA ..... Ludwig Boltzmann Institute for Health Technology Assessment
MD ..... Mean Difference
mm ..... millimetre
MRI..... Magnetic Resonance Imaging
n. s. ..... statistically not significant
NHS-EED..... NHS Economic Evaluation Database
NICE..... National Institute for Health and Care Excellence
NOS..... Newcastle-Ottawa Scale
OA ..... Osteoarthritis
OR ..... Odds Ratio
OTPG..... Organtransplantationsgesetz
PCL..... Posterior Cruciate Ligament
PCLR ..... Posterior Cruciate Ligament Reconstruction
PRICE-M..... Protection, Rest, Ice, Compression, Elevation, and Medication
QoL ..... Quality of Life
RCT..... Randomised Controlled Trial
RoB..... Risk of Bias
s. s. ..... statistically significant
SANE ..... Single Assessment Numeric Evaluation
stat. ..... statistically
WHO-ICTRP ..... World Health Organisation – International Clinical Trials Registry Platform

Executive summary

Introduction

Health problem

vordere und hintere Kreuzbänder wichtig für Stabilität des Kniegelenks

The anterior cruciate ligament (ACL) and posterior cruciate ligament (PCL) are crucial structures for providing stability in the knee joint during functional and sporting activities. The main role of the ACL is to provide restraint against the forward translation of the tibia on the femur and secondary constraint against tibial rotation and valgus and varus stress [1].

5 Indikationen zu Kreuzbandrisse in Assessment gewählt

Patients with **ruptures of the ACL/PCL, re-ruptures of the ACL/PCL** or **multi-ligament knee injuries** can be treated using arthroscopic surgery. Yet, controversy exists regarding the adequate treatment, as conservative management can also be an adequate treatment option depending, inter alia, on the specific health condition, and factors such as stability and activity level [2]. Based on the aforementioned health conditions, patients who are candidates for one of the following ligament reconstructions were selected as indications in this assessment:

- Anterior Cruciate Ligament Reconstruction (ACLR),
- Posterior Cruciate Ligament Reconstruction (PCLR),
- Revision ACLR,
- Revision PCLR or
- Cruciate ligament reconstructions in mutli-ligament knee injuries.

Inzidenz vorderer Kreuzbandriss: ca. 31-37 in 100.000 Personen, hinterer Kreuzbandriss seltener

Approximately 31-37 ACL ruptures occur per 100,000 persons annually in Germany [2]. Similarly and according to data from the United States (US), the incidence of ACL ruptures in the general population is 1 in 3,500 persons [3]. PCL injuries are less common compared to ACL injuries – approximately only 1 to 44 percent of all knee injuries are PCL injuries based on data from the US [4, 5]. Yet, relevant data on the incidence of PCL injuries by handsearching was not found. Similarly, we were unable to find any relevant incidence data on ACL or PCL re-ruptures and mutli-ligament knee injuries.

Description of technology

allogene Bandersätze als mögliche Alternative zu autogenen Bandersätzen

When reconstructing a cruciate ligament, the torn anterior cruciate ligament (ACL) or posterior cruciate ligament (PCL) is replaced using a graft – typically using tendons from the patient's body (autograft) or from another external source (allograft) [6-8].

Allografts to be used for ACLR or PCLR are the technology under investigation in this assessment. Allografts are reconstructive natural materials; they are processed cadaveric fascia lata or acellular dermal matrices of human donors [9]. Allografts are taken from a cadaver Achilles tendon, a semitendinosus, a gracilis, or a posterior tibialis tendon [10].

Both graft types are associated with benefits and harms: when using autografts, for instance, donor site morbidities and associated complications may be present. In theory, allografts offer a solution to donor site morbidities and may also lead to shorter operative time [9, 11]. Disadvantages of allografts may include potential disease transmission, immunologic reactions, slower remodelling and integration, as well as costs [7].

Research question

Allograft wirksamer und sicherer als autograft, konservatives Management bei Kreuzbandriss

Is allograft cruciate ligament reconstruction in comparison to other techniques of cruciate ligament reconstruction or conservative management in patients undergoing ACLR, PCLR, revision ACLR/PCLR or ligament reconstruction in multi-ligamentous injuries of the knee more effective and safe concerning function, activity level and symptoms, knee stability, graft failure, and complications?

Methods

systematische Übersichtsarbeit
Systematische Suche in 4 Datenbanken
alle Arbeitsschritte durch 2 WissenschafterInnen

A systematic search for relevant publications was carried out in 4 databases (Medline, Embase, the Cochrane Library, and the University of York Centre for Reviews and Dissemination). Primary studies on allografts to be used for ACLR, PCLR, revision surgery or reconstructions in patients with multi-ligament knee injuries were searched from inception to 19 December 2018. The study selection was conducted by three authors (GG, CdV, SGG). Two authors (GG, SGG) screened the abstracts. The full-text screening and the appraisal of the quality of the respective studies was conducted by GG and CdV. The risk of bias assessment of the included studies was conducted using adequate tools: the Cochrane Risk of Bias Tool [12] was utilised for randomised controlled studies, while the Newcastle-Ottawa Scale (NOS) was applied for assessing the risk of bias for cohort studies [13]. Data extraction was conducted by one researcher (GG) and verified by another researcher (CdV).

A qualitative evidence synthesis was chosen. Based on the data extraction tables, data on each selected outcome category were synthesised across studies according to GRADE (Grading of Recommendations, Assessment, Development and Evaluation) [14].

In case of disagreement, a third researcher (SGG) was consulted to resolve disagreements.

Clinical effectiveness

wesentliche Wirksamkeitsendpunkte: Funktion, Aktivität und Symptome

The crucial outcomes used as evidence to derive a recommendation on the relative effectiveness of allografts to be used for cruciate ligament reconstruction are patient-reported function, activity level and symptoms. Included are the following scores: Lysholm score, Tegner score, Cincinnati Knee score, SANE score, IKDC score (subjective), KOOS, and the Marx activity score. In addition, 3 further outcomes were selected, yet only judged as important, but not crucial, to derive a recommendation: clinical knee stability, quality of life, patient satisfaction.

Safety

wesentliche Sicherheitsendpunkte: Komplikationen, Transplantversagen, etc.

The crucial outcomes used as evidence to derive a recommendation on the relative safety of allografts to be used for cruciate ligament reconstruction included: graft failure, re-ruptures, re-operations, revisions, and other complications.

Results

Available evidence

Overall, 9 studies [15-23] were eligible to be included in this assessment. All of these studies compared allografts to autografts in cruciate ligament reconstruction. Of the included studies, 8 were randomised controlled trials [15, 17-23] with unclear-high risk of bias (mainly due to the lack of blinding and potential selective outcome reporting), and one further comparative cohort study [16] with a moderate risk of bias.

Evidenz: 9 Studien
6 RCTs zu ACLR
2 RCTs zu PCLR
1 Kohortenstudie
zu Revisions-ACLR

Clinical effectiveness and safety

When assessing the relative effectiveness of allograft cruciate ligament reconstruction in comparison to autograft cruciate ligament reconstruction, the following evidence was found for the selected indications:

Allograft vs. Autograft
Evidenz zu
ACLR & PCLR

- **Anterior cruciate ligament reconstruction (ACLR):** Low to moderate quality evidence indicating comparable effectiveness based on the crucial outcome of patient-reported function, activity level and symptoms. Moderate certainty evidence was found indicating the inferiority of allografts with regard to graft failure. Yet, with regard to the other selected crucial safety outcomes, the evidence was insufficient to clearly prove the inferiority of allografts when compared to autografts (evidence base: 6 RCTs [15, 17, 19-22] with high RoB).
- **Posterior cruciate ligament reconstruction (PCLR):** Very low to low quality evidence indicating comparable effectiveness based on the crucial outcome of patient-reported function, activity level and symptoms. Insufficient evidence to indicate superiority or inferiority on the basis of comparative safety (evidence base: 2 RCTs [18, 23] with unclear-high RoB).
- **Revision ACLR:** Insufficient evidence to support or to refute that allografts are superior or inferior on the basis of the selected effectiveness and safety outcomes (evidence base: 1 comparative cohort study [16] with moderate RoB).
- **Revision PCLR:** No evidence to support or to refute that allografts are superior or inferior on the basis of the selected effectiveness and safety outcomes.
- **ACLR/PCLR in multi-ligament knee injuries:** No evidence to support or to refute that allografts are superior or inferior on the basis of the selected effectiveness and safety outcomes.

unzureichende Evidenz
zu revision ACLR

keine Evidenz:
Multi-ligamentäre
Knieverletzung &
Revisions-PCLR

No evidence was found comparing allograft cruciate ligament reconstruction to conservative management.

Anterior cruciate ligament reconstruction (ACLR)

The scientific evidence indicates that allografts are equally effective when compared to autografts based on the outcome of **patient-reported function, activity level and symptoms** (crucial outcome; certainty: low-moderate; evidence base: 6 RCTs [15, 17, 19-22] with high RoB).

ACLR:
Evidenz weist
auf vergleichbare
Wirksamkeit hin

In addition, very low to moderate quality evidence was found indicating comparable effectiveness based on the outcome of **clinical knee stability** (important outcome; certainty: very low to moderate; evidence base: 4 RCTs [19-22] with high RoB). Yet, 1 study [22] found a statistically significant difference favouring autografts based on the Lachman test and Pivot shift test (4 studies reported on these outcomes, with the remaining studies [19-21] having not

Sicherheit:
moderate Evidenz:
Allografts weniger
sicher bezüglich
Transplantatversagen;

andere Sicherheitsendpunkte: unzureichende Evidenz

found any statistically significant difference), and 2 studies [19, 22] found a statistically significant difference favouring autografts when comparing side-to-side differences between treatment groups. No further studies that reported on this outcome [20, 21] found a statistically significant difference in side-to-side difference (measured instrumentally) and none of the studies that reported on an objective IKDC score [19-22] found a statistically significant difference of this score result between treatment groups. In addition, there is low-quality evidence that patient satisfaction is comparable between the allograft and autograft groups (important outcome; evidence base: 1 RCT [17] with high RoB). No evidence was found for the important outcome of HRQoL.

Concerning comparative safety for ACLR, moderate quality evidence was found suggesting that allografts may be less safe compared to autografts with regard to graft failures (evidence base: 2 RCTs [15, 22] with high RoB). Yet, with regard to the other selected crucial safety outcomes, the evidence was insufficient to clearly prove the inferiority of allografts when compared to autografts (evidence base: 6 RCTs [15, 17, 19-22] with high RoB).

Posterior cruciate ligament reconstruction (PCLR)

PCLR: Evidenz weist auf vergleichbare Wirksamkeit hin unzureichende Evidenz zur vergleichenden Sicherheit

The scientific evidence indicates that allografts are equally effective as autografts for PCLR based on the outcome of **patient-reported function, activity level and symptoms** (crucial outcome; certainty: very low to low; evidence base: 2 RCTs [18, 23] with unclear to high RoB). Moreover, very low-quality evidence was found for the outcome of clinical knee stability measured with the KT-arthrometer that may favour autografts. Yet, a statistically significant difference was only seen in 1 study [18] (mean difference: 3.5 ±1.1 vs. 2.1 ±1), while the other study [23] did not find a statistically significant difference of side-to-side differences between treatment groups. The other sub-outcomes measuring knee stability with clinical tests did not find any statistically significant differences between allografts and autografts (certainty: low to moderate; evidence base: 2 RCTs [18, 23] with unclear to high RoB). No evidence was found for the important outcomes patient satisfaction and HRQoL.

Concerning comparative safety for PCLR, insufficient scientific evidence was found for overall (long-term) comparative safety of allografts in comparison to autografts in PCLR (evidence base 2 RCTs [18, 23] with unclear to high RoB). There is low-quality evidence that allografts lead to fewer complications related to infections, donor site pain, and reflex sympathetic dystrophy in comparison to autografts. Yet, only 1 study [23] reported on an overall complication rate (without statistical testing), and it appears that the reported complications are related to graft harvesting and infection for autografts. As a result, the evidence was insufficient for the overall comparative safety.

Revision ACLR

Revisions-ACLR: unzureichende Evidenz

One included observational study [16] conducted a logistic regression analysis and found results from some subscales that were in favour of autografts (e.g., sports function and some further patient-reported outcomes, re-ruptures) in comparison to allografts. In the absence of evidence derived from randomised controlled trials, the evidence is insufficient to prove superiority/inferiority of allografts regarding clinical effectiveness and safety when compared to autografts in revision ACLR (evidence base: 1 comparative observational study with moderate RoB).

Upcoming evidence

7 laufende Studien:

Overall, 7 ongoing clinical trials that investigated the use of allografts for cruciate ligament reconstruction were identified (ACLR: 3 ongoing studies; PCLR: 1 ongoing study; multi-ligament knee injury: 1 ongoing study; revision reconstruction: 2 ongoing studies).

nur 2 RCTs mit geringer Fallzahl

5 laufende Beobachtungsstudien ohne Vergleich

Surprisingly, only 2 of these 7 ongoing studies were RCTs comparing allografts to autografts or a new treatment modality (Z-lig anterior cruciate ligament reconstruction). The sample size of the RCTs is 40 in one ongoing study comparing allografts to autografts, and 60 in another ongoing study comparing allografts to Z-ligs. The primary completion date of these studies already passed in 2015 and 2014, respectively. In addition, the primary outcomes were X-ray, CT-scan, and KT-1000 in one study, and KT-1000 only in the other study. The remaining 5 ongoing studies were uncontrolled, with a maximum sample size of 100 enrolled patients.

As a result, it is not expected that the evidence will change considerably according to the upcoming results of the identified ongoing studies.

Yet and according to information from the manufacturers, 2 studies (incl. 1 RCT) are currently being conducted in Austria. However, study protocols are not publicly available.

Reimbursement

Kreuzband-rekonstruktionen im Leistungskatalog, jedoch nicht mittels Allografts

In the Austrian catalogue of benefits, there is a generic code for the reconstruction of the anterior and/or posterior cruciate ligament already included in the Austrian hospital benefit catalogue [24], but not a separate/specific code for the use of allografts for reconstruction/replenishment (of the cruciate ligament).

Discussion

Wirksamkeit: vergleichbar bei ACLR & PCLR, unzureichend bei Revisions-ACLR

The evidence found in this systematic review indicates that allografts may be equally effective but less safe in ACLR with regard to graft failures. Regarding PCLR, effectiveness may be comparable, yet insufficient evidence was found for the comparative safety of allografts when compared to autografts in PCLR. The evidence is insufficient for revision ACLR, and no evidence was found for the remaining indications.

Sicherheit: weniger sicher bei ACLR (graft failure), sonst unzureichende Evidenz

The main limitations of the evidence base were in relation to the high risk of bias of the primary studies and the poor reporting on complications (e.g., differences were often reported narratively, and statistical testing was not always conducted). In addition, one further main limitation of this work, as evident with all studies investigating ACLR or PCLR, is the lack of an objective assessment of numerous outcomes (e.g., rotational knee stability, knee function, etc.).

weitere Forschung und Leitlinien wesentlich

Further research should focus on more high quality randomised controlled trials with comprehensive safety reporting. In addition, questions regarding differences between types of allografts should be addressed. Evidence-based guidelines should clearly state the role of allografts in the management of cruciate ligament reconstruction.

Recommendation

Erstattung derzeit nicht empfohlen

On the basis of the evidence identified in this assessment, the inclusion in the catalogue of benefits is currently not recommended.

In the absence of ongoing randomised controlled trials that could provide an answer to the question chosen in this assessment, it is unlikely that the evidence will change. A re-evaluation is therefore not recommended for the present.

A re-evaluation is necessary as soon as results of new RCTs are available. According to information from the manufacturers, 2 studies (incl. 1 RCT) are currently being conducted in Austria. However, study protocols are not publicly available.

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

vorderes und hinteres Kreuzband wichtig für Stabilität des Kniegelenks

Das vordere Kreuzband (engl. anterior cruciate ligament = ACL) und das hintere Kreuzband (engl. posterior cruciate ligament = PCL) sind entscheidende Strukturen für die Stabilisierung des Kniegelenks bei funktionellen und sportlichen Aktivitäten. Die Hauptaufgabe des ACL besteht darin, gegen die Vorwärtsverschiebung der Tibia am Femur und die sekundäre Zwangslage gegen die Tibia-Rotation und den Valgus- und Varus-Stress Einhalt zu leisten [1].

5 Indikationen zu Kreuzbandrisse in Assessment gewählt

PatientInnen mit Rupturen des ACL/PCL, Re-Ruptur des ACL/PCL oder Multi-Ligament-Knieverletzungen können mit einer arthroskopischen Operation behandelt werden. Kontroversen bestehen jedoch hinsichtlich der adäquaten Behandlung, da auch die konservative Behandlung unter gewissen Bedingungen eine angemesseneBehandlungsoption darstellen kann [2]. Die in diesem Assessment gewählten Indikationen sind bei PatientInnen, die aufgrund der oben beschriebenen Verletzungen KanditatInnen für eine der 5 Operationen sind:

- Rekonstruktion des vorderen Kreuzbandes (engl. Anterior Cruciate ligament reconstruction = ACLR),
- Rekonstruktion des hinteren Kreuzbandes (engl. Posterior Cruciate Ligament Reconstruction = PCLR),
- Revisionsrekonstruktionen des vorderen Kreuzbandes (engl. revision ACLR):
- Revisionsrekonstruktion des hinteren Kreuzbandes (engl. revision PCLR oder
- ACLR und/oder PCLR bei multi-ligamentären Knieverletzungen

Die jährliche Inzidenz der vorderen Kreuzbandrisse liegt in Deutschland bei etwa 31-37 pro 100.000 Personen [2]. In den Vereinigten Staaten treten die Risse der ACL in ähnlichem Ausmaß auf: Die diesbezügliche Inzidenz liegt hierbei bei 1 von 3.500 Personen [3]. Hintere Kreuzbandverletzungen treten weniger häufig auf und umfassen in etwa 1 bis 44 Prozent aller Knieverletzungen in den Vereinigten Staaten [4, 5]. Zu den anderen Indikationen wurden keine relevanten Daten zur Inzidenz gefunden.

Beschreibung der Technologie & Komparatoren

allogene Bandersätze als mögliche Alternative zu autogenen Bandersätzen

Bei allogenen Bandersätzen handelt es sich um natürliche, rekonstruktive Materialien (Allografts); also um kadaverartige fascia lata oder azelluläre dermale Matrizen menschlicher Spender [9].

Als Alternativen zu allogenen Bandersätzen können autogene Bandersätze (Autografts) zum Einsatz kommen. Invasive operative Eingriffe sind jedoch bei Kreuzbandverletzungen nicht immer notwendig [10]: Die konservative Therapie (inkl. Physiotherapie) wurde daher ebenfalls als Komparator gewählt.

Bei Kreuzbandrekonstruktionen sind die Transplantattypen mit Vor- und Nachteilen verbunden: Autogene Bandersätze sind beispielsweise mit Entnahmemorbiditäten und diesbezüglichen etwaigen Komplikationen verbun-

den. Allogene Bandersätze bieten eine Lösung für diese – mit der Entnahme des Transplantats verbundenen – Komplikationen. Zudem ist eine kürzere Operationsdauer für betroffene PatientInnen zu verzeichnen [9, 11]. Allogene Bandersätze können jedoch auch mit Nachteilen verbunden sein: langsamere Remodellierung und Integration des Transplatats, potenzielle Übertragung von Krankheiten, immunologische Reaktionen sowie erhöhte Kosten [7].

Wissenschaftliche Forschungsfrage

Allograft wirksamer und sicherer als Autograft oder konservatives Management bei Kreuzbandriss?

Sind allogene Kreuzbandrekonstruktionen im Vergleich zu Kreuzbandrekonstruktionen mittels anderer Transplantate (insb. Autografts) oder im Vergleich zur konservativen Behandlung bei PatientInnen mit Kreuzbandriss (bei denen ACLR, PCLR, Revision ACLR/PCLR, oder Kreuzbandrekonstruktionen bei multi-ligamentären Knieverletzungen indiziert ist) wirksamer und sicherer in Bezug auf Funktion, Aktivitätsniveau und Symptome sowie Kniestabilität, Transplantatversagen und Komplikationen?

Methoden

systematische Übersichtsarbeit, systematische Suche in 4 Datenbanken, alle Arbeitsschritte durch 2 WissenschafterInnen

Es wurde eine systematische Suche nach relevanten Publikationen in 4 Datenbanken durchgeführt (Medline, Embase, Cochrane Library und University of York Center for Reviews und Dissemination). Drei AutorInnen (GG, CdV, SGG) führten die Studienauswahl unabhängig voneinander durch. Das Abstract-Screening wurde von GG und SGG, und die Voll-Text-Auswahl und die Qualitätsbewertung der Studien wurde von GG und CdV durchgeführt. Das Verzerrungspotential (Risk of Bias) der eingeschlossenen Studien wurde mit geeigneten Instrumenten bewertet: Das Cochrane Risk of Bias Tool [12] wurde für randomisierte kontrollierte Studien verwendet, während die Newcastle-Ottawa-Skala (NOS) zur Bewertung des Verzerrungsrisikos für Kohortenstudien verwendet wurde [13]. Datenextraktion wurde von einer Person (GG) durchgeführt und von einer anderen Person (CdV) verifiziert. Die GRADE-Methode [14] kam im Zuge der qualitativen Evidenzsynthese zum Einsatz.

Im Falle von Meinungsverschiedenheiten wurde eine dritte Forscherin (SGG) konsultiert, um einen Konsens zu finden.

Wirksamkeit

wesentliche Wirksamkeitsendpunkte: Funktion, Aktivität und Symptome

Es wurden in diesem Assessment folgende wesentliche Wirksamkeitsendpunkte gewählt: „Funktion, Aktivität und Symptome“. Folgende Instrumente wurden dabei herangezogen: Lysholm Score, Tegner Score, Cincinnati Knee Score, SANE Score, IKDC Score (subjektiv), KOOS und der Marx-Aktivitätswert. Darüber hinaus wurden 3 weitere Wirksamkeitsendpunkte gewählt, die jedoch nicht wesentlich für die Ableitung einer Empfehlung eingestuft wurden: klinische Kniestabilität, Lebensqualität, PatientInnenzufriedenheit.

Sicherheit

wesentliche Sicherheitsendpunkte: Komplikationen, Transplantversagen, etc.

Zur Evaluierung der Sicherheit wurden folgende wesentliche Endpunkte gewählt: Transplantatversagen, Re-Rupturen, Re-Operationen, Revisionen und andere Komplikationen.

Ergebnisse

Verfügbare Evidenz

Insgesamt wurden 9 Studien [15-23] in dieser Literaturübersicht eingeschlossen. Alle eingeschlossenen Studien verglichen allogene Kreuzbandrekonstruktionen mit autogenen Kreuzbandrekonstruktionen. Von den eingeschlossenen Studien waren 8 randomisierte kontrollierte Studien [15, 17-23] mit einem unklaren bis hohen Verzerrungspotenzial (Risk of Bias) – hauptsächlich aufgrund von fehlender Verblindung und der selektiven Berichterstattung. Eine weitere vergleichende Kohortenstudie [16] mit moderatem Verzerrungspotenzial erfüllte die Einschlusskriterien für die Indikation der Revisionsrekonstruktion des vorderen Kreuzbandes.

Evidenz: 9 Studien
6 RCTs zu ACLR
2 RCTs zu PCLR
1 Kohortenstudie
zu Revisions-ACLR

Klinische Wirksamkeit und Sicherheit

Bei den gewählten Indikationen konnte folgende Evidenz hinsichtlich Überlegenheit/Unterlegenheit der allogenen Bandersätze im Vergleich zu autogenen Kreuzbandrekonstruktionen gefunden werden:

- **Rekonstruktion des vorderen Kreuzbandes (ACLR):** Es wurde Evidenz auf niedrig bis moderatem Qualitätsniveau gefunden, die – auf Basis des in diesem Assessment gewählten wesentlichen Wirksamkeits-Endpunktes „Funktion, Aktivität und Symptome“ – eine vergleichbare Wirksamkeit nahelegt. Es besteht moderate Stärke der Evidenz, die auf Unterlegenheit der Allografts im Vergleich zu Autografts hinsichtlich des Endpunktes Transplantatversagen (graft failure) hinweist. Die Evidenz war jedoch unzureichend für die Evaluation der vergleichenden Sicherheit auf Basis der anderen gewählten wesentlichen Sicherheitsendpunkte (Evidenzbasis: 6 RCTs mit hohem RoB).

  ACLR:
  Wirksamkeit:
  vergleichbar;
  Sicherheit: moderate Evidenz: höheres Risiko für graft failure bei Allografts;
  andere Sicherheitsendpunkte:
  unzureichende Evidenz

- **Rekonstruktion des hinteren Kreuzbandes (PCLR):** Es wurde Evidenz auf sehr niedrigem bis niedrigem Qualitätsniveautsniveau gefunden, die – auf Basis des in diesem Assessment gewählten wesentlichen Wirksamkeits-Endpunktes „Funktion, Aktivität und Symptome“ – eine vergleichbare Wirksamkeit nahelegt. Es wurde unzureichende Evidenz zur vergleichenden Sicherheit gefunden (Evidenzbasis: 2 RCTs mit unklarem-hohem RoB).

  PCLR:
  vergleichbare Wirksamkeit &
  unzureichende Evidenz zu Sicherheit

- **Revisionsrekonstruktionen des vorderen Kreuzbandes (revision ACLR):** unzureichende Evidenz, die eine Überlegenheit oder Unterlegenheit der Allografts im Vergleich zu Autografts nahelegt (Evidenzbasis: 1 komparative Kohortenstudie mit moderatem RoB).

  Revisions-ACLR:
  unzureichende Evidenz

- **Revisionsrekonstruktion des hinteren Kreuzbandes (revision PCLR):** keine Evidenz, die eine Überlegenheit oder Unterlegenheit der Allografts im Vergleich zu Autografts nahelegt

  Revisions-PCLR:
  keine Evidenz

- **ACLR und/oder PCLR bei mutli-ligamentären Knieverletzungen**: keine Evidenz, die eine Überlegenheit oder Unterlegenheit der Allografts im Vergleich zu Autografts nahelegt.

  keine Evidenz
  bei multi-ligament
  Knieverletzungen

Rekonstruktion des vorderen Kreuzbandes (ACLR)

Die Evidenz weist – auf Basis des in diesem Assessment gewählten wesentlichen Wirksamkeits-Endpunktes „Funktion, Aktivität und Symptome“ – auf eine vergleichbare Wirksamkeit hin (wesentlicher Endpunkt, Stärke der Evidenz: niedrig bis moderat; Evidenzbasis: 6 RCTs [15, 17, 19-22] mit hohem RoB).

Auch auf Basis des Wirksamkeitsendpunktes der klinischen Kniestabilität weist die Evidenz eher auf eine vergleichbare Wirksamkeit hin (Evidenzbasis: 4 RCTs [19-22] mit hohem RoB). Es ist hierbei aber darauf hinzuweisen, dass eine Studie [22] einen statistisch signifikanten Unterschied zu Ungunsten der allogenen Bandersätze auf Basis der Resultate des Lachman Tests und des Pivot-Shift Tests fand. Die anderen Studien, die diese Endpunkte gemessen haben [19-21], konnten jedoch keine statistisch signifikante Unterschiede dieser klinischen Tests finden. Darüber hinaus fanden 2 Studien [19, 22] einen statistisch signifikanten Unterschied zu Ungunsten der allogenen Bandersätze bei Messung der "side-to-side" Differenzen mit Hilfe des KT-Arthrometers. Die anderen Studien, die diesen Endpunkt gemessen haben [20, 21], fanden keinen statistisch signifikanten Unterschied der Resultate dieses Endpunktes zwischen Allografts und Autografts. Der objektive IKDC Score wurde von 4 Studien als Messung der Kniestabilität herangezogen und keine dieser Studien konnte einen statistisch signifikanten Unterschied zwischen Allografts und Autografts finden [19-22].

PatientInnenzufriedenheit wurde lediglich von einer Studie gemessen und es konnte Evidenz gefunden werden, die auf vergleichbare Zufriedenheit zwischen PatientInnen mit allogenen Bandersätzen versus autogenen Bandersätzen hinweist. Genaue Angaben der Messung dieser Zufriedenheit fehlten jedoch in der Studie, wodurch die Stärke der Evidenz in diesem Endpunkt als niedrig einzustufen ist (Evidenzbasis: 1 RCT [17] mit hohem RoB). Es wurde keine Evidenz hinsichtlich der vergleichenden gesundheitsbezogenen Lebensqualität gefunden.

Im Hinblick auf die vergleichende Sicherheit bei ACLR konnte Evidenz mit moderater Stärke gefunden werden, die darauf hinweist, dass allogene Bandersätze weniger sicher sind als autogene Bandersätze. Diese Evidenz, die auf Unterlegenheit der Allografts hinweist, basiert auf dem Endpunkt Transplantatversagen (graft failure). Die Evidenz war jedoch unzureichend für die Evaluation der vergleichenden Sicherheit auf Basis der anderen gewählten wesentlichen Sicherheitsendpunkte (Evidenzbasis: 6 RCTs [15, 17, 19-22] mit hohem RoB).

Posterior cruciate ligament reconstruction (PCLR)

PCLR: Evidenz weist auf vergleichbare Wirksamkeit hin, unzureichende Evidenz zur vergleichenden Sicherheit

Es wurde Evidenz auf sehr niedrigem bis niedrigem Qualitätsniveau gefunden, die – auf Basis des in diesem Assessment gewählten wesentlichen Wirksamkeits-Endpunktes „Funktion, Aktivität und Symptome" – eine vergleichbare Wirksamkeit nahelegt (Evidenzbasis: 2 RCTs [18, 23] mit unklarem bis hohem RoB).

Darüber hinaus wurde Evidenz auf sehr niedrigem Qualitätsniveau gefunden, die darauf hinweist, dass Resultate der KT-Arthrometer Testung (Kniestabilität) bei Verwendung der allogenen Bandersätze im Vergleich zur Verwendung von autogenen Bandersätzen schlechter sind. Ein statistisch signifikanter Unterschied der „side-to-side" Differenzen konnte jedoch lediglich von einer Studie gefunden werden [18]. Die andere eingeschlossene Studie [23] konnte in diesem Zusammenhang keinen statistisch signifikanten Unterschied finden. Keine der eingeschlossenen Studien [18, 23] konnte einen statistisch signifikanten Unterschied bei Endpunkten, die Kniestabilität messen (Lachman Test, Pivot-Shift Test & objektiver IKDC Test), nachweisen. Daher weist diese Evidenz eher auf eine vergleichbare Kniestabilität hin (Stärke: niedrig bis moderat; Evidenzbasis 2 RCTs [18, 23] mit unklarem bis hohem RoB). Hinsichtlich PatientInnenzufriedenheit und gesundheitsbezogener Lebensqualität wurde keine Evidenz gefunden.

Es wurde unzureichende Evidenz zur vergleichenden Sicherheit bei PCLR gefunden (Evidenzbasis: 2 RCTs [18, 23] mit unklarem-hohem RoB).

Revision ACLR

Revisions-ACLR: unzureichende Evidenz

Zur Evaluierung der vergleichenden Wirksamkeit und Sicherheit der allogenen Bandersätze bei Revisions-ACLR wurde eine Beobachtungsstudie eingeschlossen: Die prospektive komparative Kohortenstudie [16] führte eine Regressionsanalyse durch und verglich dabei wesentliche Wirksamkeits- und Sicherheitsendpunkte bei Verwendung von Allografts im Vergleich zu Autografts in einer großen Kohorte (n=1205). Die Studie präsentierte Ergebnisse zu Ungunsten von allogenen Bandersätzen bei einigen Sub-Scales (z. B. bei „sportliche Funktionalität" oder Re-rupturen). In Ermangelung an randomisierten Kontrollstudien ist die Evidenz jedoch unzureichend, um Überlegenheit oder Unterlegenheit der allogenen Bandersätzen im Vergleich zu autogenen Bandersätzen beurteilen zu können (Evidenzbasis: 1 komparative Beobachtungsstudie mit moderatem RoB).

Keine Evidenz: Allografts vs. konservatives Management

Es wurde keine Evidenz gefunden, die allogene Bandersätze mit konservativem Management verglich.

Laufende Studien

7 laufende Studien:

Insgesamt wurden 7 laufende klinische Studien identifiziert, die den Einsatz von Allografts bei Rekonstruktionen des Kreuzbandes untersuchen (ACLR: 3 laufende Studien; PCLR: 1 laufende Studie; Multi-Ligament-Knieverletzung: 1 laufende Studie; Revisionsrekonstruktion: 2 laufende Studien).

Nur 2 RCTs mit geringer Fallzahl

5 laufende Beobachtungsstudien ohne Vergleich

Allerdings sind nur zwei dieser sieben laufenden Studien RCTs, die Allografts entweder mit Autografts (1 Studie) oder mit einer anderen neuen Behandlungsmodalität (Z-lig anteriorer Cructiat-Ligment-Rekonstruktion; 1 laufende Studie) vergleichen. Die Stichprobengröße der RCTs beträgt 40 PatientInnen in einer laufenden Studie (Vergleich: Allograft vs. Autograft) und 60 PatientInnen in einer weiteren laufenden Studie (Vergleich Allograft vs. Z-Ligs). Der Zeitpunkt des voraussichtlichen Abschlusses dieser beiden Studien ist bereits verstrichen (in 2015 und 2014). Darüber hinaus ist kein in diesem Assessment wesentlicher Endpunkt in den laufenden Studien als primärer Endpunkt definiert. Die Studien betrachten insbesondere Endpunkte wie etwa Röntgen, CT-Scan und KT1000. Die restlichen 5 laufenden Studien sind unkontrolliert mit einer maximalen Stichprobengröße von 100 eingeschriebenen PatientInnen.

Es ist daher nicht zu erwarten, dass die Ergebnisse dieser Studien einen wesentlichen Einfluss auf die Wirksamkeit und Sicherheit von Allografts im Vergleich zu Autografts bei Kreuzbandrekonstruktionen haben werden.

Nach Angaben der Hersteller werden derzeit jedoch noch 2 Studien (davon 1 RCT) in Österreich durchgeführt. Die Studienprotokolle sind nicht öffentlich einsehbar und daher kann das Vorliegen der Ergebnisse zeitlich nicht abgeschätzt werden.

Kostenerstattung

Kreuzband-rekonstruktionen im Leistungskatalog, jedoch nicht mittels Allografts

Im österreichischen Leistungskatalog gibt es einen generischen Code für die Rekonstruktion des vorderen und/oder hinteren Kreuzbandes, nicht jedoch einen separaten/spezifischen Code für die Verwendung von allogenen Bandersätzen bei Kreuzbandrekonstruktionen.

Diskussion

Wirksamkeit: vergleichbar bei ACLR & PCLR, unzureichend bei Revisions-ACLR

Sicherheit: weniger sicher bei ACLR (graft failure), sonst unzureichende Evidenz

Die in dieser systematischen Übersichtsarbeit gefundene Evidenz weist darauf hin, dass Allograft bei ACLR gleichermaßen wirksam, jedoch womöglich weniger sicher sein könnte. Die Evidenz legt überdies nahe, dass die Wirksamkeit der Allografts im Vergleich zu Autografts bei PCLR vergleichbar sein könnte, es wurde jedoch keine ausreichende Evidenz für die vergleichende Sicherheit bei PCLR gefunden. Des Weiteren wurde unzureichende Evidenz gefunden, die die Wirksamkeit und Sicherheit der Allografts bei ACLR-Revisionsrekonstruktionen beurteilen könnte. Für die verbleibenden Indikationen (PCLR-Revisionsrekonstruktionen und Banderätze bei mutliligamentären Knieverletzungen) wurden keine wissenschaftlichen Nachweise der komparativen Wirksamkeit oder Sicherheit gefunden.

Limitationen: erhöhtes RoB der RCTs und unvollständige Berichterstattung

Eine wesentliche Einschränkung der Evidenzbasis bestand in Bezug auf das hohe Verzerrungspotenzial der Primärstudien und auf schlechte Berichterstattung der Komplikationen (z. B. wurden Unterschiede häufig nur narrativ berichtet und statistische Tests wurden nicht immer durchgeführt). Wie bei allen Studien, die sich mit ACLR oder PCLR befassen, ist eine weitere wesentliche Einschränkung dieser Arbeit das Fehlen einer möglichen objektiven Messung zahlreicher Endpunkte (z. B. Rotationsstabilität des Kniegelenkes, Funktion usw.) in der Primärforschung.

weitere Forschung wesentlich, um Vor- und Nachteile der Allografts weiter überprüfen zu können

Randomisierte kontrollierte Studien von hoher Qualität und geringem Verzerrungspotential sind zukünftig wesentlich, um eine valide wissenschaftliche Grundlage zu schaffen, die es ermöglicht, den Einsatz von Allografts bei Kreuzbandrekonstruktionen umfassend zu evaluieren.

Empfehlung

Erstattung derzeit nicht empfohlen

Auf Basis der vorliegenden Evidenz wird eine Aufnahme in den Leistungskatalog derzeit nicht empfohlen.

In Ermangelung laufender randomisierter Kontrollstudien, die eine Antwort auf die in dieser Bewertung gewählte Fragestellung geben können, kann derzeit kein genauer Zeitpunkt einer Re-Evaluierung empfohlen werden.

Eine Re-Evaluierung wird empfohlen, wenn Ergebnisse neuer, randomisierter Kontrollstudien vorliegen.

1 Scope

1.1 PICO question

PIKO-Frage

Is allograft cruciate ligament reconstruction in comparison to other techniques of cruciate ligament reconstruction or conservative management in patients undergoing anterior cruciate ligament reconstruction (ACLR), posterior cruciate ligament reconstruction (PCLR), revision ACLR/PCLR or cruciate ligament reconstruction in multi-ligamentous injuries of the knee, more effective and safe concerning the outcomes listed in Table 1-1?

1.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Inclusion criteria for relevant studies are summarised in Table 1-1.

Table 1-1: Inclusion criteria

Population	Patients who are – as a result of **ruptures in the anterior and/or posterior cruciate ligament,** (incl. re-ruptures) or **multi-ligament knee injuries –** candidates for one of the following ligament reconstructions: • Anterior Cruciate Ligament Reconstruction (ACLR) • Posterior Cruciate Ligament Reconstruction (PCLR) • Revision ACLR • Revision PCLR • Cruciate ligament reconstructions in mutli-ligament knee injuries International classification of diseases (ICD)-10-CM code: M23.60, M23.61, M23.62, S83.53, S83.54 **MeSH terms**: "Anterior Cruciate Ligament Injuries" [C26.558.554.213]; "Posterior Cruciate Ligament/injuries" [A02.513.514.600, A02.835.583.512.600, A10.165.669.514.600]; "Knee Injuries" [C26.558.554]
Intervention	• Allograft cruciate ligament reconstruction • **Product names**: not applicable • **MeSH terms**: ("Allografts" [A01.941.500]) AND/OR ("Anterior Cruciate Ligament Reconstruction" [E04.555.110.026, E04.680.101.026] OR "Posterior Cruciate Ligament Reconstruction" [E02.718.688, E04.555.110.557, E04.680.101.557])
Control	• Other techniques of cruciate ligament reconstruction (autograft, synthetic graft, etc.) • Conservative management **Rationale**: Both other types of cruciate ligament reconstruction and conservative management were set as control interventions since surgery may not always be required [25].

Outcomes	
Efficacy	Relevant efficacy outcomes include (crucial outcomes are highlighted in bold): • **Patient-reported function, activity level and symptoms** measured using a validated instrument (e.g., Lysholm score, Tegner score, IKDC scores) • Clinical knee stability measured using a validated instrument (e.g., KT-1000/2000 arthrometer, the Lachman test or Pivot shift test) • Health-related Quality of Life measured using a validated instrument • Patient satisfaction measured using a validated instrument **Rationale:** Appropriate clinical outcomes have been informed by one identified guideline on the management of ACL injuries [25], a meta-analysis [26], and the EUnetHTA guidelines [27].
Safety	Relevant safety outcomes include (crucial outcomes are highlighted in bold): • **Graft failure** • **Re-ruptures, re-operations and revisions** • **Complications** • Procedure-related mortality **Rationale:** Appropriate clinical outcomes have been informed by one identified guideline on the management of ACL injuries [25] and a meta-analysis [26].
Study design	
Efficacy	**ACLR**: Randomised controlled trials. If more than 10 RCTs identified, restriction to RCTs with mean FU of 5 years and more than 50 patients. **PCLR:** Randomised controlled trials. If more than 10 RCTs identified, restriction to RCTs with mean FU of 5 years and more than 50 patients. For **revision ACLR/PCLR** or ligament reconstructions in **multi-ligament knee injury**: Randomised controlled trials, if no RCTs available: prospective comparative studies.
Safety	**ACLR:** Randomised controlled trials. If more than 10 RCTs identified, restriction to RCTs with mean FU of 5 years and more than 50 patients. **PCLR:** Randomised controlled trials. If more than 10 RCTs identified, restriction to RCTs with mean FU of 5 years and more than 50 patients. For **revision ACLR/PCLR** or ligament reconstructions in **multi-ligament knee injury**: Randomised controlled trials, if no RCTs available: prospective (comparative) studies.

2 Methods

The study was undertaken in accordance with the PRISMA statement [28, 29].

2.1 Research questions

Description of the technology	
Element ID	**Research question**
B0001	What is the technology and the comparator(s)?
A0020	For which indications has the technology received marketing authorisation or CE marking?
B0002	What is the claimed benefit of the technology in relation to the comparators?
B0003	What is the phase of development and implementation of the technology and the comparator(s)?
B0004	Who administers the technology and the comparators and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use the technology and the comparator(s)?
B0009	What supplies are needed to use the technology and the comparator(s)?
A0021	What is the reimbursement status of the technology?

Health problem and current use	
Element ID	**Research question**
A0001	For which health conditions, and for what purposes is the technology used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for the disease or health condition?
A0004	What is the natural course of the disease or health condition?
A0005	What is the burden of disease for the patients with the disease or health condition?
A0006	What are the consequences of the disease or health condition for the society?
A0024	How is the disease or health condition currently diagnosed according to published guidelines and in practice?
A0025	How is the disease or health condition currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much are the technologies utilised?

Clinical effectiveness	
Element ID	**Research question**
D0001	What is the expected beneficial effect of the technology on mortality?
D0003	What is the effect of the technology on the mortality due to causes other than the target disease?
D0005	How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition?
D0006	How does the technology affect progression (or recurrence) of the disease or health condition?

Clinical effectiveness	
Element ID	**Research question**
D0011	What is the effect of the technology on patients' body functions?
D0016	How does the use of technology affect activities of daily living?
D0012	What is the effect of the technology on generic health-related quality of life?
D0013	What is the effect of the technology on disease-specific quality of life?
D0017	Was the use of the technology worthwhile?

Safety	
Element ID	**Research question**
C0008	How safe is the technology in comparison to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying the technology?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of the technology?
C0007	Are the technology and comparator(s) associated with user-dependent harms?
B0010	What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator?

2.2 Sources

Systematische Literatursuche und gezielte Handsuche

Quellen:
Leitlinien mittels Handsuche,
Deximed
UpToDate
Handsuche in PubMed

Description of the technology

- Deximed (https://deximed.de/intro)
- UpToDate (https://www.uptodate.com/home)
- Clinical practice guidelines identified by hand searching databases (Guidelines International Network)
- Hand search in PubMed, and the websites of the manufacturer
- Background publications identified in database search: see Section 2.3

Health problem and current use

- Deximed (https://deximed.de/intro)
- UpToDate (https://www.uptodate.com/home)
- Background publications identified in database search: see Section 2.3
- Documentation provided by the manufacturer

For the domains of clinical effectiveness and safety, a systematic literature search and hand search, described in detail in the following chapter (see Section 2.3), were conducted.

2.3 Systematic literature search

systematische Literatursuche in 4 Datenbanken

The systematic literature search was conducted on the 18th and 19th of December 2018 in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- CRD (DARE, NHS-EED, HTA)

The systematic search was limited to clinical trials and to articles published in English or German. No further filters applied. After deduplication, a total of 492 citations were included. The specific search strategy employed can be found in the Appendix.

Suche in Referenzlisten rezenter relevanter systematischer Übersichtsarbeiten

Before the systematic search was conducted, 7 systematic reviews/meta-analyses [26, 30-35] were identified through a hand search in PubMed. The reference lists of these publications were hand-searched to identify relevant randomised controlled trials, resulting in 13 relevant hits. The results of the hand search assisted and strengthened the systematic search: all of the potentially relevant hits were also included in the records identified through the systematic search.

insgesamt 492 Publikationen identifiziert, davon 9 Studien eingeschlossen

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on the 17th of January 2019, resulting in 17 potential relevant hits.

No additional hits were found through hand search, leading to a result of 492 identified publications overall.

2.4 Flow chart of study selection

Literaturauswahl

Overall, 492 hits were identified. The abstracts were screened by two independent researchers (GG, SGG), and the full texts were screened by GG and CdV. In case of disagreement, a third researcher (SGG) was involved to solve the differences. The selection process is displayed in Figure 2-1.

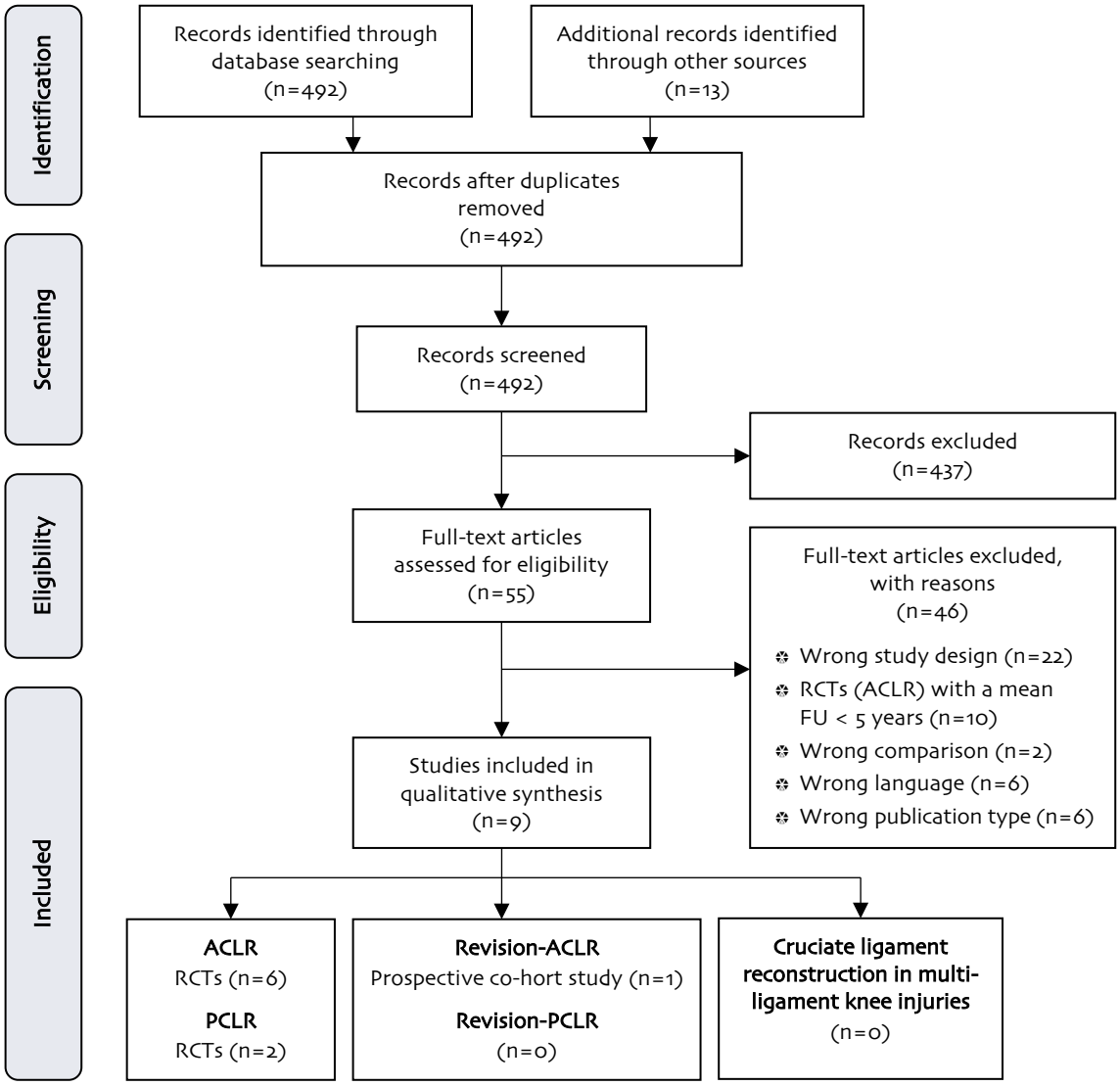

Figure 2-1: Flow chart of study selection (PRISMA Flow Diagram)[1]

[1] More than 10 RCTs were identified for ACLR. Therefore, the stricter inclusion criteria applied: min. mean FU of 5 years and at least 50 enrolled patients. No RCT, or other, at least prospective studies were identified for cruciate ligament reconstructions in patients with multi-ligament knee injuries.

2.5 Analysis

Datenextraktion und Kontrolle von 2 WissenschaftlerInnen

Relevant data from the eligible studies were systematically extracted into data extraction tables. The single-data extraction method with verification by another researcher was used: One researcher (GG) extracted the data, and one further researcher (CdV) controlled the extracted data.

Bewertung Studienqualität und Bias-Risiko durch 2 WissenschaftlerInnen mittels entsprechender Tools

Two independent researchers (GG, CdV) systematically assessed the quality of the evidence. The risk of bias assessment of the included studies was conducted using adequate tools: the Cochrane Risk of Bias Tool [12] was utilised for randomised controlled studies, while the Newcastle-Ottawa Scale (NOS) was applied for assessing the risk of bias for cohort studies [13].

2.6 Synthesis

Evidenzsynthese mittels GRADE

The questions were answered in plain text format with reference to GRADE evidence tables included in the Appendix, and the results were summarised in Table 7-1, Table 7-2, and Table 7-3.

No inferential statistical analysis was conducted. A qualitative evidence synthesis was chosen. Based on the data extraction tables, data on each selected outcome category were synthesised across studies according to GRADE (Grading of Recommendations, Assessment, Development and Evaluation) [14].

3 Description and technical characteristics of technology

Features of the technology and comparators

B0001 – What is allograft cruciate ligament reconstruction, autograft cruciate ligament reconstruction and conservative management?

Allograft Cruciate Ligament Reconstruction

Kreuzbänder bieten Unterstützung und Stabilität der Knie

Cruciate ligaments belong to structures providing support and stability in the knee. The anterior cruciate ligament (ACL) and posterior cruciate ligament (PCL) provide stability for both anterior and posterior movements, as well as with flexion and extension. Furthermore, there are medial and lateral collateral ligaments that provide support in their respective planes [36].

vordere & hintere Kreuzbandrisse können konservativ oder operativ behandelt werden

ACL and/or PCL ruptures are common sports injuries and may require surgical treatment. The reconstruction is generally performed with arthroscopy using a graft for the replacement of the ruptured ligament. Currently, there is a debate regarding graft selection among orthopaedic surgeons. The source of the grafts can be the patient's body (autologous) or from a donor body (allogenic) [6-8]

viele Transplantattypen, kein Konsens

Allografts are reconstructive natural materials. They are processed cadaveric fascia lata or acellular dermal matrices of human donors [9]. Allografts are taken from a cadaver Achilles tendon, a semitendinosus, a gracilis, or a posterior tibialis tendon [10].

Comparators of allograft cruciate ligament reconstruction

Komparatoren: Primär: Autografts & konservatives Management

Due to the existing controversy regarding the appropriate management of cruciate ligament tears [7, 8], there is also a broad variety of different comparators. In this assessment, the following comparators were used:

- Autograft cruciate ligament reconstruction and
- Conservative management.

sekundärer: synthetische Transplantate bzw. alle anderen Transplantatarten

Within **surgery**, the following graft types are common when using autografts for cruciate ligament reconstruction [10]:

- patellar tendon autograft,
- hamstring tendon autograft, or
- quadriceps tendon autograft.

In the 1970s and 1980s, the use of artificial ligaments (e.g., Gore-Tex and Proplast) in cruciate ligament reconstructions was promoted. However, the experience with these non-tissue substitutes was poor, leading surgeons to choose other, natural, graft materials [37].

In the past decades, a newer synthetic graft choice that can be used for cruciate ligament reconstructions was developed – the Ligament Augmentation and Reconstruction System (LARS). According to an advice document from the National Institute for Health and Care Excellence (NICE), however, LARS should only be used in cruciate ligament procedures after non-synthetic alternatives (e.g., autograft and allograft) have been considered as a possible treatment option by the clinician and the patient [38].

Nonsurgical treatment (conservative management) consists of progressive physiotherapy and rehabilitation. The aim of conservative management is to restore the knee to a condition close to its pre-injury state and provide the patient with the necessary knowledge on how to prevent instability. Supplementarily, a hinged knee brace may also be used [10].

Synthetic graft types were only set as a secondary comparator of less interest for the purpose of this assessment.

Conservative management vs. surgery

Konservatives Management vs. operative Eingriff

vorderer Kreuzbandriss: je nach Bedürfnisse der PatientInnen

For **ACL** tears, a conservative or surgical treatment may be used depending on the severity of the tear and the preferences of the respective patient [2].

In ACL tears, conservative management may be indicated in patients with:

- low stability,
- low level of activity,
- existing arhthrosis, and/or
- a general contra-indication for an operation [2].

Faktoren: Aktivitätslevel, Stabilität, körperliche Anstrengung im Beruf, etc.

The age of the patient may be a further indicator for the decision whether surgery should be indicated.

Bei hinterem Kreuzbandriss: Unstimmigkeiten bzgl. primärer Behandlungsmodalität

The surgical reconstruction of the ACL may be indicated if patients [2]:

- are athletes,
- have a physically demanding occupation,
- have high demands of the knee function in the future,
- suffer simultaneously from repairable meniscal injury or another ligament injury,
- suffer from a complex capsule ligament injury, and/or
- have chronic instability.

Bei multi-ligamentären Knieverletzungen: operativer Eingriff oft unmittelbar nach Unfall

However, and lastly, it must be evaluated individually whether conservative management or surgery fits most to the needs of the patient [2]. In this context and contrary to these potential indications for an ACLR, a randomised controlled trial [39] showed that in young, active adults with acute ACL tears, a strategy of rehabilitation plus early ACLR was not superior to a strategy of rehabilitation plus optional delayed ACLR. In addition, the latter strategy substantially reduced the frequency of surgical reconstructions.

The success rate of nonsurgical treatment differs significantly for ACL versus PCL ruptures. For **PCL** tears, controversy exists regarding the appropriate management. Based on limited evidence, it appears that good subjective and functional results can be achieved when using a non-operative management. Yet, it is not clear, whether conservative treatment or a surgical cruciate ligament reconstruction is the best approach to treatment for PCL ruptures [8].

Contrary to single ligament tears, surgery is often performed soon after the injury in patients with **multi-ligamentous knee injuries** [40].

A0020 – For which indications has allograft cruciate ligament reconstruction received marketing authorisation or CE marking?

Kein Medizinprodukt, daher kein CE

Human allografts for the use of cruciate ligament reconstruction are not classified as medical devices. Therefore, they are not subject to CE marking.

Gewebe- und Organspenden in EU über EUTCD geregelt

Human tissue donation is regulated by the European Union under the EU Tissue and Cells Directive (EUTCD) that was adopted in 2004 (Directive 2004/23/EC). The EUTCD outlines the legal framework for the supply of human tissues and cells within the EU, aiming at ensuring safety and quality standards of the biological samples [41, 42]. Therefore, suppliers of tissues are able to distribute allografts within the EU if they have the licence to do so.

gesetzliche Verankerung in Ö über Bundesgesetz

The Austrian legal regulation on tissue and organ donation is positioned in the "Bundesgesetz über die Transplantation von menschlichen Organen" (Organtransplantationsgesetz – OTPG) [43].

B0002 – What is the claimed benefit of allograft cruciate ligament reconstruction in relation to autograft cruciate ligament reconstruction and conservative treatment?

Vorteile von Allografts: keine Entnahme-morbidität, kürzere Behandlungszeit, etc.

In surgery, the use of allografts as a reconstructive material eliminates donor site morbidity associated with autologous fascia harvest [9, 11]. More precisely, pain – caused by obtaining the graft from the patient – and the surgery time may be reduced. The latter may also lead to smaller incisions [10]. Quick recovery of muscle strength and no increased risk of patellar fracture may be described as further advantages of allografts [11].

In addition, the clinical expert who reviewed this report stated that not only pain is reduced using allografts, but also potential weakness of the joint's range of motion due to injured tendons of the ipsi- or contralateral knee.

Nachteile: langsamere Eingliederung, immunologische Reaktionen, mögliche Infektionen, Kosten, etc.

Disadvantages of allografts may include potential disease transmission, immunologic reactions, slower remodelling and integration, as well as costs [7]. Allografts may bear a risk of disease transmission, e.g., HIV and Hepatitis C [10, 11]. Yet, the risk of infection when using an allograft is considered as extremely low [7].

Furthermore, and according to the submitting hospital, allografts are especially useful when surgery using autografts is not feasible anymore due to re-ruptures or multi-ligament knee injuries.

B0003 – What is the phase of development and implementation of allograft and autograft cruciate ligament reconstruction?

Kreuzband-rekonstruktionen nicht neu

Cruciate ligament reconstruction is, technically speaking, not a novel procedure and has been conducted since the early 20th century. However, changes in the used surgical procedure were notable. When looking at graft types, for instance, autologous fascia lata, the hamstring graft, patellar tendon grafts were introduced within the first half of the 20th century, with documented procedures using those graft types in 1912, 1934, and 1935, respectively. Later in the same century, the surgical technique using bone-patellar tendon-bone grafts (BPTB) was described in a publication in 1963. In the 1970s and 1980s, experiments with synthetic graft types followed [44]. However, the experience with these non-tissue substitutes was poor [37], with complications such as synovitis occurring in patients having undergone ACL reconstruction using synthetic graft types [44].

Rekonstruktionen mittels Allograft seit den 1980er Jahren beforscht und ist heute eine mögliche Alternative zu Autografts

In the 1980s, increasing interest in using **allografts for cruciate ligament reconstruction** was notable [44]. Since then, allografts have been the subject of research and are now considered to be a viable alternative to autografts for reconstructing a cruciate ligament [7].

Besides changes in graft type selection, there was also notable progress when looking at the arthroscopic procedure as such [45].

Administration, Investments, personnel and tools required to use the technology and the comparator(s)

B0004 – Who administers allograft and autograft cruciate ligament reconstruction and in what context and level of care are they provided?

B0008 – What kind of special premises are needed to use allograft and autograft cruciate ligament reconstruction?

B0009 – What supplies are needed to use allograft and autograft cruciate ligament reconstruction?

Durchführung: Eingriff durch orthopädische ChirurgInnen; Assistenz durch qualifiziertes Personal

Allograft cruciate ligament reconstruction is performed by an orthopaedic surgeon and assisted by qualified personnel. In addition, required structural conditions further include a surgery room and an anaesthesia work station (Information provided by the submitting hospitals).

In Europe, LifeNetHealth® [46] and Arthrex® [47] provide allografts to be used for ACLR or PCLR. Different products that may vary, inter alia, according to graft type used and sterilisation method are offered.

Regulatory & reimbursement status

A0021 – What is the reimbursement status of allograft cruciate ligament reconstruction?

Kreuzbandrekonstruktionen im Leistungskatalog, jedoch nicht mittels Allografts

A generic code for the reconstruction of the anterior and/or posterior cruciate ligament is already included in the Austrian hospital benefit catalogue[2] [24], but not a separate/specific code for the use of allografts for reconstruction/replenishment (of the cruciate ligament). In addition, a similar benefit is included in this catalogue: defect replenishment is reimbursed using homologous bone or substitute materials (PA040) [24]. According to the information of the submitting hospitals, this code is not applicable in this context.

[2] „NF050 Rekonstruktion des vorderen Kreuzbandes – arthroskopisch (LE=je Seite)“, „NF060 Rekonstruktion des hinteren Kreuzbandes – arthroskopisch (LE=je Seite)“ [24].

4 Health problem and current use

Overview of the disease or health condition

A0001 – For which health conditions, and for what purposes is allograft cruciate ligament reconstruction used?

A0002 – What is the disease or health condition in the scope of this assessment?

vordere & hintere Kreuzbänder wichtig für Stabilität des Kniegelenks

The anterior cruciate ligament (ACL) and posterior cruciate ligament (PCL) are crucial structures for providing stability in the knee joint during functional and sporting activities. The main role of the ACL is to provide restraint against the forward translation of the tibia on the femur, and secondary constraint against tibial rotation and valgus and varus stress [1]. The PCL primarily provides constraint against the posterior translation of the tibia in relation to the femur, and secondary constraint against external rotation, and protects the knee from varus and valgus stresses in extension.

Kreuzbandrisse häufig als Folge von (Sport-)Verletzungen

ACL injuries occur as a result of high energy trauma or low energy contact or non-contact sports injuries. Non-contact injuries such as sudden deceleration with cutting or change in direction, pivoting or landing from a jump account for 72% [48] of ACL injuries, with most of the injuries occurring with the knee in valgus, almost fully extended, and with internal rotation of the tibia.

Most PCL injuries occur as a result of high energy trauma such as motor traffic accidents [49-51], where a posterior shearing force is applied with the knee in a flexed position. It usually manifests as multi-ligament injuries [5], including the posterior lateral corner, ACL, and the medial collateral ligaments. Isolated PCL injuries are more common with low energy, sporting activities where the patient falls on a flexed knee with the foot in plantar flexion or a direct force on the front of the knee [8]. The PCL and posterior capsule can also be injured during varus or valgus stress on the knee or with hyperextension or hyperflexion positions with or without a posterior force.

Ligament injuries can be surgically or conservatively managed [7]. The decision to proceed with surgery is multi-factorial and should consider the patients' level of activity, functional demands on the knee, and any other associated meniscal or ligament injuries. Allograft or autograft ligament reconstructions are performed arthroscopically to repair the damaged ligaments and restore stability of the knee joint. Autografts are usually harvested from the hamstring (semitendinosis and gracilis) and patellar tendon or quadriceps tendons [7]. Allografts are typically from the Achilles tendon or patellar tendon [7], but could also be from other sources. Currently, there is controversy about the superiority/inferiority of choosing one graft over another [52].

A0003 – What are the known risk factors for anterior or posterior cruciate ligament rupture?

Risikofaktoren: Vorgeschichte einer Kreuzbandverletzung, biomechanische Faktoren, physisches Trauma bzw. körperliche Verletzung, etc.

A previous history of an ACL injury is a strong indicator for a non-contact ACL injury [53]. 70% of ACL injuries occur due to non-contact sports injuries [48, 54] and may be due to the contribution of environmental, anatomical, hormonal, neuromuscular, and biomechanical factors. Neuromuscular factors include hamstring and core muscle weakness during pivoting, landing and deceleration activities, with a higher risk of ACL injuries in female athletes [55-57].

Biomechanical factors such as dynamic knee valgus, hip internal rotation and adduction, tibial rotation and anterior translation, and ankle eversion also increase the risk of ACL injuries, in particular for female athletes [58, 59].

Gender-related differences are therefore risk factors, with females two to eight times more likely than males participating in the same sport to sustain non-contact ACL injuries [54, 60].

Trauma and high energy injuries are risk factors for multi-ligament and PCL injuries. It may also be associated with dislocation, vascular injuries, noticeable instability, and loss of range of knee motion [8].

There is a 6-25% ipsilateral re-rupture risk after reconstruction and a similar contralateral re-rupture risk of 2-25% [53].

A0004 What is the natural course of anterior or posterior cruciate ligament rupture?

The natural course of anterior or posterior cruciate ligament ruptures is explained in A0005 and A0006.

Effects of the disease or health condition on the individual and society

A0005 – What is the burden of disease for patients with anterior or posterior cruciate ligament rupture?

A0006 – What are the consequences of anterior or posterior cruciate ligament rupture for the society?

Bei Kreuzbandrissen sind Sport und Aktivitäten oft nicht möglich und Risiko der Arthrose wird erhöht

The short-term impact for younger, active patients who sustained a knee ligament injury is that they are often unable to return to sports or activities that place a high demand on the knee. ACL deficiency is associated with an increased risk of meniscal injuries, articular cartilage and chronic knee pain [7]. ACL deficiency is also associated with a higher long-term risk of the incidence of osteoarthritis (OA) [26, 60-62]. Concurrent meniscal injuries with ACL injuries are risk factors for OA after ACL injury, with a 3.54-fold increase in the incidence of OA post ACL injury [63].

It is uncertain whether the absent ACL and subsequent knee joint instability or the initial extent and degree of the joint damage during the ACL injury increase the risk of developing OA. It is most likely a combination of factors, including the severity of the initial ACL injury, the extent of the meniscal injury, the biomechanics of the knee, and the activity level of the patient [64]. The prevalence of knee OA was estimated between 0-13% in patients with isolated ACL injuries [65], and between 28-41% in patients with an ACL rupture and other injuries such as meniscal injuries [66]. Some studies suggest the occurrence of OA regardless of a surgical or conservative treatment approach after ligament injuries, and others found a higher incidence of OA in

the injured, unrepaired knee [7]. The short time frame of reported studies and the inability to account for functional levels after the injury might account for the conflicting results [7].

There is more uncertainty about the long-term complications after an isolated PCL injury. On the one hand, there is an accelerated risk of OA post PCL injury reported, justifying a PCL surgical repair. On the other hand, OA after a PCL repair is similar or worse compared to a conservative PCL rehabilitation, questioning the benefit of a repair [7].

The global burden of disease indicated hip and knee OA as the 11th highest contributor to global disability [67]. Health services might face an increase in demand of care sought in relation to hip and knee OA as a result of the ageing population and obesity [67].

Current clinical management of the disease or health condition

A0024 – How is anterior or posterior cruciate ligament rupture currently diagnosed according to published guidelines and in practice?

Kreuzbandrisse werden mittels MRI diagnostiziert

An ACL rupture is best diagnosed via Magnetic Resonance Imaging (MRI) [7]. Information in regard to any other possible ligament, meniscal and articular cartilage injuries may also be diagnosed with an MRI scan. Diagnostic studies, particular arthroscopy as the standard of care, report a sensitivity of 92 to 100% and a specificity of 95 to 100% for ACL diagnoses [68].

The examination should evaluate the timing and mechanism of the injury, any joint swelling, instability and functional inability, such as walking and descending stairs [7, 26]. This is followed by a lower limb, physical, musculoskeletal examination in comparison to the non-injured knee by a healthcare professional.

The MRI scan demonstrates an almost 100% sensitivity and specificity for accurately diagnosing an acute PCL injury [8] compared to arthroscopy as standard care. A provisional acute PCL injury can be diagnosed according to the mechanism of the injury and a physical examination using the posterior drawer test, the posterior sag sign, and the quadriceps active test. Confirmation of the diagnosis is with an MRI scan or arthroscopy. The latter (arthroscopy) can also be used for the reconstruction of a cruciate ligament as such. In chronic PCL injuries, MRI and arthroscopy might not accurately diagnose the injury, as the PCL rupture might heal over time and the PCL view is often obscured by the ACL [8].

A0025 – How are anterior or posterior cruciate ligament ruptures currently managed according to published guidelines and in practice?

1 Leitlinie zu Behandlung von vorderem Kreuzband identifiziert: hinsichtlich Auswahl eines Transplantats bei ACLR empfiehlt die Leitlinie, entweder Autografts oder Allografts zu verwenden

Only one relevant clinical practice guideline (CPG) was identified. The CPG was published in 2015 by the American Academy of Orthopaedic Surgeons (AAOS) and focused on the management of ACL injuries [25]. The AAOS recommends, inter alia, the following regarding the adequate treatment of ACL injuries:

- moderate evidence supporting surgical reconstruction in active young adult patients,
- limited evidence in skeletally immature patients, with ACL tears,
- limited evidence supporting conservative management (non-surgical therapy) for less active patients with less laxity,

- moderate evidence supporting neuromuscular training programs to reduce the risk of further ACL injuries.

According to information from the consulted clinical expert, the appropriateness of early surgical reconstruction in active young adult patients may be questioned. In this context, he referred to a randomised controlled trial [39] that showed that in young, active adults with acute ACL tears, a strategy of rehabilitation plus early ACLR was not superior to a strategy of rehabilitation plus optional delayed ACL reconstruction. In addition, the latter strategy substantially reduced the frequency of surgical reconstructions. This shows that controversy may exist regarding the appropriate management of ACL tears.

Regarding graft type selection, the AAOS [25] suggests that there is strong evidence to either use autografts or allografts in patients undergoing ACL reconstruction. The AAOS states that allograft and autograft ACL reconstruction leads to similar measured outcomes based on their systematic review conducted in 2013.

vordere & hintere Kreuzbandrisse werden konservativ oder operativ behandelt

In practice, acute ACL injuries are managed with protection, rest, ice, compression, and elevation. Ruptures may be managed conservatively or surgically, depending on the extent of the injury, patient activity levels, patient characteristics, and available resources [7]. Surgical management should take the patients' functional level, physical demands placed on the knee, and other potential injuries to the meniscus or other ligaments into consideration [7]. This option is mainly exercised by the active and younger patients or the high-level elite athletes [7] who participate in sports which require cutting, jumping, pivoting, and rapid deceleration. A significant subjective history of instability, where the knee gives way while descending stairs or during other single leg activities, would also justify a surgical management approach [7].

Acute PCL injuries are referred for immediate surgical opinion from an experienced orthopaedic surgeon if a multi-ligament injury is suspected after a traumatic incident or there is severe instability of the knee. This is due to the higher incidence of morbidity for multi-ligament injuries compared to isolated PCL injuries [8].

If an isolated PCL injury is diagnosed and no immediate referral is necessary, the standard of care should include the management of pain and disability with walking aids and braces according to the PRICE-M (protection, rest, ice, compression, elevation, and medication) principle and conservative rehabilitation [8].

Target population

A0007 – What is the target population in this assessment?

A0023 – How many people belong to the target population?

A0011 – How much are allograft cruciate ligament reconstructions utilised?

breite Zielgruppe

The target population in this assessment includes all patients who are candidates for anterior cruciate ligament reconstruction (ACLR), posterior cruciate ligament reconstruction (PCLR), revision ACLR, revision PCLR, or cruciate ligament reconstructions in patients with multi-ligament knee injuries.

Inzidenz vorderer Kreuzbandriss: 31-37 in 100.000

According to information retrieved from DexiMed [2], 31-37 per 100,000 ACL ruptures occur annually in Germany. According to data from the US, nearly 250,000 ACL ruptures occur annually [58, 69], and there is an annual inci-

dence in the general population of 1 in 3,500 [3]. PCL injuries are less common compared to ACL injuries – approximately 1 to 44 percent of all knee injuries are PCL injuries based on data from the United States [4, 5]. However, we did not identify relevant data on the incidence of PCL injuries by hand-searching. Similarly, we were unable to find any relevant incidence data on ACL or PCL re-ruptures and mutli-ligament knee injuries.

The reader must be aware that the presented incidence data do not necessarily reflect the actual target population, given that a reconstruction is not always necessary in cruciate ligament ruptures [2].

ca. 900-920 jährliche Behandlungen in Ö

In Austria, the estimated overall annual utilisation of allograft cruciate ligament reconstructions is approximately 900-920 according to information retrieved from the submission files of the submitting hospitals.

5 Clinical effectiveness

5.1 Outcomes

The following outcome was defined as crucial to derive a recommendation:

- **Patient-reported function, activity level and symptoms**

1 wesentlicher Endpunkt:

Funktion, Aktivitätslevel und Symptome

Postoperative **differences of patient-reported function, activity level and symptoms** between treatment groups were defined to be crucial to formulate a recommendation, since they are shown to be patient-centred outcomes indicating a success after anterior cruciate ligament reconstruction [70]. The following tools can be used for this crucial outcome:

- **Lysholm score**: Scale from 0-100; higher score indicates fewer symptoms/disability [71].
- **Tegner score:** Scale from 0-10; higher score indicates better activity level [72].
- **Cincinnati Knee score:** Scale from 0-100; higher score indicates better knee function [73] (score is calculated through a sum of questions in the area of pain, swelling, function, as well as activity level).
- **Single Assessment Numeric Evaluation (SANE):** Scale from 0-100; higher score indicates better function/less disability[3] [74].
- **International Knee Documentation Committee (IKDC) Subjective Knee Evaluation Form:** Scale from 0-100: higher score indicates fewer symptoms/disability – a score of 100 means no limitation with daily sporting activities and the absence of symptoms [71].
- **Knee Injury and Osteoarthritis Outcome Score (KOOS):** This composite measure consists of 5 subscales (pain, symptoms, activities of daily living, sport and recreational activities, and knee-related quality of life) scored seperately on a scale from 0-100 (0 means extreme problems and 100 no problems) [71].
- **Marx activity scale:** Scale from 0 (low activity) to 16 (highest activity) [75].

The scores of these outcomes were extracted pre- and postoperatively. However, the evidence synthesis is based on postoperative differences between patients receiving allografts and autografts because the studies only reported on the differences of the postoperative scores between groups.

Three further outcomes were judged important, but not crucial, to formulating a recommendation:

3 zusätzliche, wichtige Endpunkte: Kniestabilität, Lebensqualität, PatientInnenzufriedenheit

- Clinical knee stability
- Quality of Life
- Patient satisfaction

[3] SANE is a single-question instrument that elaborates a score by asking the patient the following question solely: "On a scale from zero to 100, how would you rate your knee today (100 being normal)?" [74]

Clinical knee stability can be measured using different tests. The **Lachman** and the **Pivot shift tests** are used to measure the knee stability of patients after a cruciate ligament injury and reconstruction. Usually, those tests use 4 grades hereby [22]:

- grade 0 (Lachman: -1 to 2 mm, Pivot shift: equal),
- grade 1 (Lachman: 3-5mm, Pivot shift: glide),
- grade 2 (Lachman: 6-10mm, Pivot shift: clunk), and
- grade 3 (Lachman: >10mm, Pivot shift: gross).

In this assessment, the grades have been dichotomised in intact (grade 0, grade I) and torn (grade II-III) [76]. The number of patients with intact knees was hereby extracted and used for evidence synthesis.

Similarly, the **objective IKDC evaluation** consists of 4 grades that are used to assess the stability of a patient's knee: normal (<3mm), nearly normal (3 to 5 mm), abnormal (6 to 10 mm), severely abnormal (>10mm) [22]. In this assessment, this sub-outcome was also dichotomised in normal stability (i.e., normal and nearly normal objective IKDC score), and abnormal (i.e., abnormal and severely abnormal objective IKDC score). The number of patients with normal knee stability was extracted and used for evidence synthesis.

In addition, **there are certain instrumented tests** that measure the outcome of clinical knee stability. The **KT arthrometer** is used to measure the side-to-side difference. A lower side-to-side difference may indicate less knee laxity (and more stability), and may be a factor indicating the superiority of one graft over the other.

The results of the objective outcomes (i.e., Lachman test, Pivot shift test, or KT arthrometer results, or objective IKDC evaluation) were only extracted postoperatively.

The tools for measuring knee stability (e.g., using the Lachman or Pivot shift test) are discussed controversially in the literature for being subjective. A recent consensus document stated that functional tests and laxity measures were not identified as important measures of successful outcome 1 or 2 years after ACL injury or reconstruction [70]. These outcomes were only considered as important, but not crucial, to formulating a recommendation.

According to information from the clinical expert from Graz, the rolimeter [77] is used in Austrian clinical practice and may be used for research to measure rotational instability. Yet, none of the studies used this instrument.

Patient satisfaction and Quality of Life are further patient-relevant outcomes that were defined as important, but not crucial, because this outcome appears to be only indirectly affected by the different graft type due to the functional and activity level.

5.2 Included studies

In total, 9 clinical studies met the inclusion criteria for the evaluation of the comparative effectiveness of allografts to be used for cruciate ligament reconstruction. All of the studies compared allografts to autografts in cruciate ligament reconstructions. Six RCTs [15, 17, 19-22] were included for anterior cruciate ligament reconstruction (ACLR), while 2 further RCTs were included for posterior cruciate ligament reconstruction (PCLR) [18, 23]. 1 further prospective comparative cohort study [16] was identified for the indication revision ACLR.

9 Studien eingeschlossen
ACLR: 6 RCTs
PCLR: 2 RCTs
Revisions-ACLR: 1 Kohortenstudie

Of the included studies, 2 were conducted in the United States [15, 16], 6 studies were conducted in China [17-22], and 1 further study was conducted in Taiwan [23].

No study comparing allografts to conservative management in either of the indications selected in this assessment was identified.

The reader is referred to Table A-1, Table A-2, Table A-3 for more information on study characteristics and results of included studies, and to the evidence profiles according to GRADE (see Table A-7, Table A-8, and Table A-9).

5.3 Results

5.3.1 Use of allografts in anterior cruciate ligament reconstruction

Study characteristics

For **ACLR**, 6 studies met the inclusion criteria [15, 17, 19-22]. All of the studies compared allograft to autograft ACLR in patients with ruptured ACL. However, there were differences regarding graft type and procedure, e.g., whether a graft was fresh-frozen, irradiated or whether bone-patellar bone tendon-bone, tibialis anterior or posterior or hamstring tendons were used.

ACLR: 6 RCTs

Of the included studies, 2 of them [19, 22] used allografts that were irradiated, while the remaining studies [15, 17, 20, 21] did not use irradiation for the purpose of disinfecting the allografts. The source of graft differed between studies (e.g., hamstring tendons, bone-patellar tendons).

Unterschiede in Transplantatart und Prozedere

Overall, the number of patients at the time of randomisation across studies resulted in 794 patients with an ACL deficiency that needed ACLR. Sample sizes at time of randomisation ranged from 99 patients to 208 patients. Of all enrolled patients across studies, 34 patients received hybrid grafts (a combination of allografts and autografts), and a further 69 patients were lost to follow-up. One study [15] did not clearly mention the number of patients included, as one patient underwent bilateral, simultaneous ACL reconstructions using an autograft on one side and an allograft on the other side; the loss to follow-up was not clearly stated; and the results refer to knees and not patients [15]. Therefore, we identified 352 patients who received allografts and 340 patients who received autografts (n=692). The reader must be aware that one entity in either the allograft or autograft group refers to a knee.

794 pts

692 pts analysiert (excl. pts mit hybrid grafts)
352 pts mit Allograft
340 pts mit Autograft

FU: 5.6-10.5 J.
Loss to FU (Allograft): 0-25.9%
Loss to FU (Autograft): 0-18.9%

The mean follow-up across studies ranged from 5.6 to 10.5 years. Loss to follow-up ranged from 3% to 22.4%. It appears that loss to follow-up in the autograft groups was higher when compared to the allograft groups, with a percentage of patients lost to follow-up ranging from 0-25.9% in the autograft groups compared to 0-18.9% in the allograft groups. The mean age of the patients receiving allografts and autografts ranged from 28 to 32.8 years and 28.9 to 31.7 years, respectively. The percentage of females within the studies ranged from 12.2% to 53.1% in patients receiving allografts and 14.6% to 47.2% in patients receiving autografts.

Baseline Characteristics in 5/6 Studien ausreichend beschrieben: vergleichbar

In 5/6 studies [15, 19-22], it was stated that most of the baseline characteristics were not statistically significantly different ($p<0.05$) between treatment groups, except for Chondral pathological abnormalities of the lateral femoral condyle being statistically significantly different in 1 study [15], with 87.8% and 72.9% with grade 0 lateral compartment in the allograft and autograft group, respectively. Co-interventions included meniscus treatment (e.g., repair, reconstruction) in 5/6 studies [15, 19-22]. The remaining study [17] neither sufficiently reported on baseline characteristics, nor on co-interventions. Patients received pre- or postoperative rehabilitation such as physiotherapy. All studies reported that the enrolled patients received the same postoperative rehabilitation programme.

In all of the included studies [15, 17, 19-22], the significance level was defined as $p<0.05$.

The reader is referred to the data extraction table (see Table A-1), the summary of findings table (see Table 7-1), and the GRADE evidence profile (see Table A-7) for more information.

Mortality

D0001 – What is the expected beneficial effect of allograft ACLR on mortality?

D0003 – What is the effect of allograft ACLR on the mortality due to causes other than the target disease?

Due to the fact that cruciate ligament tears are not life-threatening, mortality was not considered to be affected. However, procedure-related mortality can be found in the safety domain (see Chapter 6).

Morbidity

D0005 – How does allograft ACLR affect symptoms and findings (severity, frequency) of the disease or health condition?

D0006 – How does allograft ACLR affect progression (or recurrence) of the disease or health condition?

Re-ruptures may be considered as a recurrence after cruciate ligament reconstructions. In this assessment, however, this outcome was considered to be a safety-related one and the evidence regarding it was synthesised in Chapter 6.

Function

D0011 – What is the effect of allograft ACLR on patients' body functions?

D0016 – How does the use of allograft ACLR affect activities of daily living?

Answering these research questions can be based on the selected crucial outcomes of patient-reported function, activity level and symptoms, as well as on the selected, important outcome of clinical knee stability.

Patient-reported function, activity level and symptoms

Funktion, Aktivitätslevel und Symptome in 6/6 Studien

This outcome was measured by all studies using different validated instruments. The certainty of the results of these respective instruments ranged from low to moderate.

Lysholm Score in 5/6 Studien keine stat. signifikanten Unterschiede

The **Lysholm score** was reported in 5/6 included studies [17, 19-22]. In total, 595 patients (excluding 31 patients with hybrid grafts) were analysed hereby. Overall, 303 and 292 patients received an allograft and autograft, respectively. **None of the studies found a statistically significant difference in mean Lysholm scores between treatment groups postoperatively** ($p>0.05$). Postoperatively, the mean Lysholm scores ranged from 86 ±9 to 91 ±6 in the allograft groups, and 85.2 ±3.1 to 91.3+11.5 in the autograft groups across studies. These results reached **low certainty** according to GRADE.

Tegner Score in 5/6 Studien keine stat. signifikanten Unterschiede

The **Tegner score** was reported in 5/6 included studies [15, 19-22]. In total, 586 patients (excluding 31 patients with hybrid grafts) were analysed in the studies. Overall, 299 and 287 patients were in the allograft and autograft group, respectively. **None of the studies found a statistically significant difference** when comparing the mean Tegner score between treatment groups postoperatively ($p>0.05$). The mean postoperative Tegner scores ranged from 4.5 ±2.2 to 7.6 ±1.9 in the allograft groups, and 4.8 ±2.3 to 7.8 ±1.2 in the autograft groups across studies. These results reached **moderate certainty** according to GRADE.

Cincinnati Knee Score in 3/6 Studien keine stat. signifikanten Unterschiede

The **Cincinnati Knee score** was reported in 3/6 included studies [20-22]. In total, 425 patients were analysed in the studies. Of these, 218 and 207 were in the allograft and autograft group, respectively. **None of the studies found a statistically significant difference** when comparing the mean Cincinnati Knee score between treatment groups postoperatively ($p>0.05$). The mean postoperative Cincinnati Knee score ranged from 87 ±12 to 92 ±11 in the allograft groups, and 90 ±10 to 91 ±12 in the autograft groups across studies. These results reached **moderate certainty** according to GRADE.

SANE Score in 1/6 Studien keine stat. signifikanten Unterschiede

The **SANE score** was reported in 1 study [15]. In this study, 49 knees received allografts, and 48 knees received autografts[4]. No statistically significant difference was found in postoperative SANE scores ($p>0.05$). The postoperative mean score was 2.7 points lower in the allograft group when compared to the autograft group, with 78.8 ±18.8 and 81.5 ±16.4 mean SANE scores in these groups, respectively. The results from the SANE score reached **low certainty** according to GRADE.

[4] The reader is reminded that the exact number of patients in these treatment groups was unknown, given that the study did not clarify in which group the patient with 2 operated knees was.

Subjective IKDC in 6/6 Studien keine stat. signifikanten Unterschiede

The **subjective IKDC score** was reported in all 6 included studies [15, 17, 19-22]. In total, 692 patients (excl. 31 analysed patients with hybrid grafts) were analysed in the studies. Of these, 352 and 340 patients received an ACLR with allografts and autografts, respectively. **None of the studies found a statistically significant difference in mean subjective IKDC scores between groups postoperatively**. The mean postoperative subjective IKDC scores ranged from 73.7 ±25.9 to 90 ±14 in the allograft groups, and 77.2 ±25.4 to 90 ±10 in the autograft groups across studies. The results of the subjective IKDC score reached **moderate certainty** according to GRADE.

KOOS, Marx activity Scale: NR

KOOS scores (e.g., pain, symptoms) were not used by any of the included studies.

The **Marx activity scale** was not used by any of the included studies.

Clinical knee stability

Kniestabilität

The outcome of clinical knee stability was measured using a variety of different tests. In this assessment, the Lachman test, Pivot shift test, and the instrumented side-to-side difference were selected for this outcome.

Lachman Test (Grad 0-1) in 4/6 Studien keine stat. signifikanten Unterschiede in 3 Studien stat. signifikanter Unterschied in 1 Studie: 31/43 (72 %) vs. 37/40 (93 %)

The **Lachman test** was reported in 4/6 studies [19-22][5]. In total, 489 patients (excluding 31 patients with hybrid graft) were analysed in the studies. Of these, 250 received an allograft, and 239 patients received an autograft. 1 study [22] found a statistically significant difference in postoperative Lachman scores favouring autografts. That is, worse postoperative Lachman test results were found in the allograft group when compared to the autograft group, with 31/43 (72%) and 37/40 (93%) patients with grade 0-1 on the Lachman test in these groups, respectively. The remaining 3 studies [19-21] did not find any statistically significant differences in the postoperative Lachman test between treatment groups postoperatively. The proportion of patients with intact ligaments (grade 0-1) postoperatively according to the Lachman test across studies ranged from 31/43 patients (72%) to 74/80 patients (92.5%) in the allograft groups, and 84/91 patients (92.3%) to 30/32 patients (93.8%) in the autograft groups. These results reached **very low certainty** according to GRADE.

Pivot-Shift Test (Grad 0-1) in 4/6 Studien keine stat. signifikanten Unterschiede in 3 Studien stat. signifikanter Unterschied in 1 Studie: 38/43 (88.4 %) vs. 40/40 (100 %)

The **Pivot shift test** was reported in 4/6 studies [19-22][6]. In total, 489 patients (excluding 31 patients with hybrid graft) were analysed in the studies. Of these, 250 received an allograft, and 239 patients received an autograft. 1 study [22] found a statistically significant difference, with fewer patients scoring a grade 0-1 on the Pivot shift test in the allograft group when compared to the autograft group: 38/43 (88.4%) vs. 40/40 (100%). The remaining 3 studies [19-21] did not find any statistically significant differences in the postoperative Pivot shift test between the two treatment groups. The proportion of patients with intact ligaments (grade 0-1) postoperatively according to the Pivot shift test across studies ranged from 38/43 patients (88.4%) to 95/95 patients (100%) in the allograft groups, and 32/32 patients (100%) to 91/91 patients (100%) in the autograft groups. These results reached **very low certainty** according to GRADE.

[5] One further study [17] stated that the Lachman test was used, yet the data was insufficient to calculate the number of patients with intact ligaments (grade 0-1).

[6] One further study [17] stated that the Pivot shift test was used, yet the data was insufficient to calculate the number of patients with intact ligaments (grade 0-1).

Side-to-side difference in mm was reported in 4/6 included studies [19-22]. In total, 489 patients (excluding 31 patients with hybrid graft) were analysed in the studies. Of these, 250 received an allograft, and 239 patients received an autograft. 2/4 studies [19, 22] found a statistically significant difference in instrumented knee laxity favouring autografts, while the other 2/4 studies [20, 21] did not find any statistically significant difference in postoperative mean side-to-side differences measured with the KT arthrometer between treatment groups. Mean side-to-side differences (in mm) ranged from 2.5 ±0.9 to 5.5 ±1 in the allograft groups, as opposed to 2.1 ±1.6 to 2.5 ±0.7 in the autograft groups. These results reached **low certainty** according to GRADE.

Side-to-Side Difference in 4/6 Studien
2 Studien stat. signifikanter Unterschied zugunsten von Autografts
Keine stat. signifikanten Unterschiede in 2 weiteren Studien

The **objective IKDC** was reported in 4/6 included studies [19-22]. In total 489 patients (excluding 31 patients with hybrid graft) were analysed in the studies. Of these, 250 received an allograft, and 239 patients received an autograft. **None of the studies found a statistically significant difference** in the objective IKDC score between treatment groups ($p>0.05$). The proportion of normal or nearly normal scores according to the objective IKDC score across studies ranged from 38/43 patients (88.4%) to 75/80 patients (93.8%) in the allograft groups, and 29/32 patients (90.6%) to 38/40 patients (95%) in the autograft groups. These results reached **moderate certainty** according to GRADE.

Objective IKDC in 4/6 Studien (normal + nearly normal)
keine stat. signifikanten Unterschiede

The reader is referred to the data extraction table (see Table A-1), the summary of findings table (see Table 7-1), and the GRADE evidence profile (see Table A-7) for more information.

Health-related quality of life

D0012 – What is the effect of the technology on generic health-related quality of life?

No evidence was found to answer the research question.

D0013 – What is the effect of the technology on disease-specific quality of life?

No evidence was found to answer the research question.

Patient satisfaction

D0017 – Was the use of allografts worthwhile?

Only 1 out of 6 studies [17] reported on patient satisfaction and stated that there were no statistically significant difference between patients undergoing allograft ACLR (n=53) or autograft ACLR (n=53). Among the patients having undergone allograft ACLR, 46/53 (86.8%) patients were satisfied and 7 (13.2%) further patients were nearly satisfied. In the autograft group, 47/53 (88.7%) patients were satisfied and the 5 further remaining patients (9.4%) were nearly satisfied. Overall, the result of this outcome reached **low certainty** according to GRADE.

PatientInnenzufriedenheit in 1/6 Studien:
keine stat. signifikanten Unterschiede

However, this result must be interpreted with caution, since the instrument used to measure patient satisfaction was not reported.

5.3.2 Use of allografts in posterior cruciate ligament reconstruction

Study characteristics

PCLR: 2 RCTs

For **PCLR**, 2 randomised controlled studies [18, 23] were included in this assessment. Both of the studies compared allografts to autografts, but differences in graft types were used: One study [18] included 4-stranded y-irradiated tibialis anterior tendon allografts, and the other study [23] used Achilles tendon and anterior tibial tendons allografts.

145 pts

108 pts analysiert (excl. Hybrid Grafts): 50 vs. 58

Overall, the number of patients at the time of randomisation across studies resulted in 145 patients with PCL ruptures and undergoing PCLR in the included studies. Of these, 30 patients received hybrid grafts, and 7 further patients were lost to follow-up. As a result, there were 108 analysed patients receiving allografts (n=50) or autografts (n=58).

Mean FU: 2.8-5.6 Jahre

The mean follow-up time was 2.8 years in one study [23], and 5.6 in the other study [18], while the mean age between the allograft and autograft groups was 32.2 vs. 31.3 years and 30 vs. 29 years in these studies, respectively.

Co-Interventionen: Meniskus-Operation

Co-interventions in these studies included treatment of meniscal tears at the time of the PCLR and patients received pre- or postoperative rehabilitation such as physiotherapy. All studies reported that patients received the same postoperative rehabilitation programme.

In all of the included studies [18, 23], the significance level was defined as $p<0.05$.

The reader is referred to the data extraction table (see Table A-2), the summary of findings table (see Table 7-2), and the GRADE evidence profile (see Table A-8) for more information.

Mortality

D0001 – What is the expected beneficial effect of allograft PCLR on mortality?

D0003 – What is the effect of allograft PCLR on the mortality due to causes other than the target disease?

Due to the fact that neither anterior and posterior cruciate ligament ruptures, nor multi-ligament knee injuries are life-threatening, mortality was not considered to be affected. However, procedure-related mortality can be found in the safety domain (see Chapter 6).

Morbidity

D0005 – How does allograft PCLR affect symptoms and findings (severity, frequency) of the disease or health condition?

D0006 – How does allograft PCLR affect progression (or recurrence) of the disease or health condition?

Re-ruptures may be considered as a recurrence after cruciate ligament reconstructions. In this assessment, however, this outcome was considered to be a safety-related one, and the evidence regarding it was synthesised in Chapter 6.

Function

D0011 – What is the effect of allograft PCLR on patients' body functions?

D0016 – How does the use of allograft PCLR affect activities of daily living?

Answering these research questions can be based on the selected crucial outcomes of patient-reported function, activity level and symptoms, as well as on the selected, important outcome of clinical knee stability.

Patient-reported function, activity level and symptoms

Funktion, Aktivitätslevel und Symptome in 2/2 Studien

This outcome was measured by all studies using different validated instruments.

Lysholm Score in 2/2 Studien: keine stat. signifikanten Unterschiede

The **Lysholm score** was reported in 2 studies [18, 23]. In total, 108 patients (excluding 27 patients with hybrid grafts) receiving allografts (n=50) or autografts (n=58) were analysed. **None of the studies found a statistically significant difference in the mean Lysholm score between treatment groups** postoperatively (p>0.05). In one study [18], the mean postoperative Lysholm score was 85.2 ±3.9 in the allograft group (n=27), and 87.8 ±3.6 in the autograft group (n=26). In another study [23], the mean postoperative Lysholm score was 92.3 ±6.8 in the allograft group (n=23), and 87.8 ±9.6 in the autograft group (n=32). These results reached **very low certainty** according to GRADE.

Tegner Score in 2/2 Studien: keine stat. signifikanten Unterschiede

The **Tegner score** was reported in 2 included studies [18, 23]. In total, 108 patients (excluding 27 patients with hybrid grafts) receiving allografts (n=50) or autografts (n=58) were analysed. **None of the studies found a statistically significant difference in the Tegner score between treatment groups** postoperatively (p>0.05). In one study [18], the mean postoperative Tegner score was 6.2 ±1.7 in the allograft group (n=27), and 6.8 ±1.1 in the autograft group (n=26). In another study [23], the mean postoperative Tegner score was 4.7 ±1.66 in the allograft group (n=23), and 4.73 ±1.66 in the autograft group (n=32). These results reached **low certainty** according to GRADE.

Cincinnati Knee Score & SANE Score: NR

The **Cincinnati Knee score** was not reported in the included studies.

The **SANE score** was not reported in the included studies.

Subjective IKDC in 1/2 Studien: keine stat. signifikanten Unterschiede

The **subjective IKDC score** was reported in 1 of the 2 included studies [18]. In total, 53 patients (excluding 27 patients with hybrid grafts) in the study receiving allografts (n=27) and autografts (n=26) were analysed. The **study did not find a statistically significant difference** between treatment groups (p>0.05). Patients in the allograft and autograft groups had a mean postoperative subjective IKDC score of 80.2 ±6.8 and 83.5 ±6.3, respectively. These results reached **low certainty** according to GRADE.

KOOS, Marx: NR

KOOS scores were not reported in the included studies.

The **Marx activity scale** was not reported in the included study.

Clinical knee stability

Kniestabilität

The outcome of clinical knee stability was measured using a variety of different tests. In this assessment, the reverse Lachman test, reverse Pivot shift test, and the instrumented side-to-side difference were selected for this outcome.

Lachman in 1/2 Studien: keine stat. signifikanten Unterschiede

The **reverse Lachman test** was reported in 1 out of 2 included studies [23]. The study analysed 55 patients, with 23 patients receiving allografts and 32 patients receiving autografts. **The study did not find a statistically significant difference** in the reverse Lachman test postoperatively (p>0.05). The study

only reported on the mean Lachman score: the allograft and autograft groups had a mean postoperative reverse Lachman test score of 0.7 ±0.56 and 0.75 ±0.67, respectively. These results reached **low certainty** according to GRADE.

Pivot-Shift in 1/2 Studien: keine stat. signifikanten Unterschiede

The **reverse Pivot shift test** was reported in 1 out of 2 included studies [18]. In total, 53 patients (excluding 27 patients with hybrid grafts) receiving allografts (n=27) and autografts (n=26) were analysed. **The study did not find a statistically significant difference** of the Pivot shift test between treatment groups postoperatively (p>0.05). The proportion of intact ligaments (grade 0-1) according to the Pivot shift test was 26/27 patients (96.3%), and 26/26 patients (100%) in the allograft and autograft group, respectively. These results reached **moderate certainty** according to GRADE.

Side-to-Side Diff. in 2/2 Studien: stat. signifikante Unterschiede zugunsten von Autografts in 1 Studie keine stat. signifikanten Unterschiede in der anderen Studie

Side-to-side difference in mm was reported in the 2 included studies [18, 23]. In total, 108 patients (excluding 27 patients with hybrid grafts) receiving allografts (n=50) or autografts (n=58) were analysed. One study [18] found a **statistically significant difference** favouring autografts, with postoperative side-to-side differences of 3.5 ±1.1 and 2.1 ±1 in the allograft and autograft group, respectively (p<0.001). The other study [23] did not find any statistically significant difference based on the postoperative side-to-side difference between the allograft and autograft groups (2.83 ±1.7 vs. 3.16 ±2.6; p>0.05) measured with an instrumented knee laxity test. These results reached **very low certainty** according to GRADE.

Objective IKDC in 2/2 Studien: keine stat. signifikanten Unterschiede

The **objective IKDC score** was reported in the 2 included studies [18, 23]. In total, 108 patients (excluding 27 patients with hybrid grafts) receiving allografts (n=50) or autografts (n=58) were analysed. **None of the studies found a statistically significant difference in the objective IKDC score** between treatment groups postoperatively. In one study [18], the proportion of patients classified as "normal" or "nearly normal" according to the objective IKDC score between the allograft and autograft groups was 24/27 patients (88.9%) and 25/26 patients (96.2%), respectively. In another study [23], the proportion normal and nearly normal according to the objective IKDC score in the allograft and autograft groups was 14/23 patients (60.9%) and 23/32 patients (71.9%), respectively. The results of the objective IKDC score reached **low certainty** according to GRADE.

The reader is referred to the data extraction table (see Table A-2), the summary of findings table (see Table 7-2), and the GRADE evidence profile (see Table A-8) for more information.

Health-related quality of life

D0012 – What is the effect of allograft PCLR on generic health-related quality of life?

HRQoL: keine Daten

No evidence was found to answer the research question.

D0013 – What is the effect of allograft PCLR on disease-specific quality of life?

No evidence was found to answer the research question.

Patient satisfaction

D0017 – Was the use of allograft PCLR worthwhile?

PatientInnenzufriedenheit: keine Daten

No evidence was found to answer the research question.

5.3.3 Use of allografts in revision anterior cruciate ligament reconstruction

Revisions-ACLR: 1 prospektive Kohortenstudie

For revision cruciate ligament reconstruction, only one prospective cohort study [16] with patients undergoing revision ACLR was identified.

The study compared the use of allografts (various specific graft types, but all were fresh-frozen with minimal to no irradiation) and autografts (various specific graft types) in patients undergoing a revision of a previously failed ACLR. However, patients with multi-ligament knee injuries were not included in the study.

1.205 eingeschrieben
590 pts mit Allograft
583 pts mit Autograft

Overall, the study enrolled 1,205 patients. Of these, 590 received an allograft and 583 received an autograft. A further 32 patients received a combination of these grafts.

The median age of all patients was 26 (IQR: 20-34). 508 of all patients (42%) were female.

FU: 2 Jahre
Loss to FU (questionnaire): 17.9 %
Loss to FU (telephone): 7.7 %

The study followed them up after 2 years by questionnaire (989) and telephone call (1,112). The loss to follow-up using these techniques was 216 (17.9%) and 93 (7.7%), respectively.

Prior revisions ranged from 1 to 3+. That is, 1055 patients had 1 revision, 125 patients had 2 revisions, and 25 patients had 3+ revisions. Further previous surgery/ies included but was/were not limited to meniscus surgery. The pre- and postoperative rehabilitation of patients was not reported.

The reader is referred to the data extraction table (see Table A-3), the summary of findings table (see Table 7-3), and the GRADE evidence profile (Table A-9) for more information.

Mortality

D0001 – What is the expected beneficial effect of allograft revision ACLR on mortality?

D0003 – What is the effect of allograft revision ACLR on the mortality due to causes other than the target disease?

Due to the fact that neither anterior and posterior cruciate ligament ruptures, nor multi-ligament knee injuries are life-threatening, mortality was not considered to be affected. However, procedure-related mortality can be found in the safety domain (see Chapter 6).

Morbidity

D0005 – How does allograft revision ACLR affect symptoms and findings (severity, frequency) of the disease or health condition?

D0006 – How does allograft revision ACLR affect progression (or recurrence) of the disease or health condition?

Re-ruptures may be considered as a recurrence after cruciate ligament reconstructions. In this assessment, however, this outcome was considered to be a safety-related one, and the evidence regarding it was synthesised in Chapter 6.

Function

D0011 – What is the effect of allograft revision ACLR on patients' body functions?

D0016 – How does the use of allograft revision ACLR affect activities of daily living?

Answering these research questions can be based on the selected crucial outcome of patient-reported function, activity level and symptoms, as well as on the selected important outcome of clinical knee stability.

Patient-reported function, activity level and symptoms

Funktion, Aktivitätslevel und Symptome in 1/1 Studie

This outcome was measured by the included study using different validated instruments. The certainty of the results of these respective instruments was low according to GRADE.

Lysholm, Tegner, SANE, Cincinnati Knee Score: NR

The **Lysholm score** was not reported in the included study.

The **Tegner score** was not reported in the included study.

The **Cincinnati Knee score** was not reported in the included study.

The **SANE score** was not reported in the included study.

Subjective IKDC in 1 Studie: Autograft Prädiktor für verbesserten IKDC Score

The **subjective IKDC score** was reported in the included study [16]. The study only reported on the subjective IKDC score for all patients and not between allograft and autograft. The study did, however, conduct a logistic regression analysis and found that graft choice proved to be a significant predictor of 2-year IKDC scores (p=0.017). The use of an autograft for revision reconstruction, therefore, predicted an improved score on the IKDC (p=0.045; OR =1.31; 95% CI: 1.01-1.70).

KOOS Score in 1 Studie

Transplantattyp kein Prädiktor für verbesserten KOOS Score

KOOS scores were reported in the included study [16]. However, the respective scores between the different groups were not reported. The study conducted a logistic regression analysis and stated that graft choice did not predict the KOOS symptoms score (no further data reported). KOOS pain score was not reported, but the study found higher scores of the KOOS sports and recreation in the setting of an autograft compared with an allograft for revision ACLR (p=0.037; OR: 1.33; 95%CI: 1.02-1.73). The study further reported that graft choice did not predict the KOOS activities of daily living score (no further data reported).

Marx Activity Scale in 1 Studie: Kombination aus Autograft und Allograft war Prädiktor für verbesserten Score

The **Marx activity scale** was reported in the included study [16]. Results from the logistic regression analysis show that graft choice was a significant predictor of the Marx activity score (p=0.012). More precisely, the use of a combination of graft types (i.e., autograft and allograft) for revision reconstruction predicted improved scores on the Marx activity scale (p=0.005; OR: 3.33; 95%CI: 1.43-7.78). No further data were reported.

Clinical Knee stability

Kniestabilität: NR

The included study did not report on any of the clinical knee stability.

Health-related quality of life

D0012 – What is the effect of allograft revision ACLR on generic health-related quality of life (HRQoL)?

The included study [16] reported on generic HRQoL using the KOOS quality of life scale. However, only scores for all patients were reported. Results from logistic regression analysis show that the use of autografts predicted improved scores on the KOOS quality of life subscale (p=0.031; OR: 1.33; 95%CI: 1.03-1.73).

HRQoL in 1 Studie: Autograft Prädiktor für verbesserten KOOS QoL Score

D0013 – What is the effect of allograft revision ACLR on disease-specific quality of life?

No evidence was found to answer the research question.

Patient satisfaction

D0017 – Was the use of allograft revision ACLR worthwhile?

No evidence was found to answer the research question.

The reader is referred to the data extraction table (see Table A-3), the summary of findings table (see Table 7-3), and the GRADE evidence profile (see Table A-9) for more information.

PatientInnenzufriedenheit: keine Daten

5.3.4 Use of allografts in revision posterior cruciate ligament reconstruction

No evidence was identified through the systematic literature search to answer the research question.

Revisions-PCLR: keine Evidenz

5.3.5 Use of allografts for ligament reconstruction in patients with multi-ligament knee injuries

No evidence was identified through the systematic literature search to answer the research question.

Multi-ligament knee injuries: keine Evidenz

6 Safety

6.1 Outcomes

wesentliche Sicherheitsendpunkte: Komplikationen, Transplantversagen, Re-Rupturen, etc.

The following outcomes were defined as *crucial* to derive a recommendation:

- Graft failure
- Re-ruptures
- Re-operations
- Revisions
- Complications

Graft failure was chosen as a crucial outcome for the evaluation of the safety of allograft cruciate ligament reconstruction, since it may require further invasive surgeries and could, as a result, be an indicator for clinically inappropriate care. Graft failure was not defined in a standardised way by the included studies.

Re-ruptures, **re-operations,** and **revisions** are similar terms associated with graft failures. These outcomes were extracted separately and were also classified as crucial to derive a recommendation.

Complications were defined broadly in this assessment and capture routine surgical complications such as infection, anaesthesia complications, et cetera, and complications associated with cruciate ligament surgery. The latter includes, but is not limited to, postoperative loss of motion, arthrofibrosis, and donor site morbidity [25].

In addition to the crucial outcomes, one further outcome was considered to be important, but not crucial, to the decision:

- Procedure-related mortality

Procedure-related mortality is very rare, given that neither the condition nor the therapeutic procedure is life-threatening. This outcome has been included in determining whether or not there is any procedure-related mortality risk associated with the use of allograft cruciate ligament reconstruction.

6.2 Included studies

9 Studien eingeschlossen
ACLR: 6 RCTs
PCLR: 2 RCTs
Revisions-ACLR: 1 Kohortenstudie

In total, 9 clinical studies were included in this assessment. All of the studies compared allografts to autografts in cruciate ligament reconstructions. Six RCTs [15, 17, 19-22] were included for anterior cruciate ligament reconstruction (ACLR), while 2 further RCTs were included for posterior cruciate ligament reconstruction (PCLR) [18, 23]. For revision reconstruction, 1 cohort study met the inclusion criteria [16] of patients with revision ACLR.

Of the included studies, 2 were conducted in the United States [15, 16], 6 studies were conducted in China [17-22], and 1 further study was conducted in Taiwan [23].

All of the included studies compared allografts to autografts in cruciate ligament reconstructions. No study was identified comparing allografts to conservative management in either of the indications selected in this assessment.

The reader is referred to Table A-1, Table A-2 and Table A-3 for more information on study characteristics and results of included studies, as well as to the evidence profiles according to GRADE (see Table A-7, Table A-8, and Table A-9).

6.3 Results

6.3.1 Use of allografts in anterior cruciate ligament reconstruction

Study and patient characteristics

ACLR: 6 RCTs

For **ACLR**, 6 clinical studies were included [15, 17, 19-22]. All of the studies compared allograft to autograft ACLR in patients with ruptured ACL. However, differences regarding graft type and procedure were existent, e.g., whether a graft was fresh-frozen, irradiated or whether bone-patellar bone tendon-bone or hamstring tendons were used.

Of the included studies, 2 studies [19, 22] used allografts that were irradiated, while the remaining studies [15, 17, 20, 21] did not use irradiation for the purpose of disinfecting the allografts. The source of graft differed between studies (e.g., hamstring tendons, bone-patellar tendons).

794 pts

692 pts analysiert (excl. pts mit Hybrid Grafts)

352 pts mit Allograft
340 pts mit Autograft

Overall, the number of patients at the time of randomisation across studies resulted in 794 patients with an ACL deficiency that needed ACLR being enrolled in the included studies. Sample sizes at the time of randomisation ranged from 99 to 208 patients. Of all enrolled patients across studies, 34 patients received hybrid grafts (a combination of allografts and autografts), and further 69 patients were lost to follow-up. One study [15] did not clearly mention the number of patients included, as one patient underwent bilateral, simultaneous ACL reconstructions using an autograft on one side, and an allograft on the other side. Moreover, the loss to follow-up was not clearly stated, and the results refer to knees and not patients [15]. Therefore, we identified 352 patients who received allografts and 340 patients who received autografts (n=692). The reader must be aware that one entity in either allograft or autograft group refers to a knee.

The mean follow-up across studies ranged from 5.6 to 10.5 years. Loss to follow-up ranged from 3% to 22.4%. It appears that loss to follow-up in the autograft groups was higher when compared to the allograft groups, with a percentage of patients lost to follow-up ranging from 0-25.9% in the autograft groups compared to 0-18.9% in the allograft groups. The mean age of the patients receiving allografts and autografts ranged from 28 to 32.8 years and 28.9 to 31.7 years in the groups, respectively. The percentage of females within the studies ranged from 12.2% to 53.1% in patients receiving allografts, and 14.6% to 47.2% in patients receiving autografts.

Mean FU: 5.6-10.5 J.
Loss to FU (Allograft): 0-25.9 %
Loss to FU (Autograft): 0-18.9 %

In 5/6 studies [15, 19-22], it was stated that most of the baseline characteristics were not statistically significant between treatment groups, except for lateral compartment being statistically significantly different in 1 study [15], with 87.8% and 72.9% with grade 0 lateral compartment in the allograft and autograft groups, respectively. Co-interventions included meniscus treatment (e.g., repair, reconstruction) in 5/6 studies [15, 19-22]. The remaining study [17] neither sufficiently reported on baseline characteristics, nor on co-interventions. Patients received pre- or postoperative rehabilitation such as physiotherapy. All studies reported that the enrolled patients received the same postoperative rehabilitation programme.

Baseline Characteristics in 5/6 Studien ausreichend beschrieben: vergleichbar

In all of the included studies [15, 17, 19-22], the significance level was defined as $p<0.05$. Yet, for safety outcomes, it appears that differences were not always statistically tested by the included studies, since the p-value was not always reported.

The reader is referred to the data extraction table (see Table A-1), the summary of findings table (see Table 7-1), and the GRADE evidence profile (see Table A-7) for more information.

Patient safety

C0008 – How safe is allograft ACLR in comparison to autograft ACLR?

Graft failure

Graft failure was reported in 2/6 included studies [15, 22]. One study [15] reported on a graft failure rate of 13/49 (26.5%), and 4/48 (8.3%) knees in the allograft and autograft groups, respectively ($p<0.05$). The sample of this study included highly active, young patients. The other study [22] reported on a graft failure occurring in 13/43 (30.2%) patients in the (irradiated) allograft group, and 3/40 (7.5%) in the autograft group ($p<0.001$). Graft failure was measured differently in the included studies. The results of this outcome reached **moderate certainty** according to GRADE. This outcome was downgraded due to suspected applicability problems, e.g., it was unclear in how far these results are generalisable due to the fact that one study [15] only included highly active military (mostly) men, and the other study [22] only had irradiated allografts as their intervention.

Transplantversagen in 2/6 Studien berichtet:
1 RCT (Allo vs. Auto): 13/49 (26.5 %) vs. 4/48 (8.3 %), aktives junges Sample

1 RCT (bestrahlte Allo vs. Auto): 13/43 (30.2 %) vs. 3/40 (7.5 %)

Re-rupture rate

The re-rupture rate was not reported in any of the included studies.

Re-Rupturen, Re-Operationen: NR

Re-operation rate

The re-operation rate was not reported in any of the included studies.

Revisions

Revisionsrate in 2/6 Studien berichtet: 1 RCT (Allo vs. Auto): 13/49 (26.5 %) vs. 4/48 (8.3 %), aktives junges Sample 1 RCT: narrative Berichterstattung: keine PatientIn benötigte eine zusätzliche Operation wegen wiederkehrender oder verbliebener Symptome

The outcome of revisions was reported in 2/6 included studies [15, 19]. One study [15] reported on a revision ACLR rate of 13/49 knees (26.5%), and 4/48 knees (8.3%) knees in the allograft and autograft groups, respectively. The sample of this study included highly active, young patients. The other study [19] stated that no patient needed additional surgery because of recurrent or residual symptoms in 32 and 32 analysed patients receiving y-irradiated allografts and autografts, respectively (and an additional 31 patients receiving hybrid grafts). The results of this outcome reached **low certainty** according to GRADE. This outcome was downgraded because the results were not consistent, and due to applicability problems, e.g., it was unclear in how far these results are generalisable due to the fact that one study [15] only included highly active military (mostly) men, and the other study [19] used y-irradiated allografts.

Overall complications

Komplikationsrate: NR weitere Komplikationen; Arthrofibrose berichtet von 2 Studien: 0/269; Effusion: NR; Tenderness berichtet in 1 Studie: 0 % vs. 2.1 %; Infektionen berichtet in 4 Studien: 0-4.6 % vs. 0 % (P=NR); Hypoesthesia in 2 Studien berichtet: 0 % vs. 3.3-7.5% (P=NR); Synovitis: NR; Beinvenenthrombose in 3 Studien berichtet: keine DVTs in 2 Studien; 1 Studie: 2.5 % vs. 1.3 % (P=NR)

Arthrosebeschwerden in 1 Studie: stat. signifikanter Unterschied zugunsten von Autografts; Postoperatives Fieber stat. länger bei Allografts im Vergleich zu Autografts in 1 Studie; Tibia- und Femortunnelerweiterung in 2 Studien: kein stat. signifikanter Unterschied in 1 Studie, stat. signifikanter Unterschied zugunsten von Autografts in der anderen Studie

None of the studies reported on the overall complication rate.

Arthrofibrosis was reported in 2 studies (n=269) [21, 22]: No events occurred in both groups (0% vs. 0%).

Effusion was not reported in any of the included studies.

Tenderness was reported in 1 study [21], with 0/95 (0%) and 2/91 (2.1%) affected patients in allograft and autograft groups, respectively.

Infections were reported in 4 studies [19-22]: one study [19] stated that no postoperative infection occurred (0% vs. 0%), while the other studies found infections occurring in allograft patients (1.25-4.6%), as opposed to none in the autograft group (0%). No statistical testing was conducted.

Hypoesthesia was reported in 2 studies [21, 22] and favoured allografts (0% vs. 3.3-7.5%). No statistical testing was conducted.

Synovitis was not reported in any of the included studies.

Deep venous thrombosis (DVT) was reported on by 3 studies [20-22]. Of these, 2 [21, 22] stated that no DVTs occurred, and in another study [20], 3 cases with this complication occurred: 2 (2.5%) vs. 1 (1.3%). No statistical testing was conducted.

Other complications were reported in the included studies: **Arthritic progression** was mentioned in 1 study [22] and found statistically significantly **higher progression** in the allograft group when compared to the autograft group, with 14 (32.6%) and 4 (10%) in these groups, respectively ($p<0.05$). **Postoperative axillary fever time** was reported in 1 study [20], with 2.4 days longer in the allograft group (mean: 6.8 days) when compared to the autograft group (mean: 4.4 days; diff. s. s., with $p<0.05$). Two further studies [15, 17] reported that **tibial and femoral tunnel widening** was lower in the autograft group, yet only 1 of these studies [17] found a statistically significant difference ($p<0.05$) of tibial and femoral tunnel size widening between allograft and autograft. In this study [17], the postoperative mean tibial tunnel size (in mm) was 7.8 ±0.4 vs. 7.61 ±0.22, and the postoperative mean **femoral tunnel size (in mm)** was 7.64 ±0.35 vs. 7.51 ±0.42.

Furthermore, some of the included studies specifically stated that there were no cases of pain when kneeling, anterior knee pain, et cetera[7].
Overall, the outcome of complications reached **low certainty** according to GRADE.

[7] The reader is referred to the data extraction table (see Table A-1) for more information.

Procedure-related mortality

None of the included studies reported on procedure-related mortality.

C0002 – Are the harms related to dosage or frequency of applying allograft ACLR?

No evidence was found to answer the research question.

C0004 – How does the frequency or severity of harms change over time or in different settings?

No evidence was found to answer the research question.

C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of allograft ACLR?

No evidence was found to answer the research question.

C0007 – Are allograft and autograft ACLR associated with user-dependent harms?

No evidence was found to answer the research question.

Investments and tools required

B0010 – What kind of data/records and/or registry is needed to monitor the use of allograft and autograft ACLR?

No evidence was found to answer the research question.

6.3.2 Use of allografts in posterior cruciate ligament reconstruction

Study characteristics

PCLR: 2 RCTs

For **PCLR**, 2 randomised controlled studies [18, 23] were included in this assessment. Both of the studies compared allografts to autografts; however, differences in graft types were used: One study [18] included 4-stranded y-irradiated tibialis anterior tendon allografts, and the other study [23] used Achilles tendon and anterior tibial tendons allografts.

145 pts;
108 pts analysiert (excl. Hybrid Grafts):
50 vs. 58

Overall, the number of patients at the time of randomisation across studies resulted in 145 patients with PCL ruptures and undergoing PCLR. Of these, 30 patients received hybrid grafts, and 7 further patients were lost to follow-up. As a result, there were 108 analysed patients receiving allografts (n=50) or autografts (n=58).

Mean FU:
2.8-5.6 Jahre

The mean follow-up time was 2.8 years in one study [23] and 5.6 years in another study [18]. The loss to follow-up rate was 11% (10% vs. 13%) in one study [18] and not reported in another study[8] [23]. The mean age between allograft and autograft groups was 32.2 vs. 31.3 years, and 30 vs. 29 years in these studies, respectively.

[8] The study did not adequately report on the enrolment process. Therefore, the loss to follow-up rate could not have been stated.

Co-Interventionen: Meniskus-Operation

Co-interventions in the included studies included treatment of meniscal tears before PCLR and patients receiving pre- or postoperative rehabilitation such as physiotherapy. All studies reported that patients received the same post-operative rehabilitation programme.

In all of the included studies [18, 23], the significance level was defined as $p<0.05$. Yet, the differences in safety outcomes were not always statistically tested, since no p-values were reported

The reader is referred to the data extraction table (see Table A-2) the summary of findings table (see Table 7-2), and the GRADE evidence profile (see Table A-8) for more information.

Patient safety

C0008 – How safe is allograft PCLR in comparison to autograft PCLR?

Graft failure

Transplantatversagen, Re-Ruptur, Revisionen: NR

The graft failure rate was not reported in any of the included studies.

Re-rupture rate

The re-rupture rate was not reported in any of the included studies.

Re-operation rate

Re-Operationen in 1/2 Studie berichtet: kein pt benötigte zusätzliche Operation wegen wiederkehrender oder bleibender Laxität

The re-operation rate was reported in 1 study [18], yet the information of reporting on this outcome was sparse and indirect. The study only stated that no patient needed additional surgery because of recurrent or residual posterior laxity. This outcome reached **low certainty** according to GRADE.

Revisions

The outcome of revisions was not reported in any of the included studies.

Overall complications

Komplikationsrate in 1/2 Studien berichtet (Allo vs. Auto): 0 % vs. 21.9 %, aber: nicht statistisch getestet; Arthrofribrose, Effusion, Tenderness: NR

1 out of the 2 included studies [23] reported on an overall complication rate. In the allograft group, no complications occurred (0%), as opposed to 7 complications (21.9%) in the autograft group. No statistical testing was conducted, since the p-value was not reported in the study.

Arthrofibrosis was not reported in the included studies.

Effusion was not reported in the included studies.

Tenderness was not reported in the included studies.

Infektionen in 2/2 Studien berichtet: keine postoperativen Infektionen in 1 Studie, 2 Infektionen in Auto-Gruppe (6.3 %) in 1 Studie; Hypoesthesia, Synovitis: NR

Infections were reported in the 2 included studies [18, 23]: One study [18] stated that no postoperative infection occurred. Another study [23] reported on 2 infections (6.3%; 1 acute and 1 late infection) occurring in the autograft group, while no infections occurred in the allograft group. The difference was not statistically tested, since the p-value was not reported.

Hypoesthesia was not reported in any of the included studies.

Synovitis was not reported in any of the included studies.

Deep venous thrombosis was reported in 1 study [18]: the study stated that no deep venous thrombosis occurred.

Further complications were reported in the included studies: One study [23] reported on **donor site symptoms**, with an occurrence of 0% and 12.5% in the allograft and autograft groups, respectively. **Reflex sympathetic dystrophy** was reported in the same study [23], occurring in 1/32 patients (3.1%) in the autograft group versus in 0/23 patients (0%) in the allograft group. The difference was not statistically tested, since the p-value was not reported.

Moreover, 1 study [23] reported on **tibial and femoral tunnel widening** and found no statistically significant difference between the allograft and autograft groups.

Regarding complications, 1 study [18] further stated that there were no cases of major neurovascular, infectious, vascular, or wound complications.

Overall, the outcome of complications reached **low certainty** according to GRADE.

DVT in 1 Studie berichtet: keine DVT geschah; Spendersyndrom in 1 Studie berichtet: 0 % vs. 12.5 %, Reflex Sympathetic Dystrophy in 1 Studie berichtet: 0 % vs. 3.1 % Unterschied vmtl. nicht statistisch getestet; Tibia- und Femortunnel-erweiterung in 1 Studie berichtet: keine stat. signifikanten Unterschiede

Procedure-related mortality

None of the included studies reported on procedure-related mortality.

C0002 – Are the harms related to dosage or frequency of applying allograft PCLR?

No evidence was found to answer the research question.

C0004 – How does the frequency or severity of harms change over time or in different settings?

No evidence was found to answer the research question.

C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of allograft PCLR?

No evidence was found to answer the research question.

C0007 – Are allograft and autograft PCLR associated with user-dependent harms?

No evidence was found to answer the research question.

Investments and tools required

B0010 – What kind of data/records and/or registry is needed to monitor the use of allograft and autograft?

No evidence was found to answer the research question.

6.3.3 Use of allografts in revision anterior cruciate ligament reconstruction

Study characteristics

Revisions-ACLR: 1 prospektive Kohortenstudie

For revision cruciate ligament reconstruction, only 1 prospective cohort study [16] with patients undergoing revision ACLR was identified.

The study compared the use of allografts (various specific graft types, but all were fresh-frozen with minimal to no irradiation), and autografts in patients undergoing a revision of a previously failed ACLR. However, patients with multi-ligament knee injuries were not included in the study.

1205 eingeschrieben
590 pts mit Allograft
583 pts mit Autograft

Overall, the study enrolled 1,205 patients. Of these, 590 received an allograft and 583 received an autograft. A further 32 patients received a combination of these grafts.

The median age of all patients was 26 (IQR: 20-34). 508 of all patients (42%) were female.

FU: 2 Jahre
Loss to FU (questionnaire): 17.9 %
Loss to FU (telephone): 7.7 %

The study followed the enrolled patients after 2 years by questionnaire (989) and telephone call (1,112). The loss to follow-up using these techniques was 216 (17.9%) and 93 (7.7%) patients, respectively.

Prior revisions ranged from 1 to 3+. That is, 1055 patients had 1 revision, 125 patients had 2 revisions, and 25 patients had 3+ revisions. Further previous surgery/ies included but was/were not limited to meniscus surgery. Pre- and postoperative rehabilitation of patients was not reported.

The reader is referred to the data extraction table (see Table A-3), the summary of findings table (see Table 7-3), and the GRADE evidence profile (Table A-9) for more information.

Patient safety

C0008 – How safe is allograft revision cruciate ligament reconstruction in comparison to autograft revision cruciate ligament reconstruction?

Graft failure

Transplantatversagen: NR

The outcome of graft failure was not reported in the included study.

Re-rupture rate

Re-Rupture (Allo vs. Auto): 4.4 % vs. 2.2 % stat. signifikant

The outcome of re-rupture rate was reported in the included study [16]. Overall, a re-rupture occurred in 24 patients (4.4%) in the allograft group and 12 (2.2%) in the autograft group. The study used a logistic regression analysis and revealed that patients with an autograft revision were found to be 2.78 times less likely of sustaining a subsequent graft rupture when compared to the patients in the allograft group (p=0.047; 95%CI: 1.01-7.69). The results of this outcome reached **low certainty** according to GRADE.

Re-operation rate

Re-Operation: Transplantattyp war kein Prädiktor für Re-Operation; keine head-to-head Daten berichtet

The re-operation rate was reported in the included studies [16]. However, only the overall re-operation rate was reported, with 150/1112 patients (13.5%) needing a re-operation. In addition, a logistic regression analysis was conducted in the included study, showing that graft choice was not a predictor of the incidence of subsequent reoperations at 2 years after revision surgery. The results of this outcome reached **low certainty** according to GRADE.

Revisions

The outcome of revisions was not reported in the included study.

Revisionsrate, Komplikationsrate etc.: NR

Overall Complications

The outcome of overall complications was not reported in the included study.

Arthrofibrosis was not reported in the included study.

Effusion was not reported inreported in the included study.

Tenderness was not reported inreported in the included study.

Infections were not reported in the included study.

Hypoesthesia was not reported in the included study.

Synovitis was not reported in the included study.

Deep venous thrombosis was not reported in the included study.

Procedure-related mortality

The outcome of procedure-related mortality was not reported in the included study.

C0002 – Are the harms related to dosage or frequency of applying allograft revision cruciate ligament reconstruction?

No evidence was found to answer the research question.

C0004 – How does the frequency or severity of harms change over time or in different settings?

No evidence was found to answer the research question.

C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of allograft revision cruciate ligament reconstruction?

No evidence was found to answer the research question.

C0007 – Are allograft and autograft revision cruciate ligament reconstruction associated with user-dependent harms?

No evidence was found to answer the research question.

Investments and tools required

B0010 – What kind of data/records and/or registry is needed to monitor the use of allograft and autograft revision cruciate ligament reconstruction?

No evidence was found to answer the research question.

6.3.4 Use of allografts in revision posterior cruciate ligament reconstruction

No evidence was identified through the systematic literature search to answer the research question

6.3.5 Use of allografts for cruciate cruciate ligament reconstruction in patients with multi-ligament knee injuries

No evidence was identified through the systematic literature search to answer the research question

7 Quality of evidence

RoB
7 RCTs mit hohem RoB, 1 RCT mit unklarem RoB & 1 Kohortenstudie mit moderate RoB

Risk of Bias (RoB) for individual studies was assessed with the Cochrane RoB tool and the Newcastle-Ottawa Scale (NOS), and is presented in Table A-4, Table A-5 and Table A-6 in the Appendix.

Overall, 7 RCTs had high RoB, 1 RCT had unclear RoB, and 1 cohort study reached moderate RoB.

For **ACLR**, the 6 included studies had a high RoB, mainly due to the lack of blinding of the outcome assessors (attrition bias increased likelihood in 5 studies), and selective outcome reporting (high risk in 2 studies). For **PCLR**, the 2 included studies had unclear to high risk of bias. The study with high risk of bias had substantial limitations regarding the randomisation process and may only be labelled as "quasi-randomised". For **revision ACLR**, the included cohort study comparing allografts to autografts in patients undergoing revision ACLR reached a moderate RoB using the NOS scale. For revision PCLR and reconstruction of cruciate ligaments in patients with multi-ligament knee injuries, no evidence was found indicating the superiority or inferiority of allografts when compared to autografts.

Qualität der Evidenz nach GRADE:
ACLR: niedrig
PCLR: sehr niedrig
Revisions-ACLR: niedrig

The strength of evidence was rated according to the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) scheme [14] for each endpoint individually. Each study was rated by two independent researchers (GG, CdV). In case of disagreement, a third researcher (SGG) was involved to solve the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [14].

GRADE uses 4 categories to rank the strength of evidence:

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate** = We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low** = Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- **Very low** = Evidence either is unavailable or does not permit a conclusion.

The ranking according to the GRADE scheme for the research question can be found in the summary of findings table below, and in the evidence profile in Appendix (see Table A-7, Table A-8 and Table A-9)

According to GRADE, the overall strength of evidence of the selected *crucial outcomes* is as follows:

The strength of evidence for the effectiveness and safety of allograft ACLR in comparison to autograft ACLR is low.

The strength of evidence for the effectiveness and safety of allograft PCLR in comparison to autograft PCLR is very low.

The strength of evidence for the effectiveness and safety of revision allograft ACLR in comparison to revision autograft ACLR is low.

For the remaining indications (e.g., revision PCLR, cruciate ligament reconstructions in multi-ligament knee injuries), no evidence is available to assess the effectiveness and safety of allografts compared to autografts in cruciate ligament reconstruction.

Table 7-1: Summary of findings table of allografts for ACLR

Outcomes	№ of analysed patients		Anticipated absolute effects*	Relative effect (95% CI)	№ of analysed participants[9] (studies)	Certainty of the evidence (GRADE)	Comments
	Allograft	Autograft					
EFFECTIVENESS							
Patient-reported function, activity level and symptoms assessed with: Tegner score (Scale: 0-10) follow-up: mean ≥5 years	299	287	None of the studies found a statistically significant difference when comparing the Tegner activity score between treatment groups postoperatively. Postoperative mean Tegner scores (ranges): 4.5 ±2.2 to 7.6 ±1.9 vs. 4.8 ±2.3 to 7.8 ±1.2	-	586 (5 RCTs) [15, 19-22]	⊕⊕⊕◯ MODERATE [c,d,e]	Higher scores indicate better patient-reported outcome.
Patient-reported function, activity level and symptoms assessed with: Cincinnati Knee score (Scale: 0-100) follow-up: mean ≥5 years	218	207	None of the studies found a statistically significant difference when comparing the Cincinnati Knee score between treatment groups postoperatively. Postoperative mean Cincinnati Knee scores (ranges): 87 ±12 to 92 ±11 vs. 90 ±10 to 91 ±12	-	425 (3 RCTs) [20-22]	⊕⊕⊕◯ MODERATE [c,f,g]	Higher scores indicate better patient-reported outcome.
Patient-reported function, activity level and symptoms assessed with: SANE score (Scale:0-100) follow-up: mean 10.5 years	49	48	The postoperative mean score was 2.7 points lower in the allograft group when compared to the autograft group. Postoperative mean SANE score: 78.8 ±18.8 vs. 81.5 ±16.4	-	97 (1 RCT) [15]	⊕⊕◯◯ LOW [h,i]	Higher scores indicate better patient-reported outcome.
Patient-reported function, activity level and symptoms assessed with: subjective IKDC score (Scale: 0-100) follow-up: mean ≥5 years	352	340	None of the studies found a statistically significant difference in subjective IKDC scores between groups postoperatively. Postoperative mean subjective IKDC scores (ranges): 73.7 ±25.9 to 90 ±14 vs. 77.2 ±25.4 to 90 ±10	-	692 (6 RCTs) [15, 17, 19-22]	⊕⊕⊕◯ MODERATE [c,h]	Higher scores indicate better patient-reported outcome.
Patient-reported function, activity level and symptoms assessed with: KOOS score (Scales: 0-100)				-	(0 studies)	-	Higher scores indicate better patient-reported outcome.
Patient-reported function, activity level and symptoms assessed with: Marx activity scale (Scale: 0-16)				-	(0 studies)	-	Higher scores indicate better patient-reported outcome.

[9] The Number of analysed participants only refers to the number of patients receiving either allografts or autografts. Hybrid grafts were hereby excluded. In addition, the reader is reminded that in Bottoni et al. the number of patients actually refers to the number of knees.

Outcomes	№ of analysed patients		Anticipated absolute effects*	Relative effect (95% CI)	№ of analysed participants[9] (studies)	Certainty of the evidence (GRADE)	Comments
	Allograft	Autograft					
Clinical knee stability assessed with: Lachman test (Grade 0-1)	250	239	s. s. difference in Lachman scores (grade 0-1) in 1 study [22]: 31/43 (72%) vs. 37/40 (93%). No statistically significant differences in Lachman scores in 3 studies [19-21] Lachman test (grade 0-1; ranges across studies): 31/43 (72%) to 74/80 (92.5%) vs. 84/91 (92.3%) to 30/32 (93.8%)	-	489 (4 RCTs) [19-22]	⨁◯◯◯ VERY LOW [j,k]	Lachman grade 0-1 indicates an intact ligament.
Clinical knee stability assessed with: Pivot shift test	250	239	s. s. difference in Pivot shift test (Grade 0-1) in 1 study [22]: 38/43 (88.4%) vs. 40/40 (100%) No statistically significant differences in Pivot shift test in 3 studies [19-21] Pivot shift (grade 0-1; ranges across studies): 38/43 (88.4%) to 95/95 (100%) vs. 32/32 (100%) to 91/91 (100%)	-	489 (4 RCTs) [19-22]	⨁◯◯◯ VERY LOW [j,k]	Pivot shift grade 0-1 indicates an intact ligament.
Clinical knee stability (Side-to-side difference) assessed with: KT arthrometer; better indicated by lower values	250	239	2/4 studies [19, 22] found a statistically significant difference in instrumented knee laxity favouring autografts, while the other 2/4 studies [20, 21] did not find any statistically significant difference in side-to-side differences measured with the KT arthrometer between treatment groups. Mean side-to-side differences (in mm; ranges across studies): 2.5 ±0.9 to 5.5 ±1 vs. 2.1 ±1.6 to 2.5 ±0.7	-	489 (4 RCTs) [19-22]	⨁⨁◯◯ LOW [h,k]	A lower side-to-side difference indicates less knee laxity (and more stability).
Clinical knee stability assessed with: objective IKDC	250	239	None of the studies found a statistically significant difference in objective IKDC scores between treatment groups. Objective IKDC scores (normal or nearly normal scores; ranges across studies): 38/43 (88.4%) to 75/80 (93.8%) vs. 29/32 patients (90.6%) to 38/40 (95%)	-	489 (4 RCTs) [19-22]	⨁⨁⨁◯ MODERATE [h]	More patients with normal and nearly normal according to the objective IKDC may indicate better knee stability.
Patient satisfaction assessed with: NR	53	53	The instrument used to measure patient satisfaction was not reported. **Satisfied:** 46/53 (86.8%) vs. 47/53 (88.7%) **Nearly satisfied:** 7 (13.2%) vs. 5 (9.4%) Diff. n. s., with p>0.05	-	106 (1 RCT) [17]	⨁⨁◯◯ LOW [l]	
Health-related Quality of Life				-	(0 studies)	-	
SAFETY							
Graft failure follow-up: mean ≥5 years	92	88	26/92 (28.3%) vs. 7/88 (7.9%) [m] Bottoni et al. [15]: 13/49 (26.5%) vs. 4/48 (8.3%), diff. s. s. with p<0.05 Tian et al. [22]: 13/43 (30.2%) vs. 3/40 (7.5%), diff. s. s. with p<0.001	-	180 (2 RCTs) [15, 22]	⨁⨁⨁◯ MODERATE [c,i,n]	

Outcomes	№ of analysed patients		Anticipated absolute effects*	Relative effect (95% CI)	№ of analysed participants[9] (studies)	Certainty of the evidence (GRADE)	Comments
	Allograft	Autograft					
Re-rupture rate					(0 studies)	-	
Re-operations follow-up: mean ≥5 years					(0 studies)	-	
Revisions follow-up: mean ≥5 years	81	80	Bottoni et al. [15]: 13/49 (26.5%) vs. 4/48 (8.3%), diff. s. s. with p<0.05 Li et al. [19]: No patient needed additional surgery because of recurrent or residual symptoms (0/32 vs. 0/32).	-	161 (2 RCTs) [15, 19]	⨁⨁◯◯ LOW [c,i,n,o]	
Complications follow-up: mean >5 years	-	-	Overall complication rate: NR **Arthrofibrosis** (reported in 2/6 studies [21, 22]; 269 pts): 0/138 (0%) vs. 0/131 (0%) **Effusion** (0/6 studies): NR **Tenderness** (reported in 1 study [21]; 186 pts): 0/95 (0%) vs. 2/91 (2.1%) **Infections** (reported in 4 studies [19-22]; 489 pts): 5/250 (2%) vs. 0/239 (0%), range: 0-4.6% vs. 0%. **Hypoesthesia** (reported in 2 studies [21, 22]; 269 pts): 0/138 (0%) vs. 6/131 (4.6%), range: 0% vs. 3.3-7.5%. **Synovitis** was not reported in any of the included studies. **Deep venous thrombosis** (reported in 3 studies [20-22]; 425 pts): 2/218 (0.9%) vs. 1/207 (0.5%), range: 0-2.5% vs. 0-1.3% **Further reported complications:** Postoperative mean fever time in days (reported in 1 study [20]; 156 pts): 6.8 vs. 4.4 diff. s. s., with p<0.05) Arthritic progression (reported in 1 study [22]; 83 pts): 14/43 (32.6%) vs. 4/40 (10%), diff. s. s. with p<0.05. Tibial and femoral tunnel widening in mm (reported in 2 studies; 203 pts): Jia et al. [17]: Tibial (in mm), mean ±SD: 7.8 ±0.4 vs. 7.61 ±0.22, diff. s. s. with p<0.05 Femoral (in mm), mean ±SD: 7.64 ±0.35 vs. 7.51 ±0.42, diff. s. s. with p<0.05 Bottoni et al. [15]: Tibial (in mm), mean (range): 9.2 (7-10) vs. 8.9 (7-10); diff. n. s. with p=0.651 Femoral (in mm), mean (range): 8.8 (7-10) vs. 8.3 (7-10), diff n. s. with p=0.453 Furthermore, some of the included studies specifically stated that there were no cases of pain when kneeling, anterior knee pain, etc.	-	692 (6 RCTs) [15, 17, 19-22]	⨁⨁◯◯ LOW [c,p,q]	
Procedure-related mortality				-	(0 studies)	-	

GRADE Working Group grades of evidence:

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Comments:

[a] *In 4/5 studies, the risk of bias for blinding the outcome assessors was judged to be high. Therefore, we judged that this may have seriously affected the certainty.*

[b] *None of the studies showed any statistically significant differences postoperatively in the Lysholm score between the allograft and the autograft groups. Results from the non-statistically significant differences revealed that in 3/5 studies the Lysholm score was higher in the allograft group, while 2/5 studies reported a lower Lysholm score in the allograft group (comparison: allograft vs. autograft). While the general difference is small (e.g., <5-point differences between allografts and autografts), it may still be an indicator for heterogeneity. Calculation of the i-square is further needed to adequately assess how heterogeneous the results for this outcome may be.*

[c] *Differences in interventions were present across studies (e.g., irradiated vs. non-irradiated grafts, single-bundle vs. double-bundle, etc.).*

[d] *In 5/5 studies, the risk of bias for blinding the outcome assessors was judged to be high. Therefore, we judged that this may have seriously affected the certainty.*

[e] *None of the studies showed any statistically significant difference postoperatively in the Tegner score between the allograft and the autograft groups. The non-statistical findings in all study groups showed slightly higher scores in the autograft group. This may be an indicator that heterogeneity is small. Calculating the i-square may be beneficial to further assess heterogeneity.*

[f] *In 3/3 studies, the lack of blinding significantly increases the risk of bias. Given that this is a subjective outcome score, it was judged to be a very serious limitation.*

[g] *None of the studies showed any statistically significant differences in the Cincinnati Knee scores between treatment groups. The non-statistical findings showed slightly higher scores in allograft patients in 2/3 studies, and lower scores in allograft patients in 1/3 study when compared to the autograft groups, respectively. The difference of the mean scores ranged from 1 to -3.*

[h] *The lack of blinding in the study/ies may seriously affect the certainty to believe the evidence of this outcome measure.*

[i] *The overall applicability for the broad population selected in these assessment results may suffer due to the fact that numerous different graft types were used and some studies used a subpopulation of the population of interest. Bottoni et al., for instance, solely included highly active military (mostly) men, and Tian et al. used irradiated allografts. It is unclear in how far the generalisability suffers due to the aforementioned factors.*

[j] *It was judged that the lack of blinding may have very seriously affected the certainty to believe the evidence for this specific outcome.*

[k] *Heterogeneity was suspected within the included studies. It appears that the studies do not consistently show any difference/differences favouring a treatment group. A calculation of the i-square is further needed to elaborate how significant the inconsistency is.*

[l] *There were 2 substantial factors that increased the risk of bias: lack of blinding and selective outcome reporting; the latter was present insofar as it insufficiently described how patient satisfaction was measured.*

[m] *Graft failure, however, was defined differently in the studies. Tian et al. defined it as knee laxity >5mm measured with a KT-2000, and Bottoni et al. did not clearly mention how graft failure was defined.*

[n] *The lack of blinding for outcome assessors was judged to be less likely to affect this outcome.*

[o] *Bottoni et al. found a considerably large difference in the revision rate, while Li et al. stated that no additional surgeries were needed in either of the treatment groups.*

[p] *The risk of bias for selective outcome reporting was judged high in 2/6 studies, and unclear in the remaining 4/6 studies. Most of the studies, however, did not report on an overall complication rate. Instead, they were presented narratively in the studies.*

[q] *The optimal information size may have not been reached for most of the specific complications.*

Table 7-2: Summary of findings table of allografts for PCLR

Outcomes	№ of analysed patients		Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of analysed participants [10] (studies)	Certainty of the evidence (GRADE)	Comments
	Allograft	Autograft					
EFFECTIVENESS							
Patient-reported function, activity level and symptoms assessed with: Lysholm score follow-up: mean ≥2 years	50	58	None of the studies found a statistically significant difference in the Lysholm score between treatment groups postoperatively. Li et al. [18]: 85.2 ±3.9 vs. 87.8 ±3.6, diff. n. s. with p>0.05 Wang et al. [23]: 92.3 ±6.8 vs. 87.8 ±9.6, diff. n. s. with p>0.05	-	108 (2 RCTs) [18, 23]	⨁◯◯◯ VERY LOW [1,a,b,c]	Higher scores indicate better patient-reported outcome.
Patient-reported function, activity level and symptoms assessed with: Tegner score	50	58	None of the studies found a statistically significant difference in the Tegner score between treatment groups postoperatively. Li et al. [18]: 6.2 ±1.7 vs. 6.8 ±1.1, diff. n. s. with p>0.05 Wang et al. [23]: 4.7 ±1.66 vs. 4.73 ±1.66, diff. n. s. with p>0.05	-	108 (2 RCTs) [18, 23]	⨁⨁◯◯ LOW [a,b]	Higher scores indicate better patient-reported outcome.
Patient-reported function, activity level and symptoms assessed with: Cincinnati Knee score					(0 studies)	-	Higher scores indicate better patient-reported outcome.
Patient-reported function, activity level and symptoms assessed with: SANE score					(0 studies)	-	Higher scores indicate better patient-reported outcome.
Patient-reported function, activity level and symptoms assessed with: subjective IKDC score	27	26	Mean postoperative subjective IKDC score: 80.2 ±6.8 vs. 83.5 ±6.3, diff. n. s. with p>0.05	-	53 (1 RCT) [18]	⨁⨁◯◯ LOW [b,d]	Higher scores indicate better patient-reported outcome.
Patient-reported function, activity level and symptoms assessed with: KOOS score				-	(0 studies)	-	Higher scores indicate better patient-reported outcome.
Patient-reported function, activity level and symptoms assessed with: Marx activity scale				-	(0 studies)	-	Higher scores indicate better patient-reported outcome.

[10] The Number of analysed participants only refers to the number of patients receiving either allografts or autografts. Hybrid grafts were hereby excluded.

Outcomes	№ of analysed patients		Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of analysed participants [10] (studies)	Certainty of the evidence (GRADE)	Comments
	Allograft	Autograft					
Clinical knee stability assessed with: reverse Lachman test	23	32	The study did not find a statistically significant difference in the reverse Lachman test postoperatively. Mean postoperative reverse Lachman test score: 0.7 ±0.56 vs. 0.75 ±0.67, diff. n. s. with p>0.05	-	55 (1 RCT) [23]	⨁⨁◯◯ LOW [a]	Lachman grade 0-1 indicates an intact ligament.
Clinical knee stability assessed with: reverse Pivot shift test	27	26	Postoperative reverse Pivot shift (Grade 0-1): 26/27 (96.3%) vs. 26/26 (100%), diff. n. s. with p>0.05	-	53 (1 RCT) [18]	⨁⨁⨁◯ MODERATE [b]	Pivot shift grade 0-1 indicates an intact ligament.
Clinical knee stability assessed with: KT arthrometer; better indicated by lower values	50	58	1 study found a statistically significant difference favouring autografts, while another study did not find any statistically significant difference based on the side-to-side difference measured with an instrumented knee laxity test. **Side-to-side difference in mm:** Li et al. [18]: 3.5 ±1.1 vs. 2.1 ±1, diff. s. s. with p<0.001 Wang et al. [23]: 2.83 ±1.7 vs. 3.16 ±2.6, diff. n. s. with p>0.05	-	108 (2 RCTs) [18, 23]	⨁◯◯◯ VERY LOW [a,b,e]	A lower side-to-side difference indicates less knee laxity (and more stability).
Clinical knee stability assessed with: objective IKDC	50	58	None of the studies found a statistically significant difference in the objective IKDC score between treatment groups postoperatively. **Objective IKDC score (normal and nearly normal):** Li et al. [18]: 24/27 (88.9%) vs. 25/26 (96.2%) Wang et al. [23]: 14/23 (60.9%) vs. 23/32 (71.9%)	-	108 (2 RCTs) [18, 23]	⨁⨁◯◯ LOW [a,b]	More patients with normal and nearly normal scores according to the objective IKDC score may indicate better knee stability.
Patient satisfaction					(0 studies)	-	
Health-related Quality of Life					(0 studies)	-	
SAFETY							
Graft failure					(0 studies)	-	
Re-rupture rate					(0 studies)	-	
Re-operations	27	26	The study stated that no patient needed additional surgery because of recurrent or residual posterior laxity: 0% vs. 0% (further information: NR).	-	53 (1 RCT) [18]	⨁⨁◯◯ LOW [2,f,g]	
Revisions					(0 studies)	-	
Complications	-	-	**Overall complication rate** (reported in 1 study; [23]): 0/23 (0%) vs. 7/32 (21.9%). **Arthrofibrosis:** NR **Effusion:** NR **Tenderness:** NR	-	108 (2 RCTs) [18, 23]	⨁⨁◯◯ LOW [d]	

Outcomes	№ of analysed patients		Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of analysed participants [10] (studies)	Certainty of the evidence (GRADE)	Comments
	Allograft	Autograft					
Complications *(continuation)*	-	-	**Infections:** Li et al [18]: no postoperative infection; Wang et al. [23]: 0/23 (0%) vs. 2/32 (6.3%; one acute and one late infection) **Hypoesthesia:** NR **Synovitis:** NR **Deep venous thrombosis (reported in 1 study;** [18]): 0/27 (0%) vs. 0/26 (0%) **Further reported complications:** Donor site symptoms in 1 study [23]: 0/23 (0%) vs. 4/32 (12.5%); Reflex sympathetic dystrophy in 1 study [23]: 0/23 (0%) vs. 1/32 (3.1%) Li et al. [18] further stated narratively that no postoperative infection, no deep venous thrombosis, no cases of major neurovascular, infectious, vascular, deep venous thrombosis or wound complications in any of the 80 analysed patients (of which 27, 26 and 27 received allografts, autografts and hybrid grafts, respectively) occurred. Tibial and femoral tunnel enlargement in 1 study [23]: Tibial: 12 ±20 (range: 0-90) vs. 12 ±14 (range: 0-43), n. s. with p=0.64 Femoral: 5.3 ±22 (range: 0-50) vs. 13 ±19 (range: 0-55), n. s. with p=0.771	-			
Procedure-related mortality					(0 studies)	-	

GRADE Working Group grades of evidence:

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Comments:

[a] *In Wang et al., there was a high risk of bias for selection bias and an unclear risk of bias whether patients were blinded.*

[b] *In Li et al., it was unclear whether the random sequence generation was adequate (selection bias), and whether patients were blinded.*

[c] *None of the studies showed any statistically significant differences postoperatively in the Lysholm score between the allograft and the autograft groups. The non-statistically significant differences were not unanimously higher in 1 treatment group. This may be an indicator for heterogeneity. A calculation of the i-square is further needed to adequately assess how heterogeneous the results for this outcome may be.*

[d] *The optimal information size may have not been reached.*

[e] *Heterogeneity may have been present because study results were not unanimous. A further calculation of the i-square is needed to elaborate on the extent of the heterogeneity.*

[f] *The study referred to the patients who did not need additional surgery because of recurrent or residual posterior laxity. It was unclear to the review authors whether this refers to the overall re-operations rate or only the patients with recurrent or residual posterior laxity.*

[g] *The optimal information size may have not been reached.*

Table 7-3: Summary of findings table of allografts for revision ACLR

Outcomes	№ of enrolled patients		Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of enrolled participants (studies)	Certainty of the evidence (GRADE)	Comments
	Allograft	Autograft					
EFFECTIVENESS							
Patient-reported function, activity level and symptoms assessed with: Lysholm score				-	(0 studies)	-	
Patient-reported function, activity level and symptoms assessed with: Tegner score				-	(0 studies)	-	
Patient-reported function, activity level and symptoms assessed with: Cincinnati Knee score				-	(0 studies)	-	
Patient-reported function, activity level and symptoms assessed with: SANE score				-	(0 studies)	-	
Patient-reported function, activity level and symptoms assessed with: subjective IKDC score	590	583	The study conducted a logistic regression analysis and found out that graft choice proved to be a significant predictor of 2-year IKDC score (p=0.045; OR =1.31; 95% CI: 1.01-1.70).	-	1205 (1 observational study) [16]	⨁⨁◯◯ LOW	
Patient-reported function, activity level and symptoms assessed with: KOOS score follow-up: 2 years	590	583	The study conducted a logistic regression analysis and found out that graft choice did not predict KOOS symptoms, and KOOS activities and daily living. On the contrary, KOOS sports and recreation subscale demonstrated higher scores in the setting of an autograft when compared to allograft for revision reconstruction (p=0.037; OR =1.33; 95%CI: 1.02-1.73). Results from further KOOS subscales (KOOS pain from the regression analysis comparing graft types was not reported.	-	1205 (1 observational study) [16]	⨁⨁◯◯ LOW	
Patient-reported function, activity level and symptoms assessed with: Marx activity scale follow-up: 2 years	590	583	The study conducted a logistic regression and found out that graft choice was a significant predictor of 2-year Marx activity scores (p=0.012). Specifically, the use of a combination autograft plus allograft for revision reconstruction predicted improved scores on the Marx activity scale (p=0.005; OR =3.33; 95%CI: 1.43-7.78).	-	1205 (1 observational study) [16]	⨁⨁◯◯ LOW	
Clinical knee stability assessed with: Lachman test					(0 studies)	-	
Clinical knee stability assessed with: Pivot shift test					(0 studies)	-	

Outcomes	№ of enrolled patients		Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of enrolled participants (studies)	Certainty of the evidence (GRADE)	Comments
	Allograft	Autograft					
Clinical knee stability assessed with: KT arthrometer					(0 studies)	-	
Clinical knee stability assessed with: objective IKDC score					(0 studies)	-	
Patient satisfaction					(0 studies)	-	
Health-related Quality of Life	590	583	Results from the logistic regression analysis show that the use of autografts predicted improved scores on the KOOS quality of life subscale (p=0.031; OR: 1.33; 95%CI: 1.03-1.73).		1205 (1 observational study) [16]	⨁⨁◯◯ LOW	
SAFETY							
Graft failure					(0 studies)	-	
Re-rupture rate	Results from the regression analysis: Subjects with an autograft revision were found to be 2.78 times less likely of sustaining a subsequent graft rupture compared with subjects who received an allograft (p=0.047; 95%CI: 1.01-7.69).			not estimable	1205 (1 observational study) [16]	⨁⨁◯◯ LOW	
Re-operation rate	The study only reported on the overall re-operation rate for all patients including allografts, autografts or a combination of these grafts: 150/1112 (13.5%).				1205 (1 observational study) [16]	⨁⨁◯◯ LOW	
Revisions					(0 studies)	-	
Complications					(0 studies)	-	
Procedure-related mortality					(0 studies)	-	

GRADE Working Group grades of evidence:

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Comments:

[a] *Selective outcome reporting may have been present for this specific outcome, since the results from the regression analysis were not presented.*

8 Discussion

This systematic review identified evidence consisting of 9 studies [15-23] comparing allografts to autografts for ACLR, PCLR, or revision ACLR. For revision PCLR or cruciate ligament reconstruction in patients with multi-ligament knee injuries, no evidence was identified to answer the research question.

Evidenz aus 9 Studien

In this systematic review, evidence was found indicating that allografts may be as **effective** as autografts **in ACLR and PCLR** with regard to the selected crucial effectiveness outcome of patient-reported function, activity level and symptoms (certainty: very low to moderate; evidence base: 6 RCTs with high RoB for ACLR, 2 RCTs with unclear to high RoB for PCLR).

ACLR & PCLR: vergleichbare Wirksamkeit

Concerning comparative **safety for ACLR**, moderate quality evidence was found suggesting that allografts may be less safe compared to autografts with regard to graft failures. However, with regard to the other selected crucial safety outcomes, the evidence was insufficient to clearly prove the inferiority of allografts when compared to autografts in ACLR.

Concerning comparative **safety for PCLR**, insufficient evidence was found to indicate the superiority or inferiority of allografts over autografts. Low-quality evidence was found that allografts lead to fewer complications related to infections, donor site pain, and reflex sympathetic dystrophy in comparison to autografts. However, only 1 study reported on an overall complication rate (without statistical testing), and it appears that the reported complications are related to graft harvesting and, therefore, do not capture all relevant complications.

Sicherheit:
ACLR: moderate Evidenz, dass weniger sicher in Bezug auf Transplantatversagen & unzureichend bei anderen Sicherheitsendpunkten

PCLR: unzureichende Evidenz

For **revision ACLR**, insufficient evidence was found to indicate superiority or inferiority on the basis of the selected effectiveness and safety outcomes of allografts when compared to autografts. The evidence derived from 1 large cohort study found that allografts may be inferior on the basis of some patient-reported outcomes, and may also be inferior with regard to safety due to increased risks of graft re-rupture at 2 years FU.

Revision ACLR: unzureichende Evidenz

The results of the present report are in line with other published systematic reviews and meta-analyses.

Einbettung in bestehendes Wissen

1 recent systematic review [34] included 8 randomised controlled trials with 785 combined patients comparing **soft-tissue allografts to autografts** in ACLR. The study meta-analysed subjective and objective outcomes, and concluded that soft-tissue allografts are inferior to hamstring tendon autografts with respect to subjective patient evaluation and knee stability. Superiority for allografts was found on the basis of hypoesthesia for patients undergoing primary ACL reconstruction. The study noted that, overall, the principal findings showed that hamstring tendon autografts had some clinical advantages over soft tissue allografts with respect to subjective evaluation and knee laxity.

ACLR
1 SR: HS Autograft vs. Soft Tissue Allograft: einige klinische Vorteile bei Verwendung von Autografts

Another meta-analysis [78] identified 13 RCTs, comparing **allografts to autografts** in ACLR with a total sample of 1,636 participants. This review also included primary studies with a shorter follow-up. Based on a subgroup-analysis, the study concluded that autografts are superior, when compared to irradiated allografts for patients undergoing ACLR, concerning knee function and laxity. The same study found that there are no significant differences between autografts and non-irradiated allografts. Due to the lack of blinding of the primary studies used in the meta-analysis, these results must be interpreted with caution.

Meta-Analyse: Überlegenheit der Autografts bei Vergleich mit Irradiated Allo, aber: kein Unterschied im Vergleich zu Non-Irradiated Allo

1 Meta-Analyse: Non-Irradiated Allo vs. Auto kleinen klinischen Vorteil zugunsten von Auto

Another meta-analysis [79] compared non-irradiated allografts to autografts in ACLR. The review included 12 studies with an overall sample of 1,167 patients. However, only 5 studies were RCTs. Based on their analysis, the authors concluded that autografts exhibit little clinical advantage over non-irradiated allografts on the basis of knee stability, function, and side effects. Due to the lack of limited randomised controlled trials, however, the robustness of the findings must be further validated.

1 rezenter SR Auto vs. Non-Irradiated Allo: keine stat. signifikanten Unterschiede, aber: Beobachtungsstudien eingeschlossen

Similarly, a systematic review published in 2013 [80] specifically compared autografts to non-irradiated, non-chemically treated allografts in ACLR. The review included 11 studies (RCTs, NRCTs and retrospective comparative studies), and found no statistically significant differences between autografts and non-chemically processed, non-irradiated allografts in Lysholm scores, International Knee Documentation Committee (IKDC) scores, Lachman examinations, Pivot shift testing, KT-1000 measurements, or failure rates. However, the study had less strict inclusion criteria and included – besides randomised controlled trials – prospective and retrospective comparative studies, and most of these results refer to short-term to mid-term clinical outcomes.

PCLR: 1 SR: kein Unterschied bei Funktionalität Unterschiede bei Morbiditäten, Laxität, etc.

For PCLR, 1 recent systematic review [81] published in 2018 included 25 primary studies, of which 5 studies (RCTs, NRCTs and retrospective studies) compared allograft and autografts directly. Based on the identified scientific evidence, the study concludes that there would be no significant difference in postoperative functional outcomes between patients having undergone allograft and autograft PCLR. Patients with autografts have donor site morbidities that are not associated with allograft PCLR. On the contrary, some identified evidence in the review suggests that autograft reconstruction would result in reduced posterior laxity when compared to allograft PCLR. The review [81] also states clearly that the magnitude of these findings may not be clinically significant, and that decision-making based on the currently available literature is at high risk of potential bias.

Revisions-ACLR: 1 Meta-Analyse: Allo vs. Auto: vergleichbares Transplantatversagen

Another meta-analysis [82] compared the use of allografts to autografts in revision ACLR. The review identified 8 primary studies with 3,021 patients. Yet, only 2 of these studies directly compared allografts to autografts (1 prospective comparative study and 1 retrospective prognostic study). The meta-analysis found similar failure rates between allografts and autografts, with 3.6% (95% CI: 1.4%-6.7%) and 4.1% (95% CI: 2.0%-6.9%) graft failures in these treatment groups, respectively. However, the primary aim of this review was to compare revision ACLR to autograft or allograft ACLR. Therefore, and considering the limited number of primary studies, these results must be interpreted with caution.

Limitations

Limitationen: Ausschluss von Beobachtungsstudien bei ACLR & PCLR, hohes Bias-Risiko der Primärstudien

The results of this review should be interpreted in light of its limitations. Firstly, for ACLR we only included RCTs with a long follow-up (more than 5 years) and more than 50 patients, to assess the best available evidence for effectiveness and safety questions. In addition, in the presence of RCTs, we excluded prospective, non-comparative cohort studies and retrospective studies in general, which may have led to excluding several studies with a large sample size. However, these studies are – in comparison to randomised controlled trials – more prone to internal validity concerns due to the limited information on or controlling of confounding variables.

10 RCTs bei ACLR ausgeschlossen, gleiche Problematik der unzureichenden Berichterstattung der Sicherheitsendpunkte & Doppelpublikationen

As mentioned above, for ACLR, 10 publications [83-92] defined as RCTs were excluded due to a length of follow-up <5 years. It appears that overlapping samples may have been present, and some of these studies were simply re-published at a later stage and included in this review. These studies suffer from similar limitations concerning the evaluation of comparative safety as the RCTs included in this review. It seems that the differences in complications between allografts and autografts were often not statistically tested. 1 study [84], for instance, found a higher re-rupture rate in BPTB allografts (20.6%) when compared to BPTB autografts (4.8%), and concluded that, according to their data and analysis, allografts may not be suitable for young patients who are highly active (in sports), yet the p-value was not reported. Another study [83] found a graft failure rate of 8% in the hamstring allograft group (n=46) as opposed to 2% in the hamstring autograft group (n=37), yet this difference was not statistically significant (p>0.05). Furthermore, 2 publications [87, 88] that were probably the same study reported on a graft failure rate of 34.4%, 6.1%, and 8.8% for irradiated allografts, autografts, and non-irradiated allografts, respectively (p-value was not reported). However, it seems that these publications may refer to a study that was included in this assessment and was published at a later stage with a longer follow-up period [22]. The remaining publications [85, 86, 89-92] suffered from similar limitations regarding reporting on complications in a standardised, comparative manner. Therefore, and while RCTs with shorter FU are available for ACLR, it was judged to be unlikely that these RCTs may change the findings/conclusions of this review.

Ausschluss der RCTs mit kurzem FU auf Basis der "best available evidence"

Secondly, numerous different types of grafts within allogenic ligaments are available. It was unclear how far these differences (e.g., when it comes to disinfection procedures) affect clinical outcomes. The medical literature [93], describes the specific graft types to be equipped with unique advantages and disadvantages. This may affect the generalisability derived from results that were found for one specific graft type and could influence the general comparison of allograft versus autograft. Applicability concerns are described in the applicability table (see Table A-10).

Thirdly, the fact that all primary studies had unclear to high RoB (RCTs) or moderate RoB (cohort study), combined with a poor reporting on complications, must be mentioned as another significant limitation. In this context, one further main limitation of this work, as evident with all studies investigating ACLR or PCLR, is the lack of an objective assessment of numerous outcomes (e.g., rotational knee stability, knee function, etc.) within primary research. All of the aforementioned limitations manifested in the GRADE assessment, and lead, among other factors, to very low to moderate certainty to believe in the evidence of the outcomes selected in this assessment.

Finally, a minimally clinically relevant difference was not defined. It may be worthwhile to define a clinically relevant difference and use quantitative analysis to evaluate whether the statistically significant differences found within a review are also clinically relevant. In our context, most of the crucial outcomes containing sufficient data did not clearly favour one graft over the other (no statistically significant differences in patient-reported function, activity level and symptoms in ACLR and PCLR). However, evidence was found, suggesting that allografts are inferior with regard to safety for ACLR, consisting mainly of 2 studies [15, 22] that were applicable for highly active, young patients (1 study [15]), or for irradiated allografts as an intervention (1 study [22]). The other ACLR and PCLR studies did not specifically and sufficiently report on this safety outcome as mentioned above.

Economic evaluations

gesundheitsökonomische Evaluationen in Ö wesentlich

When investigating the benefits of one medical procedure over another, results from health economic evaluations may provide valuable supplementary information. Four economic evaluations [94-97] were identified and procured through the abstract screening process. Of those, 1 study was a cost-effectiveness analysis comparing different graft types, i.e., BPTB autografts, hamstring autografts, and allografts (not further specified) in the United States. In this analysis, hamstring tendon (HS) autografts were the least costly ($5,375/surgery), but the most effective, with 0.912 quality-adjusted life years (QALYs). Allograft ACLR, on the contrary, was the most costly treatment modality ($1,585/case additional to HS autograft) and least effective (0.912 QALYs). The remaining 3 studies [95-97] were simple economic cost comparisons conducted in the United States: 2 studies [96, 97] found that allografts are more costly when compared to autografts, while 1 study [95] concluded that autografts may be the pricier graft choice. Of the 2 cost-comparisons favouring autografts, 1 study [94] measured a total mean cost (incl., supply cost, case time per min, personnel, and facility cost) of $3,154 ±704 for an autograft versus $4,147 ±943 for an allograft. Another cost-comparison [95] measured a mean total cost of $5,465 for allograft ACLR and $4,872 for autograft ACLR ($p=0.009$). The latter analysis was based on retrospectively reviewing 155 patients who underwent ACLR (charges were extracted from itemised billing records; yet surgeon and anaesthesiologist fees were not included in the analysis). The other less-recent cost-comparison [96] conducted in 2005 favoured allografts and based their analysis on hospital charge data solely: the study measured a mean hospital charge for ACLR of $4,622 ±524 for allograft ACLR, as opposed to $5,694 ±809 for autografts ($p<0.0001$). Due to the fact that these economic evaluations were conducted in the United States and that no critical appraisal of these studies was conducted, these results (and its applicability) must be interpreted with caution.

Ongoing studies

The search for ongoing studies revealed that none of the studies currently being undertaken may change the evidence base significantly, given that only 2 ongoing RCTs were identified, of which only 1 was relevant, comparing allografts to autografts in ACLR. The other ongoing RCT compared allografts to animal tissues (Z-lig) used in ACLR (see Table A-11, Table A-12, Table A-13, and Table A-14 in the Appendix).

According to information from the manufacturers, 2 studies (incl. 1 RCT) are currently being conducted in Austria. However, study protocols are not publicly available.

Conclusion

For ACLR, the evidence found in this systematic review indicates that allografts may be equally effective compared to autografts, and moderate evidence indicates that it may be less safe in ACLR with regard to graft failure. However, the evidence for comparative safety was insufficient for the remaining safety outcomes.

Regarding **PCLR**, the effectiveness of allograft may be comparable to autografts, yet insufficient evidence was found for comparative safety.

Insufficient evidence was found for **revision ACLR,** and no evidence was found for the remaining indications used in this review (**revision PCLR, cruciate ligament reconstruction in multi-ligament knee injurie**s).

weitere Forschung und Leitlinien wesentlich

Further research should focus on more high-quality, randomised controlled trials with comprehensive safety reporting. In addition, questions regarding differences between types of allografts should be addressed. Evidence-based guidelines should clearly state the role of allografts in the management of cruciate ligament reconstruction.

9 Recommendations

In Table 9-1 the scheme for recommendations is displayed and the according choice is highlighted.

Table 9-1: Evidence-based recommendations

	The **inclusion** in the catalogue of benefits is **recommended**.
	The **inclusion** in the catalogue of benefits is **recommended with restrictions**.
X	The inclusion in the catalogue of benefits is ***currently*** **not recommended.**
	The **inclusion in** the catalogue of benefits is **not recommended.**

Reasoning:

The current evidence indicates that allografts may be equally effective, but less safe in ACLR with regard to graft failures. Regarding PCLR, effectiveness may be comparable, but insufficient evidence was found for the comparative safety of allografts when compared to autografts. The evidence is insufficient for revision ACLR, and no evidence was found for the remaining indications.

The overall strength of evidence for the effectiveness and safety – based on the selected crucial outcomes – of allograft ACLR in comparison to autograft ACLR is low.

The overall strength of evidence for the effectiveness and safety – based on the selected crucial outcomes – of allograft PCLR in comparison to autograft PCLR is very low.

The overall strength of evidence for the effectiveness and safety of revision allograft ACLR– based on the selected crucial outcomes – in comparison to autograft ACLR is low.

For the remaining indications (e.g., revision PCLR, cruciate ligament reconstructions in multi-ligament knee injuries), no evidence is available to assess the effectiveness and safety of allografts compared to autografts.

For the comparison of allograft cruciate ligament reconstruction to conservative management, no evidence is available to assess the effectiveness and safety of allografts compared to autografts.

In the absence of ongoing RCTs providing an answer to the question chosen in this assessment, it is unlikely that the evidence will change. A re-evaluation is, therefore, not recommended for the present.

10 References

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: Allograft versus autograft for anterior cruciate ligament reconstruction: results from randomised controlled trials

Author, year	Bottoni 2015 [15]	Sun 2009 [20]	Sun 2011 [21]	Tian 2016 [22]	Li 2015 [19]	Jia 2015 [17]
Country	United States of America	China	China	China	China	China
Sponsor	Arthrex, Inc. and the Musculoskeletal Transplant Foundation	Supported by Natural Science Foundation of China Grant No. 2004GG2202034	Research funding was provided by the Key Project of the Provincial Science Foundation of Shandong	NR	NR	Nil
Interventions/Products	Fresh-frozen, non-irradiated tibialis posterior tendon **allograft**	Fresh frozen, non-irradiated BPTB hemi-**allograft**	Fresh-frozen, non-irradiated hamstring tendon **allograft**	Fresh-frozen, irradiated hamstring tendon **allograft**	4-stranded, γ-irradiated tibialis anterior tendon **allograft**	Bone-patellar tendon-bone **allograft**[11]
Comparator	4-stranded hamstring **autograft**	BPTB **autograft**	4-stranded hamstring tendon **autograft**	Hamstring tendon **autograft**	4-stranded gracilis and semitendinosus tendon **autograft** **Hybrid graf**t (γ-irradiated tibialis anterior tendon allograft and semitendinosus tendon autograft)	Hamstring **autograft**
Surgical procedure	ACLR (not further specified)	Arthroscopic ACLR	Arthroscopic ACLR	Arthroscopic anatomic double bundle ACLR	ACLR (not further specified)	Arthroscopic ACLR
Study design	RCT	RCT	RCT	RCT	RCT	RCT
Number of pts[12]	99 pts (100 knees) 50 vs. 50 (knees)	172[13] 86 vs. 86	208[14] 104 vs. 104	107[15] 53 vs. 54	102[16] 34 vs. 34 vs. 34	106[17] 53 vs. 53

[11] Allografts were pre-soaked in gentamicin and dexamethasone.

[12] At time of randomisation.

[13] 218 pts underwent ACL reconstruction. Of those, 195 pts were eligible to participate in the study. 172 pts provided written, informed consent and were randomised to different treatment groups.

[14] 256 pts were assessed for eligibility, of which 208 were randomised to the different treatment groups.

[15] 121 pts were assessed for eligibility, of which 107 were eligible and randomised to the different treatment groups.

[16] 281 pts were assessed for eligibility, of which 102 patients were randomised to the different treatment groups.

[17] 122 pts were assessed for eligibility, of which 106 patients were randomised to the different treatment groups.

Author, year	Bottoni 2015 [15]	Sun 2009 [20]	Sun 2011 [21]	Tian 2016 [22]	Li 2015 [19]	Jia 2015 [17]
Inclusion criteria	Patients 18 years of age or older with symptomatic ACL deficiency, confirmed by MRI	Only primary unilateral reconstructions of the ACL were included in the study.[18] Patients with minor medial collateral ligament sprains (lower than grade II), previous diagnostic arthroscopy, or meniscal tears were not excluded from the study.	✵ Only primary unilateral reconstructions of the ACL were included in the study[18]. ✵ No previous injury or surgery on the affected knee, ✵ no multiple ligamentous injuries or malalignment, and ✵ ability to complete the study protocol. Patients with minor medial collateral sprains (<grade 2), meniscal tears and or previous diagnostic arthroscopes were not excluded.	Patients with acute or chronic ACL ruptures Only primary unilateral reconstructions of the ACL were included in the study[18].	Unilateral ACL rupture verified clinically by positive Lachman test and positive Pivot shift test findings. All patients had undergone a preoperative MRI scan to confirm the ACL rupture. All patients with normal preoperative CRP (<10 mg/L) and ESR (≤15 mm/h) values were included.	Diagnosis with ACL tear by physical examination and magnetic resonance imaging, normal alignment, normal contralateral knee, and willingness to join the rehabilitation programme
Exclusion criteria	✵ Multiligamentous injuries (concomitant grade I or II medial collateral ligament injuries were not excluded), ✵ previous knee ligament surgery (previous knee arthroscopic surgery was not excluded), and ✵ time remaining on the island of less than 6 months	Patients were excluded from the study if they had had ✵ a previous injury to or surgery on the affected knee, ✵ multiple ligamentous injuries, or malalignment, or ✵ if they lacked the ability to complete the study protocol. Patients undergoing revision reconstruction and those with associated injuries of the posterior cruciate ligament or posterolateral corner or with deficiency or reconstruction of the ACL in the contralateral knee were also excluded.	Revision reconstruction and patients with associated injuries of the posterior cruciate ligament or the posterolateral corner, with deficiency, or a reconstruction of the ACL in the contralateral knee were excluded.	Pts were excluded if they had ✵ a previous injury or ✵ surgery on the affected knee, ✵ had open physes present, ✵ had severe arthritic changes in the knee, ✵ had multiple ligamentous injuries, ✵ had malalignment, ✵ lacked the ability to complete the study protocol ✵ a revision reconstruction, ✵ associated injuries of the posterolateral corner, and deficiency or ✵ reconstruction of the ACL in the contralateral knee.	✵ Combined multiple-ligament injuries, ✵ previous ACL surgery, ✵ contralateral knee ligament injury, ✵ radiographically verified osteoarthritis Patients with pre-existing metabolic pathologies such as diabetes mellitus or uremia were excluded from the study. Those patients who could not finish the minimum clinical follow-up period of 5 years were also excluded.	NR

[18] All pts had an MRI scan obtained preoperatively to exclude combined, complicated ligament injuries to their knees.

Author, year	Bottoni 2015 [15]	Sun 2009 [20]	Sun 2011 [21]	Tian 2016 [22]	Li 2015 [19]	Jia 2015 [17]
Rehabilitation (before or after ACLR)	Physical therapy[19] (Standardised protocol)	Physical therapy[19] (Same protocol)	Physical therapy[19] (Same protocol)	Physical therapy[19] (Same protocol)	Physical therapy[19] (Standardised protocol)	Physical therapy[19] (Same programme)
Age of patients, mean ±SD (range), yrs	29.2 ± 5.5 (20.7-41.5) vs. 28.9 ± 5.8 (20.6-42.5)	32.8 ±7.1 (19-65) vs. 31.7 ±6.3 (20-54)[20]	31.2 ±8.3 (18-59) vs. 29.6 ±6.9 (19-56) [20]	28.6 ±7.2 (18-50) vs. 29.2 ± 6.9 (18-55)[20]	30.5 ±6.1 vs. 29.8 ±7.9 vs. 31.6 ±8.2[21] [20]	28 vs. 31[22]
Sex, n female (%)	6 (12.2) vs. 7 (14.6)	17 (21.3) vs. 15 (20)[20]	17 (17.9) vs. 20 (22)[20]	9 (20.9) vs. 8 (20)[20]	17 (53.1) vs. 15 (46.9) vs. 13 (41.9)[20]	27 (50.9) vs. 25 (47.2)
Further relevant patient characteristics at baseline & co-interventions	95% of pts were in the military (active-duty). Concomitant meniscal and chondral pathologic abnormalities, micro-fracture, and meniscal repair performed at the time of reconstruction were similar in both groups[23].	No statistically significant differences between treatment groups when considering arthroscopic findings and treatments at time of ACLR No. of pts with normal meniscus (no treatment of meniscal tears at time of ACL reconstruction): 36/80 pts (45%) vs. 36/76 pts (47%)[24]	No statistically significant differences between treatment groups when considering arthroscopic findings and treatments at time of ACLR No. of pts with normal meniscus (no treatment of meniscal tears at ACL reconstruction): 48/95 pts (50.5%) vs. 45/91 pts (49.5%)	No statistically significant differences between treatment groups when considering arthroscopic findings and treatments at time of ACLR No. of pts with normal meniscus (no treatment of meniscal tears at ACL reconstruction): 18/43 pts (41.9%) vs. 16/40 pts (40.0%)	No statistically significant differences when considering associated injuries and treatments before ACLR No. of pts. with no treatment of meniscal tears: 3/32 pts (9.4%) vs. 6/32 pts (18.8%) vs. 7/31 pts (22.6%)	Baseline characteristics insufficiently described
Mean follow-up (in yrs)	10.5, range: 10-11[25]	5.6, range: 4-8	7.8, range: 6-10 7.9 (SD: 1.1) vs. 7.6 (SD: 0.9)	6.9, range: 5.5-8 6.8 (SD: 0.8) vs. 7 (SD: 0.7)	5.9 (overall mean), range: 5-7 6.1 (SD: 0.3) vs. 5.8 (SD: 0.9) vs. 5.9, SD: 0.6	6.75, range: 2.33–7.16[26]

[19] Physical therapy may have included, but was not limited to, the following: Pre-operative therapy to restore full knee range, normal gait and eliminate knee swelling. Post-operative: Full extension range of motion, strengthening exercises, range of motion brace (for 4 weeks post surgery), and a functional brace for sport activities (for 1-2 years after surgery). Adaptations for range of motion restriction and weightbearing status applied, with accompanying meniscal and chondral surgery. 2 studies explicitly reported that physical therapy provided outside of the institution may have varied and may have been a factor that influenced the outcomes.

[20] The study only described information on the age and sex of the patients who were analysed (as opposed to the number of pts who were originally randomised). Therefore, the denominator used to calculate the percentages is the number of patients analysed in the respective treatment group.

[21] The range of the variable age was not reported in the study.

[22] SD and range were not reported.

[23] No statistically significant differences were found when comparing the respective baseline characteristics between allograft and autograft groups, except for lateral compartment: grade 0: 43 (87.8%) vs. 35 (72.9%); grade 1: 3 (6.1%) vs. 3 (6.3%); grade 2: 1 (2%) vs. 6 (12.5%); grade 3: 2 (4.1%) vs. 0 (0%); grade 4: 0 (0%) vs. 4 (8.3%). Diff. of LC category was s. s. with p=0.034.

[24] Pts with meniscal tears underwent partial meniscectomy or repair.

[25] Converted to yrs by review authors. FU reported in study: 126 months (mean), range: 120-132.

[26] Converted in yrs by review authors. FU reported in study: 81 months (mean), range: 28–86.

Author, year	Bottoni 2015 [15]	Sun 2009 [20]	Sun 2011 [21]	Tian 2016 [22]	Li 2015 [19]	Jia 2015 [17]
Loss to follow-up, n (%)[27]	Overall: 3 (3) 1 vs. 2[28]	Overall: 16 (9.3) 6 (6.9) vs. 10 (11.6)	Overall: 22 (10.6) 9 (8.7) vs. 13 (12.5)	Overall: 24 (22.4) 10 (18.9) vs. 14 (25.9)	Overall: 7 (6.8) 2 (5.9) vs. 2 (5.9) vs. 3 (8.8)	Overall: 0 (0) 0 (0) vs. 0 (0)
Pts included in analysis, n	49 vs. 48 (knees[29])	80 vs. 76	95 vs. 91	43 vs. 40	32 vs. 32 vs. 31	53 vs. 53
Outcomes						
Effectiveness						
Patient-reported function, activity level and symptoms						
✿ Lysholm score, mean ±SD (range)	NR[30]	Preoperative: 60 ±9 (32-76) vs. 59 ±11 (33-78) At final FU: 91 ±6 vs. 90 ±8; diff. n. s., with p=0.586[31]	Preoperative: 59 ±10 (33-78) vs. 60 ±12 (35-79) At final FU: 90 ±8 vs. 89 ±9; diff. n. s., p=0.595[31]	Preoperative: NR[32] At final FU: 86 ±9 (50-100) vs. 90 ± 11 (65-100); diff. n. s., with p=0.0727	Preoperative: NR[33] scores "after surgery"[34]: 88.7 ±8.6 vs. 91.3 ±11.5 vs. 90.5 ±10.2; diff. n. s., with p=0.213	Preoperative: 71.0 ± 3.6 (66–83) vs. 71.9 ± 4.2 (69–84)[35] Postoperative score: 86.8 ± 2.6 (81–90) vs. 85.2 ± 3.1 (80–95); diff. n. s., with p>0.05[36]
✿ Tegner score, mean ± SD (range)	Preoperative: NR Postoperative[37]: 4.5 ± 2.2 vs. 4.8 ± 2.3; diff. n. s, with p=0.505	Preoperative: 3.0 ±1.7 (1-6) vs. 3.1 ±1.5 (1-6) At final FU: 7.6 ±1.9 vs. 7.8 ± 1.6, diff. n.s, with p=0.871[38]	Preoperative: 3.1 ±1.5 (1-7) vs. 3.0 ±1.3 (1-6) At final FU: 7.6 ±1.5 vs. 7.7 ±1.8, diff. n. s., with p=0.936[38]	Preoperative: NR[32] At final FU: 7.3 ± 1.3 (3-9) vs. 7.8 ± 1.2 (3-9); diff. n. s. with p=0.0730	Preoperative: NR[33] Scores "after surgery"[34]: 7.0 ±2.1 vs. 7.3 ±1.3 vs. 7.5 ±1.5; diff. n. s., with p=0.416	NR

[27] Due to the fact that calculating the loss to follow-up is sometimes confused in clinical studies, the loss to FU was calculated by the review authors using consistent criteria [98]: The follow-up rate was calculated using the number of randomised patients as the denominator and the number of patients analysed as the numerator. The difference between randomised and analysed patients was therefore considered to be patients lost to FU.

[28] The review authors judged it to be spurious that the investigators switched constantly between knees and patients when reporting characteristics of patients and results. Given that it was only reported that 50 knees were randomised in two groups, the percentage for the loss to FU in each group was not estimable. Of the pts lost to FU, 2 were deceased, and 1 patient was lost to FU for other reasons.

[29] It was unclear to the review authors whether the presented results refer to 97 knees or patients, because the study did not clearly report it. Given that 3 patients were lost to FU, 97 knees must have been considered in the analysis.

[30] The study reported that the Lysholm score was measured and there was no statistically significant difference in the Lysholm score between treatment groups. However, no results of the Lysholm score were reported in the publication of the study.

[31] Significant differences were found according to the scores preoperatively and postoperatively ($p<0.05$).

[32] The study stated that preoperative subjective outcomes were measured preoperatively and at the final FU. However, preoperative scores were not reported.

[33] The study stated that there were no significant differences in the (preoperative) Lysholm score, Tegner activity score, or IKDC evaluation score (subjective, objective).

[34] Data of the subjective evaluation were reported as "after surgery" only. Significant improvements at last follow-up compared with preoperative values.

[35] Difference in baseline score between groups was n. s. ($p>0.05$).

[36] The study did not report on whether the postoperative score was statistically significantly different when compared to the baseline score.

[37] Specific time point was not mentioned.

[38] Significant differences were found according to the scores preoperatively and postoperatively ($p<0.05$).

Author, year	Bottoni 2015 [15]	Sun 2009 [20]	Sun 2011 [21]	Tian 2016 [22]	Li 2015 [19]	Jia 2015 [17]
❁ Cincinnati Knee score, mean ±SD (range)	NR	Preoperative: NR Postoperative[39]: 92 ±11 (62-100) vs. 91 ±12 (59-100); diff. n. s., with p=0.949	Preoperative: NR Postoperative[39]: 91 ±11 (58-100) vs. 90 ±10 (55-100); diff. n. s. (p=0.927)	Preoperative: NR[32] At final FU: 87 ± 12 (45-100) vs. 90 ± 10 (50-100); diff. n. s., with p=0.2214	NR	NR
❁ SANE score, mean ±SD	Preoperative: NR 10-year follow-up: 78.8 ± 18.8 vs. 81.5 ±16.4; differences n. s. with p=0.454	NR	NR	NR	NR	NR
❁ IKDC score (subjective), mean ±SD (range)	Preoperative: NR Postoperative[39]: 73.7 ± 25.9 vs. 77.2 ± 25.4, n. s. with p=0.510	Preoperative: NR Postoperative[39]: 88 ±9 (65-100) vs. 90 ±10 (64-98); differences n. s., with p=0.442	Preoperative: NR Postoperative[39]: 90 ±14 (65-100) vs. 89 ± 12 (60-100); differences n. s., with p=0.548	Preoperative: NR[32] At final FU: 85 ± 11 (60-100) vs. 89 ± 9 (65-100); differences n. s., with p=0.0748	Preoperative: NR[33] Scores "after surgery"[34]: 83.8 ±6.9 vs. 87.5 ±3.2 vs. 89.8 ±5.7; differences n. s., with p=0.353	Preoperative: 66.1 ± 3.5 (60–74) vs. 67.3 ± 2.5 (61–78)[35] Postoperative score[40]: 85.6 ± 2.9 (81–91) vs. 87.8 ± 1.6 (82–90); diff. n. s., with p>0.05[41]
❁ KOOS score (e.g., symptoms, pain, sports and activity)	NR	NR	NR	NR	NR	NR
❁ Marx activity scale	NR	NR	NR	NR	NR	NR
Clinical knee stability						
❁ Lachman test (grade 0-1), n (%)	NR	At final FU: 74 (92.5) vs. 71 (93.4) Differences n. s., with p=0.06	At final FU: 87 (91.6) vs. 84 (92.3) Differences n. s., with p=0.968	At final FU: 31 (72) vs. 37 (93) Differences s. s., with p<0.001	At final FU: 28 (87.5) vs. 30 (93.8) vs. 30 (96.8) Differences n. s., with p=0.209	**NR**[42]
❁ Pivot shift test (grade 0-1), n (%)	NR	At final FU: 80 (100) vs. 76 (100) differences n. s., with p=0.169	At final FU: 95 (100) vs. 91 (100) differences n. s., with p=0.855	At final FU: 38 (88.4) vs. 40 (100); differences s. s., with p=0.004	At final FU: 31 (96.9) vs. 32 (100) vs. 31 (100) Differences n. s., with p=0.249	**NR**[42]

[39] The time point was not clearly reported.

[40] The study did not clearly state whether the subjective or objective IKDC score was used. Due to the fact that the objective IKDC variable has 4 distinctive characteristics (normal, nearly normal, abnormal, and severely abnormal), it was assumed that the extracted numbers referred to the subjective IKDC score.

[41] The study did not report on whether the postoperative score was statistically significantly different when compared to the baseline score.

[42] The study did mention that the Lachman test was measured. Grade 1 scores can be found for the Lachman test (6/53 vs. 7/53) and Pivot shift test (13/53 vs. 11/53), but the rest of the patients were classified with a "–". Given that no explanation was provided whether those patients were negative or grade 0, we did not extract this data.

Author, year	Bottoni 2015 [15]	Sun 2009 [20]	Sun 2011 [21]	Tian 2016 [22]	Li 2015 [19]	Jia 2015 [17]
✿ Side-to-side difference in mm, mean ±SD (range)	NR	Postoperative[43] (measured with the KT-2000 arthrometer: 2.5 ±0.9 (0-5.6) vs. 2.4 ±0.7 (0-5.4); diff. n. s., with p=0.369	Postoperative[44] (measured with the KT-2000 arthrometer): 2.7 ±0.9 (0-7) vs. 2.5 ±0.7 (-1-7); diff. n. s., with p=0.314	Postoperative[45] (measured with the KT-2000 arthrometer): 5.5 ±1.0 (0-10) vs. 2.4 ±0.7 (0-7); diff. s. s., with p<0.001	At final FU (measured with the KT-1000 arthrometer): 3.5 ±1.2 (NR[46]) vs. 2.1 ±1.6 (NR[47]) vs. 2.0 ±1.5 (NR[48]) Diff. s. s. with p=0.025	NR
✿ IKDC score (objective; normal and nearly normal), n (%)[49]	NR	At final FU: 75 (93.8) vs. 72 (94.7); diff. n. s., with p=0.285	At final FU: 86 (90.5) vs. 85 (93.4) Diff. n. s., with p=0.707	At final FU: 38 (88.4) vs. 38 (95) Difference in objective IKDC scores between groups n. s., with p=0.435	At final FU: 29 (90.6) vs. 29 (90.6) vs. 28 (90.3); differences n. s., with p=0.880	NR
Patient satisfaction	NR	NR	NR	NR	NR	Satisfied: 46/53 (86.8%) vs. 47/53 (88.7%) Nearly satisfied: 7 (13.2%) vs. 5 (9.4%) Diff. n. s.; p>0.05[50]
Health-related Quality of Life	NR	NR	NR	NR	NR	NR
Safety outcomes						
Graft failure rate, n (%)	13 (26.5) vs. 4 (8.3), diff. s. s., with p=0.031[51]	NR	NR	Defined as knee laxity >5mm (KT-2000): 13 (30.2) vs. 3 (7.5), diff. s. s., with p<0.001	NR	NR[52]

[43] Unclear time point.

[44] Unclear time point.

[45] Unclear time point.

[46] 95%CI was reported instead of the range: 3.1-4.1.

[47] 95%CI was reported instead of the range: 1.6-2.6.

[48] 95%CI was reported instead of the range: 1.4-2.6.

[49] The overall IKDC score has 4 qualitative characteristics regarding knee functionality: normal, nearly normal, abnormal, and severely abnormal. In this assessment, only the number of pts with normal and nearly normal characteristics were extracted and summarised.

[50] The study only stated that **patient satisfaction** was measured using a questionnaire. The instrument was not reported.

[51] The study stated that 17 patients failed their index operation and sustained graft failure, requiring revision ACL reconstruction. The study did not state how graft failure was defined. It appears that revision ACL reconstruction may have been an indicator for graft failure for the investigators. The authors of the study were contacted for further information, but no information was provided by them.

[52] The study reported that "(…) graft failure proportions were larger for allografts than for autografts, but after statistical analysis, the differences were not significant". Further information was not reported.

Author, year	Bottoni 2015 [15]	Sun 2009 [20]	Sun 2011 [21]	Tian 2016 [22]	Li 2015 [19]	Jia 2015 [17]
Re-rupture rate	NR [53]	NR	NR	NR	NR	NR[54]
Re-operation rate, n (%)	NR[55]	NR	NR[56]	NR[57]	NR[58]	NR
Revisions, n (%)	13 (26.5) vs. 4 (8.3), diff. s. s., with p=0.031	NR	NR	NR	The study stated that no patient needed additional surgery because of recurrent or residual symptoms.	NR
Overall complications, n (%)	NR	NR	NR	NR	NR	NR
❁ Arthrofibrosis, n (%)	NR	NR	0 (0) vs. 0 (0)	0 (0) vs. 0 (0)	NR	NR[59]
❁ Effusion, n (%)	NR	NR	NR	NR	NR	NR
❁ Tenderness, n (%)	NR	NR	0 (0) vs. 2 (2.1)[60]; p=NR	NR	NR	NR
❁ Infection, n (%)	NR	Postoperative infection: 1 (1.25)[61] vs. 0 (0); p=NR	2 (2.1) vs. 0 (0)[62]; p=NR	2 (4.6) vs. 0 (0)[62]; p=NR	The study stated that no postoperative infection occurred.	NR
❁ Hyposthesia, n (%)	NR	NR	0 (0) vs. 3 (3.3); p=NR	0 (0) vs. 3 (7.5); p=NR	NR	NR
❁ Synovitis, n (%)	NR	NR	NR	NR	NR	NR
❁ Deep venous thrombosis, n (%)	NR	2 (2.5) vs. 1 (1.3); p=NR	0 (0) vs. 0 (0)	0 (0) vs. 0 (0)	NR	NR

[53] The 17 patients who failed their index operation sustained graft failure and required revision ACL reconstruction. This number may also represent the re-rupture rate, given that the patients needed revision ACL reconstruction.

[54] The study stated that the rate of ligament rupture after primary reconstruction was higher in the allograft group, but the difference was not statistically significant. Further information was, however, not reported.

[55] The data only refers to revision ACL reconstruction and may not include other re-operations.

[56] The study did mention that no postoperative complications required reoperation or readmission. The authors judged this information to be insufficient to calculate the re-operation rate.

[57] The study did mention that no complications required reoperation. The authors judged this information to be insufficient to calculate the overall re-operation rate.

[58] The study stated that no patient needed additional surgery because of recurrent or residual symptoms. This information was judged insufficient to calculate the re-operation rate.

[59] The study stated that no statistically significant differences were found when comparing the incidence of arthrofibrosis between groups at the final FU. However, further information was not reported.

[60] The 2 patients in the autograft group had tenderness or irritation at the graft harvest site.

[61] There was 1 patient (1.25%) in the allograft group with a late infection that required antibiotic treatment.

[62] There were 2 patients with a superficial wound infection in the allograft group at the incision area who needed antibiotic treatment and healed well soon after.

Author, year	Bottoni 2015 [15]	Sun 2009 [20]	Sun 2011 [21]	Tian 2016 [22]	Li 2015 [19]	Jia 2015 [17]
✿ Other complications	Tibial and femoral tunnel widening was higher, yet not s. s. different, in the allograft group at final follow-up. **Tibial (in mm), mean (range):** 9.2 (7-10) vs. 8.9 (7-10); diff. n. s. with p=0.651 **Femoral (in mm), mean (range):** 8.8 (7-10) vs. 8.3 (7-10), diff n. s. with p=0.453	The mean postoperative fever time (axillary temperature >38°C, which was taken by nurses for 10 minutes) in the allograft group (mean, 6.8 days; range, 4.4 to 9.8 days) was 2.4 days longer than that in the autograft group (mean, 4.4 days; range, 3.5 to 6.9 days). Diff. s. s., with p<0.05	The study stated that there were **no cases of the following complications** in either treatment group during the study: ✿ arthrofibrosis, ✿ anterior knee pain ✿ pain on kneeling, ✿ deep infection, ✿ deep venous thrombosis, ✿ failure of fixation, ✿ blowout fracture, ✿ reoperation issues such as removal of staples, or ✿ failed meniscal repairs.	There were no cases of ✿ deep venous thrombosis, ✿ deep infection, arthrofibrosis, ✿ pain when kneeling, ✿ anterior knee pain, ✿ failure of fixation, or ✿ blowout fracture in either treatment group during the study. Arthritic progression: 14 (32.6%) vs. 4 (10%), diff. s. s., with p<0.05[63]	Regarding complications, the study stated that there **were no cases of** major neurovascular, infectious, vascular, or wound complications.	Tibial and femoral widening was s. s. higher in the allograft group (p<0.05). Scores at final follow-up: **Tibial (in mm), mean ±SD:** 7.8 ±0.4 vs. 7.61 ±0.22, **Femoral (in mm), mean ±SD:** 7.64 ±0.35 vs. 7.51 ±0.42
Procedure-related mortality, n (%)	NR	NR	NR	NR	NR	NR

Abbreviations *ACL – anterior cruciate ligament;* ***ACLR – anterior cruciate ligament reconstruction; BPTB – bone-patellar tendon-bone;*** *CI – confidence interval; diff. – difference; FU – follow-up; IKDC – International Knee Documentation Committee; KOOS – Knee injury and Osteoarthritis Outcome Score;* ***MRI – magnetic resonance imaging;*** *n. s. – not statistically significant; NR – not reported; Pts – patients;* ***RCT – randomised controlled trial;*** *s. s. – statistically significant;* ***SANE – Single Assessment Numerical Evaluation;*** *SD – standard deviation; vs. – versus; yrs – years.*

[63] It appears that a typing error occurred in the included study: in the abstract, the study reports that "(…) 32.6% (19/43)" patients had arthritic progression in the allograft group (note: wrong calculation, since this should be 44.2% then), while in the text it is written that 14/43 (32.6%) had arthritic progression in the allograft group.

Table A-2: Allograft versus autograft for posterior cruciate ligament reconstruction: results from randomised controlled trials

Author, year	Li 2016 [18]	Wang 2004 [23]
Country	China	Taiwan
Sponsor	NR	NR
Interventions/Products	4-stranded y-irradiated tibialis anterior tendon **allograft**	**Allograft** (incl. Achilles tendon and anterior tibial tendons)
Comparator	Gracilis and semitendinosus tendon **autograft** **Hybrid graf**t (y-irradiated tibialis anterior tendon allograft and semi-tendinosus tendon autograft	**Autograft** (incl. quadriceps tendon-patellar bones and quadruple hamstrings)
Surgical procedure	Arthroscopic single-bundle PCLR	Arthroscopic single-bundle PCLR
Study design	RCT	RCT
Number of pts	90[64] 30 vs. 30 vs. 30	55 23 vs. 32
Inclusion criteria	✿ persistent posterior laxity greater than or equal to grade 2, ✿ lack of response to conservative treatment (medication and physical therapy) for more than 3 months, and ✿ objective evidence of PCL rupture by MRI.	NR[65]
Exclusion criteria	✿ concomitant injury to other knee ligaments, ✿ previous surgery on the injured knee, or ✿ articular cartilage lesions greater than Outerbridge grade II based on the preoperative MRI scan and diagnostic arthroscopic examination	Patients with PCL avulsion fracture and combined ligament injuries were not included.
Rehabilitation (before or after PCLR)	The 3 groups of patients followed the same postoperative rehabilitation programme. Physiotherapy[66] Rehabilitation outside the hospital was not controlled.	Patients received the same postoperative rehabilitation (incl. e.g., exercise, functional knee braces, etc.). Physiotherapy: NR
Age of patients, mean ±SD (range), yrs	32.2 ±7.8 (20-40) vs. 31.3 ±6.2 (20-40) vs. 30.6 ±7.5 (20-40)[67]	30 ±12 (16-64) vs. 29 ±12 (16-54)
Sex, n female (%)	11 (40.7) vs. 9 (34.6) vs. 10 (37) [67]	7 (30.4) vs. 7 (21.9)

[64] 116 pts were assessed for eligibility. Of those, 90 pts were randomised in the 3 treatment groups.

[65] The study only reported that it consisted of patients who underwent PCLR. In this context, the study states that the indication for surgery included pain and instability because of high-energy posterior cruciate ligament injury with failure of conservative treatments for 3 months.

[66] Post-operative physiotherapy may have included, but was not limited to, the following: a functional brace (6-12 weeks), passive range of motion exercises, progressive weight bearing after 2 weeks, and closed kinetic chain exercises.

[67] The study reported on demographic data using the analysed (not the enrolled) patients. Therefore, the denominator(s) are the analysed patients within the groups.

Author, year	Li 2016 [18]	Wang 2004 [23]
Further relevant patient characteristics	Pts with tears of the meniscus underwent partial meniscectomy (if irreparable) or repair. No. of pts. with no treatment of meniscal tears: 10/30 pts (33.3%) vs. 9/30 pts (30%) vs. 9/30 pts (30%); diff. n. s.	Associated injuries were treated accordingly before PCLR. **Concomitant treatments[68]:** 5 meniscectomies 3 meniscus repairs 3 debridement for chondral lesions
Mean follow-up in yrs ±SD	Overall[69]: 5.6 5.7 ±0.3 vs. 5.5 ±0.2 vs. 5.6 ±0.5	Overall[70]: 2.83 2.83 vs. 2.75
Loss to follow-up, n (%)	Overall: 10 (11) 3 (10) vs. 4 (13.33) vs. 3 (10)	NR[71]
Pts included in analysis, n	27 vs. 26 vs. 27	23 vs. 32
Outcomes		
Effectiveness		
Patient-reported function, activity level and symptoms		
✿ Lysholm score, mean ±SD (range)	Pre-operative: 64.1 ±10.8 vs. 63.8 ±11.2 vs. 62.3 ±12.9; diff. n. s. with p=0.721 Postoperative[72]: 85.2 ±3.9 vs. 87.8 ±3.6 vs. 86.9 ±4.3; diff. n. s., with p=0.193	Preoperative: NR Postoperative[73]: 92.3 ±6.8 vs. 87.8 ±9.6; diff. n. s., with p=0.077
✿ Tegner score, mean ± SD	Pre-operative: 2.6 ±1.1 vs. 2.7 ±1.2 vs. 2.9 ±1.3; diff. n. s., with p=0.662 Postoperative [72]: 6.2 ±1.7 vs. 6.8 ±1.1 vs. 6.5 ±1.8; diff. n. s., with p=0.096	4.70 ±1.66 vs. 4.73 ±1.66; diff. n.s., with p=0.976
✿ Cincinnati Knee score, mean ±SD	NR	NR
✿ SANE score, mean ±SD	NR	NR
✿ **IKDC score (subjective) , mean ±SD (range)**	Pre-operative: 65.9 ±9.3 vs. 66.5 ±10.1 vs. 65.5 ±11.5; diff. n. s., with p=0.586 Postoperative[72] 80.2 ±6.8 vs. 83.5 ±6.3 vs. 82.8 ±5.7; diff. n. s., with p=0.153	NR

[68] Differences between treatment groups were not reported.

[69] The overall mean was calculated by the review authors based on the mean FU time of the respective treatment groups.

[70] The study only reported on the FU time in months. Overall: 34±10 (34 ±11 vs. 33 ±12)

[71] The study did not adequately report on the enrolment process. Therefore, the loss to follow-up rate could not have been calculated.

[72] There were significant differences ($p<0.05$) between baseline scores and the last follow-up scores after surgery.

[73] The time point was not clearly reported.

Author, year	Li 2016 [18]	Wang 2004 [23]
❁ KOOS score (e.g., symptoms, pain, sports and activity)	NR	NR
❁ Marx activity scale	NR	NR
Clinical knee stability		
❁ Lachman test (grade 0-1), n (%)	NR	Reverse Lachman Preoperative: NR Postoperative[74]: mean ±SD (range)[75]: 0.70 ±0.56 (0-2) vs. 0.75 ±0.67 (0-3); diff. n. s., with p=0.898
❁ Pivot shift test (grade 0-1), n (%)	Reverse Pivot shift (postoperative at final FU): 26 (96.3) vs. 26 (100) vs. 27 (100); diff. n. s., with p=0.407	NR
❁ Side-to-side difference in mm, mean ±SD (range)	Measured with Instrumented Anteroposterior Measurements Postoperative: 3.5 ±1.1 (NR[76]) vs. 2.1 ±1.0 (NR[77]) vs. 2.6 ±1.2 (NR[78]); diff. s. s., with p<0.001	Measured with the KT-1000 arthrometer Preoperative: NR Postoperative[79]: 2.83 ±1.70 (1-6) vs. 3.16 ±2.60 (1-10); diff. n. s., with p=0.605
❁ IKDC score (objective; normal and nearly normal), n (%)[80]	Postoperative (at Final FU): 24 (88.9) vs. 25 (96.2) vs. 25 (92.6); diff. n. s., with p=0.716	Preoperative: NR Postoperative[81]: 14 (60.9) vs. 23 (71.9); diff. n. s., with p=0.391
Patient satisfaction	NR	NR
Health-related Quality of Life	NR	NR
Safety		
Graft failure rate, n (%)	NR	NR
Re-ruptures	NR	NR

[74] The time point was not clearly reported.

[75] The study only reported on the mean and range of the Lachman test.

[76] 95%CI was reported: 3.083-3.9200

[77] 95%CI was reported: 1.6946-2.4941

[78] 95%CI was reported: 2.1028-3.0397

[79] The time point was not clearly reported.

[80] The overall IKDC score has 4 qualitative characteristics regarding knee functionality: normal, nearly normal, abnormal, and severely abnormal. In this assessment, only the number of pts with normal and nearly normal characteristics were extracted and summed up.

[81] The time point was not clearly reported.

Author, year	Li 2016 [18]	Wang 2004 [23]
Re-operation rate, n (%)	The study stated that no patient needed additional surgery because of recurrent or residual posterior laxity.	NR
Revisions, n (%)	NR	NR
Overall complications, n (%)	NR	0 (0) vs. 7 (21.9)
❁ **Arthrofibrosis, n (%)**	NR	NR
❁ **Effusion, n (%)**	NR	NR
❁ **Tenderness, n (%)**	NR	NR
❁ **Infection, n (%)**	The study stated that no postoperative infection occurred.	0 (0) vs. 2 (6.3)[82]
❁ **Hyposthesia, n (%)**	NR	NR
❁ **Synovitis, n (%)**	NR	NR
❁ **Deep venous thrombosis, n (%)**	The study stated that no deep venous thrombosis occurred.	NR
❁ **Other complications**	Regarding complications, the study reported that there were no cases of major neurovascular, infectious, vascular, deep venous thrombosis, or wound complications.	Donor site pain: 0 (0) vs. 4 (12.5) Reflex sympathetic dystrophy (RSD): 0 (0) vs. 1 (3.1) Tibial and femoral tunnel Enlargement was comparable between the allograft and autograft groups with no significant difference at final follow-up: **Tibial**[83]: 12 ±20 (range: 0-90) vs. 12 ±14 (range: 0-43), with p=0.64 **Femoral**[83]**:** 5.3 ±22 (range: 0-50) vs. 13 ±19 (range: 0-55), with p=0.771
Procedure-related mortality, n (%)	NR	NR

Abbreviations: *BPTB – bone-patellar tendon-bone; diff. – difference; FU – follow-up; IKDC – International Knee Documentation Committee; KOOS – KOOS – Knee injury and Osteoarthritis Outcome Score; MRI – magnetic resonance imaging; n. s. – not statistically significant; NR – not reported; PCL – posterior cruciate ligament; PCLR – posterior cruciate ligament reconstruction; pts – patients; RCT – randomised controlled trial; s. s. – statistically significant; SANE – Single Assessment Numerical Evaluation; SD – standard deviation; vs. – versus; yrs – years.*

[82] Of the 2 infections, one was an acute infection and the other was a late infection.

[83] Femoral and tibia tunnel enlargements are presented in percentage of the tunnel width at follow-up over the width postoperative in A-P view X-ray.

Table A-3: Allograft versus autograft for anterior cruciate ligament revision surgery: results from observational studies

Author, year	MARS Group [16]
Country	United States of America
Sponsor	AOSSM, Smith and Nephew (Andover, Massachusetts) National Football League Charities (New York, New York) Musculoskeletal Tissue Foundation (MTF; Edison, New Jersey) Project was partially funded by a grant from the **National Institutes of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIH/NIAMS)**.
Interventions/Products	**Allograft**: various specific graft types[84] (n=590)
Comparator	**Autograft**: various specific graft types (n=583) **Autograft+Allograft**: various specific graft types (n=32)
Surgical procedure	Revision anterior cruciate ligament (ACL) reconstruction (not further specified)
Study design	Prospective cohort study
Number of pts	1205
Inclusion criteria	Patients undergoing revision of a previously failed ACL reconstruction who agreed to participate and filled out an informed consent and a series of patient-reported outcome instruments
Exclusion criteria	Multiligament reconstructions
Rehabilitation (before or after ACLR)	NR
Age of patients, mean ±SD (range), yrs	Mean age: NR 26, median (IQR: 20-34)
Sex, n female (%)	508 (42)
Further relevant patient characteristics	**Previous surgery included, n (%):** Number of previous medial meniscus surgery: 743 (62) Number of previous lateral meniscus surgery: 958 (80) Number of previous articular cartilage surgeries: 1059 (88) **Prior revisions** ranged from 1 to 3+ (with 1055, 125 and 25 pts, respectively) **Prior graft type, n (%):** Autograft: 816 (68) Allograft: 348 (29) Both autograft + allograft: 29 (2) Other/unknown: 12 (<1)
Follow-up in yrs	2

[84] All of the grafts were fresh frozen and had minimal to no irradiation.

Author, year	MARS Group [16]
Loss to follow-up, n (%)	Questionnaire loss to FU: 216 (17.9) FU by telephone: 93 (7.7)[85]
Pts included in analysis, n	Questionnaire: 989 FU by telephone: 1112
Outcomes	
Effectiveness	
Patient-reported function, activity level and symptoms	
❁ Lysholm score, mean ±SD (range)	NR
❁ Tegner score, mean ± SD	NR
❁ Cincinnati Knee score, mean ±SD	NR
❁ SANE score, mean ±SD	NR
❁ IKDC score (subjective), mean ±SD (range)	Scores were only reported for all pts: Baseline score vs. score at 2 years FU: 52 (median, IQR: 38-63) vs. 77 (median, IQR: 61-86); diff. s. s., with p<0.001 **Results from logistic regression analysis:** Graft choice proved to be a significant predictor of 2-year IKDC scores (p=0.017). Specifically, the use of an autograft for revision reconstruction predicted an improved score on the IKDC (p=0.045; OR, 1.31; 95% CI: 1.01-1.70).
❁ KOOS symptoms	Scores were only reported for all pts: Baseline score vs. score at 2 years FU: 68 (median; IQR: 54-82) vs. 79 (mean; IQR: 64-89); diff. s. s., with p<0.001 **Results from logistic regression analysis:** It is stated that graft choice did not predict the outcome score (no further data reported).
❁ KOOS pain	Scores were only reported for all pts: Baseline score vs. score at 2 years FU: 75 (median; IQR: 58-86) vs. 89 (median; IQR: 75-94); diff. s. s., with p<0.001 **Results from logistic regression analysis: NR**
❁ KOOS sports and recreation	Scores were only reported for all pts: Baseline score vs. score at 2 years FU: 45 (median; IQR: 25-65) vs. 75 (median; IQR: 55-90); diff. s. s., with p<0.001 **Results from logistic regression analysis:** The KOOS sports and recreation subscale demonstrated higher scores in the setting of an autograft compared with allograft for revision reconstruction (p=0.037; OR, 1.33; 95% CI, 1.02-1.73).
❁ KOOS activities of daily living	Scores were only reported for all pts: Baseline score vs. score at 2 years FU: 87 (median; IQR: 69-96) vs. 97 (median; IQR: 88-100); diff. s. s., with p<0.001 **Results from logistic regression analysis:** It is stated that graft choice did not predict this outcome score.

[85] There was some inconsistency regarding the reporting of the number of patients analysed in the study. It is not clearly stated how many patients were analysed in the respective treatment groups. However, the denominator is described narratively for some of the results of the outcomes of interest. That is, regarding re-ruptures, it is stated that 540, 542 and 29 patients were described as the denominator for re-ruptures, leading to an overall sample of 1,111 analysed patients. Yet, it is also stated that overall 1,112 patients were analysed after loss to FU.

Author, year	MARS Group [16]
❁ Marx activity score	Scores were only reported for all pts: Baseline score vs. score at 2 years FU: 11 (median; IQR: 4-16) vs. 7 (median; IQR: 2-12); diff. s. s., with p<0.001 **Results from logistic regression analysis:** Graft choice was a significant predictor of 2-year Marx activity scores (p=.012). Specifically, the use of a combination autograft plus allograft for revision reconstruction predicted improved scores on the Marx (p =.005; OR, 3.33; 95% CI, 1.43-7.78). No further data were reported.
Clinical knee stability	
❁ Lachman test (grade 0-1), n (%)	NR
❁ Pivot shift test (grade 0-1), n (%)	NR
❁ Side-to-side difference in mm, mean ±SD (range)	NR
❁ IKDC score (objective; normal and nearly normal), n (%)[86]	NR
Patient satisfaction	NR
Health-related Quality of Life	KOOS QoL subscale (scores were only reported for all pts): Baseline score vs. score at 2 years FU: 31 (median; IQR: 19-44) vs. 56 (median; IQR: 38-75) diff. s. s., with p<0.001 **Results from logistic regression analysis**: Use of an autograft predicted improved scores on the KOOS quality of life subscale (p=0.031; OR =1.33; 95% CI, 1.03-1.73).
Safety	
Graft failure rate, n (%)	NR
Re-rupture rate, n (%)	Graft re-ruptures: 24 (4.4) vs. 12 (2.2) vs. 1 (3.4) **Results from logistic regression analysis**: Subjects with an autograft revision were found to be 2.78 times less likely of sustaining a subsequent graft rupture compared with subjects who received an allograft (p=0.047; 95%CI: 1.01-7.69).
Re-operation rate, n (%)	Overall: 150 (13.5) No further data were reported, but it is stated that the multivariate regression analysis showed that graft choice was not a predictor of reoperation[87] at 2 years FU.
Revisions, n (%)	NR
Overall complications, n (%)	NR
❁ Arthrofibrosis, n (%)	NR
❁ Effusion, n (%)	NR

[86] The overall IKDC score has 4 qualitative characteristics regarding knee functionality: normal, nearly normal, abnormal, and severely abnormal. In this assessment, only the number of pts with normal and nearly normal characteristics were extracted and summed up.

[87] The included re-operations in the analysis were chondroplasty and other articular cartilage treatment procedures, meniscectomy, meniscal repair, and hardware removal.

Author, year	MARS Group [16]
❁ Tenderness, n (%)	NR
❁ Infection, n (%)	NR
❁ Hyposthesia, n (%)	NR
❁ Synovitis, n (%)	NR
❁ Deep venous thrombosis, n (%)	NR
❁ Other complications	NR
Procedure-related mortality, n (%)	NR[88]

Abbreviations: ACL – anterior cruciate ligament; CI – confidence interval; diff. – difference; FU – follow-up; IKDC – International Knee Documentation Committee; IQR – interquartile range; KOOS – Knee injury and Osteoarthritis Outcome Score; n. s. – not statistically significant; NR – not reported; QoL – quality of life; SANE – Single Assessment Numerical Evaluation; s. s. – statistically significant; SD – standard deviation; vs. – versus; yrs – years.

[88] 1 patient died and was not eligible for the analysis. It was deemed unlikely that this patient died due to the procedure, since it was not stated that this death was procedure-related.

Risk of bias tables and GRADE evidence profile

Internal validity of the included studies was judged by two independent researchers. In case of disagreement a third researcher was involved to solve the differences. The Cochrane Risk of Bias Tool was used for randomised controlled trials [12], while the Newcastle-Ottawa Scale (NOS) was utilised for the included cohort studies[13].

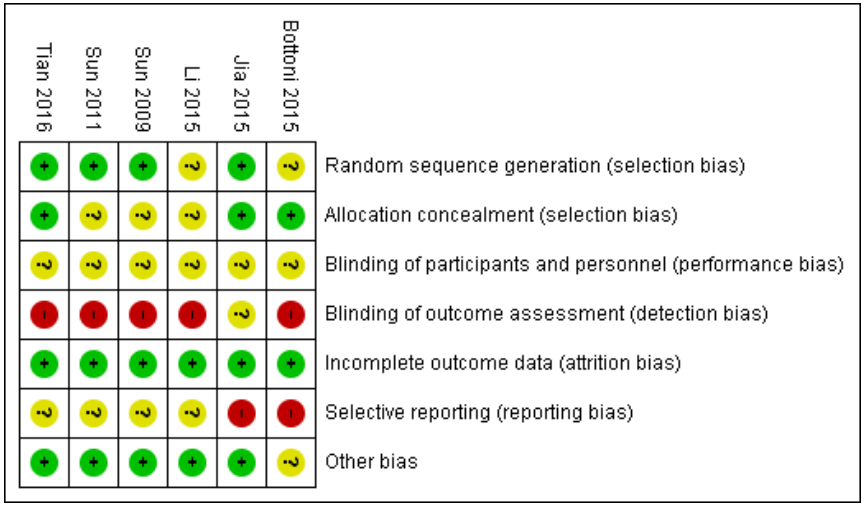

Figure A-1: Risk of bias summary for studies comparing allografts to autografts in ACLR[89]

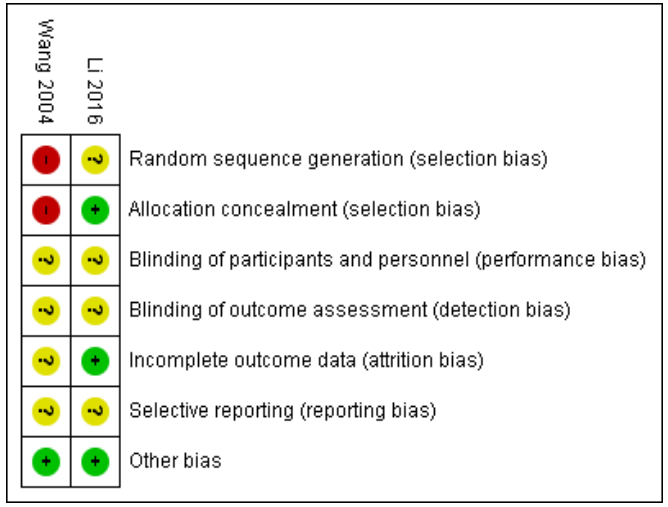

Figure A-2: Risk of bias summary for studies comparing allografts to autografts in PCLR[89]

[89] The figures, summarising the risk of bias of the included studies, were created with the computer program Review Manager (version 5.3).

Table A-4: Risk of bias assessment for studies comparing allografts to autografts in ACLR: review authors' judgements about each risk of bias item for each included study (study level: RCTs, see [2])

RoB Assessment for Bottoni 2015 [15]	Author's judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The investigators of the study did not sufficiently describe the random component in the sequence generation process. They did state that participating patients were randomised by study design, but it was unclear to the review authors what kind of sequence generation process is meant hereby. Therefore, the review authors judged the risk of bias to be unclear.
Allocation concealment (selection bias)	Low risk	The investigator stated that sealed envelopes were used. Therefore, the review authors judged it to be unlikely that patient assignment could have somehow been foreseen.
Blinding of participants and personnel (performance bias)	Unclear risk	Although the authors stated that patients were, once randomised, not blinded as to their graft type, the personnel (e.g., the physical therapists) seemed to have been blinded to the graft type. Overall, the review authors judged it to be unclear whether the outcomes may be influenced by the lack of blinding of personnel or participants.
Blinding of outcome assessment (detection bias)	High risk	It was not clearly stated whether the outcome assessors were blinded to the graft type that was used. It was reported that the participants, once randomised, were not blinded to their graft types. The physical therapist was, on the contrary, blinded to their graft types. Given that subjective outcome measurements were also used in the study and the patients were not blinded, the review authors judged this to be potentially increasing the risk of bias in the study.
Incomplete outcome data (attrition bias)	Low risk	The percentage of patients lost to FU was considerably small.
Selective reporting (reporting bias)	High risk	The review authors did not find a protocol or supplementary material showing the full spectrum of measured outcomes. Therefore, it was not possible to adequately assess whether reporting bias occurred. However, numerous outcomes were insufficiently reported (for the Lysholm score, e.g., it was only written narratively that no statistically significant differences were found between treatment groups without reporting on the respective scores). Overall, the review authors judged the risk of selective outcome reporting to be increased, since outcomes of interest (e.g., the Lysholm score) are reported incompletely so that they cannot be entered in a meta-analysis, or adequately considered in a qualitative evidence synthesis.
Other bias	Unclear risk	The study was funded by Arthrex Inc. and the Musculosceletal Transplant Foundation. In addition, the primary investigator of the study was a consultant for Arthrex Inc. However, it was unclear to which degree funding bias may have been present due to the consultant role of the primary investigator.
RoB Assessment for Jia 2015 [17]	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The investigators of the study describe an adequate random component in the sequence generation process. That is, the investigators state that 106 patients were randomised into two groups using computer-generated, randomised numbers which were put in sealed opaque envelopes.
Allocation concealment (selection bias)	Low risk	The investigator described that sealed opaque envelopes were used. Therefore, the review authors judged it to be unlikely that patient assignment could have somehow been foreseen.
Blinding of participants and personnel (performance bias)	Unclear risk	The investigator did not report on whether participants and personnel were blinded. The participants and personnel may have had knowledge of the allocated interventions.
Blinding of outcome assessment (detection bias)	Unclear risk	No information on whether outcome assessors had knowledge on the allocated intervention was found.

RoB Assessment for Jia 2015 [17] *(continuation)*	**Author's judgement**	**Support for judgement**
Incomplete outcome data (attrition bias)	Low risk	Once randomised, all patients were considered in the analysis and no patient was lost to FU.
Selective reporting (reporting bias)	High risk	The review authors did not find a protocol or supplementary material showing the full spectrum of measured outcomes. Therefore, the review authors could not adequately assess whether reporting bias occurred. Some outcomes of interest (e.g., complications) were reported incompletely, so that they could not be entered in a meta-analysis or considered in the evidence synthesis. Therefore, the review authors judged the risk of selective outcome reporting to be increased.
Other bias	Low risk	The review authors could not find any other potential sources of bias that may have distorted the results.
RoB Assessment for Li 2015 [19]	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The investigators did not report on the random component in the sequence generation process. Therefore, the risk of selection bias is unclear.
Allocation concealment (selection bias)	Unclear risk	The investigators did not report on the concealment of allocations prior to assignment. Therefore, the risk of selection bias is unclear.
Blinding of participants and personnel (performance bias)	Unclear risk	The participants were not blinded to the received graft type. It is unclear to which extent this may have biased the results.
Blinding of outcome assessment (detection bias)	High risk	The investigator described that "(...) all of the examinations were performed by the senior physicians (...) twice at each time point, neither of whom was the operating surgeon, and both of whom were blinded to the clinical findings". Therefore, the review authors judged the risk of detection bias for objective outcomes and complications to be low. However, and given that there were also subjective outcome measurements used in the study and the patients were not blinded, the review authors judged this to be potentially increasing the risk of bias in the study, leading to a high risk of bias for the likelihood of a detection bias for the subjective outcome scores.
Incomplete outcome data (attrition bias)	Low risk	Although some patients were lost to FU, the review authors judged the risk of attrition bias to be low due to the relatively small number of patients that were not considered in the analysis after randomisation and the fact that loss to FU was judged to be not related to differences between treatment groups.
Selective reporting (reporting bias)	Unclear risk	The review authors did not find a protocol or supplementary material showing the full spectrum of measured outcomes. Therefore, the review authors could not adequately assess whether reporting bias occurred.
Other bias	Low risk	The review authors could not find any other potential sources of bias that may have distorted the results.
RoB Assessment for Sun 2009 [20]	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The investigators of the study describe an adequate random component in the sequence generation process. That is, a computer was used to generate a random component in the sequence generation: "Written informed consent to participate in the study was provided by 172 patients. These 172 patients were randomised on the day of surgery by use of a computer to either BPTB autograft (number 1 to 86) or BPTB allograft (number 87 to 172)".
Allocation concealment (selection bias)	Unclear risk	It was unclear to the review authors whether the investigators of the study used a concealed allocation schedule (a list of random numbers).

RoB Assessment for Sun 2009 [20] *(continuation)*	Author's judgement	Support for judgement
Blinding of participants and personnel (performance bias)	Unclear risk	The study reported that the participants had knowledge of the allocated interventions and the personnel could have guessed the type of intervention due to the incisions. However, the review authors judged it to be unclear in how far the risk of bias increased due to the lack of blinding participants and personnel.
Blinding of outcome assessment (detection bias)	High risk	The likelihood of detection bias is high in the study due to the fact that data were collected in an unblinded fashion by 1 fellowship-trained surgeon at 1 institution. The investigators themselves mention that observer bias was a limitation of the study: "The data were collected by only 1 fellowship-trained surgeon at 1 institution and were not collected in a blinded fashion. Patients were informed as to the type of surgery by the surgeon postoperatively, so the data collector may also have been aware at the time of follow-up". In addition, subjective outcome measurements were also used in the study, and the patients were not blinded, so the review authors judged this to be potentially increasing the risk of bias in the study.
Incomplete outcome data (attrition bias)	Low risk	While not all randomised patients were analysed (172 randomised patients; 156 analysed patients), the review authors judged the risk of attrition bias to be low due to the fact that loss to FU was judged to be comparable between treatment groups. Moreover, the review authors judged it to be unlikely that missing data were somehow related to treatment groups.
Selective reporting (reporting bias)	Unclear risk	The review authors did not find a protocol or supplementary material showing the full spectrum of measured outcomes. Therefore, it was not possible to adequately assess whether reporting bias occurred.
Other bias	Low risk	The review authors could not find any other potential sources of bias that may have distorted the results.
RoB Assessment for Sun 2011 [21]	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The investigators of the study describe an adequate random component in the sequence generation process. That is, a computer was used to generate a random component in the sequence generation: patients "(...) were randomised on the day of surgery using a computer to either the hamstring tendon autograft group (numbers 1 to 104) or allograft group (numbers 105 to 208)".
Allocation concealment (selection bias)	Unclear risk	It was unclear to the review authors whether the investigators of the study used a concealed allocation schedule (the list of random numbers).
Blinding of participants and personnel (performance bias)	Unclear risk	The study reported that neither the participants nor the personnel had knowledge of the allocated interventions. However, the review authors judged it to be unclear in how far the risk of bias increased due to the lack of blinding participants and personnel.
Blinding of outcome assessment (detection bias)	High risk	The likelihood of detection bias is high in the study due to the fact that data were collected in an unblinded fashion by 1 fellowship-trained surgeon at 1 institution. The investigators themselves mention that observer bias was a limitation of the study: "These data were collected by only 1 fellowship-trained surgeon at 1 institution and were not collected in a blinded fashion. Patients were informed as to the type of surgery by the surgeon after surgery, so the data collector may also have been aware at the time of the follow-up. Additionally the incisions could also tip off the observer to the type of surgery". In addition, subjective outcome measurements were also used in the study and the patients were not blinded, so the review authors judged this to be potentially increasing the risk of bias in the study.
Incomplete outcome data (attrition bias)	Low risk	The review authors judged it to be unlikely that missing data were somehow related to treatment groups.
Selective reporting (reporting bias)	Unclear risk	The review authors did not find a protocol or supplementary material showing the full spectrum of measured outcomes. Therefore, it was not possible to adequately assess whether reporting bias occurred.
Other bias	Low risk	The review authors could not find any other potential sources of bias that may have distorted the results.

RoB Assessment for Tian 2016 [22]	Author's judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators of the study describe an adequate random component in the sequence generation process. That is, the investigators state that a computer software programme was used to generate the random allocation sequence.
Allocation concealment (selection bias)	Low risk	The investigator described that the random allocation sequence remained concealed from those enrolling patients into the study to minimise the effect of bias. Therefore, the review authors judged it to be unlikely that patient assignment could have somehow been foreseen.
Blinding of participants and personnel (performance bias)	Unclear risk	The study reported that the participants had knowledge of the allocated interventions and the personnel could have guessed the type of intervention due to the incisions. However, the review authors judged it to be unclear in how far the risk of bias increased due to the lack of blinding of participants and personnel.
Blinding of outcome assessment (detection bias)	High risk	Detection bias may have occurred in the study due to the fact that the outcome assessor was not blinded: "(...) the data were collected by only 1 surgeon at 1 institution and were not collected in a blinded fashion. Patients were informed as to the type of surgical procedure that they underwent by the surgeon after surgery, so the data collector may also have been aware at the time of the follow-up". In addition, there were also subjective outcome measurements used in the study and the patients were not blinded, so the review authors judged this to be potentially increasing the risk of bias in the study as well.
Incomplete outcome data (attrition bias)	Low risk	The risk of attrition bias was judged to be low. 83 out of 107 enrolled patients (77.5%) were analysed. 14/54 (25.9%) and 10/53 (18.9%) of patients were lost to FU in the autograft and allograft groups, respectively. However, the reported reasons for missing outcome data were judged unlikely to be systematically related to differences of treatment groups.
Selective reporting (reporting bias)	Unclear risk	The review authors did not find a protocol or supplementary material showing the full spectrum of measured outcomes. Therefore, it was not possible to adequately assess whether reporting bias occurred.
Other bias	Low risk	The review authors could not find any other potential sources of bias that may have distorted the results.

Table A-5: Risk of bias assessment for studies comparing allografts to autografts in PCLR: review authors' judgements about each risk of bias item for each included study (study level: RCTs, see [2])

RoB Assessment for Li 2016 [18]	Author's judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The investigators of the study did not sufficiently describe the random component in the sequence generation process. Therefore, the review authors judged the risk of bias to be unclear.
Allocation concealment (selection bias)	Low risk	The investigators stated that all patients were randomly allocated by sealed envelopes into 1 of 3 groups: autograft group, hybrid graft group, or γ-irradiated allograft group. Therefore, the review authors judged the risk of bias to be low.
Blinding of participants and personnel (performance bias)	Unclear risk	The investigators did not report on whether participants or personnel were adequately blinded. The review authors judged the risk of performance bias to be unclear.
Blinding of outcome assessment (detection bias)	Unclear risk	No information was found on whether outcome assessors had knowledge on the allocated intervention.
Incomplete outcome data (attrition bias)	Low risk	Although some patients were lost to FU, the review authors judged the risk of attrition bias to be low due to the relatively small number of patients who were not considered in the analysis after randomisation, and the comparable loss to FU between groups. It was judged to be unlikely that missing data were somehow related to treatment groups.
Selective reporting (reporting bias)	Unclear risk	The review authors did not find a protocol or supplementary material showing the full spectrum of measured outcomes. Therefore, it was not possible to adequately assess whether reporting bias occurred.
Other bias	Low risk	The review authors could not find any other potential sources of bias that may have distorted the results.
RoB Assessment for Wang 2004 [23]	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	It appears to the review authors that there was a lack of randomisation process in the study. The study described a randomisation according to hospital admission. Therefore, the review authors judged the randomisation to be solely quasi-randomised, increasing the risk of selection bias considerably.
Allocation concealment (selection bias)	High risk	It appears that the allocation was not concealed. We, therefore, judged the risk of selection bias to be high.
Blinding of participants and personnel (performance bias)	Unclear risk	Insufficient information was provided to judge whether performance bias occurred.
Blinding of outcome assessment (detection bias)	Unclear risk	The study did not report on (whether) a blinding process was present.
Incomplete outcome data (attrition bias)	Unclear risk	The loss to follow-up rate was not reported in the included study. It was unclear to the review authors whether attrition bias occurred.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to judge the risk of reporting bias (no protocol available).
Other bias	Low risk	No other potential bias was detected according to the information of the study's publication.

Table A-6: Risk of bias – study level (observational studies) using the Newcastle-Ottawa Scale (NOS) [13]

Study reference/ID	Selection				Comparability	Outcome			Comments
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow-up of cohorts	Overall risk of bias
MARS Group 2014 [16]	1[90]	1	0	1	2	0	1[91]	0	Moderate

* *A study can be awarded a maximum of 1 point (=star) for each numbered item within the Selection and Outcome categories. A maximum of 2 points (star)s can be given for Comparability.*

[90] While the baseline characteristics were not homogenous (e.g., prior graft type, presence of other prior surgery such as meniscus surgery), it was still judged that the subjects derived from groups are representative of patients with re-ruptures of the ACL who need a revision ACL reconstruction.

[91] While it is important to see the long-term benefits of each graft type, it was argued that 2 years FU are long enough for outcomes to occur in this patient population.

Table A-7: Evidence profile: efficacy and safety of allografts for ACLR

Certainty assessment							№ of analysed patients[92 93]		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allograft	Autograft			
EFFECTIVENESS											
Patient-reported function, activity level and symptoms (follow-up: mean ≥5 years; assessed with: Lysholm score)											
5 [17, 19-22]	randomised trials	serious[a]	serious [b]	not serious [c]	not serious	none	303	292	None of the studies found a statistically significant difference in Lysholm scores between treatment groups postoperatively. Postoperative mean Lysholm scores (ranges): 86 ±9 to 91 ±6 vs. 85.2 ±3.1 to 91.3+11.5	⊕⊕◯◯ LOW	CRITICAL
Patient-reported function, activity level and symptoms (follow-up: mean ≥5 years; assessed with: Tegner score)											
5 [15, 19-22]	randomised trials	serious [d]	not serious [e]	not serious [c]	not serious	none	299	287	None of the studies found a statistically significant difference when comparing the Tegner activity score between treatment groups postoperatively. Postoperative mean Tegner scores (ranges): 4.5 ±2.2 to 7.6 ±1.9 vs. 4.8 ±2.3 to 7.8 ±1.2	⊕⊕⊕◯ MODERATE	CRITICAL
Patient-reported function, activity level and symptoms (follow-up: mean ≥5 years; assessed with: Cincinnati Knee score)											
3 [20-22]	randomised trials	serious [f]	not serious [g]	not serious [c]	not serious	none	218	207	None of the studies found a statistically significant difference when comparing the Cincinnati Knee score between treatment groups postoperatively. Postoperative mean Cincinnati Knee scores (ranges): 87 ±12 to 92 ±11 vs. 90 ±10 to 91 ±12	⊕⊕⊕◯ MODERATE	CRITICAL
Patient-reported function, activity level and symptoms (follow-up: mean 10.5 years; assessed with: SANE score)											
1 [15]	randomised trials	serious [h]	not serious	serious [i]	not serious	none	49	48	The postoperative mean score was 2.7 points lower in the allograft group when compared to the autograft group. Postoperative mean SANE score: 78.8 ±18.8 vs. 81.5 ±16.4	⊕⊕◯◯ LOW	CRITICAL
Patient-reported function, activity level and symptoms (follow-up: mean ≥5 years; assessed with: subjective IKDC score)											
6 [15, 17, 19-22]	randomised trials	serious [h]	not serious	not serious [c]	not serious	none	352	340	None of the studies found a statistically significant difference in subjective IKDC scores between groups postoperatively. Postoperative mean subjective IKDC scores (ranges): 73.7 ±25.9 to 90 ±14 vs. 77.2 ±25.4 to 90 ±10	⊕⊕⊕◯ MODERATE	CRITICAL

[92] The reader is reminded that in Bottoni et al. the number of patients actually refers to the number of knees.

[93] Excluding patients with hybrid grafts.

Certainty assessment							№ of analysed patients[92 93]		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allograft	Autograft			
Patient-reported function, activity level and symptoms (assessed with: KOOS score)											
0										-	CRITICAL
Patient-reported function, activity level and symptoms (assessed with: Marx activity scale)											
0										-	CRITICAL
Clinical knee stability (assessed with: Lachman test)											
4 [19-22]	randomised trials	very serious [j]	serious [k]	not serious	not serious	none	250	239	s. s. difference in Lachman scores (grade 0-1) in 1 study [22]: 31/43 (72%) vs. 37/40 (93%). No statistically significant differences in Lachman scores in 3 studies [19-21] Lachman test (grade 0-1; ranges across studies): 31/43 (72%) to 74/80 (92.5%) vs. 84/91 (92.3%) to 30/32 (93.8%)	⊕◯◯◯ VERY LOW	IMPORTANT
Clinical knee stability (follow-up: mean ≥5 years; assessed with: Pivot shift test)											
4 [19-22]	randomised trials	very serious [j]	serious [k]	not serious	not serious	none	250	239	s. s. difference in Pivot shift test (Grade 0-1) in 1 study [22]: 38/43 (88.4%) vs. 40/40 (100%) No statistically significant differences in Pivot shift test in 3 studies [19-21] Pivot shift (grade 0-1; ranges across studies): 38/43 (88.4%) to 95/95 (100%) vs. 32/32 (100%) to 91/91 (100%)	⊕◯◯◯ VERY LOW	IMPORTANT
Clinical knee stability (follow-up: mean ≥5 years; assessed with: KT arthrometer; better indicated by lower values)											
4 [19-22]	randomised trials	serious [h]	serious [k]	not serious	not serious	none	250	239	2/4 studies [19, 22] found a statistically significant difference in instrumented knee laxity favouring autografts, while the other 2/4 studies [20, 21] did not find any statistically significant difference in side-to-side differences measured with the KT arthrometer between treatment groups. Mean side-to-side differences (in mm; ranges across studies): 2.5 ±0.9 to 5.5 ±1 vs. 2.1 ±1.6 to 2.5 ±0.7	⊕⊕◯◯ LOW	IMPORTANT
Clinical knee stability (follow-up: mean ≥5 years; assessed with: objective IKDC score)											
4 [19-22]	randomised trials	serious [h]	not serious	not serious	not serious	none	250	239	None of the studies found a statistically significant difference in the objective IKDC score between treatment groups. Objective IKDC score (normal or nearly normal scores; ranges across studies): 38/43 (88.4%) to 75/80 (93.8%) vs. 29/32 patients (90.6%) to 38/40 (95%)	⊕⊕⊕◯ MODERATE	IMPORTANT

Certainty assessment							№ of analysed patients[92 93]		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Impre-cision	Other con-siderations	Allo-graft	Auto-graft			
Patient satisfaction (assessed with: NR)											
1 [17]	randomised trials	very serious [l]	not serious	not serious	not serious	none	53	53	Patient satisfaction was analysed in 106 patients from 1 study. The study found no statistically significant difference between patients undergoing allograft ACLR (n=53) or autograft ACLR (n=53). The instrument used to measure patient satisfaction was not reported. **Satisfied**: 46/53 (86.8%) vs. 47/53 (88.7%) **Nearly satisfied:** 7 (13.2%) vs. 5 (9.4%) Diff. n. s.; p>0.05	⊕⊕◯◯ LOW	IMPORTANT
Health-related Quality of Life											
0										-	IMPORTANT
SAFETY											
Graft failure (follow-up: mean ≥5 years)											
2 [15, 22]	randomised trials	not serious [m]	not serious	serious [c i]	not serious	none	92	88	26/92 (28.3%) vs. 7/88 (7.9%) [n] Bottoni et al. [15]: 13/49 (26.5%) vs. 4/48 (8.3%), diff. s. s. with p<0.05 Tian et al. [22]: 13/43 (30.2%) vs. 3/40 (7.5%), diff. s. s. with p<0.001	⊕⊕⊕◯ MODERATE	CRITICAL
Re-rupture rate											
0										-	CRITICAL
Re-operations											
0										-	CRITICAL
Revisions (follow-up: mean ≥5 years)											
2 [15, 19]	randomised trials	not serious [m]	serious[o]	serious [c i]	not serious	none	81	80	Bottoni et al. [15]: 13/49 (26.5%) vs. 4/48 (8.3%), diff. s. s. with p<0.05 Li et al. [19]: no patient needed additional surgery because of recurrent or residual symptoms (0/32 vs. 0/32)	⊕⊕◯◯ LOW	CRITICAL

Certainty assessment							№ of analysed patients[92 93]		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Impre-cision	Other con-siderations	Allo-graft	Auto-graft			
Complications (follow-up: mean ≥5 years)											
6 [15, 17, 19-22]	randomised trials	serious [p]	not serious	not serious [c]	serious [q]	none	352	340	Overall complication rate: NR **Arthrofibrosis** (reported in 2/6 studies [21, 22]; 269 pts): 0/138 (0%) vs. 0/131 (0%) **Effusion** (0/6 studies): NR **Tenderness** (reported in 1 study [21]; 186 pts): 0/95 (0%) vs. 2/91 (2.1%) **Infections** (reported in 4 studies [19-22]; 489 pts): 5/250 (2%) vs. 0/239 (0%), range: 0-4.6% vs. 0% **Hypoesthesia** (reported in 2 studies [21, 22]; 269 pts): 0/138 (0%) vs. 6/131 (4.6%), range: 0% vs. 3.3-7.5%. **Synovitis** was not reported in any of the included studies. **Deep venous thrombosis** (reported in 3 studies [20-22]; 425 pts): 2/218 (0.9%) vs. 1/207 (0.5%), range: 0-2.5% vs. 0-1.3% **Further reported complications:** Postoperative mean fever time in days (reported in 1 study [20]; 156 pts): 6.8 vs. 4.4 diff. s. s., with p<0.05) Arthritic progression (reported in 1 study [22]; 83 pts): 14/43 (32.6%) vs. 4/40 (10%), diff. s. s. with p<0.05. Tibial and femoral tunnel widening in mm (reported in 2 studies; 203 pts): Jia et al. [17]: Tibial (in mm), mean ±SD: 7.8 ±0.4 vs. 7.61 ±0.22, diff. s. s. with p<0.05 Femoral (in mm), mean ±SD: 7.64 ±0.35 vs. 7.51 ±0.42, diff. s. s. with p<0.05 Bottoni et al. [15]: Tibial (in mm), mean (range): 9.2 (7-10) vs. 8.9 (7-10); diff. n. s. with p=0.651 Femoral (in mm), mean (range): 8.8 (7-10) vs. 8.3 (7-10), diff n. s. with p=0.453 Furthermore, some of the included studies specifically stated that there were no cases of pain when kneeling, anterior knee pain, etc.	⨁⨁◯◯ LOW	CRITICAL
Procedure-related mortality											
0										-	IMPORTANT

MD: *Mean difference*

Comments:

[a] *In 4/5 studies, the risk of bias for blinding the outcome assessors was judged to be high. Therefore, we judged that this may have seriously affected the certainty.*

[b] *None of the studies showed any statistically significant differences postoperatively in the Lysholm score between the allograft and the autograft groups. Results from the non-statistically significant differences revealed that in 3/5 studies the Lysholm score was higher in the allograft group, while 2/5 studies reported a lower Lysholm score in the allograft group (comparison: allograft vs. autograft). While the general difference is small (e.g., <5 point differences between allografts and autografts), it may still be an indicator for heterogeneity. A calculation of the i^2 is further needed to adequately assess how heterogenous the results for this outcome may be.*

[c] *Differences in interventions were present across studies (e.g., irradiated vs. non-irradiated grafts, single-bundle vs. double-bundle, etc.).*

[d] *In 5/5 studies, the risk of bias for blinding the outcome assessors was judged to be high. Therefore, we judged that this may have seriously affected the certainty.*

[e] *None of the studies showed any statistically significant difference postoperatively in the Tegner score between the allograft and the autograft groups. The non-statistical findings in all study groups showed slightly higher scores in the autograft group. This may be an indicator that heterogeneity is small. Calculating the i^2 may be beneficial to further assess heterogeneity.*

f *In 3/3 studies, the lack of blinding significantly increases the risk of bias. Given that this is a subjective outcome score, it was judged to be a very serious limitation.*

g *None of the studies showed any statistically significant differences in Cincinnati Knee scores between treatment groups. The non-statistical findings showed slightly higher scores in allograft patients in 2/3 studies, and lower scores in allograft patients in 1/3 study/studies when compared to the autograft groups, respectively. The difference of the mean scores ranged from 1 to -3.*

[h] *The lack of blinding in the study/studies may seriously affect the certainty to believe in the evidence of this outcome measure.*

[i] *The overall applicability for the broad population selected in these assessment results may suffer due to the fact that numerous different graft types were used and that some studies used a subpopulation of the population of interest. Bottoni et al., for instance, only included highly active military (mostly) men, and Tian et al. used irradiated allografts. It is unclear in how far the generalisability suffers due to the aforementioned factors.*

[j] *It was judged that the lack of blinding may have very seriously affected the certainty to believe this specific outcome.*

[k] *Heterogeneity was suspected within the included studies. It appears that the studies do not consistently show any difference/difference favouring a treatment group. A calculation of the i^2 is further needed to elaborate how significant the inconsistency is.*

[l] *There were 2 substantial factors that increased the risk of bias: lack of blinding and selective outcome reporting; the latter was present insofar as it was insufficiently described how patient satisfaction was measured. In addition, no scores were reported, but it was stated that no statistically significant differences between treatment groups was found.*

[m] *Lack of blinding for outcome assessors was judged to be less likely to affect this outcome.*

[n] *Graft failure, however, was defined differently in the studies. Tian et al. defined it as knee laxity >5mm measured with a KT-2000, and Bottoni et al. did not clearly mention how graft failure was defined.*

[o] *Bottoni et al. found a considerably large difference in the revision rate, while Li et al. stated that no additional surgeries were needed in either of the treatment groups.*

[p] *The risk of bias for selective outcome reporting was judged high in 2/6 studies, and unclear in the remaining 4/6 studies. Most of the studies, however, did not report on an overall complication rate. Instead, they were presented narratively in the studies.*

[q] *The optimal information size may have not been reached for most of the specific complications.*

Table A-8: Evidence profile: efficacy and safety of allografts for PCLR

Certainty assessment							№ of analysed patients[94]		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allograft	Autograft			
EFFECTIVENESS											
Patient-reported function, activity level and symptoms (follow-up: mean >2 years; assessed with: Lysholm score)											
2 [1,2] [18, 23]	randomised trials	very serious [1,a,b]	serious [c]	not serious	not serious	none	50	58	None of the studies found a statistically significant difference in the Lysholm score between treatment groups postoperatively. Li et al. [18]: 85.2 ±3.9 vs. 87.8 ±3.6, diff. n. s. with p>0.05 Wang et al. [23]: 92.3 ±6.8 vs. 87.8 ±9.6, diff. n. s. with p>0.05	⊕◯◯◯ VERY LOW	CRITICAL
Patient-reported function, activity level and symptoms (follow-up: mean >2 years; assessed with: Tegner score)											
2 [1,2] [18, 23]	randomised trials	very serious [a,b]	not serious	not serious	not serious	none	50	58	None of the studies found a statistically significant difference in the Tegner score between treatment groups postoperatively. Li et al. [18]: 6.2 ±1.7 vs. 6.8 ±1.1, diff. n. s. with p>0.05 Wang et al. [23]: 4.7 ±1.66 vs. 4.73 ±1.66, diff. n. s. with p>0.05	⊕⊕◯◯ LOW	CRITICAL
Patient-reported function, activity level and symptoms (assessed with: Cincinnati Knee score)											
0										-	CRITICAL
Patient-reported function, activity level and symptoms (assessed with: SANE score)											
0										-	CRITICAL
Patient-reported function, activity level and symptoms (follow-up: mean 5.6 years; assessed with: subjective IKDC score)											
1 [2][18]	randomised trials	serious [b]	not serious	not serious	serious [d]	none	27	26	Mean postoperative subjective IKDC score: 80.2 ±6.8 vs. 83.5 ±6.3, diff. n. s. with p>0.05	⊕⊕◯◯ LOW	CRITICAL
Patient-reported function, activity level and symptoms (assessed with: KOOS score)											
0										-	CRITICAL
Patient-reported function, activity level and symptoms (assessed with: Marx activity scale)											
0										-	CRITICAL

[94] Excluding patients with hybrid grafts. The number of patients refers to the analysed patients, not the enrolled ones.

Certainty assessment							№ of analysed patients[94]		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Impre-cision	Other con-siderations	Allo-graft	Auto-graft			
Clinical knee stability (follow-up: mean 2.8 years assessed with: Reverse Lachman test)											
1 [23]	randomised trials	very serious [a]	not serious	not serious	not serious	none	23	32	The study did not find a statistically significant difference in the reverse Lachman test postoperatively. Mean postoperative reverse Lachman test score: 0.7 ±0.56 vs. 0.75 ±0.67, diff. n. s. with p>0.05	⊕⊕◯◯ LOW	IMPORTANT
Clinical knee stability (assessed with: Reverse Pivot shift test)											
1 [18]	randomised trials	serious [b]	not serious	not serious	not serious	none	27	26	Postoperative reverse Pivot shift (Grade 0-1): 26/27 (96.3%) vs. 26/26 (100%), diff. n. s. with p>0.05	⊕⊕⊕◯ MODERATE	IMPORTANT
Clinical knee stability (follow-up: mean >2 years; assessed with: KT arthrometer; better indicated by lower values)											
2 [18, 23]	randomised trials	very serious [a,b]	serious [e]	not serious	not serious	none	50	58	1 study found a statistically significant difference favouring autografts, while another study did not find any statistically significant difference based on the side-to-side difference measured with an instrumented knee laxity test. **Side-to-side difference in mm:** Li et al. [18]: 3.5 ±1.1 vs. 2.1 ±1, diff. s. s. with p<0.001 Wang et al. [23]: 2.83 ±1.7 vs. 3.16 ±2.6, diff. n. s. with p>0.05	⊕◯◯◯ VERY LOW	IMPORTANT
Clinical knee stability (follow-up: mean >2 years; assessed with: objective IKDC)											
2 [18, 23]	randomised trials	very serious [a,b]	not serious	not serious	not serious	none	50	58	None of the studies found a statistically significant difference in the objective IKDC score between treatment groups postoperatively. **Objective IKDC (normal and nearly normal):** Li et al. [18]: 24/27 (88.9%) vs. 25/26 (96.2%) Wang et al. [23]: 14/23 (60.9%) vs. 23/32 (71.9%)	⊕⊕◯◯ LOW	IMPORTANT
Patient satisfaction											
0										-	IMPORTANT
Health-related Quality of Life											
0										-	IMPORTANT
SAFETY											
Graft failure											
0										-	CRITICAL
Re-rupture rate											
0										-	CRITICAL

Certainty assessment							№ of analysed patients[94]		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Allograft	Autograft			
Re-operations (follow-up: mean 5.6 years)											
1 [18]	randomised trials	not serious	not serious	serious [2,f]	serious [g]	none	27	26	The study stated that no patient needed additional surgery because of recurrent or residual posterior laxity: 0% vs. 0% (further information: NR).	⨁⨁◯◯ LOW	CRITICAL
Revisions											
0										-	CRITICAL
Complications (follow-up: mean >2 years)											
2 [18, 23]	randomised trials	serious	not serious	not serious	serious [d]	none	50	58	**Overall complication rate** (reported in 1 study; [23]): 0/23 (0%) vs. 7/32 (21.9%). **Arthrofibrosis:** NR **Effusion:** NR **Tenderness:** NR **Infections:** Li et al [18]: no postoperative infection; Wang et al. [23]: 0/23 (0%) vs. 2/32 (6.3%; one acute and one late infection) **Hypoesthesia:** NR **Synovitis:** NR **Deep venous thrombosis (reported in 1 study;** [18]): 0/27 (0%) vs. 0/26 (0%) **Further reported complications:** Donor site symptoms in 1 study [23]: 0/23 (0%) vs. 4/32 (12.5%); Reflex sympathetic dystrophy in 1 study [23]: 0/23 (0%) vs. 1/32 (3.1%) Li et al. [18] further stated narratively that no post-operative infection, no deep venous thrombosis, no cases of major neurovascular, infectious, vascular, deep venous thrombosis or wound complications in any of the 80 analysed patients (of which 27, 26 and 27 received allograft, autografts and hybrid grafts respectively) occurred. Tibial and femoral tunnel enlargement in 1 study [23]: Tibial: 12 ±20 (range: 0-90) vs. 12 ±14 (range: 0-43), n. s. with p=0.64 Femoral: 5.3 ±22 (range: 0-50) vs. 13 ±19 (range: 0-55), n. s. with p=0.771	⨁⨁◯◯ LOW	CRITICAL
Procedure-related mortality											
0										-	IMPORTANT

CI: *Confidence interval;* ***MD:*** *Mean difference*

Comments:

[a] *In Wang et al., there was high risk of bias for selection bias and unclear risk of bias whether patients were blinded.*

[b] *In Li et al., it was unclear whether the random sequence generation was adequate (selection bias), and whether patients were blinded.*

[c] *None of the studies showed any statistically significant differences postoperatively in the Lysholm score between the allograft and the autograft groups. The non-statistically significant differences were not unanimously higher in one treatment group. This may be an indicator for heterogeneity. A calculation of the i-square is further needed to adequately assess how heterogeneous the results for this outcome may be.*

[d] *The optimal information size may have not been reached.*

[e] *Heterogeneity may have been present because study results were not unanimous. Further calculation of the i-square is needed to elaborate on the extent of the heterogeneity.*

[f] *The study referred to the patients who did not need additional surgery because of recurrent or residual posterior laxity. It was unclear to the review authors whether this refers to the overall re-operations rate or only the patients with recurrent or residual posterior laxity.*

[g] *The optimal information size may have not been reached.*

Table A-9: Evidence profile: efficacy and safety of allografts for revision ACLR

Certainty assessment							№ of analysed patients[95]		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Impre-cision	Other con-siderations	Allo-graft	Auto-graft			
EFFECTIVENESS											
Patient-reported function, activity level and symptoms (assessed with: Lysholm score)											
o										-	CRITICAL
Patient-reported function, activity level and symptoms (assessed with: Tegner score)											
o										-	CRITICAL
Patient-reported function, activity level and symptoms (assessed with: Cincinnati Knee score)											
o										-	CRITICAL
Patient-reported function, activity level and symptoms (assessed with: SANE score)											
o										-	CRITICAL

[95] Excluding patients with a combination of allografts and autografts.

Certainty assessment							№ of analysed patients[95]		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Impre-cision	Other con-siderations	Allo-graft	Auto-graft			
Patient-reported function, activity level and symptoms (follow-up: 2 years; assessed with: subjective IKDC score)											
1 [16]	observational studies	not serious	not serious	not serious	not serious	none	590	583	The study conducted a logistic regression analysis and found that graft choice proved to be a significant predictor of 2-year IKDC score. Specifically, the use of an autograft for revision reconstruction predicted improved score on the IKDC (p=0.045; OR =1.31; 95% CI: 1.01-1.70).	⨁⨁◯◯ LOW	CRITICAL
Patient-reported function, activity level and symptoms (follow-up: 2 years; assessed with: KOOS)											
1 [16]	observational studies	not serious	not serious	not serious	not serious	none	590	583	The study conducted a logistic regression analysis and found that graft choice did not predict KOOS symptoms, and KOOS activities of daily living. On the contrary, KOOS sports and recreation subscale demonstrated higher scores in the setting of an autograft when compared to allograft for revision reconstruction (p=0.037; OR =1.33; 95%CI: 1.02-1.73). Results from further KOOS subscales (KOOS pain, from the regression analysis comparing graft types, was not reported.	⨁⨁◯◯ LOW	CRITICAL
Patient-reported function, activity level and symptoms (follow-up: 2 years; assessed with: Marx activity scale)											
1 [16]	observational studies	not serious	not serious	not serious	not serious	none	590	583	The study conducted a logistic regression and found that graft choice was a significant predictor of 2-year Marx activity scores (p=0.012). Specifically, the use of a combination autograft plus allograft for revision reconstruction predicted improved scores on the Marx (p=0.005; OR =3.33; 95%CI: 1.43-7.78).	⨁⨁◯◯ LOW	CRITICAL
Clinical knee stability (assessed with: Lachman test)											
0										-	IMPORTANT
Clinical knee stability (assessed with: Pivot shift test)											
0										-	IMPORTANT
Clinical knee stability (assessed with: KT arthrometer)											
0										-	IMPORTANT
Clinical knee stability (assessed with: objective IKDC)											
0										-	IMPORTANT
Patient satisfaction											
0										-	IMPORTANT

Certainty assessment							№ of analysed patients[95]		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Incon-sistency	Indirect-ness	Impre-cision	Other con-siderations	Allo-graft	Auto-graft			
Health-related Quality of Life											
1 [16]	observational studies	not serious	not serious	not serious	not serious	none	590	583	Results from the logistic regression analysis show that the use of an autograft predicted improved scores on the KOOS quality of life subscale (p=0.031; OR: 1.33; 95%CI: 1.03-1.73).	⊕⊕◯◯ LOW	IMPORTANT
SAFETY											
Graft failure											
0										-	CRITICAL
Re-rupture rate (follow-up: 2 years)											
1 [16]	observational studies	not serious	not serious	not serious	not serious	none	24/540 (4.4%)	12/542 (2.2%)	Results from regression analysis: Subjects with an autograft revision were found to be 2.78 times less likely of sustaining a subsequent graft rupture compared with subjects who received an allograft (p=0.047; 95%CI: 1.01-7.69)	⊕⊕◯◯ LOW	CRITICAL
Re-operation rate (follow-up: 2 years)											
1 [16]	observational studies	not serious	not serious	not serious	not serious	none	The study only reported on the overall re-operation rate for all patients including allografts, autografts or a combination of these grafts: 150/1112 (13.5%)			⊕⊕◯◯ LOW	CRITICAL
Revisions											
0										-	CRITICAL
Complications											
0										-	CRITICAL
Procedure-related mortality											
0										-	IMPORTANT

CI: *Confidence interval;* ***OR:*** *Odds ratio*

Comments:

[a] *Selective outcome reporting may have been present for this specific outcome, since the results from the regression analysis were not presented.*

Applicability table

Table A-10: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	The target population in this review included all patients of any age receiving allografts. Age and activity level of the patients may affect the applicability of the results: For ACLR, the mean age of the patients receiving allografts and autografts ranged from 28 to 32.8 years and 28.9 to 31.8 years, respectively. For PCLR, the mean age between allograft and autograft groups was 32.2 vs. 31.3 years, and 30 vs. 29 years in these studies, respectively. For revision ACLR, the median age of all patients was 26 (IQR: 20-34). 508 of all patients (42%) were female. In addition, there were (most likely highly active) predominantly military men enrolled in 1/6 studies. The applicability is restricted insofar as some outcomes were only measured by the study that only enrolled (mostly) military men.
Intervention	All of the included studies (9/9 studies) used allograft cruciate ligament reconstruction as an intervention. Differences were present with specific graft types, e.g., some studies used 4-stranded grafts, others used tibialis anterior tendons or Achilles tendons, and the allograft (processing) techniques varied between the included studies as well (e.g., irradiated or not, fresh-frozen or not). Within allografts, there are numerous different graft types with unique advantages and disadvantages. Given that the evidence base is sometimes dominated by a specific graft type (for ACLR, for instance, graft failure rate was measured by 2/6 studies of which 1 had only irradiated allografts as an intervention), the applicability may be limited. Concerns regarding specific applicability of the evidence were highlighted in text and in the GRADE evidence tables.
Comparators	All of the included studies used autograft cruciate ligament reconstruction as a comparator. Some additional comparators were hybrid grafts (i.e., a combination of allograft and autograft; 2/9 studies had 3 treatment groups, of which 1 group received hybrid grafts). Within autografts, there are numerous different graft types with unique advantages and disadvantages. These further differences may limit conclusions in this context. None of the included studies used conservative management as a comparator of allograft cruciate ligament reconstruction.
Outcomes	All of the included studies (ACLR: 6/6 studies; PCLR: 2/2 studies; revision reconstruction: 1/1 study) reported on the crucial outcomes of patient-reported function, activity level and symptoms. The important outcome of clinical knee stability was reported in 4/6 studies for ACLR, in 2/2 studies for PCLR, and 0/1 studies for revision reconstruction. Other important outcomes, such as HRQoL or patient satisfaction, were hardly reported (1/9 included studies, respectively). Regarding safety outcomes, no standardised reporting of complications or graft failure was available. Therefore, it may be that different definitions were present and different complications were judged worthwhile to be reported. As a result, the applicability for safety is limited and must be interpreted with caution.
Setting	It is not expected that the applicability of the results are limited by geographic settings. However, the setting of the patients may reduce the applicability of the results. As such, patients in settings that require highly active behaviour may be differently affected by allografts/autografts when compared to environments in which less activity is required.

List of ongoing randomised controlled trials

Table A-11: List of ongoing trials of allografts for ACLR

Identifier/ Trial name	Patient population	Study design	Number of patients	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT00510848	Rupture of the Anterior Cruciate Ligament with Instability of the Knee Joint	Randomised controlled trial: parallel assignment, open label	40	Reconstruction with an autograft tendon (hamstrings)	Reconstruction with an allograft tendon (tibialis posterior)	X-ray, CT-scan, KT1000 [Time frame: 12 months]	July 2015	University Hospital, Ghent
NCT01245400	Patients with Ruptured Anterior Cruciate Ligaments	Randomised controlled trial: single group assignment, quadruple masking (participant, care provider, investigator, outcome assessor	60	Z-Lig Anterior Cruciate Ligament Reconstruction (ACLR) graft implantation performed under anesthesia during an arthroscopic procedure.	Allograft bone/ tendon graft implantation performed under anaesthesia during an arthroscopic procedure.	KT-1000 [Time frame: baseline, 3,6, 12 & 24 months]	April 2014	Aperion Biologics, Inc.
NCT00975845	Patients with Anterior Cruciate Ligament Rupture	Prospective cohort study	43	BioCleanse Tibialis Tendon Allograft	-	Objective International Knee Documentation Committee (IKDC) Exam [Time frame: pre-op, 2 months, 4 months, 6 months, 12 months, 24 months]	November 2017	RTI Surgical

Table A-12: List of ongoing trials of allografts for PCLR

Identifier/ Trial name	Patient population	Study design	Number of patients	Intervention	Comparison	Primary outcome	Primary completion date	Sponsor
NCT00991588	Complete ruptures to the posterior cruciate ligament (PCL) and posterolateral structures of the knee joint	Prospective cohort study	20	Procedure: PCL, posterolateral reconstruction	-	Elimination of knee giving-way [Time frame: Minimum 2 years postoperatively]	December 2019	Sue Barber-Westin

Table A-13: List of ongoing trials of allografts in multi-ligament knee injuries

Identifier/ Trial name	Patient population	Study design	Number of patients	Intervention	Comparison	Primary outcome	Primary completion date	Sponsor
NCT01440348	Rupture of Posterior Cruciate Ligament|Rupture of Anterior Cruciate Ligament	Intervention Model: Single Group Assignment|Masking: None (Open Label)|Primary Purpose: Treatment	51	Procedure: cruciate ligament reconstruction	-	circumference and length of the Achilles allograft [Time frame: day 1]	September 2011	National Police Hospital

Table A-14: List of ongoing trials of allografts in revision cruciate ligament reconstruction

Identifier/ Trial name	Patient population	Study design	Number of patients	Intervention	Comparison	Primary outcome	Primary completion date	Sponsor
UMIN000003599	Re-injury after the anterior cruciate ligament reconstruction	Single arm, non-randomised open label uncontrolled study	1[96]	Re-reconstruction of ligament with allogenic graft	-	Knee function and safety	NR	Department of Ortho-paedic Surgery, Shimane University
ACTRN12612000631808	Patients undergoing ACL reconstruction	Prospective uncontrolled longitudinal study	100	Anterior Cruciate Ligament (ACL) reconstruction with Live Donor Allograft	-	Clinical and subjective outcome as assessed by the International Knee Documentation Committee (IKDC) Evaluation, KT1000 arthrometer, Lysholm Knee Score, effusion, and kneeling pain (time point: 2 years)	NR	Friends of the Mater Foundation

[96] The number of patients may have been incorrectly entered in the database. The description of the study leads to the impression that this study is not a case report.

Literature search strategies

Search strategy for Cochrane

ID	Search
#1	(cruciate ligament*) (Word variations have been searched)
#2	MeSH descriptor: [Anterior Cruciate Ligament Injuries] explode all trees
#3	MeSH descriptor: [Posterior Cruciate Ligament] explode all trees and with qualifier(s): [injuries – IN]
#4	((knee* NEAR ligament* NEAR (defect* or injur* or lesion* or rupture* or rerupture* or re-rupture* or tear* or dislocat* or damage*))) (Word variations have been searched)
#5	(multiligament* knee*) (Word variations have been searched)
#6	(multi*ligament* knee*) (Word variations have been searched)
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6 (Word variations have been searched)
#8	MeSH descriptor: [Allografts] explode all trees
#9	(Allograft*) (Word variations have been searched)
#10	MeSH descriptor: [Transplantation, Homologous] explode all trees
#11	("allogeneic transplant*") (Word variations have been searched)
#12	#8 OR #9 OR #10 OR #11 (Word variations have been searched)
#13	MeSH descriptor: [Anterior Cruciate Ligament Reconstruction] explode all trees
#14	MeSH descriptor: [Posterior Cruciate Ligament Reconstruction] explode all trees
#15	(ligament* NEAR reconstruct*) (Word variations have been searched)
#16	((ACL or PCL) NEAR (repair* or reconstruct*)) (Word variations have been searched)
#17	(ACLR):ti,ab,kw (Word variations have been searched)
#18	(PCLR):ti,ab,kw (Word variations have been searched)
#19	#13 OR #14 OR #15 OR #16 OR #17 OR #18 (Word variations have been searched)
#20	#12 AND #19 (Word variations have been searched)
#21	(allograft* NEAR (ligament* NEAR (repair* or reconstruct*))) (Word variations have been searched)
#22	(allograft* NEAR (repair* or reconstruct*)) (Word variations have been searched)
#23	#20 OR #21 OR #22
#24	#7 AND #23
Total: 117 Hits	

Search strategy for CRD

ID	Search
1	MeSH DESCRIPTOR Allografts EXPLODE ALL TREES
2	(allograft*)
3	MeSH DESCRIPTOR Transplantation, Homologous EXPLODE ALL TREES
4	(allogeneic)
5	(allogenic)
6	#1 OR #2 OR #3 OR #4 OR #5
7	MeSH DESCRIPTOR Anterior Cruciate Ligament Reconstruction EXPLODE ALL TREES
8	MeSH DESCRIPTOR Posterior Cruciate Ligament Reconstruction EXPLODE ALL TREES
9	(ligament* NEAR reconstruct*)
10	((ACL or PCL) NEAR (repair* or reconstruct*))
11	(ACLR)
12	(PCLR)

13	#7 OR #8 OR #9 OR #10 OR #11 OR #12
14	#6 AND #13
15	(allograft* NEAR (ligament* NEAR (repair* or reconstruct*)))
16	(allograft* NEAR (repair* or reconstruct*))
17	#14 OR #15 OR #16
Total: 22 Hits	

Search strategy for Embase

Session Results			
No.	Query Results	Results	Date
#31.	#28 OR #30	181	18 Dec 2018
#30.	#27 AND #29	162	18 Dec 2018
#29.	'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti	2,331,671	18 Dec 2018
#28.	#8 AND #26 AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim)	87	18 Dec 2018
#27.	#8 AND #26	1,443	18 Dec 2018
#26.	#23 OR #24 OR #25	4,091	18 Dec 2018
#25.	(allograft* NEAR/5 (repair* OR reconstruct*)):ti,ab,de	3,328	18 Dec 2018
#24.	(allograft* NEAR/5 ligament* NEAR/5 (repair* OR reconstruct*)):ti,ab,de	672	18 Dec 2018
#23.	#14 AND #22	1,574	18 Dec 2018
#22.	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	16,394	18 Dec 2018
#21.	'knee ligament surgery'/exp	8,975	18 Dec 2018
#20.	pclr:ti,ab	43	18 Dec 2018
#19.	aclr:ti,ab	1,078	18 Dec 2018
#18.	((acl OR pcl) NEAR/1 (repair* OR reconstruct*)):ti,ab,de	8,442	18 Dec 2018
#17.	(ligament* NEAR/1 reconstruct*):ti,ab,de	14,38	18 Dec 2018
#16.	'posterior cruciate ligament reconstruction'/exp	543	18 Dec 2018
#15.	'anterior cruciate ligament reconstruction'/exp	8,221	18 Dec 2018
#14.	#9 OR #10 OR #11 OR #12 OR #13	135,928	18 Dec 2018
#13.	'allogenic transplant*':ti,ab,de	724	18 Dec 2018
#12.	'allogeneic transplant*':ti,ab,de	7,823	18 Dec 2018
#11.	'allotransplantation'/exp	35,383	18 Dec 2018
#10.	'allograft*':ti,ab,de	102,644	18 Dec 2018
#9.	'allograft'/exp	38,808	18 Dec 2018
#8.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	28,634	18 Dec 2018
#7.	'multiligament knee*':ti,ab,de	89	18 Dec 2018
#6.	'multi-ligament knee*':ti,ab,de	27	18 Dec 2018
#5.	'multiligament knee injury'/exp	11	18 Dec 2018
#4.	('cruciate ligament*' NEAR/5 (defect* OR injur* OR lesion* OR rupture* OR rerupture* OR 're-rupture*' OR tear* OR dislocat* OR damage*)):ti,ab,de	13,794	18 Dec 2018
#3.	'cruciate ligament*':ti,ab,de	28,57	18 Dec 2018
#2.	'posterior cruciate ligament injury'/exp	238	18 Dec 2018
#1.	'anterior cruciate ligament injury'/exp	8,189	18 Dec 2018

Search strategy for Medline

Database: Ovid MEDLINE(R) <1946 to December Week 1 2018>, Ovid MEDLINE(R) Epub Ahead of Print <December 17, 2018>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 17, 2018>, Ovid MEDLINE(R) Daily Update <December 17, 2018>	
Search Strategy:	
1	cruciate ligament*.mp. (22511)
2	exp Anterior Cruciate Ligament Injuries/ (8582)
3	exp *Posterior Cruciate Ligament/in [Injuries] (567)
4	(knee* adj5 ligament* adj5 (defect* or injur* or lesion* or rupture* or rerupture* or re-rupture* or tear* or dislocat* or damage*)).mp. (2154)
5	multi* ligament* knee*.mp. (58)
6	multiligament* knee*.mp. (117)
7	1 or 2 or 3 or 4 or 5 or 6 (23447)
8	exp Allografts/ (6321)
9	allograft*.mp. (66706)
10	exp Transplantation, Homologous/ (83841)
11	allogen?ic transplant*.mp. (4932)
12	8 or 9 or 10 or 11 (128836)
13	exp Anterior Cruciate Ligament Reconstruction/ (3818)
14	exp Posterior Cruciate Ligament Reconstruction/ (44)
15	(ligament* adj reconstruct*).mp. (10356)
16	((ACL or PCL) adj (repair* or reconstruct*)).mp. (7019)
17	ACLR.ti,ab. (844)
18	PCLR.ti,ab. (43)
19	13 or 14 or 15 or 16 or 17 or 18 (12772)
20	12 and 19 (1172)
21	(allograft* adj5 (ligament* adj5 (repair* or reconstruct*))).mp. (365)
22	(allograft* adj5 (repair* or reconstruct*)).mp. (2528)
23	(surg* adj reconstruct*).mp. (4678)
24	20 or 21 or 22 or 23 (7796)
25	7 and 24 (1467)
26	limit 25 to clinical trial, all (120)
27	((randomized controlled trial or controlled clinical trial).pt. or randomi#ed.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/ not humans.sh.) (3765350)
28	25 and 27 (359)
29	26 or 28 (384)
30	remove duplicates from 29 (384)
31	(knee* adj5 ligament* adj5 (defect* or injur* or lesion* or rupture* or rerupture* or re-rupture* or tear* or dislocat* or damage*)).mp. (2154)
32	1 or 2 or 3 or 5 or 6 or 31 (23447)
33	24 and 32 (1467)
34	limit 33 to clinical trial, all (120)
35	27 and 33 (359)
36	34 or 35 (384)
Search date: 18.12.2018	

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