Allograft for use in primary anterior cruciate ligament reconstruction

Evidence-based review

July 2016

Requested by:	Clinical Services Directorate
Date Requested:	April 2016
Date Completed:	August 2016
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Version	Final (external)

Acknowledgements

ACC Research would like to acknowledge the valuable feedback received from the following peer reviewers:

- Dr. Gisela Sole, Senior Lecturer at the School of Physiotherapy, University of Otago
- Mr. Andrew Vincent, Orthopaedic Surgeon, Fellow of the NZ Orthopaedic Association and member of the NZ Knee Society

Important note

- *The purpose of this report is to outline and interpret the best current evidence about the effectiveness and safety of allograft for primary knee ACL reconstruction, including failure rates and complications, in order to facilitate a purchasing decision for ACL reconstruction with allograft tissue.*

- *It is not intended to replace clinical judgement or be used as a clinical protocol.*

- *A reasonable attempt has been made to find and review papers relevant to the focus of this report; however, it does not claim to be exhaustive.*

- *This document has been prepared by the staff of the Evidence Based Healthcare Team, ACC Research. The content does not necessarily represent the official view of ACC or represent ACC policy.*

- *This report is based upon information supplied up to June 2016.*

Revision History

Date	Version	Description	Author
21 July 2016	V1.0		Meagan Stephenson
31 July 2016	V1.2	Revised draft sent to peer reviewers	Meagan Stephenson
22 Aug 2016	V1.3	Revised draft based on peer review comments	Meagan Stephenson
6 Dec 2016	Final (external)	Final draft for external release	Meagan Stephenson

1 Executive Summary

1.1 Background

Anterior cruciate ligament (ACL) ruptures are a relatively common knee injury. Following an ACL rupture, patients can experience ongoing instability of the knee and functional restrictions. The purpose of surgery is to restore stability, offer an opportunity to return to sports activities and reduce the likelihood of further injury to the knee (ACC 2002). Currently, the gold standard option for repair of the ACL is the use of autograft tissue, where tissue from another part of the patients own body (usually the patellar or hamstring tendon), is used to replace the ruptured ACL. More recently, allograft tissue has been used, where tendon tissue is taken from a donor cadaver for the repair. The Clinical Services Directorate (CSD) at the Accident Compensation Corporation (ACC) requested a review of the performance of autograft versus allograft for primary ACL reconstruction to inform purchasing decisions for ACL repair.

1.2 Methodology

A systematic search was conducted of Ovid Medline, Embase and Google Scholar by two EBH researchers from January 2000 up to May 2016. Systematic reviews and meta-analyses which compared outcomes from primary ACL reconstruction with autograft tissue versus allograft tissue were included. Systematic reviews investigated outcomes from revision ACL surgery or which compared two types of autograft or two types of allograft were excluded. Included studies were appraised for quality using the Scottish Intercollegiate Guideline Network (SIGN) levels of evidence system and the methodology and findings of each study were summarized in evidence tables.

1.3 Main results

Twelve systematic reviews were included in this report; all of them conducted a meta-analysis of various outcome measures. Studies were of moderate quality and the systematic reviews were limited by a lack of high quality primary research. Some reviews included data from clinical series as well as comparative studies, which increased the risk of biased findings. Six reviews reported compared outcomes from ACL reconstruction with autograft tissue versus irradiated or nonirradiated allograft tissue. Four reviews excluded studies of irradiated allograft tissue and compared outcomes using autograft tissue versus nonirradiated allograft tissue only. One study compared outcomes in younger (<25 years) and highly active patient groups and one study compared low-dose irradiated allograft with fully irradiated allograft.

When autograft was compared with any type of allograft (irradiated or nonirradiated), there was consistent evidence of higher graft failure rates for primary ACL reconstruction using allograft tissue, but little difference in patient-reported outcome measures or instrumented laxity measures. When autograft was compared with nonirradiated allograft in adult patients (mean age ~late 20s/early 30s) there was consistent evidence of no significant difference in graft failure rate or any other outcomes. Low-dose irradiated allograft tissue performed worse than nonirradiated tissue and is not sufficient to eliminate the risk of disease transmission. Allograft tissue performed significantly worse in younger patients with significantly higher graft failure rates reported in one systematic review.

1.4 Conclusions

The evidence suggests that ACL reconstruction using nonirradiated, fresh-frozen allograft tissue performs no better than autograft tissue in terms of graft failure rate or other outcomes. The evidence also indicates that ACL reconstruction with irradiated allograft tissue is associated with a significantly higher risk of graft failure than autograft tissue. The evidence from one meta-analysis suggests that ACL reconstruction with allograft tissue is associated with a higher graft rupture rate in younger, more active patient groups (e.g. military populations, athletes) than autograft tissue.

1.5 Recommendations

Considering ACL reconstruction with allograft tissue is associated with increased cost, a risk of disease transmission and no significant difference in clinical and patient-reported outcomes for most patient groups, autograft remains the best first option for primary ACL reconstruction in most patients. In young patient groups and those who are highly active, primary ACL reconstruction with allograft tissue is associated with higher graft failure rates and should not be used. Appropriately processed (nonirradiated, fresh-frozen) allograft may be an option for patients whose own tissue is not suitable for repair of an ACL rupture.

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2 Background

2.1 Purpose

Anterior cruciate ligament (ACL) injuries are a relatively common knee injury. They are often associated with sports which involve rapid changes in direction or pivoting and jumping actions (ACC 2002; Gianotti et al 2009). Following an ACL rupture, patients can experience ongoing instability of the knee and functional restrictions. The goal of surgery is to restore stability, offer an opportunity to return to sports activities and reduce the likelihood of further injury to the knee (ACC 2002).

Currently, the gold standard option for repair of the ACL is the use of autograft tissue, where tissue from another part of the patients own body (usually the patellar or hamstring tendon), is used to replace the ruptured ACL. More recently, allograft tissue has been proposed as a good alternative to autograft, where tendon tissue is taken from a donor cadaver for the repair. There is some debate however, about the performance of allograft tissue compared with autograft tissue, and there are also concerns about the risk of disease transmission and the cost and quality of the donor tissue. The Clinical Services Directorate (CSD) at the Accident Compensation Corporation (ACC) requested a review of the performance of autograft versus allograft for primary ACL reconstruction to inform purchasing decisions for ACL repair.

2.2 Anterior cruciate ligament reconstruction

Surgery to repair the ACL following a complete rupture involves the replacement of existing damaged tissue with a substitute. Several options for replacement are available. Autograft involves harvesting the patient's own tissue from another part of their body, usually the patellar tendon or the hamstring tendon, to replace the ruptured ACL (Zeng et al 2016).

Bone Patellar Tendon Bone (BPTB) autografts involve harvesting the middle third of the patellar tendon, plus bone plugs at either end of the section which are used to fix the replacement tendon in place. BPTB autografts are associated with good outcomes, including a low graft failure rate, and are considered the gold standard option for primary ACL reconstruction (Lamblin et al 2013). Autograft tissue can also be harvested from the patients hamstring tendon. Hamstring tendons are less painful to harvest than BPTB autografts but may take longer to heal as soft tissue to bone healing is slower than bone to bone healing (Zeng et al 2016). The disadvantages of autograft are that the treatment involves healing of both the donor site and the repair of the ACL, and the ability to use the patient's own tissue relies on good quality donor material. BPTB autograft can also be associated with subsequent anterior knee pain (Thompson et al 2016).

Allograft involves obtaining replacement tendons from a donor cadaver. Its advantages are that there is no donor site, so no need to recover from harvesting the replacement tendon, and shorter surgical times (Lamblin et al 2013). It has been proposed as a good option for people whose own donor material is not of good enough quality to replace their ruptured ACL. The disadvantages are that outcomes rely on the quality of donor material and there is a risk of serious disease transmission, including bacterial infection, hepatitis and human immunodeficiency virus (HIV) (NZ Knee Society 2015). Methods of sterilization and preservation involve the use of fairly high levels of radiation to kill bacteria and viruses in the tissue. Unfortunately, exposing the tissue to radiation affects its structure and tensile strength and may contribute to a higher rate of graft failure with allograft tissue (Park et al 2014; Lamblin et al 2013). Lower levels of radiation have been proposed as an alternative method of sterilization but these are not sufficient to kill HIV and may not improve graft failure and other outcomes (Park et al 2014). In addition, allograft tissue at present is sourced outside of New Zealand and is associated with significantly greater costs than ACL reconstruction using autograft tissue. The current cost of the tissue is $4000 - $7500 New Zealand dollars (NZ Knee Society 2015) in addition to the costs of the surgery itself.

2.3 Epidemiology

A report based on ACC claims for knee ligament injuries between 2000 and 2005 (Gianotti et al 2009) indicated that over a five year period over 238,000 knee ligament injuries were accepted by ACC, of which 7,375 (3.1%)

resulted in ACL surgery. The incidence of ACL surgery peaked in the 15 – 30 year old age group with the highest incidence in males aged 20 – 29 years. There is a clear association with sports and recreational activities, with approximately 65% of injuries resulting in ACL surgery occurring in sports or recreation settings (Gianotti et al 2009). Knee injuries requiring ACL surgery involve a high number of visits to health practitioners over the course of treatment and rehabilitation. According to ACC data the median number of treatments for ACL surgery was 24 (S.E. = 0.2) with a median cost of $8574.25 (S.E. = $110.67).

2.4 Objective of this report

The main purpose of this evidence-based review is to provide the ACC Clinical Advisory Panel with an overview of the evidence regarding the efficacy and safety of allograft compared with autograft for ACL reconstruction. A number of systematic reviews have been published in the last fifteen years summarizing the outcomes of both prospective and retrospective comparative studies of allograft and autograft. These reviews have overlapped, but not included the same set of primary studies because of differences in the inclusion and exclusion criteria. Some studies have included clinical series, some only patellar tendon autografts, and some only nonirradiated allografts. For this reason, this report focuses on a summary of the systematic reviews and meta-analyses rather than the original primary studies. The appropriateness of different graft sources varies depending on patient subgroups, so where possible, subgroup analyses of different patient subgroups have also been reported.

To this end, this report utilizes EBH tools and methodologies to:

- identify best available secondary evidence using standard EBH research methods (described in methods section below) and appraise articles found in peer-reviewed medical journals, guided by the Scottish Intercollegiate Guideline Network (SIGN) criteria (section 3.3 below),
- clearly outline the quality and consistency of evidence for and against allograft compared with autograft tissue for ACL reconstruction
- clearly outline the caveats within the included evidence that need to be taken into consideration by the Clinical Advisory Panel when using this report as a guide for decisions about the appropriate source of graft material for ACL reconstruction

3 Methods

3.1 Search Strategy

A search was conducted by two EBH researchers within ACC Research using the following databases up to 25 May 2016

- Ovid MEDLINE In-Process & Other Non-Indexed Citations
- Ovid MEDLINE <1946 to Present>,
- Embase
- Cochrane Library databases
- Google scholar

Full search strategies are presented in Appendix A.

3.2 Inclusion and Exclusion Criteria

An initial scan and scoping of the evidence base identified that a large number of systematic reviews and meta-analyses had been completed comparing allograft with autograft for ACL reconstruction. A decision was thus made to include systematic reviews and meta-analyses but not appraise the original primary studies (controlled trials or case series). The full text of potentially eligible secondary studies were retrieved and screened by one researcher using predetermined inclusion and exclusion criteria.

3.2.1 Inclusion Criteria

- *Study design*: Systematic reviews with or without meta-analyses published from January 2006 – May 2016
- *Types of participant:* People with a diagnosed ACL disruption/tear/rupture
- *Types of intervention:* Allograft for primary knee ACL reconstruction
- *Types of comparison:* Autograft for primary knee ACL reconstruction
- *Types of outcome measures:* Rates of success, failure (e.g. re-injury, laxity), revision and complications; patient-reported outcomes (e.g. self-reported stability, satisfaction, quality of life); return to work; return to activity
- *Types of prognostic factors:* age, level of activity, tissue sterilization, tissue preservation, type of graft and donor site, rehabilitation programme or plan

3.2.2 Exclusion Criteria

- Non-systematic reviews, literature reviews
- Articles that did not provide a description of the method of diagnosis of ACL disruption
- Studies where it was not possible to extract the findings for people with knee ACL disruption e.g. studies that reported on the use of allograft or autograft for shoulder, or hip reconstruction
- Systematic reviews and meta-analyses which only included clinical series or did not report the characteristics of included studies
- Studies of revision ACL reconstruction
- Animal or laboratory study
- Non-English studies

3.3 Level of Evidence

Studies meeting the criteria for inclusion in this report were assessed for their methodological quality using the Scottish Intercollegiate Guideline Network (SIGN; http://www.sign.ac.uk/guidelines/fulltext/50/annexoldb.html) methodological checklists and level of evidence system (see table 1 below). The number (1 – 4) indicates the level of evidence based on study design. The +/++/- indicates the quality of evidence for that study design based on the risk of bias. SIGN uses four categories to grade the quality of a systematic review or meta-analysis. These grades are obtained by completing a checklist of criteria for each study and making an overall qualitative assessment of the likely risk of bias:

High quality (++)

Moderate (+)

Low quality (-)

Unacceptable – reject 0

In the current review, systematic reviews which included at least one randomised trial were graded 1- to reflect the inclusion of RCTs with a high risk of bias. Systematic reviews which included prospective or retrospective comparative studies were graded 2++ and systematic reviews which included the findings of non-comparative clinical series in their analyses were graded 2-, to reflect the high risk of error in these analyses. Evidence tables summarising the methodology and findings of each included study and a brief outline of any limitations are presented in Appendix D.

Table 1. Levels of evidence based on the Scottish Intercollegiate Guideline Network (SIGN) level of evidence system

Levels of evidence	
1++	High quality meta analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well conducted meta analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

4 Results

4.1 Study Overview

The initial search identified 51 potentially relevant studies of which 39 were excluded, leaving 12 systematic reviews and meta-analyses which fulfilled inclusion criteria. These were published between 2007 and 2015, with all 12 performing a meta-analysis. There was some overlap of included studies, but there was also considerable variability depending on the focus of the review and whether non-comparative studies were included. Tables 3A, 3B, and 3C summarise the inclusion criteria and the types of studies included in each review. In general, the systematic reviews which included non-comparative studies were considered low quality, graded 2- (Podromos et al 2007; Kraeutler et al 2013; Park et al 2014) because these reviews included studies which have a high risk of bias, for example, case series. These studies also did not perform any sensitivity analyses and it was therefore difficult to interpret their findings. The remaining nine reviews included either only prospective comparative studies (Krych et al 2008; Cvetanovich et al 2014; Hu et al 2013; Wei et al 2014) or prospective and retrospective comparative studies (Carey et al 2009; Wasserstein et al 2015; Yao et al 2015; Lamblin et al 2013; Mariscalco et al 2013). These were all graded as moderate quality.

The number of studies included in each review also varied depending on the focus of the review and the year of publication. Four randomized trials and one partially randomized trial of autograft and allograft for ACL reconstruction were published between 2008 and 2012 so some of the earlier reviews did not include some or all of these studies (Podromos et al 2007; Carey et al 2009; Krych et al 2008). There were also differences in the focus of each review. Three reviews compared any type of allograft, including both studies of irradiated and nonirradiated graft tissue, with any type of autograft (BPTB grafts and hamstring grafts). One of these (Wasserstein et al 2015) focused solely on patients younger than 25 years of age or with a high activity level. Four reviews focused on a specific autograft and allograft comparison. Three of these compared BPTB autografts and BPTB allografts (Krych et al 2008; Kraeutler et al 2013; Yao et al 2015) and one compared hamstring autografts with soft tissue allografts (Cvetanovich et al 2014). The remaining four reviews focused on a comparison of any type of autograft (BPTB or hamstring) with nonirradiated allograft of any type (BPTB or soft tissue) (Hu et al 2013; Lamblin et al 2013; Mariscalco et al 2013; Wei et al 2014). Two of these reviews included subgroup analyses of different types of grafts (Hu et al 2013; Wei et al 2014). Almost all the reviews completed quality assessments of the included primary studies and described them as being of low to moderate quality. Some heterogeneity was present but sensitivity analyses were often completed where there was an outlying study.

All of the reviews stated as part of their inclusion criteria that at least two years follow-up of patients was required. However, for some studies this meant an average follow-up of two years, whereas for others a minimum of two years for all included patients was required. Not all reviews stated the mean age of participants, however, where stated, it was approximately 28 – 29 years of age in most cases. The review by Wasserstein and colleagues (2015) focused on young and highly active patients and included only studies of patients aged 25 years and under. The preinjury activity level of patients was not described in any of the reviews, other than Wasserstein et al (2015) where high activity levels (military/Marx activity level >12/collegiate or semiprofessional athlete) were a prerequisite for inclusion.

Table 3. Overview of included secondary studies of autograft compared with allograft for primary ACL reconstruction

A) Autograft (any type) v allograft (any type)

Reference	Inclusion criteria		Included studies	Rehabilitation Protocol and Follow-Up	Quality of evidence
Podromos et al (2007)	Autograft v allograft (any type) Comparative studies and clinical series Subgroup analyses of irradiated v nonirradiated allograft	20	*Prospective cohort studies: n=5:* *Retrospective cohort studies: n=2* *Clinical series: n=13*	Not stated At least two years follow-up Mean age not stated	Low 2-
Carey et al (2009)	Autograft v allograft (any type) Prospective and retrospective	9	*Prospective comparative studies: n=5*	Not stated At least two	Moderate

	comparative studies Subgroup analyses of BPTB autograft v BPTB allograft		*Retrospective comparative studies: n=4*	years follow-up Mean age not stated	2++
Wasserstein et al (2015)	Autograft v allograft (all types) **Patients < 25 years of age or of high activity level** Prospective and retrospective comparative studies Subgroup analyses of irradiated and nonirradiated allograft	7	*RCTs: n=1* *Prospective comparative studies: n=2* *Retrospective comparative studies: n=4*	Not stated At least two years follow-up Mean age = 21.7 years	Moderate 1-

B) BPTB autograft v BPTB allograft and QHS autograft v soft tissue allograft

Reference	Inclusion criteria		Included studies	Rehabilitation Protocol and Follow-Up	Quality of evidence
Krych et al (2008)	BPTB autograft v BPTB allograft Prospective comparative studies Subgroup analyses of irradiated and nonirradiated allografts	6	*Prospective cohort studies: n=6*	Return to full activity in 6-12 months At least two years follow-up Mean age = 32.9 years	Moderate 2++
Kraeutler et al (2013)	BPTB autograft v BPTB allograft Comparative studies and clinical series No subgroup analyses	76	*Characteristics of included studies were not described*	Not stated At least two years follow-up Mean age = 30 years	Low 2-
Yao et al (2015)	BPTB autograft v BPTB allograft Prospective or retrospective comparative studies Subgroup analyses of irradiated v nonirradiated allograft	13	*Prospective cohort studies: n=6* *Retrospective cohort studies: n=7*	Not stated At least two years follow-up Mean age = ~28 years	Moderate 2++
Cvetanovich et al (2014)	QHS autograft v soft tissue allograft Prospective comparative studies Subgroup analyses of irradiated and nonirradiated allografts	5	*RCTs: n=4* *Partially randomised comparative studies: n=1*	Not stated At least two years follow-up Mean age = 29.9 years	Moderate 1-

C) Autograft v nonirradiated allograft

Reference	Inclusion criteria		Included studies	Rehabilitation Protocol and Follow-Up	Quality of evidence
Hu et al (2013)	Autograft v nonirradiated allograft Prospective comparative studies Subgroup analyses of BPTB and QHS grafts	9	*RCTs: n=4* *Cohort studies: n=5*	Not stated At least two years follow-up Mean age = 28.5 years	Moderate 1-
Lamblin et al (2013)	Autograft v nonirradiated allograft Prospective and retrospective comparative studies No subgroup analyses	11	*RCTs: n=4* *Prospective cohort studies: n=5* *Retrospective cohort studies: n=2*	Return to running 3-6 months postoperatively Return to sports activities 6-12 months	Moderate 1-

				postoperatively At least two years follow-up Mean age – not stated	
Mariscalco et al (2013)	Autograft v nonirradiated allograft Prospective and retrospective comparative studies No subgroup analyses	9	*RCTs: n=3* *Prospective cohort studies: n=3* *Retrospective cohort studies: n=3*	Not stated At least two years follow-up Mean age = 31 years	Moderate 1-
Wei et al (2014)	Autograft v nonirradiated allograft Prospective comparative studies Subgroup analyses of BPTB and soft tissue grafts	12	*RCTs: n=5* *Prospective comparative studies: n=7*	Not stated At least two years follow-up Mean age = 30 years	Moderate 1-
Park et al (2014)	Autograft v low-dose irradiated allograft (< 2.5 Mrad) Comparative studies and clinical series	21	*Comparative studies: n=2* *Clinical series: n=19*	Not stated At least two years follow-up Mean age = 32 years	Low 2-

4.2 Definition of key outcome measures

Both patient-reported outcome measures and objective clinical measures of laxity and graft failure were included in the reviews. Patient-reported outcome measures included Lysholm scores, overall and subjective IKDC scores and Tegner scores, all of which are standardized and validated outcome measures. Clinical outcomes also used standardized measures for measures of laxity, however there were some differences in the classification of instability. For instance, KT 1000 outcomes were classified in some studies as a fail if there was 3mm or greater difference in laxity compared with the contralateral knee, where other studies used a cut-off of 5mm difference. Similarly, there were differences in the classification of graft failure across the reviews, with some including only re-ruptures, reoperations or revision surgery, and others also including failures on the basis of clinical laxity outcomes.

Generally, the reviews included both patient-reported and clinical outcomes, but they were not always able to complete a meta-analysis of all included outcomes. For instance, some studies were unable to provide summary scores for Lysholm and Tegner questionnaires, but were able to provide IKDC data. Similarly, some studies reported summary Lachman scores, KT-1000 scores and hop test scores where others did not. Data which was easily categorized as a pass or fail (e.g. Lachman scores) were presented as summary odds ratios or relative risk ratios. If the 95% confidence interval of an odds ratio or relative risk ratio cross 1, this is considered not statistically significant, and suggests there is no significant difference in the risk of a particular outcome for the two groups. Continuous data (e.g. Tegner score) was most often presented as a standardized or weighted mean difference in scores between the autograft and allograft groups.

4.3 Autograft compared with irradiated and nonirradiated allograft

Five systematic reviews compared the performance of autograft with irradiated or nonirradiated allograft (see Tables 4, 5, 6, 7 below). One of these reviews was considered low quality because it included a large number of non-comparative studies, mainly clinical series (Kraeutler et al 2013). The remaining four reviews were considered moderate quality.

4.3.1 Graft Failure

In reviews of both irradiated and nonirradiated allograft tissue, the risk of graft failure was reported as being significantly higher for allograft compared with autograft in three studies (Table 4). Both Krych et al (2008) (OR 5.03, 95% CI 1.38 – 18.33) and Kraeutler et al (2013) (OR 3.24, 95% CI 2.41 – 4.36) reported a significantly higher

odds of graft failure when BPTB allograft tissue was used compared to autografts. Yao et al (2015) reported a significantly lower odds (OR 0.31, 95% CI 0.13 – 0.78) of graft failure when BPTB autograft tissue was used. The remaining two reviews reported no significant differences in graft failure outcomes. Cvetanovich et al (2014) focused on hamstring autograft compared with soft tissue allograft and reported a non-significant relative risk of graft failure favouring autograft (RR 1.14, 95% CI 0.40 – 3.25).

Table 4. Summary results of graft failures comparing autograft with irradiated or nonirradiated allograft

Outcome *Definition*	References	Comparison	Results of the meta-analysis Std Mean Difference/RR/OR (95% CI)	P-value
Clinical failure rate *Reoperation/re-rupture*	*Krych et al (2008)*	*BPTB autograft v BPTB allograft*	*OR = 5.03 (1.38, 18.33) (favours autograft)*	*0.01*
	Carey et al (2009)	*Autograft v allograft*	*OR = 0.61 (0.21, 1.79)*	*NS*
	Kraeutler et al (2013)	*BPTB autograft v BPTB allograft*	*OR = 3.24 (2.41, 4.36) (favours autograft)*	*NR*
	Cvetanovich et al (2014)	*QHS autograft v soft tissue allograft*	*RR = 1.14 (0.40, 3.25)*	*NS*
	Yao et al (2015)	*BPTB autograft v BPTB allograft*	*OR = 0.31 (0.13, 0.78) (favours autograft)*	*0.01*

4.3.2 Patient-Reported Outcome Measures

There was some variability in the inclusion of patient-reported outcome measures across the reviews of irradiated and nonirradiated allograft tissue (Table 5). Where these measures were included, the reviews mostly reported no significant odds ratios or mean differences between the groups. The only significant differences between autograft and allograft were reported by a low quality meta-analysis which included non-comparative clinical series (Kraeutler et al 2013). Three of these measures favoured autograft (Lysholm score, Tegner score and subjective IKDC) and one favoured allograft (objective IKDC).

Table 5. Summary results of patient-reported outcome measures comparing autograft with irradiated or nonirradiated allograft

Outcome *Definition*	References	Comparison	Results of the meta-analysis Std Mean Difference/Weighted Mean Difference/RR/OR (95% CI)	P-value
Lysholm score *Normal or nearly normal*	*Kraeutler et al (2013)*	*BPTB autograft v BPTB allograft*	*OR = 2.61 (2.13, 3.19) (favours autograft)*	*NR*
	Cvetanovich et al (2014)	*QHS autograft v soft tissue allograft*	*SMD = -0.07 (-0.28, 0.15)*	*NS*
	Yao et al (2015)	*BPTB autograft v BPTB allograft*	*WMD = 1.57 (-1.09, 4.24)*	*NS*
Overall IKDC	*Krych et al (2008)*	*BPTB autograft v BPTB allograft*	*OR = 1.49 (0.21, 10.38)*	*NS*
	Kraeutler et al (2013)	*BPTB autograft v BPTB allograft*	*OR = 0.45 (0.30, 0.68) (favours allograft)*	*NR*
	Cvetanovich et al (2014)	*QHS autograft v soft tissue allograft*	*RR = 1.01 (0.96, 1.05)*	*NS*
	Yao et al (2015)	*BPTB autograft v BPTB allograft*	*OR = 1.37 (0.80, 1.37)*	*NS*
Subjective IKDC	*Kraeutler et al (2013)*	*BPTB autograft v BPTB allograft*	*OR = 1.64 (1.26, 2.14) (favours autograft)*	*NR*
Tegner score	*Kraeutler et al (2013)*	*BPTB autograft v BPTB allograft*	*OR 1.35 (1.07, 1.70) (favours autograft)*	*NR*

Cvetanovich et al (2014)	*QHS autograft v soft tissue allograft*	*SMD = 0.11 (-0.15, 0.36)*	*NS*
Yao et al (2015)	*BPTB autograft v BPTB allograft*	*WMD = 0.40 (-0.29, 1.09)*	*NS*

4.3.3 Instrumented Laxity and Stability Outcomes

There was some variability in the included clinical measures of laxity and stability across the different reviews. In general, where summary odds ratios or relative risk ratios were reported, they were not significant, indicating no difference in risk between the two groups (Table 6). A low quality meta-analysis (Kraeutler et al 2013) reported some differences in KT-1000 scores (OR <3mm difference = 2.02, 95% CI 1.67 – 2.44) favouring autograft and in pivot-shift test scores (OR 0.74, 95% CI 0.58 – 0.95) and hop test scores (OR 4.09, 95% CI 2.99 – 5.60) favouring allograft. The only other significant difference in outcomes was by Krych et al (2008) who reported an increased odds of a successful hop test outcome (hop index >90%) with BPTB autograft (OR 5.66, 95% CI 3.09 – 10.36) when compared with BPTB allograft.

Table 6. Summary results of instrumented laxity scores comparing autograft with irradiated or nonirradiated allograft

Outcome *Definition*	References	Comparison	Results of the meta-analysis Std Mean Difference/RR/OR (95% CI)	P-value
Lachman (anterior laxity) *Negative*	*Krych et al (2008)*	*BPTB autograft v BPTB allograft*	*OR = 2.75 (0.70, 10.81)*	*NS*
	Cvetanovich et al (2014)	*QHS autograft v soft tissue allograft*	*RR = 1.37 (0.88, 2.14)*	*NS*
	Yao et al (2015)	*BPTB autograft v BPTB allograft*	*OR = 0.95 (0.49, 1.85)*	*NS*
KT1000 assessment *<3mm difference in laxity*	*Kraeutler et al (2013)*	*BPTB autograft v BPTB allograft*	*OR = 2.02 (1.67, 2.44) (favours autograft)*	*NR*
	Cvetanovich et al (2014)	*QHS autograft v soft tissue allograft*	*RR = 1.11 (0.89, 1.39)*	*NS*
	Yao et al (2015)	*BPTB autograft v BPTB allograft*	*OR = 0.90 (0.14, 5.72)*	*NS*
Pivot shift test (rotational laxity) *Negative*	*Krych et al (2008)*	*BPTB autograft v BPTB allograft*	*OR = 1.23 (0.51, 2.98)*	*NS*
	Kraeutler et al (2013)	*BPTB autograft v BPTB allograft*	*OR = 0.74 (0.58, 0.95) (favours allograft)*	*NR*
	Cvetanovich et al (2014)	*QHS autograft v soft tissue allograft*	*RR = 1.05 (0.92, 1.20)*	*NS*
	Yao et al (2015)	*BPTB autograft v BPTB allograft*	*OR = 0.61 (0.29, 1.25)*	*NS*
Hop test *Hop index >90%*	*Krych et al (2008)*	*BPTB autograft v BPTB allograft*	*OR = 5.66 (3.09, 10.36) (favours autograft)*	*P=0.01*
	Kraeutler et al (2013)	*BPTB autograft v BPTB allograft*	*OR = 4.09 (2.99, 5.60) (favours allograft)*	*NR*
	Yao et al (2015)	*BPTB autograft v BPTB allograft*	*OR = 0.69 (0.39, 1.23)*	*NS*

4.3.4 Complications

Very few reviews included an analysis of other complications such as anterior knee pain and patellofemoral crepitus. Where they were included (Table 7), there were no significant differences reported except in one low quality meta-analysis which reported a significant difference in the odds of anterior knee pain favouring allograft (OR 0.29, 95% CI 0.20 – 0.42).

Table 7. Summary results of complications comparing autograft with irradiated or nonirradiated allograft

Outcome *Definition*	References	Comparison	Results of the meta-analysis Std Mean Difference/RR/OR (95% CI)	P-value
Anterior knee pain	*Kraeutler et al (2013)*	*BPTB autograft v BPTB allograft*	*OR = 0.29 (0.20 – 0.42) (favours allograft)*	*NR*
	Yao et al (2015)	*BPTB autograft v BPTB allograft*	*OR = 0.97 (0.52, 1.82)*	*NS*
Patellofemoral Crepitus *Presence v absence*	*Krych et al (2008)*	*BPTB autograft v BPTB allograft*	*OR = 2.34 (0.76, 7.27)*	*NS*
	Yao et al (2015)	*BPTB autograft v BPTB allograft*	*OR = 0.99 (0.55, 1.76)*	*NS*

4.4 Autograft (all types) compared with nonirradiated allograft

4.4.1 Graft Failure

Four reviews reported summary odds or relative risk ratios for the likelihood of clinical graft failure following ACL reconstruction with autograft or nonirradiated allograft tissue (Table 8). All four reported no significant differences in the risk of failure, and all were within a close range (OR/RR range 0.67 – 0.76). However, the definitions of failure varied between studies. Lamblin et al (2013) based their classification of graft failure on laxity measures where the remaining studies used rates of reoperation, revision or re-rupture. Mariscalco et al (2013) completed analyses of failure risk using two different definitions for comparison. In the first, clinical failure was defined by the author of each primary study, and suggested that the overall failure rate was 3.0% and 2.4% for the autograft and allograft groups respectively. In the second, failure was defined as anterior laxity of at least 5mm greater than the unaffected knee, with an overall failure rate of 6% for autograft and 5.5% for allograft. In both cases these differences were not statistically significant.

Mariscalco et al (2013) reported no overall difference in the relative risk of graft failure between autograft and allograft (OR = 0.75, 95% CI 0.25 – 2.24), however, a subgroup analysis of BPTB autograft versus BPTB allograft revealed a significant difference in favour of autograft (SMD = 0.5, 95% CI 0.15 to 0.85, p=0.005).

Table 8. Summary results of graft failures comparing autograft with nonirradiated allograft

Outcome *Definition*	References	Comparison	Weighted Mean Difference/Standardised Mean Difference/Relative Risk/Odds Ratio (95% CI)	P-value
Clinical failure rate *Reoperation/re-rupture except Lamblin which was based on laxity*	*Mariscalco et al (2013)*	*Autograft v nonirradiated allograft*	RR = 0.75 (0.25, 2.24)*	*NS*
	Hu et al (2013)	*Autograft v nonirradiated allograft*	RR = 0.67 (0.1, 4.36)	*NS*
	Lamblin et al (2013)	*Autograft v nonirradiated allograft*	OR = 0.76 (0.36, 1.59)	*NS*
	Yao et al (2015)	*BPTP autograft v nonIR BPTB allograft*	OR = 0.76 (0.11, 5.31)	*NS*

** subgroup analysis: BPTB autograft versus BPTB nonirradiated allograft (SMD = 0.5, 95% CI 0.15 to 0.85, p=0.005)*

4.4.2 Patient-Reported Outcome Measures

Three reviews completed meta-analyses of patient-reported outcomes following ACL reconstruction with autograft or nonirradiated allograft tissue (Hu et al 2013; Lamblin et al 2013; Yao et al 2015). No significant differences in the odds or relative risk of poor Lysholm or overall IKDC scores were reported by any of the reviews (Table 9). Two studies reported differences in Tegner scores in favour of autograft. Hu et al reported a summary relative risk of 0.25 (95% CI -0.01 to 0.52, p=0.06) and Yao et al (2015) reported a significant difference in the weighted mean difference in Tegner scores for BPTB autograft compared with BPTB allograft (WMD = 0.38, 95% CI 0.11 – 0.65). While statistically significant, the absolute difference is very small and may not be clinically significant. Lamblin et al (2013) completed a subgroup analysis of BPTB autograft v BPTB allograft and reported a significant difference in Lysholm scores in favour of autograft (SMD = 0.5, 95% CI 0.15 to 0.85, p=0.005).

Table 9. Summary results of patient-reported outcomes comparing autograft with nonirradiated allograft

Outcome *Definition*	References	Comparison	Weighted Mean Difference/Standardised Mean Difference/Relative Risk/Odds Ratio (95% CI)	P-value
Lysholm score *Normal or nearly normal*	*Hu et al (2013)*	*Autograft v nonirradiated allograft*	RR = 0.3 (-1.97, 2.57)	*NS*
	Lamblin et al (2013)	*Autograft v nonirradiated allograft*	SMD = 0.8	*NS*
	Yao et al (2015)	*BPTP autograft v nonIR BPTB allograft*	WMD = 0.04 (-1.63, 1.56)	*NS*
Overall IKDC	*Hu et al (2013)*	*Autograft v nonirradiated allograft*	*RR = 0.96 (0.6, 1.54)*	*NS*
	Lamblin et al (2013)	*Autograft v nonirradiated allograft*	*OR = 1.03 (0.64, 1.66)*	*NS*
	Yao et al (2015)	*BPTB autograft v nonIR BPTB allograft*	*OR = 1.47 (0.77, 2.78)*	*NS*
Tegner score	*Hu et al (2013)*	*Autograft v nonirradiated allograft*	*RR = 0.25 (-0.01, 0.52)(autograft)*	*0.06*
	Wei et al (2014)	*Autograft v nonirradiated allograft*	*OR 1.35 (1.07, 1.70) (autograft)*	*NR*
	Yao et al (2015)	*BPTB autograft v nonIR BPTB allograft*	*WMD = 0.38 (0.11, 0.65)*	*0.006*

4.4.3 Instrumented Laxity and Stability Outcomes

Four reviews completed meta-analyses of instrumented laxity and stability outcomes following ACL reconstruction with autograft or nonirradiated allograft tissue (Mariscalco et al 2013; Hu et al 2013; Lamblin et al 2013; Yao et al 2015). There were no significant differences in the risk of poor outcomes across any of the measures (Table 10). The classification of a failure using the KT-1000 assessment was >5mm laxity compared with the unaffected knee, a higher cut-off than that used in studies which included irradiated allograft tissue.

Table 10. Summary results of instrumented laxity comparing autograft with nonirradiated allograft

Outcome *Definition*	References	Comparison	Weighted Mean Difference/Standardised Mean Difference/Relative Risk/Odds Ratio (95% CI)	P-value
Lachman *Grade > 0*	*Mariscalco et al (2013)*	*Autograft v nonirradiated allograft*	*RR = 1.11 (0.79, 1.57)*	*NS*
	*Hu et al (2013)**	*Autograft v nonirradiated allograft*	*RR = 0.88 (0.64, 1.20)*	*NS*

	Lamblin et al (2013)	*Autograft v nonirradiated allograft*	*OR = 0.99 (0.54, 1.80)*	*NS*
	Yao et al (2015)	*BPTB autograft v nonIR BPTB allograft*	*OR = 0.78 (0.34, 1.77)*	*NS*
KT1000 assessment	*Hu et al (2013)*	*Autograft v nonirradiated allograft*	*RR = 1.19 (0.63, 2.24)*	*NS*
	Lamblin et al (2013)	*Autograft v nonirradiated allograft*	*OR = 0.57 (0.22, 1.53)*	*NS*
>5mm laxity difference	*Yao et al (2015)*	*BPTB autograft v nonIR BPTB allograft*	*OR = 1.05 (0.55, 2.03)*	*NS*
	Mariscalco et al (2013)	*Autograft v nonirradiated allograft*	*RR = 1.06 (0.66, 1.70)*	*NS*
Pivot shift test	*Hu et al (2013)*	*Autograft v nonirradiated allograft*	*RR = 0.97 (0.64, 1.46)*	*NS*
Grade > 0	*Lamblin et al (2013)*	*Autograft v nonirradiated allograft*	*OR = 0.77 (0.43, 1.37)*	*NS*
	Yao et al (2015)	*BPTB autograft v nonIR BPTB allograft*	*OR = 0.95 (0.37, 2.44)*	*NS*
Hop test	*Wei et al (2014)*	*BPTB autograft v BPTB allograft*	*OR = 0.52 (0.25, 1.97)*	*NS*
Hop index >90%				

4.4.4 Complications

There were no significant differences in the risk of anterior knee pain or patellofemoral crepitus for autograft or nonirradiated allograft in two meta-analyses (Mariscalco et al 2013; Yao et al 2015). See Table 11 for a summary of these findings.

Table 11. Summary results of complications comparing autograft with nonirradiated allograft

Outcome *Definition*	References	Comparison	Weighted Mean Difference/Standardised Mean Difference/Relative Risk/Odds Ratio (95% CI)	P-value
Anterior knee pain	*Yao et al (2015)*	*BPTB autograft v BPTB allograft*	*OR = 1.35 (0.42, 4.33)*	*NS*
Patellofemoral Crepitus	*Mariscalco et al (2013)*	*Autograft v nonirradiated allograft*	*OR = 2.34 (0.76, 7.27)*	*NS*
	Yao et al (2015)	*BPTB autograft v BPTB allograft*	*OR = 0.80 (0.29, 2.25)*	*NS*
Presence v absence				

4.5 Low-dose allograft v nonirradiated allograft

Park et al (2014) completed a systematic review of the performance of low-dose (<2.5 Mrad) irradiated allograft compared with nonirradiated allograft. Studies were required to have a minimum average follow-up of two years. Both comparative studies and clinical series were included, with two included studies directly comparing autograft and low-dose irradiated allograft. Outcomes were compared from the pooled results of all included studies. This study was not fully critically appraised as it was primarily a comparison of low-dose irradiated and nonirradiated allograft and did not meet inclusion criteria, but as it is the only identified systematic review of the performance of low-dose irradiated allograft, it was included in the summary of findings. The findings indicated that low-dose

irradiated allograft tissue performed significantly worse than autograft tissue in terms of revision surgery, Lysholm scores, KT-1000 arthrometer scores and Lachman scores.

4.6 Autograft compared with allograft in young (<25 years of age) and highly active people

Wasserstein et al (2015) conducted a meta-analysis of the graft failure rate following ACL reconstruction with autograft or allograft tissue in young people (</= 25 years) or those with a high activity level (military/Marx activity level >12/collegiate or semiprofessional athlete). The data from one randomized trial and six cohort studies were included in the analyses.

In this study, the authors reported a clear difference in relative risk in favour of autograft for both BPTB and hamstring tendon autografts (overall RR = 0.36, 95% CI 0.24 – 0.53). Overall graft failure rates were 9.6% for autograft and 25% for allograft.

When subgroups were analysed, a similar pattern of results was reported for BPTB autografts versus allograft and hamstring autografts versus soft tissue allografts. When autografts were compared with nonirradiated allografts, the results were in the same direction as for other subgroups, but were no longer significant (Failure rate autograft = 9%; failure rate nonirradiated allograft = 19.5%). The single randomized trial (Bottoni et al 2014) included in these analyses indicated that the failure rate for allograft was three times that of autograft (failure rate autograft = 8.3%, failure rate nonirradiated allograft = 26.5%; RR = 0.31, 95% CI 0.11 – 0.90). There were no significant differences in the overall Lysholm score based on three primary studies. The authors were unable to calculate summary risk ratios for any other measures.

Table 12. Summary results of graft failures comparing autograft and allograft in young people (<25 years of age) (Wasserstein et al 2015)

Outcome *Definition*	**Comparison**	**Results of the meta-analysis** **Std Mean Difference/RR/OR (95% CI)**	**Significant**
Clinical failure rate *Reoperation/re-rupture*	*All autograft v all allograft*	RR = 0.36 (0.24, 0.53) (favours autograft)	*P < 0.01*
	BPTB autograft v allograft	RR = 0.42 (0.28, 0.63) (favours autograft)	*P < 0.01*
	QHS autograft v allograft	RR = 0.37 (0.17, 0.81) (favours autograft)	*P < 0.01*
	Autograft v irradiated allograft	RR = 0.22 (0.06, 0.85) (favours autograft)	*P < 0.03*
	Autograft v nonirradiated allograft	RR = 0.57 (0.14, 2.27)	*NS*
Lysholm score *Proportion classified as normal or nearly normal*	*All autograft v all allograft*	SMD = 1.87 (-0.44, 4.18)	*NS*

4.7 Rehabilitation protocols

There were no meta-analyses comparing different intensity rehabilitation protocols following ACL reconstruction with autograft and allograft tissue. For nonirradiated allograft studies, the authors of the meta-analyses comparing autograft and nonirradiated allograft, reported that all the included primary studies utilized similar rehabilitation protocols. These involved a return to running in 3-6 months and a return to sports activities in 6-12 months. All rehabilitation protocols allowed early motion, early weight bearing and mobility with the assistance of a postoperative brace. The summary results for clinical failure and laxity outcomes should not be applied to situations where a shorter rehabilitation protocol was implemented. In addition, there is considerable debate in the literature around the ideal time for return to sports following ACL reconstruction, with some evidence suggesting

that an early return within 1-2 years of reconstruction may be associated with higher rates of a second ACL injury, especially in younger, more active people (Nagelli and Hewitt 2016).

4.8 Guidelines and other insurance jurisdictions

Both Cigna and AETNA do not consider the use of allograft tissue for primary ACL reconstruction medically necessary unless at least one of the following criteria are met:

- Previous reconstruction has failed and requires revision
- Surgical reconstruction requires the use of multiple ligament transfers
- Individual has a medical condition (e.g. collagen disease, anatomic anomaly, prior knee injury or prior knee surgery) that precludes the use of autograft tissue

There is a paucity of information in clinical guidelines about the use of allograft tissue for ACL reconstruction. The American Academy of Orthopedic Surgeons (AAOS 2012) recommends the use of autograft or appropriately processed (nonirradiated) allograft tissue for most patients, but not young people or athletes.

The New Zealand Knee and Sports Society does not support the use of allograft tissue for primary ACL reconstruction because it has been associated with higher graft failure rates, especially in younger populations; heals at a slower rate; is associated with a small but real risk of disease transmission; and is costly to obtain in New Zealand (NZOA 2015).

5 Discussion

5.1 Nature and quality of the evidence

There were noticeable differences in findings between systematic reviews which included clinical series and those which included only comparative studies and randomised trials. Ethical concerns with randomly allocating people to receive cadaveric material and strong patient preferences meant that there were few randomised trials included in the meta-analyses. Allocation to autograft or allograft groups was therefore based on patient and surgeon preference. The systematic reviews were mostly of a moderate quality and were graded 1- to 2++ depending on whether they included randomised trial data or not. The five randomised controlled trials comparing autograft and allograft for ACL reconstruction focus only on nonirradiated fresh-frozen allograft tissue (see appendix 8.3 for a summary). There are no randomised trials comparing autograft with irradiated allograft. There were limitations in the quality of included studies, databases searched, and whether the reviews took heterogeneity into account when completing their analyses. While the direction of the findings was mostly consistent, there were often marked differences in the size of the summary odds ratios or relative risk ratios. The mean age of included patients was late 20s to early 30s in most cases, with one review focussing on younger patients aged under 25. No other reviews were able to complete subgroup analyses for older and younger patients. However, many authors advised that their findings should not be applied to younger, more active patient groups.

Where a quality appraisal of included primary studies was completed, the main limitations were a lack of randomisation and a lack of blinding of patients, surgeons and those assessing outcome measures. This means that the included primary studies had a high risk of biased findings.

5.2 Summary of findings

Meta-analyses which compared autograft with irradiated allograft tissue indicated that allograft performed significantly worse than autograft tissue in graft failure rate, but there were few differences in other outcome measures. When studies of irradiated allograft tissue were excluded from analyses, there were no significant differences between autograft and allograft in graft failure rates, except for one subgroup analysis comparing BPTB autograft with BPTB allograft. There were also no significant differences in patient-reported outcome measures, instrumented laxity and complications. In addition, one systematic review compared the outcomes of nonirradiated and low dose irradiated (<2.5 Mrad) allograft tissue for primary ACL reconstruction. The review indicated that low-dose irradiated allograft tissue was associated with higher rates of revision surgery, and worse patient-reported and

instrumental laxity outcomes. This suggests that irradiating allograft tissue as part of the sterilisation process may reduce its structural integrity, whether low-dose or full irradiation is used. Other methods of sterilization and preservation are available, but may be associated with a risk of disease transmission which may be unacceptable for some patients.

One systematic review focussed solely on a comparison of autograft and allograft for primary ACL reconstruction in younger patients under the age of 25, or those who were highly active (military and athletic populations). This review suggested that allograft had a significantly higher graft failure rate than autograft for these patient groups.

No review was able to perform an analysis comparing the outcomes of ACL reconstruction with autograft and allograft using different rehabilitation protocols. However, several authors noted that all the prospective comparative studies utilised a standard rehabilitation protocol which involved early weightbearing and motion, return to running in 2-3 months and return to sporting activities in 6-12 months. The authors cautioned that they could not extrapolate their findings to situations where an accelerated rehabilitation protocol was used.

6 Conclusion

6.1 Evidence statement

There is moderate quality evidence, based on five moderate quality and two low quality meta-analyses, of a significant difference in graft failure rate favouring autograft, between primary ACL reconstruction completed using autograft tissue and reconstruction completed using irradiated (low-dose or full) allograft tissue.

There is moderate quality evidence, based on four moderate quality meta-analyses, of no significant differences in graft failure rate, patient-reported outcomes, or instrumented laxity outcomes between primary ACL reconstruction completed with autograft tissue and that completed with nonirradiated allograft tissue. It should be noted that irradiating allograft tissue is used as a means of reducing the risk of disease transmission.

There is moderate quality evidence, based on one moderate quality meta-analysis, of a significant difference in graft failure rate favouring autograft, between primary ACL reconstruction completed with autograft tissue and that completed with allograft tissue in young patients under the age of 25 and patients who are highly active.

This evidence does not take into account the risk of disease transmission with low or nonirradiated allograft tissue, ethical considerations associated with using cadaver tissue or the significantly greater costs associated with obtaining allograft tissue in Aotearoa/New Zealand.

6.2 Recommendations:

- Given the lack of evidence of any improvement in outcomes relative to autograft, and also considering the higher cost and the potential risk of disease transmission, allograft is not recommended for primary ACL reconstruction as a first option.
- Autograft remains the gold standard and should be the first option for primary ACL reconstruction in most cases. Poorer outcomes are associated with the use of irradiated allograft tissue (including low-dose irradiated tissue) for primary ACL reconstruction. There are risks around the performance of other methods of sterilization to prevent disease transmission.
- In particular, allograft is not recommended for young people, where there is evidence of worse outcomes including a higher rate of graft failure and revision surgery in young people under the age of 25 years who undergo an ACL reconstruction using allograft tissue.
- For some patients whose own tissue is not of high enough quality, allograft may be a suitable option. However, patients would need to be fully informed of the source of the donor tissue, and the potential risks, including the risks of graft failure and disease transmission. In addition, patients would need to understand and commit to the recommended standardized rehabilitation protocol, as the included reviews were unable to extrapolate their findings to situations where a standard rehabilitation protocol (2-3 months return to running, 6-12 months return to sports activities) was not followed.

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8 Appendices

8.1 Appendix A: Search Strategies

8.1.1 Cochrane Library searched 9 May 2016

#1 MeSH descriptor: [Allografts] explode all trees

#2 allograft*

#3 MeSH descriptor: [Anterior Cruciate Ligament] explode all trees

#4 Anterior Cruciate Ligament* or ACL:ti,ab,kw (Word variations have been searched)

#5 (#1 or #2) and (#3 or #4) Publication Year from 2006 to 2016

8.1.2 Ovid Medline & Ovid Epub Ahead of Print searched 10 May 2016

1. Anterior Cruciate Ligament/
2. exp Anterior Cruciate Ligament Reconstruction/
3. (Anterior Cruciate Ligament$ or acl).tw.
4. Allografts/
5. Transplantation, Homologous/
6. allograft$.tw.
7. (1 or 2 or 3) and (4 or 5 or 6)
8. limit 7 to yr="2006 -Current"
9. limit 8 to (english language and humans)
10. limit 9 to "review articles"
11. limit 9 to ("reviews (best balance of sensitivity and specificity)" or "prognosis (best balance of sensitivity and specificity)")
12. limit 9 to (consensus development conference or consensus development conference, nih or evaluation studies or government publications or guideline or meta analysis or practice guideline or systematic reviews)
13. or/10-12

8.1.3 Ovid Embase searched 11 May 2016

1. *anterior cruciate ligament/ or anterior cruciate ligament reconstruction/
2. ((Anterior Cruciate Ligament$ or acl) adj3 (reconstruct$ or repair$)).tw.
3. 1 or 2
4. *allograft/
5. *allotransplantation/
6. allograft$.ti,sh.
7. or/4-6
8. 3 and 7
9. limit 8 to (human and english language and yr="2006 -Current")

10. limit 9 to (meta analysis or "systematic review")

11. limit 9 to ("reviews (best balance of sensitivity and specificity)" or "prognosis (best balance of sensitivity and specificity)")

12. "systematic review"/

13. meta analysis/

14. exp practice guideline/

15. or/12-14

16. 15 and 9

17. 10 or 11 or 16

8.1.4 Medline In-Process searched 18 May 2016

1. (Anterior Cruciate Ligament$ or acl).tw.

2. allograft$.tw.

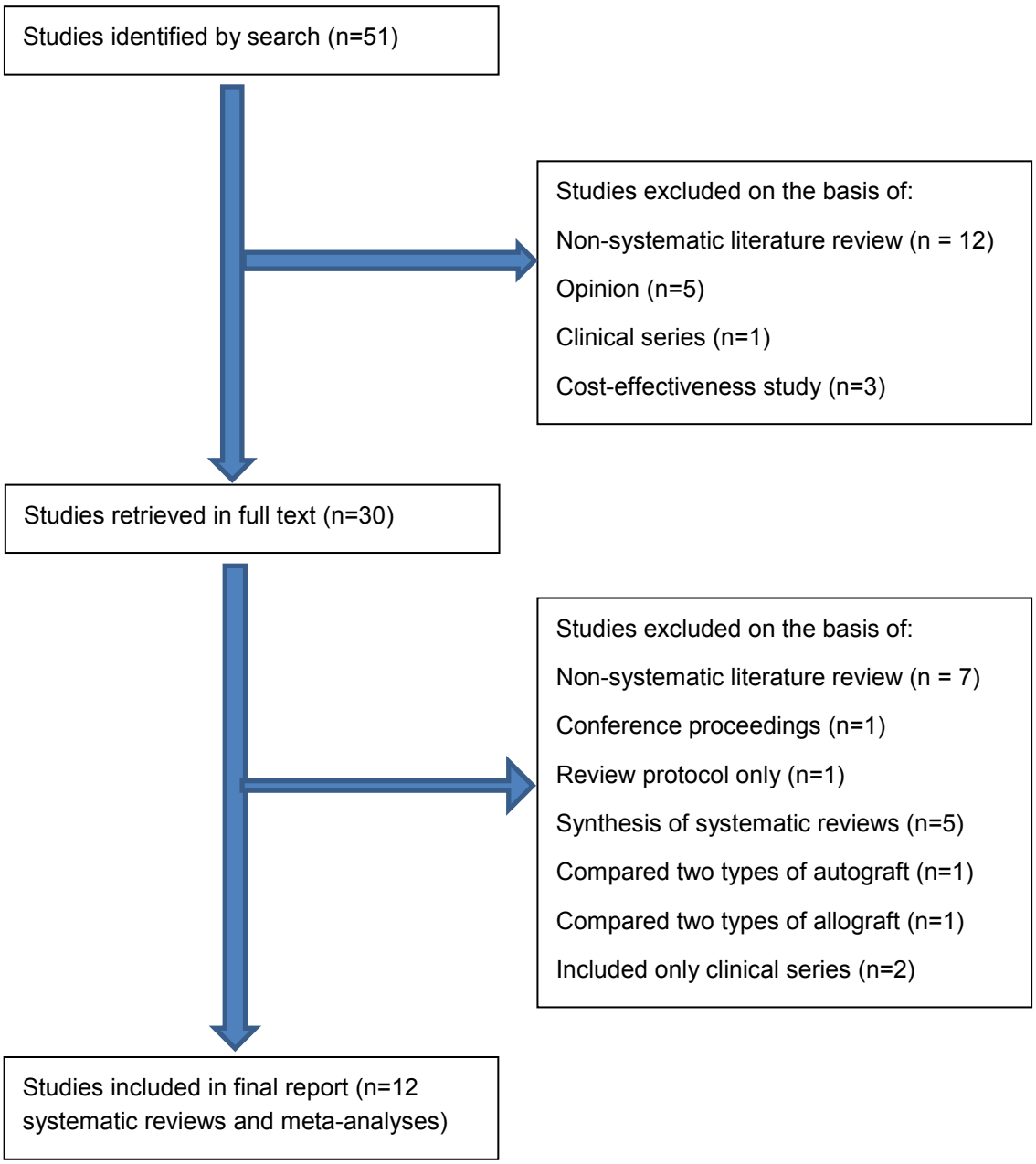
3. (homologous adj2 transplant$).tw.

4. 1 and (2 or 3)

5. limit 4 to english language

6. limit 5 to yr="2006 -Current"

8.2 Appendix B: Included and Excluded Studies Flow Diagram



8.3 Appendix C: Characteristics of randomized controlled trials comparing autograft and allograft for primary ACL reconstruction

Author	Enrolled patients	Follow-up duration (average months)	Mean age auto/allo (years)	Autograft type	Allograft type	Rehabilitation	Definition of graft failure	Failure rates
Sun et al (2009)	N=156	67	31.7/32.8	Patellar tendon	Patellar tendon – FF/NI	Standardised	Laxity >5mm	Auto: 6.6% Allo: 7.5%
Sun et al (2011)	N=186	94	29.6/31.2	Hamstring	Hamstring – FF/NI	Standardised	Laxity >5mm	Auto: 7.7% Allo: 8.4%
Noh et al (2011)	N=65	29.8	23.0/22.0	Hamstring	Achilles – FF/NI	Standardised	Reoperation	Auto: 3.0% Allo: 0.0%
Lawhorn et al (2012)	N=102	24	30.0/33.3	Hamstring	Tibialis Anterior – FF/NI	Standardised	Reoperation	Auto: 5.6% Allo: 8.3%
Bottoni et al (2014)	N=97 Military cadets	120	28.6	Hamstring	Tibialis Posterior – FF/NI	Standardised	Reoperation	Auto: 8.3% Allo: 26.5%

FF/NI = fresh frozen, nonirradiated

8.4 Appendix D: Evidence tables

Systematic Reviews

Study	Methodology	Outcomes & results	Paper Grading		Reviewer comments & evidence level
Carey et al (2009) Journal of Bone and Joint Surgery, 91: 2242 - 2250 **Study design:** Systematic review **Research Question** To investigate the short-term clinical outcomes of ACL with allograft versus autograft **Funding** National Institute of Health Smith and Nephew, DonJoy	**Search strategy** Embase, Medline searched up to March 2009 **Inclusion criteria** Prospective or retrospective comparative study with at least 15 patients in each study arm Patients of any age Unilateral anterior cruciate ligament reconstruction All patients followed-up for at least two years (average of two years follow-up across the participants was not sufficient) **Exclusion criteria** Case series Data from same patients reported in another study with longer follow-up **Review Process** Quality assessed by two authors – no specific instrument used Heterogeneity assessed qualitatively by comparing study design, populations, interventions, outcomes etc., and quantitatively using chi-square testing. Failure of these tests resulted in exclusion from the meta-analysis	**Included Studies** N = 9 primary studies included (1 excluded from the meta-analysis because it failed tests of homogeneity) RR and 95% CIs were calculated for nominal variables Sensitivity analyses performed 6 North American and 3 European studies, procedures performed between 1986 and 2000 5 prospective and 4 retrospective comparative studies Treatment determined by a combination of patient choice and allograft availability **Findings** **Graft failure** Failure not defined identically in all studies OR = 0.61 (95% CI 0.21 – 1.79) Outcomes much worse for the one study which included irradiated allograft tissue (45% clinical failure), so it was omitted from the meta-analysis. **Patient-reported outcomes** No significant differences between autograft and allograft. Lysholm scores pooled according to graft source. Meta-analysis indicated a mean difference of 1.5 favouring autograft (95% CI -1.1 to 4.1, p>0.25) **Instrumented Laxity**	Clearly defined research question Two people selected studies and extract data Comprehensive literature search carried out Authors clearly state how review is limited by publication type Included and excluded studies listed Characteristics of included studies are provided Scientific quality of included studies assessed and documented Scientific quality of included studies assessed appropriately Appropriate methods used to combine individual study	**Y** **Y** **Y** **Y** **N** **Y** **Y** **Y** **Y**	Limited by a lack of high quality studies and high drop-out rates in some of the included comparative studies. A strength was the use of tests of homogeneity to decide which studies should be included in the meta-analyses. The authors noted that none of the included studies stratified outcomes by age and there were significant age differences in the allograft and autograft groups for some studies. The authors suggested that the results of this review may not be generalizable to elite athletes, very young patients or very old patients. **Level of evidence: 2++**

		No significant differences in Lachman test, pivot-shift test, flexion deficit, one-leg-hop test, thigh circumference <u>Lachman test >5mm laxity cut-off</u> No significant differences within each study between autograft and allograft. Pooled data for 7 studies produced an odds ratio of 1.23 (95% CI 0.52 to 2.92, p=0.63). **Complications** No significant differences in anterior knee pain, patellofemoral pain, retropatellar pain, deep infection rate, arthrofibrosis, reoperation rates Incisional site complaints greater for autograft **Authors conclusions** Short term (two year) clinical outcomes of ACL reconstruction with allograft are not significantly different from those with autograft. Important to note that none of the included studies stratified outcomes by age or controlled for age or any other confounders in their analyses.	findings Likelihood of publication bias assessed Conflicts of interest declared Are results of study directly applicable to patient group targeted by guideline?	**Y** **Y** **Y**	

Study	Methodology	Outcomes & results	Paper Grading		Reviewer comments & evidence level
Prodromos et al (2007) **Knee Surgery Sports Traumatology Arthroscopy, 15: 851 - 856** **Study design:**	**Search strategy** PubMed searched to 2006 **Inclusion criteria** English language Prospective or retrospective comparative study, case series Used allograft for anterior cruciate ligament reconstruction Minimum follow-up of two years	**Included studies** N = 20 studies (including clinical series) **Assessment of studies** IKDC stability criteria used: Side to side difference of </= 2mm = normal A side to side difference of >5mm is classified as abnormal **Findings**	Clearly defined research question Two people selected studies and extract data Comprehensive literature search carried out Authors clearly state how review is limited	**Y** **N** **N**	Poor quality systematic review and meta-analysis. No appraisal of included studies – quality of studies not taken into account in analysis of findings. Case series included. Measures of instability varied. Literature search limited to one database (PubMed) The statistical methods used

Systematic review **Research question:** To investigate stability outcomes for allograft compared with autograft **Funding** Not stated	Stratified arthrometric stability rate reporting (not just averages) 30lb or maximum manual arthrometric testing force **Exclusion criteria** Amount of arthrometric force not specified **Review Process** Study selection and appraisal process not described	<u>Normal stability rate</u> Autograft = 72% Allograft = 59%, p<0.001 <u>Abnormal stability rate</u> Autograft = 5.3% Allograft = 14%, p<0.001 <u>BPTB autograft v BPTB allograft</u> *Normal stability* Autograft = 66% Allograft = 57% *Abnormal stability* Autograft = 5.9% Allograft = 16% <u>Hamstring autograft v soft tissue allograft</u> *Normal stability* Autograft = 77% Allograft = 64% *Abnormal stability* Autograft = 4.7% Allograft = 12% **Authors conclusions** Autografts have significantly better outcomes (clinical failure and laxity/stability outcomes) than allograft and are the graft of choice for routine primary ACL reconstruction.	by publication type Included and excluded studies listed Characteristics of included studies are provided Scientific quality of included studies assessed and documented Scientific quality of included studies assessed appropriately Appropriate methods used to combine individual study findings Likelihood of publication bias assessed Conflicts of interest declared Are results of study directly applicable to patient group targeted by guideline?	**N** **N** **Y** **N** **N** **?** **N** **N** **Y**	in this study have been criticised by other authors (Carey et al 2009) . **Level of evidence: 2-**

Study	Methodology	Outcomes & results	Paper Grading		Reviewer comments & evidence level
Wasserstein et al (2015)[8] Sports Health, 7(3): 207 – 216. **Study design:** Systematic review and meta-analysis **Research Question** To compare the failure rates of autograft and allograft for ACL reconstruction in young, active patients **Conflicts of interest** None	**Search strategy** Embase, Cochrane trials registry and Medline searched 1980 - 2014 Handsearching of included articles reference lists **Inclusion criteria** Prospective or retrospective comparative study Study population competitive athletes, active military, Marx score >12, varsity/college semi-professional or professional Patients aged <25 years old or stratified age outcomes if older patients included Unilateral primary ACL reconstruction with autograft compared with allograft Any clinically relevant outcome (patient-reported outcomes, physical examination, reoperation, failure) Minimum follow-up two years Minimum of 15 patients per treatment arm **Exclusion criteria** Case series, conference proceedings Average follow-up of two years not sufficient (needed all patients to be followed up for at least two years) Study superseded by longer follow-	**Included Studies** N = 874 studies identified of which 866 excluded N = 7 studies included in review: 1 RCT, 2 prospective cohort and 4 retrospective cohort studies Mean age across studies = 21.7 years Follow-up ranged from 24 – 51 months **Findings** **Graft Failures** Autograft = 9.6% Allograft = 25.0% RR = 0.36 (95% CI 0.24 – 0.53, p<0.0001) **Patient-reported outcomes** *Lysholm scores* No difference in Lysholm scores *Other patient-reported outcomes* Too much heterogeneity to pool results for other outcome measures **Authors conclusions** Higher rate of failure with use of allograft compared with autograft in a young, or highly active, population. Caution should be applied in using allograft with these patient subgroups. There is a paucity of data regarding whether this difference persists with non-irradiated allografts compared with autograft.	Clearly defined research question Two people selected studies and extract data Comprehensive literature search carried out Authors clearly state how limited review by publication type Included and excluded studies listed Characteristics of included studies are provided Scientific quality of included studies assessed and documented Scientific quality of included studies assessed appropriately Appropriate methods used to combine individual study findings Likelihood of publication bias	**Y** **Y** **Y** **Y** **Y** **Y** **Y** **Y** **N**	Good quality review. Limited by a lack of high quality studies. Only one study of nonirradiated allograft in young/active patient groups. Authors unable to conduct meta-analysis of many outcomes because of high heterogeneity. Overall findings with regards to graft failure rates echo those of the only included RCT which reported a failure rate of ~8% for autograft and ~26% for allograft. **Level of evidence: 1-**

	up with the same patients **Review processes** Two authors retrieved and selected references for inclusion Study quality assessed using validated checklists Heterogeneity tested for using Chi-squared test, random effects model used to pool data		assessed Conflicts of interest declared Are results of study directly applicable to patient group targeted by guideline?	 **N** **Y**	

Study	Methodology	Outcomes & results	Paper Grading		Reviewer comments & evidence level
Mariscalco et al (2014) American Journal of Sports Medicine, 42(2): 492 - 499 **Study design:** Systematic review and meta-analysis **Research Question:** To compare outcomes with autograft and non-irradiated allograft tissue **Funding:** National Institute	**Search strategy** Scopus, Embase, CINAHL, Cochrane Systematic Reviews searched up to October 2012 **Inclusion criteria** Prospective or retrospective comparative studies Compared outcomes of primary ACL reconstruction with autograft vs non-irradiated allograft tissue. Patients of all ages included Minimum of 15 patients in each group Mean follow-up of at least 2 years **Exclusion criteria** Did not state whether allograft tissue was irradiated or included irradiated tissue Cost-effectiveness studies	**Included Studies** N = 649 studies identified in the search of which N=640 excluded N = 9 studies included 3 randomised trials, 3 prospective cohort, 3 retrospective cohort BPTB autograft v BPTB allograft, n=6 Quadrupled hamstring tendon autograft v quadrupled hamstring tendon allograft, n=2 Quadrupled hamstring tendon autograft v anterior tibialis allograft, n=1 Mean patient age ranged from 24.5 to 32 years in 7 of 9 studies. 1 study had a patient age range of 40 – 54 years Mean follow-up ranged from 24 – 94 months **Findings** **Failure Risk (n=6 studies)** Defined as anterior laxity at least 5mm greater	Clearly defined research question Two people selected studies and extract data Comprehensive literature search carried out Authors clearly state how limited review by publication type Included and excluded studies listed Characteristics of included studies are provided Scientific quality of included studies assessed and	**Y** **Y** **Y** **Y** **N** **Y** **Y**	Well-conducted review limited by a lack of high quality studies. Authors cautioned against extrapolating the findings to younger, more active patient groups. **Level of evidence: 1-**

of Health	Not a comparative study Did not include minimum number of patients Follow-up too short **Review process** Two authors retrieved and selected references for inclusion Methodological quality of studies assessed using Delphi scoring system Two authors extracted data independently	than contralateral side Autograft = 6% Allograft = 5.5% **Instrumented Laxity (n=5 studies)** Anterior laxity – Lachman examination used in 5 studies. No statistical difference between autograft and allograft groups. Rotational laxity – pivot-shift examination used in 5 studies. No significant difference in autograft and allograft groups. **Patient-reported outcomes (n=9 studies)** Lysholm scores or subjective IKDC score used in 9 studies. No significant difference in any patient-reported outcome scores in any study. **Authors conclusions** No significant difference between autografts and nonirradiated allografts with regard to failure risk, post-operative laxity, or patient-reported outcome scores. These findings apply to patients in their late 20s and early 30s. We caution against extrapolating these findings to younger, more active cohorts.	documented Scientific quality of included studies assessed appropriately Appropriate methods used to combine individual study findings Likelihood of publication bias assessed Conflicts of interest declared Are results of study directly applicable to patient group targeted by guideline?	**Y** **Y** **N** **Y** **Y**	

Study	Methodology	Outcomes & results	Paper Grading		Reviewer comments & evidence level
Cvetanovich et al (2014) Arthroscopy, 30(12): 1616-1624 **Study design:** Systematic review	**Search strategy** PubMed, Cochrane Central Register of Controlled Trials, Embase searched. Dates not specified. **Inclusion criteria** RCTs comparing hamstring autograft with soft-tissue allograft in ACL	**Included Studies** N = 16 studies identified in the search of which N=11 excluded N = 5 randomised trials included Methodological quality of the studies was rated as poor – main limitation was a lack of blinding of patients and observers	Clearly defined research question Two people selected studies and extract data Comprehensive literature search	**Y** **Y** **Y**	Question regarding quality of search strategy but further hand searching of reference lists did not yield any additional studies. Dates of search not specified. Many different types of allograft used in the different studies. Also differences in inclusion of patients with co-existent meniscal

and meta-analysis **Research Question:** To compare outcomes with hamstring autograft versus soft-tissue allograft **Funding:** Not stated Several potential conflicts of interest declared	reconstruction Minimum of 6 months follow-up **Exclusion criteria** Studies including BTB grafts Less than 6 months follow-up Conference abstracts, case reports, retrospective studies, review articles Data superseded by a later publication from the same study **Review process** Two authors retrieved and selected references for inclusion Methodological quality of studies assessed using Modified Coleman Methodology Score and Jadad scale Two authors extracted data independently Data pooled and meta-analysis performed with RevMan software	Mean age of patients 29.9 ± 2.2 years Mean follow-up 47.4 ± 26.9 months (follow-up ranged from 24 – 93 months) Allografts for the studies were fresh-frozen hamstring, irradiated hamstring, mixture of fresh-frozen and cryo-preserved hamstring, fresh-frozen of tibialis anterior, fresh-frozen Achilles tendon **Findings** **Graft failures** Significantly longer operative time for autograft than allograft (n= 2 studies). Mean = 77.1 ± 2.0 mins v 59.9 ± 0.9 mins Reoperations: Allograft = 6; autograft = 7 Revision ACL reconstruction due to failure: Allograft = 2; autograft = 3 No cases in any study of deep infection, nerve injury, deep venous thrombosis, failure of fixation **Instrumented Laxity** No significant difference between allograft and autograft for the Lachman test, pivot-shift test, KT arthrometer testing. One study used irradiated allograft and showed greater laxity compared with autograft. When this study was removed from analyses it reduced heterogeneity but did not alter the results of the meta-analyses for all tests. **Patient-reported outcomes** No significant difference between autografts and allografts for any of the other outcome measures, including Lysholm score, Tegner score, IKDC grade.	carried out Authors clearly state how limited review by publication type Included and excluded studies listed Characteristics of included studies are provided Scientific quality of included studies assessed and documented Scientific quality of included studies assessed appropriately Appropriate methods used to combine individual study findings Likelihood of publication bias assessed Conflicts of interest declared Are results of study directly applicable to patient group targeted by guideline?	 **Y** **N** **Y** **Y** **Y** **Y** **N** **Y** **Y**	or cartilage surgery. **Level of evidence: 1-** **Grade of evidence:**

		Authors conclusions No significant differences in clinical outcome measures, laxity or reoperations in patients undergoing ACL reconstruction with hamstring allograft or soft-tissue autograft. Results may not extrapolate to younger populations.			

Study	Methodology	Outcomes & results	Paper Grading		Reviewer comments & evidence level
Hu et al (2013) International Orthopaedics, 37: 311 - 320 **Study design:** Systematic review and meta-analysis **Research Question:** To compare clinical outcomes for primary ACL reconstruction using allograft and autograft **Funding:** National Natural Science Foundation of China No conflicts of interest declared	**Search strategy** PubMed, Cochrane Central Register of Controlled Trials, Embase, Scopus, Cochrane Database of Systematic Reviews searched up to 31 October 2012 **Inclusion criteria** Prospective studies comparing allograft with autograft for primary ACL reconstruction Patients with unilateral ACL rupture BPTB autograft compared with BPTB allograft OR soft tissue autograft compared with soft tissue allograft No language restrictions Minimum of 2 years follow-up Use of non-irradiated allografts **Exclusion criteria** Case-control or retrospective cohort study, conference abstracts, case series, review articles Use of gamma-irradiated allografts BPTB grafts versus soft tissue grafts	**Included Studies** N = 406 studies identified in the search of which N=397 excluded N = 9 prospective comparative studies included Mean age of patients ranged from 23 to 32 years Mean age = 29.9 ± 2.2 years Mean follow-up ranged from 24 – 95 months Five studies compared BPTB grafts, 2 compared hamstring grafts, 1 compared hamstring autograft and anterior tibialis allograft, 1 compared hamstring autograft with free tendon Achilles allograft. Allografts for the studies were fresh-frozen or cryo-preserved. **Findings** **Graft failures and complications** <u>Anterior knee pain</u> (n=3 studies) No significant difference between autograft and allograft in 3 studies <u>Rate of incisional site complaints</u> 53% autograft and 7% allograft (Peterson et al.) <u>Knee range of motion</u> (n=7 studies) No significant difference between autograft and allograft in 6 studies, 1 study reported	Clearly defined research question Two people selected studies and extract data Comprehensive literature search carried out Authors clearly state how limited review by publication type Included and excluded studies listed Characteristics of included studies are provided Scientific quality of included studies assessed and documented Scientific quality of included studies	**Y** **Y** **Y** **Y** **N** **Y** **Y** **Y**	Limited comparisons to BPTB autograft v BPTB allograft and soft tissue autograft v soft tissue allograft. Authors suggested two years follow-up may be too short. Impacts of patient characteristics such as age, gender, activity level could not be analysed due to a lack of data. Overall a well-conducted review limited mainly by heterogeneity in reported outcomes and a lack of long-term follow-up. **Level of evidence: 1-**

	Review process Two authors retrieved and selected references for inclusion Methodological quality of studies assessed using Detsky Scale for RCTs and Newcastle-Ottawa Scale for prospective cohort studies Two authors extracted data independently Data pooled and meta-analysis performed with RevMan software	significantly more extension loss with autograft compared with allograft. <u>Infection/arthrofibrosis/reoperation</u> No significant difference between autograft and allograft. <u>Graft Failure (n=6 studies)</u> Clinical failures reported in 4/286 patients in the autograft group (1.4%) and 6/280 patients in the allograft group (2.1%). No significant difference in risk ratio of graft failure (RR = 0.67, 95% CI 0.1 to 4.36, p=0.68) **Instrumented Laxity** <u>KT-Arthrometer test</u> (n=6 studies) No significant difference in risk ratio for side-to-side difference >5mm (RR=1.19, 95% CI 0.63 – 2.24, p=0.59) <u>Lachman Test</u> (n=6 studies) No significant difference in risk ratio for abnormal Lachman test (grade>0) (RR = 0.88, 95% CI 0.64 – 1.2, p=0.41) <u>Pivot Shift Test</u> (n=7 studies) No significant difference in risk ratio for abnormal pivot shift test (RR = 0.97, 95% CI 0.64 – 1.46, p=0.88) **Patient-reported outcomes** No significant difference in risk ratio for abnormal IKDC score (RR=0.96, 95% CI 0.6 - 1.54, p=0.87) No significant difference in Lysholm scores (Mean difference 0.3, 95% CI -1.97 to 2.57, p=0.79). Mean difference in Tegner scores = 0.25 (95% CI -0.01 to 0.52, p=0.06) in favour of autograft. **Subgroup Analyses** BPTB graft only – no change in findings except	assessed appropriately Appropriate methods used to combine individual study findings Likelihood of publication bias assessed Conflicts of interest declared Are results of study directly applicable to patient group targeted by guideline?	 **Y** **N** **Y** **Y**	

		Tegner scores. Tegner scores (4 studies) showed a mean difference of 0.5 in favour of autograft (95% CI 0.15 – 0.85, p=0.005) **Authors conclusions** No significant differences in outcomes between allograft and autograft. Only five of the nine studies reported donor-site morbidity and these symptoms were measured differently across studies, making it difficult to conduct a meta-analysis of findings.			

Study	Methodology	Outcomes & results	Paper Grading		Reviewer comments & evidence level
Krych et al (2008) Arthroscopy, 24(3): 292 - 298 **Study design:** Systematic review and meta-analysis **Research Question:** To compare outcomes with patellar tendon autograft versus patellar tendon allograft **Funding:** Mayo Clinic No conflicts of	**Search strategy** Medline, Scopus, Web of Science, Embase up to April 2006 **Inclusion criteria** Prospective studies comparing BPTB autograft with BPTB allograft in ACL reconstruction With identical rehabilitation protocols Minimum of 2 years follow-up **Exclusion criteria** Allografts other than BPTB Less than 2 years follow-up Non-prospective comparative study **Review process** Two authors retrieved and selected references for inclusion Not stated whether methodological quality of papers was assessed or	**Included Studies** N = 548 studies identified in the search of which N=542 excluded N = 6 prospective studies included N= 534 patients in total (256 autograft and 278 allograft) Mean age of patients 29.9 ± 2.2 years Mean follow-up 47.4 ± 26.9 months (follow-up ranged from 24 – 93 months) **Postoperative treatment** Postoperative management varied between studies but was relatively consistent within studies. It generally included early weightbearing and ROM exercises, with return to full activity between 6 – 12 months. **Findings** **Graft Failures** Rate of Reoperations (n = 3 studies) Allograft = 13; autograft = 8	Clearly defined research question Two people selected studies and extract data Comprehensive literature search carried out Authors clearly state how limited review by publication type Included and excluded studies listed Characteristics of included studies are provided Scientific quality of included studies assessed and	**Y** **Y** **Y** **Y** **N** **Y** **Y**	Review was limited by a lack of high quality studies. Included studies were not appraised for quality. **Level of evidence: 1-**

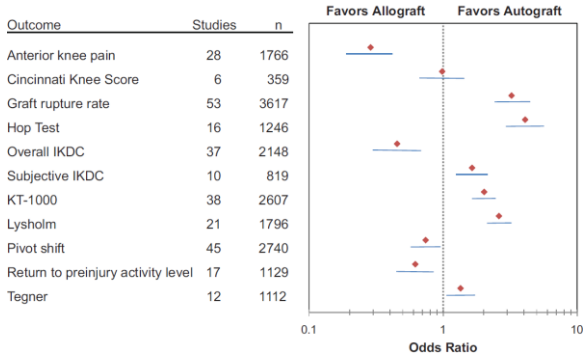
interest	with what scale Two authors extracted data independently Data pooled and meta-analysis performed – odds ratios calculated	No significant difference (OR = 1.2, 95% CI 0.44 – 3.27) Graft rupture (n=5 studies) Significantly more ruptures in allograft group OR = 5.03 (95% 1.38 – 18.33, p=0.01) **Instrumented Laxity (n=4 studies)** No significant difference between allograft and autograft for the Lachman test, pivot-shift test, patellofemoral crepitus. Return to pre-injury activity level (n=3 studies) No significant difference for return to sports in any of the studies. Hop Test (n=3 studies) OR = 5.66 (95% CI 3.09 – 10.36, P<0.01) significantly favoured autograft **Patient-reported outcomes** IKDC scores (n=3 studies) No significant differences between autograft and allograft. **Heterogeneity** One study included irradiated grafts with acetone drying process. This study showed significantly worse outcomes than the other studies. When this study was excluded, heterogeneity tests were no longer significant and there were no significant differences in outcomes between autograft and allograft groups. **Authors conclusions** "Studies in the literature have shown allograft rupture rates from 7% to 13%, 9 and autograft rupture rates between 5% and 7%.1,24 Salmon et al.25 report that risk factors for ACL graft rupture include return to competitive side-stepping, pivoting, or jumping sports, and the contact	documented Scientific quality of included studies assessed appropriately Appropriate methods used to combine individual study findings Likelihood of publication bias assessed Conflicts of interest declared Are results of study directly applicable to patient group targeted by guideline?	 **Y** **Y** **N** **Y** **Y**	

		mechanism of the index injury" In this meta-analysis, graft failure and functional outcome as measured by single-leg hop test favored ACL reconstruction with BPTB autograft over BPTB allograft. However, when irradiated and chemically processed grafts were excluded, no significant differences were found in all measurable outcomes."			

Study	Methodology	Outcomes & results	Paper Grading		Reviewer comments & evidence level
Lamblin et al (2013) Arthroscopy , 29(6): 1113 - 1122 **Study design:** Systematic review and meta-analysis **Research Question:** To compare outcomes with autograft and nonirradiated, non-chemically treated allograft **Funding:** Fremont Orthopedic Associates No conflicts of	**Search strategy** PubMed, Cochrane databases, CINAHL, and Embase searched 1980 - 2012 **Inclusion criteria** Prospective studies comparing autograft with nonirradiated allograft in primary ACL reconstruction Minimum 25 patients in each arm Minimum of 2 years follow-up **Exclusion criteria** Used irradiated tissue Insufficient follow-up Insufficient outcome measures **Review process** Three authors retrieved and selected references for inclusion Studies assessed for quality but method/scale not stated Three authors extracted data	**Included Studies** N = 596 studies identified in the search of which N=585 excluded N = 11 studies included Mean age of patients ranged from 24 – 37 years Mean follow-up ranged from 24 – 94 months **Postoperative treatment** All studies used a standard rehabilitation protocol with return to running 3-6 months postoperatively and a return to full activity between 6 – 12 months. All protocols allowed early weightbearing, early motion, and mobility with the assistance of a postoperative brace **Findings** **Graft Failures** Defined as persistent instability, 2 or 3+ on pivot shift testing, 10mm or greater laxity on KT-1000 evaluation, or revision ACL reconstruction No significant difference between allograft and autograft Autograft failure range 0 – 8.1%; Mean = 2.8%	Clearly defined research question Two people selected studies and extract data Comprehensive literature search carried out Authors clearly state how limited review by publication type Included and excluded studies listed Characteristics of included studies are provided Scientific quality of included studies assessed and documented	**Y** **Y** **Y** **Y** **N** **Y** **Y**	Well conducted review, although the details of the quality assessment of included studies was not provided. The authors discussed the shortcomings of included primary studies, including a lack of randomisation, blinding and small samples in single institution studies. Of particular importance, the authors pointed out that all the included studies used a standardised rehabilitation protocol. **Level of evidence: 1-**

interest declared	independently Data pooled and meta-analysis performed – odds ratios calculated	Allograft failure range 0 – 9.1%, Mean = 3.6% **Instrumented Laxity (n=4 studies)** No significant difference between allograft and autograft for the Lachman test, pivot-shift test, or KT-1000 evaluation **Patient-reported outcomes** IKDC scores (n=3 studies) No significant differences between autograft and allograft in IKDC scores or Lysholm scores. **Authors conclusions** No significant differences in various functional and objective outcome measures after ACL reconstruction with autografts and nonirradiated allografts. All of the included studies used a standardised rehabilitation protocol. Lack of data investigating the use of allograft in young or athletic populations. There were various limitations in study quality which may have affected outcomes.	Scientific quality of included studies assessed appropriately Appropriate methods used to combine individual study findings Likelihood of publication bias assessed Conflicts of interest declared Are results of study directly applicable to patient group targeted by guideline?	**N** **Y** **N** **Y** **Y**	

Study	Methodology	Outcomes & results	Paper Grading		Reviewer comments & evidence level
Kraeutler et al (2013) American Journal of Sports Medicine, 41 (10): 2439 – 2448. **Study design:** Systematic review and meta-analysis **Research**	**Search strategy** Medline searched January 1998 to April 2012 **Inclusion criteria** Studies reporting data on BPTB grafts for primary ACL reconstruction – studies were not required to be comparative or prospective Minimum of 2 years follow-up	**Included Studies** N = 76 studies included including 5182 patients (4276 autograft and 906 allograft patients) Mean age (autograft) = 27.6 years Mean age (allograft) = 32.3 years Mean follow-up at least 52 months for each outcome. Surgical procedure reported in 69/76 studies - anteromedial, transtibial and outside-in techniques used. Only 1 study used the contralateral patellar tendon for autograft.	Clearly defined research question Two people selected studies and extract data Comprehensive literature search carried out Authors clearly state how limited review by	**Y** **Y** **N** **N**	The use of one database (Medline) reduced the search quality overall, and the authors did not indicate how many papers they identified in total in the search, or how many were excluded. Included non-comparative studies with no assessment of data quality. The results presented were for all allograft types, without sub-

Question: To compare outcomes with bone-patellar tendon-bone autograft and bone-patellar tendon-bone allograft in ACL reconstruction **Funding:** Department of Orthopaedics, University of Colorado No conflicts of interest declared	**Exclusion criteria** Studies which focussed specifically on older populations e.g. 40 years or older; workers' compensation cases Less than 2 years follow-up Data on revision ACLR **Review process** Two authors retrieved and selected references for inclusion Methodological quality of studies assessed using Modified Coleman Methodology Score and Jadad scale Two authors extracted data independently Data pooled and meta-analysis performed with RevMan software	Allografts included those fresh-frozen and irradiated. **Findings** **Clinical Outcomes** **Graft Rupture Rate (n=53 studies)** Overall rate = 4.3% autograft, 12.7% allograft OR = 3.24 (95% CI 2.41 – 4.36) **Returned to Pre-Injury Activity Level (n=17 studies)** Mean (autograft) = 57.1% Mean (allograft) = 68.3% OR = 0.62 (95% CI 0.45 – 0.85) **Patient Satisfaction Outcomes** 1 study directly compared patient satisfaction with allograft and autograft. The authors suggested the subjective IKDC and Lysholm scores could be used as proxies for patient satisfaction – both of these outcomes were significantly in favour of autograft. **Physical Laxity Outcomes**  **Authors conclusions** Of the 11 outcomes evaluated in this meta-analysis, we found that 6 of them significantly	publication type Included and excluded studies listed Characteristics of included studies are provided Scientific quality of included studies assessed and documented Scientific quality of included studies assessed appropriately Appropriate methods used to combine individual study findings Likelihood of publication bias assessed Conflicts of interest declared Are results of study directly applicable to patient group targeted by guideline?	**N** **Y** **N** **N** **Y** **N** **Y** **Y**	analyses for irradiated versus non-irradiated v partially irradiated graft tissue. Given the poorer outcomes for irradiated tissue reported in some other studies, the findings reported here may not provide a full representation of the performance of BPTB allograft compared with autograft. **Level of evidence: 1-**

		favored the use of patellar tendon autografts for ACL reconstruction, while 4 of them significantly favored patellar tendon allografts. We have reasonably shown that autograft patients have a lower rate of graft rupture and a lower level of knee laxity, can jump farther, and may be more generally satisfied compared with allograft patients. For most patients, especially those who are younger and more active, we recommend BPTB autograft for ACLR, primarily because of its lower rupture rate and higher patient satisfaction.			

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Yao et al (2015) European Journal of Orthopaedic Surgical Traumatology, 25: 355 - 365 **Study design:** Systematic review and meta-analysis **Research Question:** To compare outcomes with patellar tendon autograft versus patellar tendon allograft in ACL reconstruction **Funding:**	**Search strategy** PubMed, Cochrane Library, Embase searched up to June 2013 **Inclusion criteria** Prospective or retrospective comparative studies comparing BPTB autograft with BPTB allograft in primary ACL reconstruction Minimum of 2 years follow-up Included subjective and objective outcome measures **Exclusion criteria** Studies including BPTB grafts v any other graft Less than 2 years follow-up Case-control study design or below Patients younger than 18 years **Review process** Two authors retrieved and selected	**Included Studies** N = 578 studies identified in the search of which N=565 excluded N = 6 prospective and N=7 retrospective cohort studies included Mean age of patients ranged from 21 to 47 years Follow-up ranged from 24 to 78 months **Findings** **Clinical Outcomes** Graft failure/reoperation: OR = 0.31 (95% CI 0.13 to 0.78, p=0.01) in favour of autograft Total events (autograft) =4 Total events (allograft) = 18 No significant difference in post-operative anterior knee pain or crepitus. **ACL Laxity on Physical Examination (n=5 studies)** No significant difference in one-hop test, range of	Clearly defined research question Two people selected studies and extract data Comprehensive literature search carried out Authors clearly state how limited review by publication type Included and excluded studies listed Characteristics of included studies are provided Scientific quality of included studies assessed and	**Y** **Y** **Y** **Y** **N** **Y** **Y**	Reasonably good review limited mainly by the lack of randomised trials. No information about the effect of different rehabilitation protocols. The authors rated all of the included studies as high quality (Newcastle-Ottowa score >/= 7). The authors state that autograft provides earlier firm fixation, thereby allowing patients to return more quickly to more intense activity without a feeling of instability. This is represented by the significant difference in Tegner scores. The difference in graft failure disappeared when irradiated allograft studies were excluded, suggesting irradiation weakens the allograft tissue structure. **Level of evidence: 1-**

Not stated No conflicts of interest declared	references for inclusion Methodological quality of studies assessed using Newcastle-Ottawa Scale Two authors extracted data independently Data pooled and meta-analysis performed with RevMan software	motion, overall IKDC, Lysholm score, Tegner score, KT-1000 score, Lachman test or pivot-shift test. **Fresh-frozen v irradiated allograft sensitivity analyses** Results for two subgroups (irradiated and fresh-frozen allograft tissue) were compared. Results for fresh-frozen allograft samples were similar to those of the main analyses, except there was a significant difference in Tegner scores, in favour of autograft (WMD = 0.38, 95% CI 0.11 – 0.65, p = 0.006). **Authors conclusions** No differences in most clinical outcomes. Compared with BPTB allograft, BPTB autograft has a lower rate of graft failure, but this finding disappeared in the subgroup analysis which excluded irradiated allograft studies.	documented Scientific quality of included studies assessed appropriately Appropriate methods used to combine individual study findings Likelihood of publication bias assessed Conflicts of interest declared Are results of study directly applicable to patient group targeted by guideline?	 **Y** **Y** **N** **Y** **Y**	

Study	Methodology	Outcomes & results	Paper Grading		Reviewer comments & evidence level
Wei et al (2014) The Knee, 22: 372 - 379 **Study design:** Systematic review and meta-analysis **Research Question:** To compare outcomes for	**Search strategy** Medline, Cochrane Library databases, Embase searched up to July 2013 References lists of identified studies also searched for additional references Current controlled trials website searched for ongoing and unpublished studies	**Included Studies** N = 664 studies identified in the search of which N= 54 were retrieved as full text papers. A further 42 studies were excluded once the full text had been screened. N = 5 RCTs and N=7 prospective cohort studies included Mean age of patients ranged from 24 to 47 years Follow-up ranged from 24 to 94 months Autografts were mostly BPTB (n=8) and	Clearly defined research question Two people selected studies and extract data Comprehensive literature search carried out Authors clearly state how limited review by	**Y** **Y** **Y** **Y**	Comprehensive search and assessment of study qualities. No examination of the effect of rehabilitation protocols. **Level of evidence: 1-**

autograft and non-irradiated allograft for primary ACL reconstruction **Funding:** Not stated No conflicts of interest declared	**Inclusion criteria** Prospective comparative studies (Level I or II) comparing autograft with nonirradiated allograft Primary ACL reconstruction Arthroscopic reconstruction English language **Exclusion criteria** Used irradiated allograft tissue Same trial but data superseded by a longer follow-up **Review process** Two authors retrieved and selected references for inclusion Methodological quality of studies assessed using modified Oxford scale and the "Evaluation System for Non-randomised studies" Two authors extracted data independently Data pooled and meta-analysis performed with RevMan software	hamstring tendon (n=4). Allograft sources were anterior tibialis, hamstring tendon, BPTB, and Achilles tendon **Findings** **Clinical Outcomes** Graft failure/reoperation: RR = 0.93 (95% CI 0.5 to 1.73, p=0.82), not significant No other significant differences in complication rates **ACL Laxity on Physical Examination** No significant difference in one-leg hop test, range of motion, overall IKDC, subjective IKDC, anterior drawer test, Tegner score, KT-1000 score, Lachman test or pivot-shift test. Significant difference in Lysholm score favouring autograft (WMD = -1.46, 95% CI -2.46 to -0.07, p=0.004). This was not considered clinically significant by the authors. **Soft tissue v BPTB sensitivity analyses** Results for two subgroups (soft tissue and BPTB) were compared. The significant differences in Lysholm scores and instrumented laxity tests were repeated for the soft tissue autograft v allograft analyses. The BPTB autograft v allograft analyses showed no significant differences in any measures. **Authors conclusions** Patients with autografts exhibited little clinical advantage over those with nonirradiated allografts with respect to knee stability, function, and side effects.	publication type Included and excluded studies listed Characteristics of included studies are provided Scientific quality of included studies assessed and documented Scientific quality of included studies assessed appropriately Appropriate methods used to combine individual study findings Likelihood of publication bias assessed Conflicts of interest declared Are results of study directly applicable to patient group targeted by guideline?	**N** **Y** **Y** **Y** **Y** **Y** **Y**	